The GALE ENCYCLOPEDIA *of* NEUROLOGICAL DISORDERS

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VOLUME

A-L

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The Gale Encyclopedia of Neurological Disorders

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PLEASE READ—IMPORTANT INFORMATION

The Gale Encyclopedia of Neurological Disorders is a medical reference product designed to inform and educate readers about a wide variety of diseases, syndromes, drugs, treatments, therapies, and diagnostic equipment. Thomson Gale believes the product to be comprehensive, but not necessarily definitive. It is intended to supplement, not replace, consultation with a physician or other healthcare practitioner. While Thomson Gale has made substantial efforts to provide information that is accurate, comprehensive, and up-to-date, Thomson Gale 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 are advised to seek professional diagnosis and treatment for any medical condition, and to discuss information obtained from this book with their healthcare providers.

INTRODUCTION

The Gale Encyclopedia of Neurological Disorders (GEND) is a one-stop source for medical information that covers diseases, syndromes, drugs, treatments, therapies, and diagnostic equipment. It keeps medical jargon to a minimum, making it easier for the layperson to use. *The Gale Encyclopedia of Neurological Disorders* presents authoritative and balanced information and is more comprehensive than single-volume family medical guides.

SCOPE

Almost 400 full-length articles are included in *The Gale Encyclopedia of Neurological Disorders.* Articles follow a standardized format that provides information at a glance. Rubrics include:

Diseases

- Definition
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INCLUSION CRITERIA

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

ABOUT THE CONTRIBUTORS

The essays were compiled by experienced medical writers, physicians, nurses, and pharmacists. GEND medical advisors reviewed most of the completed essays to insure that they are appropriate, up-to-date, and medically accurate.

HOW TO USE THIS BOOK

The *Gale Encyclopedia of Neurological Disorders* has been designed with ready reference in mind:

- Straight **alphabetical arrangement** allows users to locate information quickly.
- Bold faced terms function as print hyperlinks that point the reader to full-length entries in the encyclopedia.
- A list of **key terms** is provided where appropriate to define unfamiliar words or concepts used within the context of the essay.
- **Cross-references** placed throughout the encyclopedia direct readers to where information on subjects without their own entries can be found. Cross-references are also used to assist readers looking for information on diseases that are now known by other names; for example, there is a cross-reference for the rare childhood disease commonly known as Hallervorden-Spatz disease that points to the entry entitled Pantothenate kinase-associated neurodegeneration.
- A **Resources** section directs users to sources of further information, which include books, periodicals, websites, and organizations.
- A **glossary** is included to help readers understand unfamiliar terms.
- A comprehensive **general index** allows users to easily target detailed aspects of any topic.

GRAPHICS

The Gale Encyclopedia of Neurological Disorders is enhanced with over 100 images, including photos, tables, and customized line drawings.

ADVISORY BOARD

An advisory board made up of prominent individuals from the medical and healthcare communities provided invaluable assistance in the formulation of this encyclopedia. They defined the scope of coverage and reviewed individual entries for accuracy and accessibility; in some cases they contributed entries themselves. We would therefore like to express our great appreciation to them:

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Abetalipoproteinemia *see* **Bassen-Kornzweig syndrome**

Abulia

Definition

Abulia is a state in which an individual seems to have lost will or motivation.

Description

Abulia is not a separate condition; rather, it is a symptom associated with various forms of brain injury. It may occur in association with a variety of conditions, including **stroke**, brain tumor, traumatic brain damage, bleeding into the brain, and exposure to toxic substances.

Causes and symptoms

Some research suggests that abulia occurs due to malfunction of the brain's dopamine-dependent circuitry. Injuries to the frontal lobe (the area of the brain responsible for higher thinking) and/or the basal ganglia (the area of the brain responsible for movement) can interfere with an individual's ability to initiate speech, movement, and social interaction. Abulia has been noted in patients who have suffered brain injuries due to stroke, bleeding into the brain from a ruptured aneurysm, trauma, brain tumor, neurological disease (such as **Parkinson's disease**), psychiatric condition (such as severe **depression** or **schizophrenia**), and exposure to toxic substances (such as cyclosporin-A).

An individual with abulia may not appear to have much will or motivation to pursue activities or initiate conversation. Such an individual may appear apathetic, disinterested, asocial, quiet or mute, physically slowed or still (hypokinetic), and emotionally remote.

Key Terms

Basal ganglia A group of brain structures that are responsible for movement.

Dopamine A brain chemical (neurotransmitter) responsible for carrying messages throughout the nervous system, particularly messages regarding movement.

Frontal lobe The area of the brain responsible for higher thinking.

Diagnosis

Abulia is not an individual diagnosis; it is a symptom that usually occurs as part of a constellation of symptoms accompanying a specific disorder. Diagnosis of the underlying disorder depends on the kinds of symptoms that co-exist with abulia. Psychiatric interview, **magnetic resonance imaging (MRI)**, ultrasound, or computed tomography (**CT**) imaging of the brain, EEG, blood tests, and neurological testing may all be used to diagnose an underlying condition.

Treatment team

Treatment of abulia is usually part of a program of general rehabilitation for the symptoms accompanying the underlying condition. A **neurologist** or psychiatrist may lead a treatment team. Other professionals that may be involved include physical therapists, occupational therapists, recreational therapists, and speech and language therapists.

Treatment

There are no specific treatments for abulia. The underlying condition should be treated such as administering antidepressants or electroconvulsive therapy to depressed patients or antipsychotic medications to schizophrenic patients. Patients who have suffered brain injury due to

stroke, bleeding, or trauma will benefit from rehabilitation programs that provide stimulation and attempt to re-teach skills.

Research has looked at the possibility of treating abulia with medications that boost the activity of dopamine throughout the brain, but this is far from becoming a standard treatment.

Prognosis

The prognosis of abulia depends on the prognosis of the underlying condition.

Resources

BOOKS

Friedman, Joseph H. "Mood, Emotion, and Thought." In *Textbook of Clinical Neurology*, edited by Christopher G. Goetz. Philadelphia: W. B. Saunders Company, 2003.

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Al-Adawi, Samir. "Abulia: The Pathology of 'Will' and Dopaminergic Dysfunction in Brain-Injured Patients." *Medical Sciences* 1 (1999): 27–40.

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Pantoni, L. "Abulia and Cognitive Impairment in Two Patients with Capsular Genu Infarct." *Acta Neurologica Scandinavia* 104, no. 3 (1 September 2001): 185–190.

Vijayaraghavan. "Abulia: A Delphi Survey of British Neurologists and Psychiatrists." *Movement Disorders* 17, no. 5 (September 2002): 1052–1057.

Rosalyn Carson-DeWitt, MD

Acanthocytosis *see* **Bassen-Kornzweig syndrome**

Acetazolamide

Definition

Acetazolamide (a-set-a-ZOLE-a-mide) is a carbonic anhydrase inhibitor. Carbonic anhydrase is an enzyme that shifts the rate of reaction to favor the conversion of carbon dioxide and water into carbonic acid, bicarbonate ions, and free protons. Carbonic anhydrase activity is key to the regulation of pH and fluid balance in many different reactions throughout the body.

Fluid buildup can alter the shape of the eye and cause pressure on the optic nerve. Clinically, this condition is described as glaucoma. Inhibition of the enzymatic work of carbonic anhydrase activity (e.g., through the action of a carbonic anhydrase inhibitor) can lower fluid pressure in the eye.

Purpose

Acetazolamide is used to treat a number of disorders, including the control of epileptic **seizures** in those individuals who suffer **epilepsy**.

Acetazolamide is also used to treat non-neurological disorders such as glaucoma (acetazolamide decreases pressure in the eye), and to reduce the symptoms of edema (an excess storage of water by the body that leads to localized swelling or puffiness) and altitude sickness.

Description

Acetazolamide is prescription medication and is available only with a licensed physician's prescription. Acetazolamide is available in oral form in extended release capsules and tablets. Acetazolamide can also be administered by injection.

Recommended dosage

For both adults and children the recommended dosage for use in epilepsy cases is based upon actual body weight. In all cases, the exact dosage is determined by an experienced physician and/or pharmacist. In the most common cases, the normal recommended dosage is 4.5 mg per pound of body weight (10 mg per kg of body weight) and is administered in multiple (divided) doses delivered in the form of tablets or capsules.

Doses must be taken on a regular schedule but individuals should not double dose to make up for a missed dose.

When used to control anticonvulsive seizures, acetazolamide doses should not be stopped all at once. In most cases, physicians usually curtail (gradually lower) the dose an individual takes over time.

Precautions

As with most prescription medicines, acetazolamide should stored in a safe place—away from the reach of children. Acetazolamide should also be stored in a dry area away from excessive heat or light. Outdated medicine (medicines past their expiration date) should be discarded in a container that is safe from the reach of children.

Women who are pregnant, plan to become pregnant, or who are breast-feeding infants should inform their physician of this fact before taking acetazolamide.

Side effects

Unwanted side effects while taking acetazolamide include drowsiness, **fatigue**, or a dizzy lightheaded feeling. Individuals who experience these side effects should not

Key Terms

Carbonic anhydrase An enzyme that shifts the rate of reaction to favor the conversion of carbon dioxide and water into carbonic acid, bicarbonate ions, and free protons.

Optic nerve The bundle of nerve fibers that carry visual messages from the retina to the brain.

operate machinery or drive while experiencing these symptoms. Other common side effects include shortness of breath.

Acetazolamide can also lead to excessive depletion (loss) of potassium from the body. To counter this potential loss, many physicians recommend that patients eat food or drink beverages such as orange juice to replace lost potassium. The loss of potassium does not occur in every case, however, and high levels of potassium can also be dangerous. Individuals who show signs of potassium loss—including, but not limited to, dryness of mouth, increased thirst, or muscle cramps—should alert their physician. Because diet can impact a number of health factors, individuals should only alter their diet after consulting their physician.

Individuals who are diabetic and who take acetazolamide may experience elevated sugar levels in their urine and blood.

Individuals who experience changes in their vision should also consult their physician.

In some rare cases, individuals may suffer **depression**, pains in the area of the kidneys, and bloody or black tarry stools.

Interactions

Physicians and pharmacists are trained to evaluate the potential for adverse interactions by prescription drugs with other drugs. In the case of acetazolamide physicians evaluate potential adverse reactions with a range of drugs that include—but are not limited to—amphetamines, over-the-counter aspirins, cyclosporine, mood altering drugs (e.g., lithium), drugs used to control mental depression, drugs used to control irregular heartbeats, digoxin, diuretics (also known as water pills), and vitamins.

Resources

PERIODICALS

Varadkar S., J. S. Duncan, and H. Cross. "Acetazolamide and Autosomal Dominant Nocturnal Frontal Lobe Epilepsy." *Epilepsia* 44 (July 2003): 986.

OTHER

Medline Plus. U.S. National Library of Medicine and the National Institutes of Health. <http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202114.html> (May 9, 2004).

ORGANIZATIONS

National Eye Institute. 2020 Vision Place, Bethesda, MD 20892-3655. (301) 496-5248. <http://www.nei.nih.gov/>.

Paul Arthur

Acupuncture

Definition

Acupuncture, one of the main forms of therapy in traditional Chinese medicine (TCM), has been practiced for at least 2,500 years. In acupuncture, certain points on the body are stimulated by the insertion of fine needles. Unlike the hollow hypodermic needles used in mainstream medicine to give injections or to draw blood, acupuncture needles are solid. The points can be needled between 15° and 90° relative to the skin's surface, depending on treatment.

Acupuncture is thought to restore health by removing energy imbalances and blockages in the body. Practitioners of TCM believe that there is a vital force or energy called *qi* (pronounced "chee") that flows through the body and between the skin surface and the internal organs, along channels or pathways called meridians. There are 12 major and eight minor meridians. *Qi* regulates the spiritual, emotional, mental, and physical harmony of the body by keeping the forces of yin and yang in balance. Yang is a principle of heat, activity, brightness, outwardness, while yin represents coldness, passivity, darkness, interiority, etc. TCM does not try to eliminate either yin or yang, but rather keep them in harmonious balance. Acupuncture may be used to raise or lower the level of yin or yang in a specific part of the body in order to restore the energy balance.

Acupuncture was virtually unknown in the United States prior to President Richard Nixon's trip to China in 1972. A reporter for the *New York Times* named James Reston wrote a story for the newspaper about the doctors in Beijing who used acupuncture to relieve his **pain** following abdominal surgery. By 1993, Americans were making 12 million visits per year to acupuncturists, and spending $500 million annually on acupuncture treatments. By 1995, there were an estimated 10,000 certified acupuncturists practicing in the United States; as of 2000, there were 20,000. About a third of the credentialed acupuncturists in the United States as of 2002 are MDs.

Acupuncture's record of success has stimulated a number of research projects investigating its mechanisms

Key Terms

Cardiac tamponade A condition in which blood leaking into the membrane surrounding the heart puts pressure on the heart muscle, preventing complete filling of the heart's chambers and normal heartbeat.

Electroacupuncture A variation of acupuncture in which the practitioner stimulates the traditional acupuncture points electronically.

Endorphins A group of peptide compounds released by the body in response to stress or traumatic injury. Endorphins react with opiate receptors in the brain to reduce or relieve pain.

Hyperemesis gravidarum Uncontrollable nausea and vomiting associated with pregnancy. Acupuncture appears to be an effective treatment for women with this condition.

Meridians In traditional Chinese medicine, a network of pathways or channels that convey *qi* (also sometimes spelled "ki"), or vital energy, through the body.

Moxibustion A technique in traditional Chinese medicine that involves burning a "Moxa," or cone of dried wormwood leaves, close to the skin to relieve pain. When used with acupuncture, the cone is placed on top of the needle at an acupuncture point and burned.

Neurotransmitter A chemical in the brain that transmits messages between neurons, or nerve cells.

Opioids Substances that reduce pain and may induce sleep. Some opioids are endogenous, which means that they are produced within the human body. Other opioids are produced by plants or formulated synthetically in the laboratory.

Pneumothorax A condition in which air or gas is present in the chest cavity.

Qi The Chinese term for energy, life force, or vital force.

Yin and yang In traditional Chinese medicine and philosophy, a pair of opposing forces whose harmonious balance in the body is necessary to good health.

as well as its efficacy. Research has been funded not only by the National Center for Complementary and Alternative Medicine (NCCAM), but also by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute of Dental Research, the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute on Drug Abuse. In 1997, a consensus panel of the National Institutes of Health (NIH) presented a report in which it described acupuncture as a sufficiently promising form of treatment to merit further study. In 2000, the British Medical Association (BMA) recommended that acupuncture should be made more readily available through the National Health Service (NHS), and that family doctors should be trained in some of its techniques.

Purpose

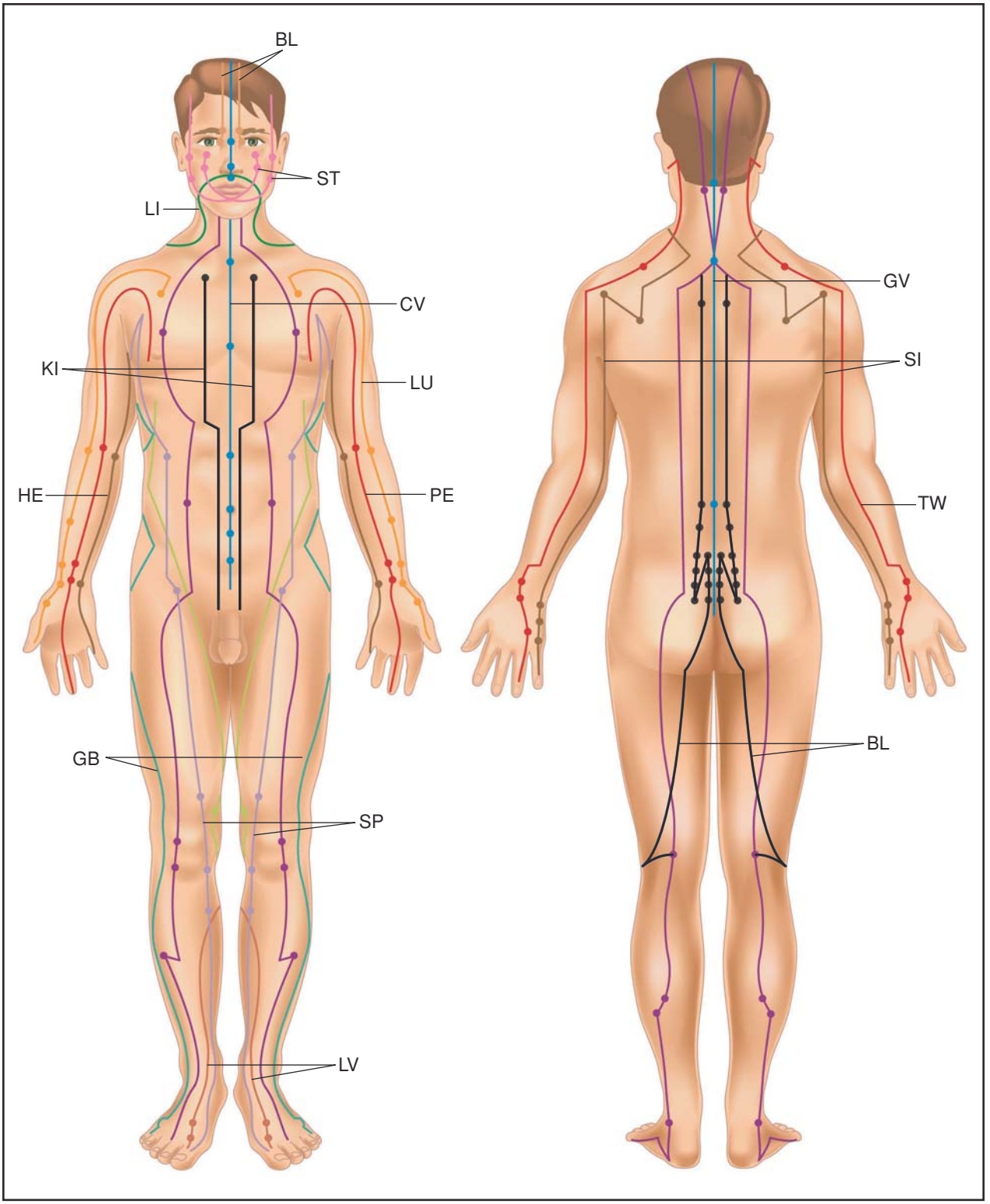
The purpose of acupuncture in TCM is the rebalancing of opposing energy forces in different parts of the body. In Western terms, acupuncture is used most commonly as an adjunctive treatment for the relief of chronic or acute pain. In the United States, acupuncture is most widely used to treat pain associated with musculoskeletal disorders, but it has also been used in the treatment of headaches, other painful disorders, and nausea and vomiting. In addition to these disorders, acupuncture has been used to treat a variety of disorders such as asthma, infertility, **depression**, anxiety, HIV infection, and fibromyalgia, although its efficacy in relieving these disorders is largely unproven. Acupuncture should not be used to treat traumatic injuries and other emergency conditions requiring immediate surgery. Also, while it appears to have benefits in relieving symptoms such as pain under the proper circumstances, it has not been shown to alter the underlying course of a disease.

The exact mechanism by which acupuncture works is not known. Studies have demonstrated a variety of physiologic effects such as release in the brain of various chemicals and hormones, alteration of immune function, blood pressure, and body temperature.

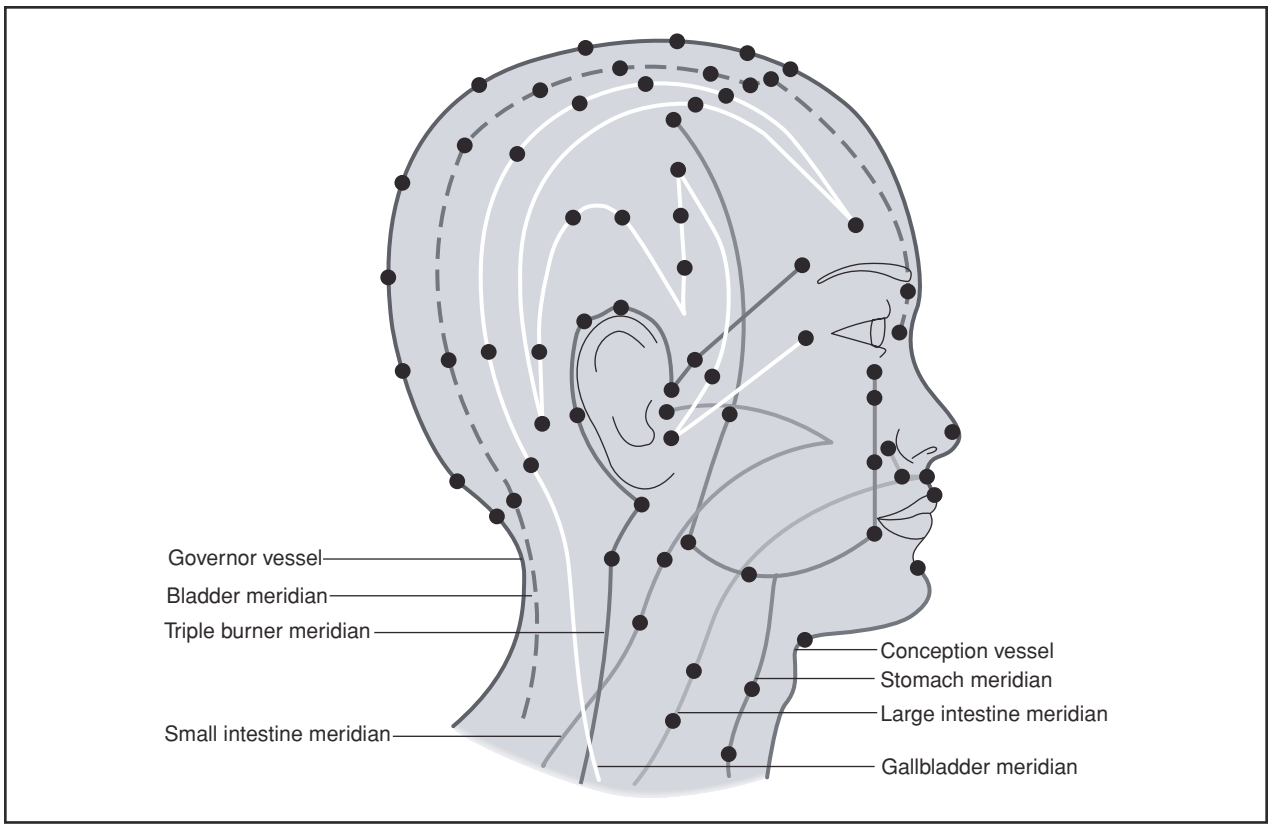
Precautions

The risk of infection in acupuncture is minimal if the acupuncturist uses sterile disposable needles. In the United States, the Food and Drug Administration (FDA) mandates the use of sterilized needles made from nontoxic materials. The needles must be clearly labeled as having their use restricted to qualified practitioners.

Patients should also inquire about the practitioner's credentials. People who would prefer to be treated by an MD or an osteopath can obtain a list of licensed physicians



Traditional Chinese medicine teachings state that channels of energy flow throughout the body, and that disease is caused by too much or too little flow of energy along these channels. Points along the channels, called meridians, are manipulated in acupuncture. In the illustration, points are shown on the bladder (BL), conception vessel (CV), gallbladder (GB), governing vessel (GV), heart (HE), kidney (KI), large intestine (LI), liver (LV), lung (LU), pericardium (PE), small intestine (SI), spleen (SP), stomach (ST), and triple warmer (TW) meridians. *(Illustration by Electronic Illustrators Group.)*



Acupuncture sites and meridians on the face and neck. *(Illustration by Hans & Cassady, Inc.)*

who practice acupuncture in their area from the American Academy of Medical Acupuncture. With regard to nonphysician acupuncturists, 31 states have established training standards that acupuncturists must meet in order to be licensed in those states. In Great Britain, practitioners must qualify by passing a course offered by the British Acupuncture Accreditation Board.

People seeking acupuncture treatment should provide the practitioner with the same information about their health conditions and other forms of treatment that they would give their primary care doctor.

As is true with other forms of medical treatment, a minority of patients do not respond to acupuncture. The reasons for nonresponsiveness are not known at the present stage of research.

Description

In traditional Chinese practice, the needles are twirled or rotated as they are inserted. Many patients feel nothing at all during this procedure, while others experience a prickling or aching sensation, and still others a feeling of warmth or heaviness.

The practitioner may combine acupuncture with moxibustion to increase the effectiveness of the treatment. Moxibustion is a technique in which the acupuncturist lights a small piece of wormwood, called a moxa, above the acupuncture point above the skin. When the patient begins to feel the warmth from the burning herb, it is removed. Cupping is another technique that is a method of stimulation of acupuncture points by applying suction through a metal, wood, or glass jar, and in which a partial vacuum has been created. Cupping produces blood congestion at the site, and the site is thus stimulated.

In addition to the traditional Chinese techniques of acupuncture, the following are also used in the United States:

- Electroacupuncture. In this form of acupuncture, the traditional acupuncture points are stimulated by an electronic device instead of a needle.
- Japanese meridian acupuncture. Japanese acupuncture uses thinner, smaller needles, and focuses on the meridians rather than on specific points along their course.
- Korean hand acupuncture. Traditional Korean medicine regards the hand as a "map" of the entire body, such that

any part of the body can be treated by stimulating the corresponding point on the hand.

- Western medical acupuncture. Western physicians trained in this style of acupuncture insert needles into so-called trigger points in sore muscles, as well as into the traditional points used in Chinese medicine.
- Ear acupuncture. This technique regards the ear as having acupuncture points that correspond to other parts of the body. Ear acupuncture is often used to treat substance abuse and chronic pain syndromes.

A standard acupuncture treatment takes between 45 minutes to an hour and costs between $40 and $100, although initial appointments often cost more. Chronic conditions usually require 10 treatment sessions, but acute conditions or minor illnesses may require only one or two visits. Follow-up visits are often scheduled for patients with chronic pain. As of 2000, about 70–80% of health insurers in the United States reimbursed patients for acupuncture treatments.

Preparation

Apart from a medical history and physical examination, no specific preparation is required for an acupuncture treatment. In addition to using sterile needles, licensed acupuncturists will wipe the skin over each acupuncture point with an antiseptic solution before inserting the needle.

Aftercare

No particular aftercare is required, as the needles should not draw blood when properly inserted. Many patients experience a feeling of relaxation or even a pleasant drowsiness after the treatment. Some patients report feeling energized.

Risks

Most complications from acupuncture fall into one of three categories: infections, most often from improperly sterilized needles; bruising or minor soft tissue injury; and injuries to muscle tissue. Rarely, serious side effects from improper application of the needle may result in pneumothorax and cardiac tamponade.

Normal results

Normal results from acupuncture are relief of pain and/or improvement of the condition being treated.

Abnormal results

Abnormal results from acupuncture include infection, a severe side effect, or worsening of the condition being treated.

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Acute disseminated encephalomyelitis

Definition

Acute disseminated encephalomyelitis (ADE) is a neurological disorder involving inflammation of the brain and spinal cord. A hallmark of the disorder is damage to the myelin sheath that surrounds the nerve fibers in the brain, which results in the inflammation.

Description

Acute disseminating encephalomyelitis was first described in the mid-eighteenth century. The English physician who first described the disorder noted its association with people who had recently recovered from smallpox. Symptoms often develop without warning. As well, mental disorientation can occur. The disorder is also known as postinfectious encephalomyelitis and immune-mediated encephalomyelitis. The nerve demyelination that occurs in ADE also occurs in **multiple sclerosis**. However, the two maladies differ in that multiple sclerosis is long lasting and can recur over time, while ADE has a monophasic course, meaning that once it is over, further attacks rarely occur.

Demographics

ADE can occur in both children and adults, although it occurs more commonly in children. ADE is not rare, accounting for approximately 30% of all cases of encephalitis (brain inflammation).

Causes and symptoms

Acute disseminating encephalomyelitis can occur as a consequence of a bacterial or viral infection (including HIV), following recovery from infection with the malarial protozoan, or as a side effect of vaccination or another inoculation. ADE is usually a consequence of a viral illness, and occurs most often after measles, followed by rubella, chicken pox, Epstein-Barr, mumps and pertussis (whooping cough). Typically, symptoms appear two to three weeks after the precipitating infection or immunization. Alternatively, ADE may develop with no known associations.

Despite the different causes, the symptoms that develop are similar. A number of non-specific symptoms, which vary from one person to another, include **headache**, stiff neck, fever, vomiting, and weight loss. These symptoms are quickly followed by lethargic behavior, **seizures**, hallucinations, sight difficulties, and even coma. Paralysis can occur in an arm or leg (monoparesis) or along an entire side of the body (hemiplegia).

These symptoms can last a few weeks to a month. In some people, symptoms can progress from the appearance of symptoms to coma and death in only a few days. Brain damage is largely confined to the white matter. Microscopic examination will typically reveal invasion of white blood cells into small veins. The nerve myelin damage occurs in the regions where the white blood cells accumulate. Examination of the brains of patients who have died of the disorder has not yielded consistent results. Some brains appear normal, while others display the nerve damage and white blood cell congestion.

Key Terms

Encephalitis Inflammation of the brain, usually caused by a virus. The inflammation may interfere with normal brain function and cause seizures, sleepiness, confusion, personality changes, weakness in one or more parts of the body, and even coma.

Myelin A fatty sheath surrounding nerves throughout the body that helps them conduct impulses more quickly.

Diagnosis

Diagnosis is made based on the above symptoms and the patient's medical history (i.e., recent infection or vaccination). In the early stages of the disorder, diagnosis can be confused with diseases including acute meningitis, acute viral encephalitis, and multiple sclerosis. Often, the latter can be ruled out using **magnetic resonance imaging** (**MRI**) and examination of the cerebrospinal fluid (CSF). Typically, in acute disseminating encephalomyelitis, CSF contains abnormally elevated levels of white blood cells and protein; and magnetic resonance imaging can reveal brain alterations.

Treatment team

The treatment team typically consists of a primary care physician and, when hospitalization is necessary, nurses and specialized medical care personnel.

Treatment

Corticosteroid medication is often prescribed in order to lessen the nerve inflammation. Use of high doses of steroids can often produce a rapid diminishing of the symptoms. Other kinds of treatment depend on the nature of the symptoms that develop. Supportive care includes keeping a patient comfortable and hydrated.

Recovery and rehabilitation

Persons recovering from acute disseminated encephalomyelitis need time to recover their normal consciousness and movements. Problems with memory, especially short-term memory, may be present. The recovering person sometimes has trouble controlling their emotions and is easily frustrated. Frequent periods of rest, alternating with shorter periods of mental and physical **exercise** are prescribed during initial recovery. The maximum possible recovery of brain and motor function may take a period of weeks or months.

Clinical trials

There are no **clinical trials** for the study of ADE recruiting patients or being planned in the United States, as of January 2004. However, organizations such as the National Institute for Neurological Disorders and Stroke undertake and fund studies on disorders that involve damage to the myelin sheath of nerve cells. By understanding the nature of the disorders, it is hoped that detection can be improved and strategies will evolve to prevent or reverse the nerve damage.

Prognosis

Prognosis varies from person to person. Some patients may recover fully, with no residual effects. Others may have some residual damage. Seldomly, ADE is fatal. Early detection and treatment improves a patient's outlook.

Special concerns

Although the incidence of ADE occurring after vaccination is rare, in recent years, public debate has led some parents to choose that their children not receive the recommended childhood vaccinations. The American Academy of Pediatrics asserts that, despite concerns about vaccine safety, vaccination is far safer than accepting the risks for the diseases that the vaccines prevent.

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ADHD *see* **Attention deficit hyperactivity disorder**

Adrenoleukodystrophy

Definition

Adrenoleukodystrophy (ALD) is a progressive condition that affects both the adrenal glands (located atop the kidneys and responsible for the production of adrenalin) and myelin (the substance that insulates the nerves in the brain, spinal cord, and the limbs).

Description

First described in the early 1900s, adrenoleukodystrophy was originally called Schilder-Addision disease. "Adreno" refers to the adrenal glands, "leuko" is the Greek word for white (myelin is the main component of the white matter in the brain and spinal cord), and "dystrophy" means impaired growth. This disease affects the adrenal glands and the growth of the myelin.

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) The CNS 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 that 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 acid (VLCFA) A type of fat that is normally broken down by the peroxisomes into other fats that can be used by the body.

Types of ALD

There are three types of ALD, each with a different severity of symptoms and age of onset of ALD. All varying degrees of severity have been seen within the same family. Therefore, a family who has many mildly affected members could still have a more severely affected member. Some patients do not fall neatly into one of the three 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**. Other children become hyperactive and have behavioral problems that may initially be diagnosed as **attention deficit/hyperactivity disorder** (**ADHD**). 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. Affected children usually develop clumsiness, difficulty in reading and comprehension of written material, aggressive or uninhibited behavior, and various personality and behavioral changes. Most affected 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 AMN. 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 lifespan. About 70% of men with AMN will have problems with their adrenal glands when other symptoms are initially 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 they 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 of ADL, 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.

Demographics

ALD is found in all ethnic groups. About one in every 100,000 people suffers from ALD. Because the most severe form, called classic ALD, is X-linked, many more males than females are affected. Women are carriers of this X-linked form of the disease and may exhibit no or only mild symptoms. Another form of the disease is called neonatal ALD; this form of ALD is not X-linked and therefore both male and female babies exhibit symptoms. An adult-onset type of the disease is commonly called adrenomyeloneuropathy.

Causes and symptoms

ALD causes problems in the peroxisomes, tiny cellular structures that are involved in breaking down large molecules of fats into smaller ones that can be used by the body. In ALD, the peroxisomes cannot break down a type of fat called very long chain fatty acid (VLCFA). As a result, VLCFAs accumulate throughout the body, particularly in the brain and adrenal glands. This accumulation interferes with the adrenal glands' conversion of cholesterol into steroids, and prompts deterioration of the myelin

covering nerve cells within the white matter of the brain, thus interfering with nerve function. Additionally, fats that are usually made from the breakdown products of VLCFAs cannot be produced. Because these fats would usually be utilized in the synthesis of myelin, nerve function is further compromised.

The adrenal glands of almost all individuals affected with ALD do not secret a sufficient amount of hormones; this is called adrenal insufficiency. Symptoms 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 coma, which can be potentially life threatening. As this aspect of ALD is readily treatable, identifying these patients helps prevent these complications.

Diagnosis

When the diagnosis of ALD is suspected, the results of a test called **magnetic resonance imaging (MRI)** are sometimes abnormal. In this test, pictures of the brain are taken. In people with symptoms of ALD, there are usually detectable changes in the white matter. While an MRI can be helpful in making the diagnosis of ALD, a normal MRI does not exclude the diagnosis and an abnormal MRI does not definitively make the diagnosis of ALD.

A more definitive diagnosis of ALD can be made by measuring the level of the VLCFA in the blood. In nearly all males with ALD, the level of the VLCFA in blood is very high.

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. 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.

Treatment team

A number of professionals can provide supportive (though not curative) care for patients with adrenoleukodystrophy: neurogeneticists, to help with diagnosis; pediatric or adult neurologists (depending on the type of ALD and age of onset) to monitor and manage the neurological effects; pediatric or adult endocrinologists to manage the adrenal complications; and pediatric or adult urologists to manage bladder complications in both children and adults and sexual problems in adults. In addition, physical therapists, occupational therapists, speech therapists, learning specialists, and behavioral psychologists may be helpful.

Treatment

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 lifesaving. Adrenal function should be tested periodically.

Lorenzo's oil

In the early 1990s, a film called *Lorenzo's Oil* presented a fictionalized account of a real ALD patient, a young boy named Lorenzo, and his family's search to find a cure for him. A possible treatment was found and was named Lorenzo's oil. 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 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 had their condition stabilize and a few 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 risk that complications will develop from the transplant. Early data suggests that bone marrow transplant is most effective when it is performed at an early stage of the disease when neurological abnormalities are mild. 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 tested 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 performed 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 fetus and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with it. 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.

Clinical Trials

A number of **clinical trials** are underway, including testing the efficacy of Lorenzo's oil (combination glyceryl trierucate and glyceryl trioleate), oral bile acid therapy with cholic acid, chenodeoxycholic acid, and ursodeoxycholic acid, and bone marrow or umbilical cord blood transplantation.

Prognosis

The prognosis for people with ALD is highly variable. Those diagnosed with childhood ALD usually have a very rapid course. Symptoms typically progress very fast and these children usually 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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Affective disorders

Definition

Affective disorders are psychiatric diseases with multiple aspects, including biological, behavioral, social, and psychological factors. Major depressive disorder, bipolar disorders, and anxiety disorders are the most common affective disorders. The effects of these disorders—such as difficulties in interpersonal relationships and an increased susceptibility to substance abuse—are major concerns for parents, teachers, physicians, and the community. Affective disorders can result in symptoms ranging from the mild and inconvenient to the severe and life-threatening; the latter account for more than 15% of deaths due to suicide among those with one of the disorders.

Major depressive disorder (MDD), also known as monopolar **depression** or unipolar affective disorder, is a common, severe, and sometimes life-threatening psychiatric illness. MDD causes prolonged periods of emotional, mental, and physical exhaustion, with a considerable risk of self-destructive behavior and suicide. Major studies have identified MDD as one of the leading causes of work disability and premature death, representing an increasingly worldwide health and economic concern.

Bipolar affective diseases are divided into various types according to the symptoms displayed: Type I (bipolar I, or BPI) and Type II (bipolar II or BPII) disease, cyclothymic disorder, and hypomania disorder. Other names for bipolar affective disease include manic-depressive disorder, cyclothymia, manic-depressive illness (MDI), and bipolar disorder. People with bipolar diseases experience periods of manic (hyper-excitable) episodes alternating with periods of deep depression. Bipolar disorders are chronic and recurrent affective diseases that may have degrees of severity, tending however to worsen with time if not treated. Severe crises can lead to suicidal attempts during depressive episodes or to physical violence against oneself or others during manic episodes. In many patients, however, episodes are mild and infrequent. Mixed states may also occur with elements of mania and depression simultaneously present. Some people with bipolar affective disorders show a rapid cycling between manic and depressive states.

Anxiety disorders are also common psychiatric disorders, and are considered one of the most under-treated and overlooked health problems. Among its common manifestations are panic syndromes, phobias, chronic generalized anxiety disorder, obsessive-compulsive disorder, and post-traumatic disorder. Anxiety disorders are important contributors to other diseases such as hypertension, digestive and eating disorders, and cardiac arrhythmia. Severe anxiety disorders often lead to tobacco addiction, alcohol abuse, and drug abuse.

Key Terms

Anxiety disorder A psychiatric disorder involving the presence of anxiety that is so intense or so frequently present that it causes difficulty or distress for the individual.

Bipolar disorder A psychiatric disorder marked by alternating episodes of mania and depression. Also called bipolar illness, manic-depressive illness.

Depressive disorder A psychiatric disorder of varying degrees characterized by feelings of hopelessness, physical responses such as insomnia, and withdrawal from normal activities.

Dysthymia A chronic mood disorder characterized by mild depression.

Manic A period of excess mental activity, often accompanied by elevated mood and disorganized behavior.

Phobia A persistent abnormal fear of an object, experience, or place.

Description

People with major depressive disorder (MDD) experience periods of at least two weeks of symptoms that often include sadness, emotional heaviness, feelings of worthlessness, hopelessness, guilt, anguish, fear, loss of interest for normal daily activities, social withdrawal, inability to feel pleasure, physical apathy, difficulty in concentrating, and recurrent thoughts about death. Changes in sleeping pattern, with insomnia during the night and **hypersomnia** (excessive sleep) during the day, chronic **fatigue**, and a feeling of being physically drained and immobile may also occur. Irritability and mood swings may be present, and loss of appetite or overeating are common features. In severe cases, MDD may last for months, with those affected experiencing profound despair and spending most of their time isolated or prostrate in bed, considering or planning suicide. Approximately 50% of MDD patients attempt suicide at least once in their lives.

In bipolar I disease (BPI), the manic episodes are severe, lasting from one week to three months or more if untreated, and often require hospitalization. Manic episodes are characterized by hyperactivity, feelings of grandiosity or omnipotence, euphoria, constant agitation, obsessive work or social activity, increased sexual drive, racing thoughts and surges of creativity, distractibility, compulsive shopping or money spending, and sharp mood swings and aggressive reactions, which may include physical violence against others. Depressive episodes may not occur in some BPI patients, but when present, the signs are similar to those of MDD and tend to last for months if untreated.

In bipolar II disease (BPII), milder and fewer manic episodes occur than for those people suffering from BPI, and at least one major depressive episode is experienced. BPII depression is the most common form of bipolar disease. Depressive episodes are usually more frequent than manic episodes, and can also last for extended periods if untreated.

Cyclothymia disorder is less severe, but tends to be chronic with frequent mood swings and single episodes lasting for at least two years. In some individuals, cyclothymic disorder is the precursor to a progressive bipolar disease. In others, the cyclothymic disorder remains chronic.

Hypomania is a mild degree of mania, manifested as brief and mild episodes of inflated self-esteem and excitability, irritability, impatience, and demanding attitude. Those with hypomania often find it disturbing or impossible to relax or to remain idle. Feelings of urgency to work longer hours and accomplish several tasks simultaneously are common.

Demographics

MDD is a leading cause of suicide, with more than 100,000 attempts per year in the United States alone. Affective disorders account for more than 200,000 suicide attempts in the United States, with an estimated mortality rate of 15%. Affective disorders are, however, a worldwide problem, and there are no racial differences, though Caucasian and Japanese males have been shown to be at higher risk of committing suicide. Suicide due to affective disorders is the second leading cause of mortality in teenagers in the United States and, among young adults, it accounts for 10–30% of deaths.

Causes and symptoms

Cultural influences and social pressures in achievement-oriented societies are important risk factors in affective disorders symptoms. Wars, catastrophic events, severe economic recession, accidents, personal loss, and urban violence are other contributing or triggering factors. Alcohol and drug abuse have a direct impact on brain neurochemistry, as well as some diseases, medical interventions, and medications, constituting a risk factor as well. However, in most cases, alcoholism, tobacco use, and/or drug abuse are the clinical symptoms of an underlying affective disorder that is inherently predisposed to substance abuse. Adaptive neurochemical and structural brain changes occurring in childhood give rise to the symptoms of many affective disorders; the diseases tend to run in families, although specific genetic factors causing the diseases have not yet been identified. Malnutrition and nutritional deficiencies are also important triggering factors in many psychiatric and affective disorders, as well as brain contamination with toxic levels of heavy metals such as methyl-mercury, lead, and bismuth.

The age of onset of bipolar diseases varies from childhood to middle adulthood, with a mean age of 21 years. MDD onset is highly variable, due to the presence of different possible factors such as family history, traumatic childhood, hormonal imbalance or seasonal changes, medical procedures, diseases, stress, menopause, emotional trauma and affective losses, or economical and social factors such as unemployment or social isolation.

Children with one parent affected by MDD or bipolar disease are five to seven times more prone to develop some affective or other psychiatric disorder than the general population. Although an inherited genetic trait is also under suspicion, studies over the past 20 years, as well as ongoing research on brain development during childhood, suggest that many cases of affective disorder may be due to the impact of repetitive and prolonged exposure to stress on the developing brain. Children of bipolar or MDD parents, for instance, may experience neglect or abuse, or be required to cope in early childhood with the emotional outbursts and incoherent mood swings of adults. Many children of those with affective disorders feel guilty or responsible for the dysfunctional adult. Such early exposure to stress generates abnormal levels of toxic metabolites in the brain, which have been shown to be harmful to the neurochemistry of the developing brain during childhood.

The neurochemical effects of stress alter both the quantities and the baseline systems of substances responsible for information processing between neurons such as **neurotransmitters** and hormones. Moreover, the stress metabolites such as **glucocorticoids** cause atrophy and death of neurons, a phenomenon known as neuronal crop, which alters the architecture of a child's brain. Neurotransmitters have specific roles in mood and in behavioral, cognitive, and other physiological functions: serotonin modulates mood, satiety (satisfaction in appetite), and

sleeping patterns; dopamine modulates reward-seeking behavior, pleasure, and maternal/paternal and altruistic feelings; norepinephrine determines levels of alertness, danger perception, and fight-or-flight responses; acetylcholine controls memory and cognition processes; gamma amino butyric acid (GABA) modulates levels of reflex/stimuli response and controls or inhibits neuron excitation; and glutamate promotes excitation of neurons. Orchestrated interaction of proper levels of different neurotransmitters is essential for normal brain development and function, greatly influencing affective (mood), cognitive, and behavioral responses to the environment.

Low levels of the neurotransmitters serotonin and norepinephrine were found in people with affective disorders, and even lower levels of serotonin are associated with suicide and compulsive or aggressive behavior. Depressive states with mood swings and surges of irritability also point to serotonin depletion. Lower levels of dopamine are related to both depression and aggressive behavior. Norepinephrine synthesis depends on dopamine, and its depletion leads to loss of motivation and apathy. GABA is an important mood regulator because it controls and inhibits chemical changes in the brain during stress. Depletion of GABA leads to phobias, panic attacks, chronic anxiety pervaded with dark thoughts about the dangers of accidents, hidden menaces, and feelings of imminent death. Acute and prolonged stress, as well as alcohol and drug abuse, leads to GABA depletion. Acetylcholine depletion causes attention and concentration deficits, memory reduction, and **learning disorders**.

Chronic stress or highly traumatic experiences cause adaptive or compensatory changes in brain neurochemistry and physiology, in order to provide the individual with defense and survival mechanisms. However, such adaptive changes come with a high cost, in particular when they are required for an extended period such as in war zones, or other prolonged stressful situations. The adaptive chemicals tend to outlast the situation for which they were required, leading to some form of affective and behavioral disorder.

These adaptive neurochemical changes are especially harmful during early childhood. For instance, neglected or physically, sexually, or emotionally abused children are exposed to harmful levels of glucocorticoids (comparable to those found in war veterans) that lead to neuron atrophy (wasting) and cropping (reduced numbers) in the hippocampus region of the brain. Neuronal atrophy and crop often cause cognitive and memory disorders, anxiety, and poor emotional control. Neuronal crop also occurs in the frontal cortex of the brain's left hemisphere, leading to fewer nerve-cell connections with several other brain areas. These decreased nerve-cell connections favor epilepsy-like short circuits or microseizures in the brain that occur in association with bursts of aggressiveness, self-destructive behavior, and cognitive or attention disorders. These alterations are also seen in the brains of adults who were abused or neglected during childhood. Time and recurrence of exposure and severity of suffered abuse help determine the extension of brain damage and the severity of psychiatric-related disorders in later stages of life.

Diagnosis

Well-known sets of clinical characteristics associated with MDD, bipolar diseases, or anxiety disorders provide the physician the necessary data for an initial diagnosis of affective disorder. The psychiatrist analyzes the person's pattern of mood, behavioral, and cognitive symptoms, along with the family history and environmental-contributing factors.

Abnormal atrophy, or loss of volume, in the hippocampus and cortex areas of the brain are detectable on **magnetic resonance imaging (MRI)** and computed tomography (**CT**) **scans**. Postmortem neuropathological (brain tissue) analysis demonstrates reduced cells and/or neuron size reductions in several brain regions of those with affective disorders.

Treatment team

The treatment team for people with affective disorders is primarily the psychiatrist, a medical doctor specializing in mood diseases and chemistry of the brain. Psychologists may also provide counseling and behavioral strategies for coping with the illness. Nurses administer prescribed medicine, along with monitoring behavior and physical condition during acute phases of the illness in the hospital setting. Mental health nurses also support treatment plans for clients in the community and provide a ready link to the psychiatrist. Additional community resources may include school psychologists, counselors, and support groups for affected people, as well as their family.

Treatment

Psychotherapy alone is rarely sufficient for the treatment of affective disorders, as the existing neurochemical imbalance impairs the ability of a person with an affective disorder to respond. However, psychotherapy is important in helping to cope with guilt, low self-esteem, and inadequate behavioral patterns once the neurochemistry is stabilized and more normal levels of neurotransmitters are at work.

Understanding of the devastating effects of stress in the brain of highly stressed or abused children made evident the need of medication as well as psychotherapy in

early intervention. Administration of clonidine, a drug that inhibits the fight-or-flight response, and of other medications—or GABA supplementation—that interfere with levels of glucocorticoids in the brain can prevent both harmful neurochemical and architectural changes in the child's **central nervous system**. Family and parental therapy is also crucial in order to reduce the presence of emotional stressors in the child's life.

Teenagers and adults suffering from affective disorders may benefit from prescribed antidepressant medications that reduce symptoms. Recent studies have shown that antidepressants also encourage neuron cells in certain areas of the brain to mature, thus protecting the number of neurons in this area and preventing stress-induced neuronal crop. Lithium is beneficial to some bipolar and MDD patients, and also shows a protective effect against several neural injuries.

Antidepressants that inhibit the fast removal (i.e., reuptake) of serotonin from the receptors in neurons and that regulate norepinephrine concentrations in the neuronal networks of the brain are very effective in mood stabilization. After a few days of medication, symptoms often recede. Nutrient supplementation, especially with B-complex vitamins, GABA, and essential amino acids, optimizes the synthesis of neurotransmitters and important neuropeptides, which are important for balanced neurochemistry in the central nervous system.

Recovery and rehabilitation

Helping individuals with an affective disorder to recognize their particular symptoms and mood states is essential for recovery and rehabilitation. With recognition, a person may seek additional treatment during recurring episodes early enough to deter the harmful consequences of the disease.

Clinical trials

As of early 2004, the National Institute of Mental Health (NIMH) is offering several **clinical trials** for adults and children with many types of affective disorders. People may participate at the institute's main facility in Bethesda, Maryland, or at several locations throughout the United States. Further information and updates may be found at the NIMH clinical trials web site.

Prognosis

Because affective disorders are usually long-term, cyclic conditions, ongoing treatment should be considered to prevent or modulate episodes of depression, mania, or severe anxiety. With preventative drug therapy, most people with affective disorders can expect to experience stabilization of their moods and anxiety, and can maintain an active role in work and social settings. Without treatment, daily activities and work are usually difficult to maintain within the cycles of mood disturbances, and social isolation, drug abuse, and suicide are often long-term consequences.

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Depression and Related Affective Disorders Association (DRADA). 2330 West Joppa Rd., Suite 100, Lutherville, MD 21093. (410) 583-2919. drada@hmi.edu. <http://www.drada.org/Facts/general.html>.

Sandra Galeotti

Agenesis of the corpus callosum

Definition

Agenesis of the corpus callosum (ACC) is an abnormality of brain structure, present at birth, that is characterized by partial or complete absence of the corpus callosum. The corpus callosum is a bundle of nerve fibers

that connects the two hemispheres (halves) of the brain and allows information to pass back and forth between both sides.

Description

Agenesis of the corpus callosum is one form of abnormal corpus callosum development. Other corpus callosum disorders include hypoplastic (thin or underdeveloped) corpus callosum and dysgenesis (abnormal formation) of the corpus callosum. In complete ACC, the corpus callosum is entirely missing. In partial ACC, some portion, usually the posterior portion, is absent. Agenesis of the corpus callosum is often found in combination with other brain abnormalities and some degree of mental impairment. Birth defects involving other parts of the body (especially the eyes, face, heart, and skeletal system) may also be present. ACC can occur alone, without other obvious brain abnormalities. In some of these cases, the affected person is healthy and has an IQ (intelligence quotient) in the normal range. Even in these cases however, subtle neuropsychological and cognitive abnormalities may exist.

Demographics

Estimates of the frequency of ACC range between 0.0005% and 0.7% of children. An incidence of 2–3% has been reported in children with developmental disabilities. Between one-half to three-quarters of cases of ACC occur in males. ACC is a feature of Aicardi syndrome, an X-linked (caused by a gene on the X chromosome) condition that occurs almost exclusively in females and is thought to be lethal in males.

Causes and symptoms

The corpus callosum forms during the fifth to sixteenth week of pregnancy. It is thought that ACC occurs when one or more factors interfere with the migration (movement) of cells in the brain that eventually form the corpus callosum. An underlying cause for ACC is found in about one-half of cases. Factors that may affect normal corpus callosum development include:

- prenatal infections, viruses, or toxic exposures such as rubella or fetal alcohol syndrome
- chromosome abnormalities such as trisomy 8, trisomy 13, and trisomy 18
- genetic syndromes such as Aicardi syndrome, acrocallosal syndrome, Andermann syndrome, Shapiro syndrome, and Menkes disease
- blocked growth of the corpus callosum due to cysts or other abnormal structures
- a cerebral dysgenesis syndrome, in which there is abnormal formation of the brain such as **Dandy-Walker syndrome**, **Arnold-Chiari malformation**, **holoprosencephaly**, or **hydrocephalus**

The symptoms of ACC largely depend on the presence or absence of other medical conditions. The majority of children with ACC with other brain abnormalities usually show signs of a neurological disorder by age two. Symptoms in these children can include:

- **seizures**
- developmental delay or mental retardation
- increased or decreased head size
- hydrocephalus (abnormal accumulation of cerebrospinalfluid in the spaces of the brain)
- **cerebral palsy**
- hypotonia (decreased muscle tone)
- failure to thrive

In children with ACC who otherwise have limited neurological problems, there are slight differences in cognition (thought processes) and psychosocial functioning compared with children without ACC. **Neuropsychological testing** has shown that such individuals can have any of the following:

- motor, language, or cognitive delays
- poor motor coordination
- sensitivity to tactile sensations
- high **pain** tolerance
- cognitive and social challenges

Cognitive and social challenges may become more apparent with age. Examples of these challenges include difficulties using language in social settings and with performing tasks that require complex reasoning, creativity, or problem-solving skills. Patients with ACC may display limited insight into one's own behavior, a lack of awareness of others' feelings, misunderstanding of social cues, limited sophistication of humor, and difficulty imagining consequences of behavior.

Diagnosis

A health professional suspicious of ACC may recommend a neurological evaluation that includes imaging studies. The more subtle cognitive and psychosocial problems found in individuals with isolated ACC are less likely to lead to the diagnosis. In some cases, the diagnosis of ACC is incidental, made in the course of an evaluation for other reasons. There may well be many asymptomatic individuals with partial or complete agenesis who never come to medical attention.

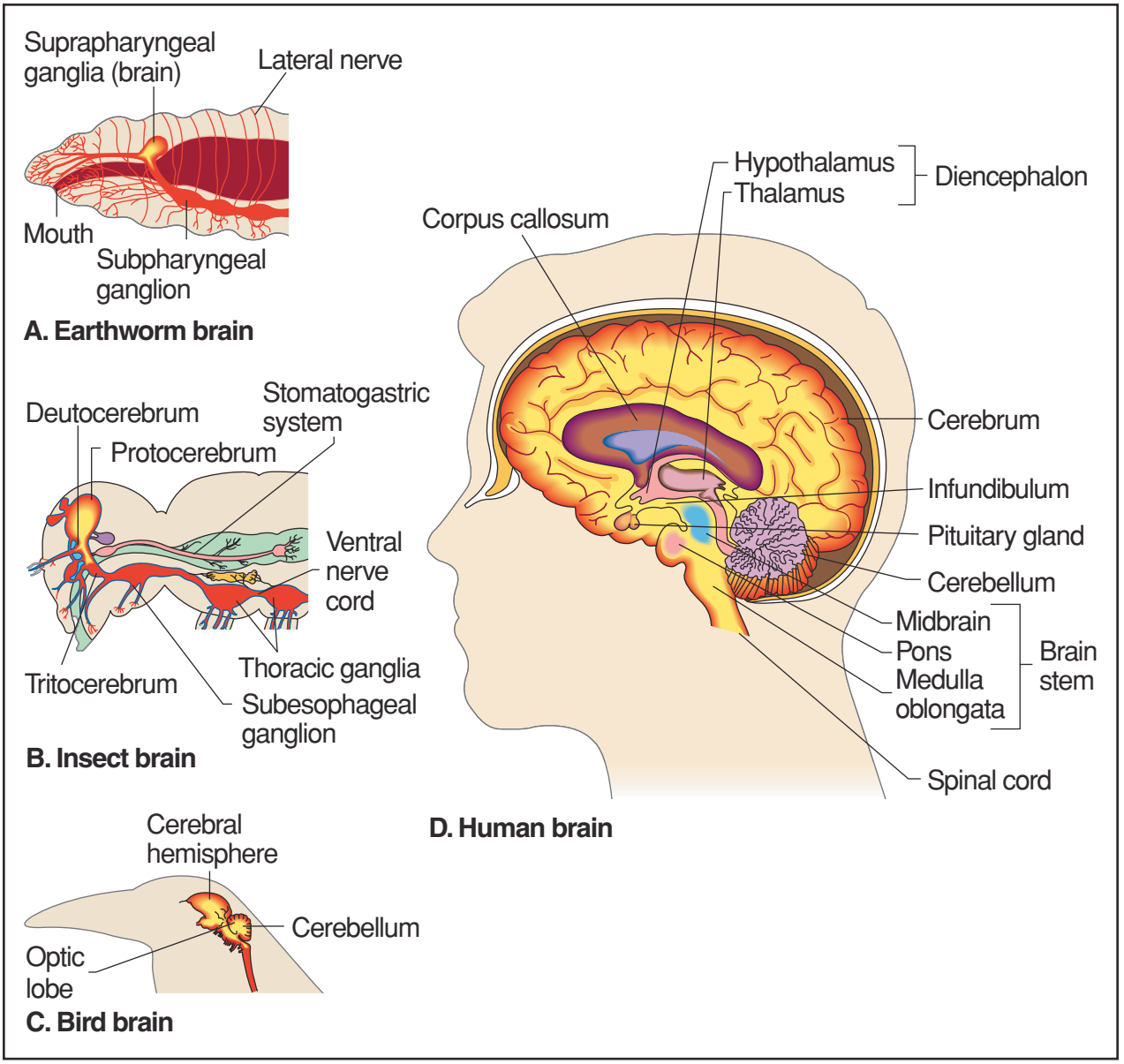

Diagram of the human brain (and others) with the corpus callosum indicated. *(Illustration by Electronic Illustrators Group.)*

Diagnosis of ACC relies on imaging studies such as ultrasound (prenatal or postnatal), **magnetic resonance imaging (MRI)**, or computerized axial tomography (**CT** or CAT) scan. Diagnostic findings include:

- absence of the corpus callosum
- widely displaced and parallel lateral ventricles
- selective dilatation of the posterior horns
- widely spaced frontal horns
- upward displacement and enlargement of the third ventricle
- displaced orientation of gyral markings

Fetal ultrasound can detect some but not all cases of ACC, beginning at about 20 weeks of pregnancy. The prenatal or postnatal diagnosis of ACC should be followed by studies aimed to determine the cause for the ACC. Such studies may include chromosome analysis, metabolic screening, and genetic and ophthalmologic consultations.

Treatment team

Treatment for patients with ACC is highly individualized because the severity of symptoms varies from patient to patient. Depending upon the symptoms, many

Key Terms

Arnold-Chiari malformation A condition in which the cerebellum, a structure in the brain, protrudes into the spinal canal.

Cerebral palsy A brain injury that results in inability to use some muscles in the usual way.

Chromosome Thin, rod-like fibers in the nucleus of a cell that contain the genes.

Dandy-Walker syndrome A cyst in the cerebellum that involves the fourth ventricle (a space in the brain) and that may interfere with the body's ability to drain cerebral spinal fluid.

Failure to thrive Failure to grow and gain weight at the expected rate.

Holoprosencephaly Brain, cranial, and facial malformations present at birth that are caused by incomplete cleavage of the brain during embryologic development.

Hydrocephalus Abnormal accumulation of cerebrospinal fluid in the ventricles of the brain.

medical specialists can assist the patient's primary physician or nurse practitioner, including a **neurologist**, ophthalmologist, geneticist, **neuropsychologist**, behavioral psychologist, occupational therapist, physical therapist, speech-language pathologist, and experts in special education and early intervention.

Treatment

There is no cure for ACC. Treatment primarily includes management of associated problems such as seizures, hydrocephalus, and cerebral palsy.

Recovery and rehabilitation

Limited information is available about the optimal remedial strategies for individuals with ACC. Speech therapy, occupational therapy, physical therapy, and early intervention are common services provided to patients with ACC. The goal of these therapies is to maximize the patient's success in school, work, and life in general. Speech therapy can help patients with speech delays, **apraxia** (the inability to make voluntary movements despite normal muscle function), and difficulties with pragmatics or social language use. Occupational therapy can help patients with sensory integration problems. Physical therapy can help address problems such as impaired coordination, motor delays, and **spasticity** (abnormally increased muscle stiffness and restricted movement).

Clinical trials

There are currently no **clinical trials** for patients with agenesis of the corpus callosum. Patients and families may elect to participate in genetic research. Laboratories searching for genes associated with agenesis of the corpus callosum include the laboratory of Elliott H. Sherr M.D., Ph.D, at the University of California, San Francisco, and the Harvard Institutes of Medicine. Both labs accept contact from patients and families.

Prognosis

The prognosis for ACC varies according to the presence and severity of associated problems such as **microcephaly** (small head), seizures, cerebral palsy, and cerebral dysgenesis. In the case of a fetus diagnosed with isolated ACC, prediction of outcome remains imprecise. Estimates of the chance for a normal developmental outcome for a case detected prenatally range from 35–85%. It has also been stated that a so-called "normal" or "asymptomatic" outcome for ACC does not exist. Subtle or cognitive and psychosocial differences have been found in patients with ACC and a normal IQ.

Special concerns

The special educational needs of children with ACC vary. Children with ACC may be eligible for an individual education plan (IEP). An IEP provides a framework from which administrators, teachers, and parents can meet the educational needs of a child with ACC. Depending upon severity of symptoms and the degree of learning difficulties, some children with ACC may be best served by special education classes or a private educational setting.

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Key Terms

Alzheimer's disease A progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions such as memory and learning. Formerly called presenile dementia.

Anoxia Lack of oxygen.

Asperger syndrome A developmental disorder of childhood characterized by autistic behavior but without the same difficulties acquiring language that children with autism have.

Autism A syndrome characterized by a lack of responsiveness to other people or outside stimulus. Often occurs in conjunction with a severe impairment of verbal and non-verbal communication skills.

Huntington's disease A rare hereditary disease that causes progressive chorea (jerky muscle movements) and mental deterioration that ends in dementia. Huntington's symptoms usually appear in patients in their 40s. Also called Huntington's chorea.

Parietal lobe One of two brain hemispheres responsible for associative processes.

Temporal lobes A large lobe of each hemisphere of the brain that is located on the side of the head, nearest the ears. It contains a sensory area associated with hearing.

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Aicardi Syndrome Foundation. P.O. Box 3202, St. Charles, IA 60174. (800) 374-8518. aicardi@aol.com. <http://www.aicardisyndrome.org>.

National Organization for Disorders of the Corpus Callosum (NODCC). 18032-C Lemon Drive PMB 363, Yorba Linda, CA 92886. (714) 717-0063. <http://www.corpuscallosum.org>.

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Agnosia

Definition

Agnosia is a neuropsychological disorder characterized by the inability to recognize common objects, persons, or sounds, in the absence of perceptual disability. There are three major types of agnosia: visual agnosia, auditory agnosia, and tactile agnosia. Agnosia is caused by lesions to the parietal and temporal lobes of the brain, regions involved in storing memories and associations of objects. The condition may arise following head trauma or **stroke**, or following carbon monoxide poisoning or anoxia.

Description

Agnosia, from the Greek "not knowing," describes a collection of disorders where the ability to recognize objects or sounds or retrieve information about them is impaired, in the absence of other perceptual difficulties, including memory, intellectual capabilities, and the capacity for communication. The disorder can affect visual, auditory or tactile object recognition, but visual agnosia is the most common form of the condition, and most often expressed as an inability to recognize people.

Visual Agnosia

In addition to being the most common form of agnosia, visual agnosias are also the best understood. Lissauer was the first scientist to provide a detailed account of agnosia (1888). He hypothesized that disorders in visual object recognition could be classified as either apperceptive agnosia or associative agnosia. This classification continues to be used today although there is some debate as to whether the deficits occur as a dichotomy or as a spectrum.

Apperceptive agnosics can see, but they lack higher-level visual perception, which interferes with object information gathering. Apperceptive agnosics fail shape-recognition and shape-copying tests. In an attempt to copy a drawing of a circle, a patient with apperceptive agnosia my draw a series of concentric scribbles. Conversely, associative agnosics have normal perception, but fail to draw on stored memories or knowledge associated with the object, such as its name, or the way it feels when picked up.

APPERCEPTIVE VISUAL AGNOSIA Carbon monoxide poisoning is a frequent cause of apperceptive visual agnosia. The ensuing brain damage is frequently profuse and located in the posterior region of the brain. Simultanagnosia, a syndrome related to apperceptive visual agnosia, describes a condition where scenes containing multiple objects cannot be interpreted as a whole. Instead patients with simultanagnosia, recognize only portions of the scene at one time, and fail to describe the overall nature of the scene and comprehend its meaning.

Individuals capable of seeing only one object at a time are said to have dorsal simultanagnosia. The condition is associated with lesions in the posterior parietal cortex, which are frequently bilateral. Patients with ventral simultanagnosia retain the ability to recognize whole objects, but the rate of recognition is impaired. The left inferior temporo-occipital cortex is generally implicated in the deficit.

ASSOCIATIVE VISUAL AGNOSIA Even when perception remains intact, some people have difficulty recognizing objects. For these people, who lack language or communication disorders or intellectual impairment, and who are able to create good copies of objects, the deficit lies in retrieving stored information about the object that would permit identification. However, many people can provide semantic information about the object without being able to provide the name. For example, the word "kangaroo" may remain elusive, but descriptors, such as "found in Australia" and "has a pouch" may be offered in its place. Many associative visual agnosics have difficulty recognizing faces (prosopagnosia) or words (pure alexia), others specific types of objects, such as tools, or animals.

Prosopagnosia was first described by Quaglino and Borelli in 1867. Although deficits in face recognition occur in a variety of neurological diseases, including **Alzheimer**'s and **Huntington**'s diseases, Asperger's syndrome and **autism**, the term is best reserved for situations where impaired face recognition appears in absence of other neurological symptoms. Patients are often uncomfortable in social situations, although many learn to recognize people using other visual cues, such as hairstyles, glasses, or scars.

Prosopagnosia can be diagnosed using the Warrington Memory Test for faces, or the Benton Face Recognition test. Although the latter will not indicate prosopagnosia, failing the test does help quantify the degree of impairment. Neuroimaging of the adult with prosopagnosia often reveals lesions in the lingual and fusiform gyri of the medial occipitotemporal cortex, which are frequently bilateral. Children who have acquired the condition *in utero* or genetically, however, may not show these cortical lesions.

Auditory agnosia

Auditory agnosics fail to ascribe values to verbal or non-verbal sounds. Individuals with pure word deafness have intact hearing, but are unable to understand the spoken word, typically the result of bilateral trauma to the temporal cortico-subcortical regions of the brain. Nonverbal auditory agnosics fail to associate sounds with specific objects or events, such as a dog's bark or the slamming of a door. In these patients, the lesions tend to locate to the right hemisphere.

Tactile agnosia

Tactile agnosia, also called astereognosis, is often difficult to recognize as we rarely identify objects solely by feel. Information about the object, including its weight, size, and texture are not given any value. Lesions in the somatosensory cortex are thought to be responsible for the condition.

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National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health. Bldg. 31, Rm. 3C35, Bethesda, MD 20892-2320, (301) 496-7243. nidcdinfo@nidcd.nih.gov. <http://www.nidcd.nih.gov>.

National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203)744-0100 or (800) 999-NORD (6673); Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Hannah M. Hoag, MSc

Aicardi syndrome *see* **Agenesis of the corpus callosum**

AIDS

Key Terms

Hemophiliac A person with the blood disorder hemophilia, an inherited deficiency in blood-clotting ability. Hemophiliacs require regular administration of blood products, and were especially at risk of acquiring AIDS from HIV-contaminated blood during the early years of the evolving AIDS epidemic, before tests were developed to identify the HIV virus in donated blood.

Opportunistic infection An infection in a person with an impaired immune system caused by an organism that does not usually cause disease in people with healthy immune systems.

Pandemic Widespread epidemic.

Western blot A sensitive laboratory blood test for specific antibodies; useful in confirming the diagnosis of AIDS.

Definition

Acquired immunodeficiency syndrome (AIDS) is the final and most serious stage of the disease caused by the human immunodeficiency virus. Symptoms begin when an HIV-positive person presents a CD4-cell (also called T cell, a type of immune cell) count below 200. AIDS happens concurrently with numerous opportunistic infections and tumors that are normally associated with the HIV infection.

The most common neurological complications of AIDS involve opportunistic infections of the brain such as progressive multifocal leucoencephalopathy (PML) and meningitis, other opportunistic infections such as herpes zoster (**shingles**), **peripheral neuropathy**, **depression**, and AIDS-related **dementia**.

Description

AIDS was first recognized in 1981 and has since become a major worldwide pandemic. Abundant evidence indicates that the human immunodeficiency virus (HIV), discovered in 1983, causes AIDS. By leading to the destruction and/or functional impairment of immune cells, notably CD4+ T cells, HIV progressively destroys the body's ability to fight infections and to resist certain cancer formation.

Before the HIV infection became widespread in the human population, AIDS-like syndromes occurred extremely rarely, and almost exclusively in individuals with known causes of immune suppression, such as those receiving chemotherapy or those with underlying cancers. A marked increase in unusual infections and tumors characteristic of severe immune suppression was first recognized in the early 1980s in homosexual men who had been otherwise healthy and had no recognized cause for immune suppression. An infectious cause of AIDS was suggested by geographic clustering of cases, a sexual link among cases, mother-to-infant transmission, and transmission by blood transfusion.

Isolation of the HIV from patients with AIDS strongly suggested that this virus was the cause of AIDS. Since the early 1980s, HIV and AIDS have been repeatedly associated; the appearance of HIV in the blood supply has preceded or coincided with the occurrence of AIDS cases in every country and region where AIDS has been noted. Individuals of all ages from many risk groups, including homosexual men, infants born to HIV-infected

mothers, heterosexual women and men, hemophiliacs, recipients of blood and blood products, health care workers and others occupationally exposed to HIV-tainted blood, and injection drug users have all developed AIDS with only one common denominator: HIV.

HIV destroys CD4+ T cells, which are crucial to the normal function of the human immune system. In fact, depletion of CD4+ T cells in HIV-infected individuals is an extremely powerful predictor of the development of AIDS. Studies of thousands of individuals have revealed that most HIV-infected people carry the virus for years before enough damage is done to the immune system for AIDS to develop; however, with time, a near-perfect correlation has been found between infection and the subsequent development of AIDS.

Demographics

In the United States, more than 733,000 people have AIDS, and an estimated one to two million people have HIV infection without the symptoms of AIDS.

Internationally, since the AIDS epidemic began, more than 16 million deaths have been attributed to AIDS. The current estimate of worldwide disease prevalence is more than 33 million HIV infections. Ninety-five percent of these cases are in developing countries, generally in sub-Saharan Africa and Southeast Asia.

Most HIV infections still occur in men; however, the frequency of infection in women is increasing, especially in developing countries. In the United States, fewer than 16% of all HIV cases are in women, whereas worldwide an estimated 46% of all HIV patients are women.

Causes and symptoms

The cause of primary AIDS is infection with the HIV virus, transmitted via infected blood or body fluids. Methods of transmission of the virus include unprotected sex, especially anal intercourse; occupational needle stick or body fluid splash, which has an estimated transmission rate of less than 0.3%; sharing of needles in drug abuse; and receiving contaminated blood products.

Opportunistic infections occur in individuals whose CD4 count is less than 200 cells/mm^3 and those not taking preventative drugs.

Symptoms of AIDS include:

- cough and shortness of breath
- **seizures** and lack of coordination
- difficult or painful swallowing
- confusion and forgetfulness
- severe and persistent diarrhea
- fever
- vision loss
- nausea, abdominal cramps, and vomiting
- weight loss and extreme fatigue
- severe **headaches** with neck stiffness

Neurological complications of AIDS

Almost 30% of people with AIDS develop peripheral neuropathy, causing tingling, numbness, and weakness in the arms and legs due to nerve damage. If severe, peripheral neuropathy can cause difficulty walking. Several drugs used to treat people with AIDS can contribute to the development of peripheral neuropathy.

Several opportunistic infections experienced by people with AIDS involve the nervous system. Progressive multifocal leucoencephalopathy (PML) is a serious viral infection of the brain, most often caused by the JC virus. PML is fatal in more than 90% of cases within six months of diagnosis. Nearly 4% of people with AIDS, especially those with T-cell counts below 100, will develop the disease. Meningitis is an infection of the lining of the spinal cord and brain, and also occurs in some people with AIDS. Cryptococcus, a fungus that normally occurs in the soil and seldom affects persons with intact immune systems, can cause recurring meningitis in people with AIDS whose T-cell count is below 100. The common parasite *Toxoplasma gondii* often present in cat feces, raw meat, raw vegetables, and the soil can also cause encephalitis, or inflammation of the brain, in AIDS patients. Shingles is a painful nerve inflammation caused by a reactivation of the herpes varicella zoster virus, the same virus that causes chicken pox. Although not directly linked to HIV, shingles seems to occur more frequently in people with AIDS.

Other neurological conditions associated with AIDS include depression, occurring at any time during the disease, and dementia, which sometimes occurs in the later stages of AIDS. Depression can stem from living with a chronic and progressive disease. AIDS-related dementia involves problems with thinking, memory, and usually also with controlling the arms and legs, and can stem from direct infection in the brain with the HIV virus. In the initial stages of the pandemic, almost 20% of persons with AIDS developed severe dementia. With the development of combination **antiviral drugs**, the rate of severe dementia in AIDS has been reduced by more than half. The number of persons with HIV and milder dementia has increased, however, as people with HIV live longer.

Diagnosis

In the early stages of infection, HIV often causes no symptoms and the infection can be diagnosed only by testing a person's blood. Two tests are available to diagnose

HIV infection, one that looks for the presence of antibodies produced by the body in response to HIV and the other that looks for the virus itself. Antibodies are proteins produced by the body whenever a disease threatens it. When the body is infected with HIV, it produces antibodies specific to HIV. The first test, called ELISA (enzyme-linked immunosorbent assay), looks for such antibodies in the blood.

A positive ELISA has to be confirmed by another test called western blot or immunofluorescent assay (IFA). All positive tests by ELISA are not accurate and hence, western blot and repeated tests are necessary to confirm a person's HIV status. A person infected with HIV is termed HIV positive or seropositive.

Rapid tests that give results in five to 30 minutes are increasingly being used worldwide. The accuracy of rapid tests is stated to be as good as that of ELISA. Though rapid tests are more expensive, researchers have found them to be more cost effective in terms of the number of people covered and the time the tests take.

The HIV antibodies generally do not reach detectable levels in the blood until about three months after infection. This period, from the time of infection until the blood is tested positive for antibodies, is called the window period. Sometimes, the antibodies might take up to six months to be detected. Even if the tests are negative, during the window period the amount of virus is very high in an infected person. If a person is newly infected, therefore, the risk of transmission is higher.

Another test for HIV is called polymerase chain reaction (PCR), which looks for HIV itself in the blood. This test, which recognizes the presence of the virus' genetic material in the blood, can detect the virus within a few days of infection. There are also tests like radio immuno precipitation assay (RIPA), a confirmatory blood test that may be used when antibody levels are difficult to detect or when western blot test results are uncertain.

Treatment team

The treatment team often includes personal caregivers, physical therapists, dietitians, specialists (infectious disease specialists, dermatologists, nephrologists, ophthalmologists, pediatrists, psychiatrists, and neurologists), and **social workers**.

Treatment

Since the early 1990s, several drugs to fight both the HIV infection and its associated infections and cancers have become available, including:

- Reverse transcriptase inhibitors: They interrupt the virus from making copies of itself. These drugs are AZT (zidovudine [Retrovir]), ddC (zalcitabine [Hivid], dideoxyinosine), d4T (stavudine [Zerit]), and 3TC (lamivudine [Epivir]).
- Nonnucleoside reverse transcriptase inhibitors (NNRTIS): These medications are used in combination with other drugs to help keep the virus from multiplying. Examples of NNRTIS are delavirdine (Rescriptor) and nevirapine (Viramune).
- Protease inhibitors: These medications interrupt virus replication at a later step in its lifecycle. These include ritonavir (Norvir), a lopinavir and ritonavir combination (Kaletra), saquinavir (Invirase), indinavir sulphate (Crixivan), amprenavir (Agenerase), and nelfinavir (Viracept). Using both classes of drugs reduces the chances of developing resistance in the virus.
- Fusion inhibitors: This is the newest class of anti-HIV drugs. The first drug of this class (enfuvirtide [Fuzeon]) has recently been approved in the United States. Fusion inhibitors block HIV from entering the human immune cell.
- A combination of several drugs called highly active antiretroviral therapy (HAART): This treatment is not a cure. The virus still persists in various body sites such as in the lymph glands.

The antiretroviral drugs do not cure people of the HIV infection or AIDS. They stop viral replication and delay the development of AIDS. However, they may also have side effects that can be severe. These include decrease of red or white blood cells, inflammation of the pancreas, and painful nerve damage. Other complications are enlarged or fatty liver, which may result in liver failure and death.

Recovery and rehabilitation

As there is no cure for AIDS, the focus is on maintaining optimum health, activity, and quality of life rather than on complete recovery.

Occupational therapy can have a crucial role in assisting people living with HIV/AIDS to reengage with life, particularly through vocational rehabilitation programs. Occupational therapy can provide the patient with a series of learning experiences that will enable the individual to make appropriate vocational choices.

Clinical trials

There are many ongoing **clinical trials** for AIDS. "HIV Vaccine Designed for HIV Infected Adults Taking Anti-HIV Drugs," "When to Start Anti-HIV Drugs in Patients with Opportunistic Infections," and "Outcomes of Anti-HIV Therapy during Early HIV Infection" are some trials that are currently recruiting patients at the National

Institute of Allergy and Infectious Diseases (NIAID). Updated information on these and other trials for the study and treatment of AIDS can be found at the National Institutes of Health website for clinical trials at <http://www.clinicaltrials.gov>.

Prognosis

Presently, there is no cure for HIV infection or AIDS, nor is there a vaccine to prevent the HIV infection. However, there are new medications that help slow the progression of the infection and reduce the seriousness of HIV consequences in many people.

Special concerns

The surest way to avoid AIDS is to abstain from sex, or to limit sex to one partner who also limits his or her sex in the same way (monogamy). Condoms are not 100% safe, but if used properly they will greatly reduce the risk of AIDS transmission. Also, avoiding the use of intravenous drugs (drug abuse, sharing contaminated syringes) is highly recommended.

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Alcohol-related neurological disease

Definition

Alcohol-related neurological disease represents a broad spectrum of conditions caused by acute or chronic alcohol intake.

Description

Alcohol, or ethanol, is a poisonous chemical that has direct and toxic effects on nerve and muscle cells. The effects can be profound, and symptoms can include incoordination, weakness, **seizures**, memory loss, and sensory deficits. Alcohol has a profoundly negative effect on both the **central nervous system** (i.e., the brain and spinal cord) and the **peripheral nervous system** (i.e., nerves that send impulses to peripheral structures such as muscles and organs). Alcohol can have negative effects on neurological centers that regulate body temperature, sleep, and coordination.

Alcohol can significantly lower body temperature. It disrupts normal sleep patterns because it decreases rapid eye movement (REM) during the dreaming stage of sleep. It also adversely affects muscle coordination, causing imbalance and staggering—alcohol is a toxic insult to the **cerebellum**, which is responsible for balance.

Additionally, the chronic use of alcohol can cause a broad spectrum of abnormalities in mental functioning. Generally, persons exhibit poor attention, difficulty with abstraction and problem solving, difficulty learning new materials, reduced visuospatial abilities (capacity to discriminate between two-dimensional or three-dimensional space), and often require extra time to integrate visual information. Other related problems include thiamine deficiency (vitamin B-1) and liver disease (liver cirrhosis and possibly liver cancer).

Acute effects of alcohol

When alcohol is ingested, it moves from the bloodstream into every part of the body that contains water, including the brain, lungs, kidneys, and heart. Alcohol distributes itself equally both inside and outside cells. Ninety-five percent of alcohol is eliminated from the body by breakdown in the liver, and 5% is eliminated through urine, sweat, and breath. Alcohol is broken down (metabolized) in the liver by a complex process called zero-order kinetics (broken down at a certain amount at a time). This means that alcohol is metabolized at a rate of 0.3 oz (8.8 ml) of pure ethanol per hour. Within moments after ingestion, alcohol reaches the brain and produces acute effects such as euphoria, sedation (calmness), anesthesia,

Key Terms

Cerebellum Part of the brain that is responsible for muscle control and maintenance of balance.

Cortical atrophy A wasting away and decrease in size of the outer portion of the brain, or cerebral cortex.

Diencephalon The relay station of the brain for impulses concerning sensation and movement.

Euphoria An exaggerated state of psychological and physical well being.

Gray matter Area deep in the brain that functions during thinking and contains nerve cells that have an insulation membrane called a myelin sheath.

Incoordination Loss of voluntary muscle control resulting in irregular movements.

Limbic system Part of the brain that functions in motivational and mood states.

and a sleepy hypnotic state. Further effects include release of inhibitions and judgment, blunting of sexual desire, aggressiveness, and mood changes. Physical effects of intoxication (with continued consumption) include impairment of motor ability, muscle function, eyesight, reaction time, night vision, and depth perception. Continued consumption can be lethal because alcohol can depress heart and lung function, which can slow breathing and circulation. Lethality occurs when levels are high enough to paralyze breathing. However, death due to alcohol consumption is rare because body defenses tend to eliminate the chemical by vomiting or the person becomes comatose. Alcohol "hangovers" usually cause persons to have **headache** (due to dilation of blood vessels in the head), dehydration (alcohol acts as a diuretic increasing urine output), and upset stomach (due to irritation of stomach lining).

Specific neurological damage

The effects of alcohol can include damage or impairment to brain systems and to specific regions in the brain. The limbic system, located deep inside the brain, has several functions, including memory. Long-term users of alcohol often exhibit memory loss due to damage of the limbic system structures called the amygdala and hippocampus, located in the temporal lobes. Damage to other parts of the limbic system can produce symptoms such as abnormalities in emotional functioning and in the ability to use one of the senses (e.g., eyesight or the sense of smell) or in the ability to learn using the senses (e.g., learning through the sense of touch). Damage to the **diencephalon** (major relay station for nerve signals moving within the brain, associated with memory functioning) occurs and is associated with chronic usage and malnutrition (a late-onset condition). The cerebral cortex (folded outer layer of the brain) is composed of nerve cells called gray matter, which functions as the center of intelligent behavior and higher consciousness. Neuroimaging studies reveal that there are definitive signs of morphological change such as cortical atrophy (a decrease in size of the cerebral cortex). Cortical atrophy induced by alcoholism is associated with deficits in spatial memory and visual associations, learning related to or caused by touch, and problem solving. Alcoholic subjects also exhibit a decrease in blood nourishing the frontal lobe (portion of the brain behind the forehead), whose functions include planning, carrying out, and monitoring goal-directed and socially acceptable behaviors.

Neurotransmitter deficits and the progression of alcoholism

Neurotransmitters are brain chemicals that allow nerve cells to communicate. These chemicals are released and picked up by specialized structures (receptors) in a space between nerve cells called a synapse. Alcohol can cause "up"-regulation or "down"-regulation effects on neurotransmitters. Over prolonged periods of alcohol abuse, the levels of receptors change. Genes that produce molecular copies of receptors may by turned off (decreasing activity) or on (increasing activity). Levels of glutamate (an amino acid that is an excitatory neurotransmitter in the brain) are abnormally altered. Glutamate is correlated with long-term potentiation (mechanism vital for learning and memory) in the brain. Even minute amounts of alcohol have profound effects on brain glutamate action. Interference with glutamate chemistry in the brain can cause memory impairment and may account for the short-lived condition called "blackouts." Because alcohol suppresses the excitatory effect of glutamate on nerve cells, this can result in strokes and seizures.

Another neurochemical that is altered due to chronic intake of alcohol is gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the brain. Initially, alcohol increases the effects of GABA, which produces a state of mild sedation. Over time with continued abuse, the GABA system is down regulated and, when alcohol is not present in the system, the inhibitory effects are lost and overexcitation of the brain results.

Alcoholism is a chronic disease, with a natural history that progresses to death if the intake does not completely

stop. The progress consists of three stages. During the beginning stage, the alcoholic becomes dependent on the mood-altering effects of alcohol. In the middle stage, drinking starts earlier and there is tolerance (when more alcohol is needed to produce effects); during this stage, alcohol consumption is out of control and alcoholics frequently exhibit denial. Heavy consumption causes symptoms of anxiety, **depression**, **fatigue**, anger, rage, lack of self-esteem, and self-loathing. Symptoms worsen as the disease progresses, and alcoholics develop hand **tremors** and shaking (**delirium** tremens) and morning hangover. The final stages of alcoholism progress to round-the-clock consumption despite extremely negative personal and social consequences. The disease progresses with symptoms of intense guilt and remorse (suppressed by more drinking), fear of crowds and public places, financial debt, legal problems, and ill health (including malnutrition). Late-stage disease typically involves liver degeneration (cirrhosis) and severe, even life-threatening, clinical signs (shakes and convulsions) during withdrawal without treatment. Insanity due to brain damage or death may occur during this stage.

Alcohol can cause thiamine deficiency (vitamin B-1). The Wernicke-Korsakoff syndrome is a late complication due to vitamin B deficiency, resulting from malnutrition. These alcoholics have a condition called hepatic **encephalopathy**, caused by diminished capacity of the liver to metabolize and detoxify chemicals in the body. Symptoms of Wernicke-Korsakoff syndrome include agitation, confusion, and altered personality. There is **peripheral neuropathy** (damage to peripheral nerves), which is symmetrical and affects the lower extremities. If untreated, this syndrome can further cause brain (cerebellum) degeneration, abnormal gait (walking), memory deficits (retrograde amnesia), and difficulty with abstract thinking and the acquisition of new learning (anterograde amnesia). Even if successfully treated with vitamin therapy, patients may still have amnesia (a condition called Korsakoff Syndrome).

Fetal alcohol syndrome is a condition that occurs in infants born to alcoholic mothers. Prenatal exposure to alcohol can impair and retard fetal development and growth. Affected infants have a characteristic appearance that consists of a flat nose, flat mid face, small head size, short stature, and a thin upper lip. Approximately 50% are mentally deficient and most others exhibit intellectual deficits. Affected babies typically suffer from poor coordination, decreased adipose (fat) tissue, cleft palate, **attention deficit hyperactivity disorder** (ADHD), decreased muscle tone, heart defects, eye/ear defects, and smaller jaw.

Alcoholic **myopathy** (disorder affecting muscle tissue) can be either acute (rapid onset of symptoms) or chronic (slower onset to develop symptoms). Acute alcoholic myopathy can involve symptoms such as muscular cramps, weakness, swelling, and tenderness in affected areas of muscle. Chronic alcoholic myopathy can be painless, but is associated with weakness due to nerve atrophy.

Demographics

Alcoholism is a widespread and costly problem. Even though use has declined since 1981, two of three American adults drink alcoholic beverages. Approximately 6.5% to 10% of the total U.S. population are heavy drinkers and they consume 50% of all the alcohol ingested annually. Alcohol is heavily implicated in tragic events and is involved in 50% of all crimes, 50% of all fatal car accidents, 33% of all boat/aviation deaths and drowning, and 50% of all accidental death, suicides, and murder. Approximately 50% of alcoholics are not diagnosed, because alcoholics rarely admit to excessive consumption. In approximately 50% of Chinese, Japanese, and Koreans, an enzyme called aldehyde dehydrogenase is absent. This is the enzyme that breaks down alcohol in the liver. Thus in populations who do not have the enzyme, alcohol-related problems are less likely, because persons with this deficiency will become sick (face flushing, racing heart rate) when they consume alcohol. Persons who develop nerve damage as a result of chronic alcoholism have a greater mortality rate than the general population. Fetal alcohol syndrome is estimated to occur in 5.2 per 10,000 live births in the United States. Women are more likely to develop alcoholic myopathy more than men, because women can develop the complication with 40% less consumption than males.

Causes and symptoms

Studies of adopted twins reveal that children of alcoholics have a greater propensity for alcoholism even though they were adopted away from the alcoholic parents. Additionally, research indicated that children of nonalcoholic parents are less likely to develop alcoholism even when adopted into families with an alcoholic parent(s). Adopted children of alcoholic parents have four times a greater risk of developing alcoholism than those born of nonalcoholic parents. The cause is ultimately a combination of genetic and environmental factors, and poor prevention programs among high-risk target populations.

Diagnosis

Diagnosis of neurologic disease is based on clinical signs and symptoms. Psychometric testing, psychological evaluation, and appropriate medical tests (neuroimaging, blood chemistry, liver profiles, differential cell count) can help establish the diagnosis. Alcoholics can exhibit disorders in multiple organ systems, and careful, comprehensive examination is necessary in order to stage the disease

and execute an effective interventional treatment plan. No single test can diagnose alcoholism. The diagnosis can be made once a careful evaluation of all the clinical data is available. Criminal information related to drunk driving can also help establish the diagnosis.

Treatment team

The treatment for medical-related disorders can include a psychiatrist, **neurologist**, and members of an inpatient medical ward in a hospital or psychiatric unit. Professional psychotherapist services are necessary to initiate an interventional treatment program. Monitoring and follow-up care with primary care practitioners and specialists is part of a well-integrated treatment program.

Treatment

Acute management of alcohol intoxication is supportive in nature, and patients are monitored and treated if heart or lung problems develop. Patients may require intravenous fluid replacement (due to fluid loss from sweating and fever). Agitation can be treated with medications called **benzodiazepines**. Wernickes' syndrome can be reversed with IV thiamine replacement, and withdrawal seizures can be treated with antiepileptic medication. Damage to muscles (chronic alcoholic myopathy) can be treated by supplementation of deficient vitamins and special diets. This initial management of detoxification usually requires inpatient treatment ranging from three to 10 days. Patients must undergo intensive inpatient or outpatient psychotherapy, and a long process of recovery and rehabilitation.

Recovery and rehabilitation

Involvement in nonprofessional community-centered support groups such as Alcoholics Anonymous (AA) that utilize the "12-step" recovery approach is helpful for maintaining sobriety. During early recovery, patients still exhibit mood swings and compulsions to drink. Patients should attempt to receive positive support from family and friends, take rest and good nutrition, and seek to share experiences with other alcoholics (e.g., through self-help groups). Patients should also receive professional psychotherapy treatment from a clinician with special certifications in addictions counseling, or from a specialist in forensic psychotherapy. Typical treatment using psychological techniques include cognitive behavioral therapy and motivational enhancement therapy.

Clinical trials

Clinical trials are currently recruiting patients for government-sponsored medical research (National Institute on Alcohol Abuse and Alcoholics). Studies include the role of dopamine in response to alcohol, and the effects of another neurotransmitter, serotonin, in alcoholism.

Prognosis

The prognosis depends on the motivation of the patient to stop drinking alcohol, and the extent of organ damage, which varies with each case. The prognosis can be favorable in some patients (with minimal organ damage) that successfully complete long-term intensive psychotherapy and stop drinking.

Special concerns

Psychotherapy treatment may be long term and complicated. Frequently, there may be psychological problems that occur within families who have an alcoholic. Alcoholics may cause violence to or abuse of family members.

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National Council on Alcoholism and Drug Dependence, Inc., 20 Exchange Place, Suite 2902, New York, NY 10005. (212) 269-7797 or (800) NCA-CALL; Fax: (212) 269-7510. <http://www.ncadd.org/>.

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 for analysis. 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.

Astrocytes Types of neuroglial cells in the central nervous system that help support other nerve cells.

Chorionic villus sampling A medical procedure done during weeks 10-12 of a pregnancy. A needle is inserted into the placenta and a small amount of fetal tissue is withdrawn for analysis.

Chromosome A structure in the nucleus of a cell that contains a thread of DNA containing the genetic information (genes). Humans have 46 chromosomes in 23 pairs.

DNA Deoxyribonucleic acid; the genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Histologic Pertaining to histology, the study of cells and tissues at the microscopic level.

Hydrocephalus An abnormal accumulation of cerebrospinal fluid within the brain. This accumulation can be harmful by pressing on and damaging brain structures.

Quadriparesis Partial or incomplete paralysis of all four limbs.

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Alexander disease

Definition

Alexander disease (ALX) is a rare and often fatal nervous system disorder that primarily occurs in infants and children.

Description

The main features of Alexander disease are progressive mental impairment and loss of motor control. Based on the age of onset and type of symptoms present, ALX has been classified into three forms: infantile, juvenile, and adult. Alexander disease is named for Dr. W. Stewart Alexander, an Australian pathologist who first described an infantile case in 1949. Since that time, 80% of cases described have also been the infantile form. About 14% of patients have the juvenile form, and adult cases are rare. All three forms of ALX are unified by the presence of Rosenthal fibers (RF), microscopic protein aggregates that are found in astrocytes in the brain and spinal cord. Though Rosenthal fibers are associated with other conditions, the numbers and distribution of RF-containing astrocytes are unique to Alexander disease. ALX is one of the leukodystrophies, a group of disorders characterized by imperfect formation or maintenance of white matter, the myelin sheath (insulation) that covers the nerves in the brain and spinal cord. Patients with ALX usually display loss of white matter, most prominently in the frontal lobes of the brain.

Demographics

Alexander disease is thought to be quite rare with approximately 200 cases described. Although there are no known prevalence estimates, the disease has been reported in both males and females and in various ethnic and racial groups.

Causes and symptoms

Most cases of Alexander disease are genetic, caused by a dominant mutation (change) in the glial fibrillary acidic protein (GFAP) gene on chromosome 17. Usually this mutation occurs randomly in an individual without a family history of the disease. There are reports of rare familial cases with affected siblings. Therefore, unaffected parents of a child with ALX are at a low risk to have another affected child. Individuals with ALX who live long enough to reproduce have a 50% chance for an affected child. Since GFAP mutations have not been found in all cases of ALX, there may rarely be other genetic or non-genetic explanations for this disease.

The glial fibrillary acidic protein gene encodes a protein by the same name. GFAP helps to provide structural stability to the astrocytes, which are supporting cells in the brain similar to blood vessels. GFAP is found in Rosenthal fibers. Reports have suggested that GFAP gene mutations

result in a toxic gain of function of the protein (GFAP) that leads to a minimal or absent production of myelin. As of 2003, the precise mechanisms by which GFAP mutations cause ALX were unresolved.

In the infantile form of the disease, average age of onset is six months, with a range of birth to two years. Affected children tend to have progressive physical and **mental retardation** with loss of previously attained milestones. Head size becomes increasingly large and the forehead appears prominent as a result of **megalencephaly** (enlarged head and brain). Other disease manifestations include **seizures**, **spasticity** (stiffness of the arms and legs), quadriparesis, feeding problems, and **ataxia** (poor coordination). **Hydrocephalus** may also occur, especially in children with early onset of symptoms.

The juvenile form of ALX usually presents between age four and the early teens. Patients may develop some or all of the following symptoms: speech problems, difficulty swallowing, frequent vomiting, spasticity of the legs, ataxia, gradual intellectual decline, seizures, megalencephaly, or breathing problems. White matter abnormalities in the juvenile form are less prominent than in the infantile form.

The adult form of ALX represents the most variable and least common form of the disorder. Patients with the adult variant may have symptoms that mimic **multiple sclerosis**, or may display symptoms similar to the juvenile form of the disease, except with later onset and slower progression. White matter changes may or may not be present. Some adult cases have been discovered by chance when an autopsy reveals Rosenthal fibers, a characteristic finding of this disease.

Diagnosis

A diagnosis of Alexander disease is usually based on radiologic findings and/or genetic test results in an individual who has symptoms suggestive of this condition. Radiologic studies that may aid in diagnosis include **magnetic resonance imaging (MRI)**, a computerized tomography (**CT**) **scan**, or a head ultrasound. For example, an MRI of an individual with the infantile form typically reveals white matter loss that involves the frontal lobes of the brain, abnormalities of the basal ganglia and thalamus, and possibly, enlargement of the ventricles. Genetic testing is accomplished by looking for known or detectable mutations in the GFAP gene. In up to 94% of cases of ALX, a GFAP mutation is found. Prenatal diagnosis for couples with an affected child can be performed when the mutation responsible for ALX is known. The DNA of a fetus can be tested using cells obtained from chorionic villus sampling (CVS) or amniocentesis.

Prior to the discovery of the gene responsible for the disease, diagnosis of ALX was made by demonstration of Rosenthal fibers in a **biopsy** or autopsy sample from the brain. Though genetic testing has largely replaced these histologic studies, a brain biopsy or autopsy may be indicated in select cases if the diagnosis cannot be made through other means.

Treatment team

Management of ALX usually involves the services of multiple medical specialists. In addition to primary health care professionals, patients may require the care of specialists in neurology, neurosurgery, physical therapy, occupational therapy, social services, orthopedics, and gastroenterology. A genetic specialist, such as a clinical geneticist or a genetic counselor, may be helpful to the patient and family, especially at the time of diagnosis or prior to genetic testing. Families may also benefit from psychological counseling and contact with other families affected by ALX or another **leukodystrophy**.

Treatment

There is no cure for Alexander disease. Treatment, which is symptomatic and supportive, primarily consists of attention to general care and nutritional needs, antibiotic therapy for infections, and management of associated complications such as anti-epileptic drug therapy for seizures. Surgical interventions, including placement of a feeding tube and/or shunting for hydrocephalus, may also be required. Orthopedic surgery for scoliosis has been reported in a case of Alexander disease.

Recovery and rehabilitation

Given the rarity of ALX, the potential for rehabilitation in this disorder is unknown. Depending upon the type, severity, and rate of progression of symptoms in a given individual, interventions such as physical, occupational, and speech therapy may be recommended for management of disease-related complications. In severe cases of ALX, consideration may be given to placement in a residential care facility that can provide 24-hour care and support services.

Clinical trials

As of 2003, there were no **clinical trials** for patients with Alexander disease. As more is learned about how mutations in the GFAP gene cause disease, it is hoped that new therapies may be developed in the future. As of December 2003, two laboratories were conducting research on the GFAP gene; both accept contact from patients and

families. They are the Children's National Medical Center—Center for Genetic Medicine (202-884-6065 or <egordon@cnmcresearch.org>) and the University of Alabama at Birmingham, Michael Brenner Research Lab (608-263-9191 or <messing@waisman.wisc.edu>).

Prognosis

The course of Alexander disease is generally one of regression and progressive neurologic degeneration. Prognosis varies according to the form of the disease. Lifespan for patients with the infantile from is significantly reduced; affected individuals live anywhere from one to 10 years of age. For the juvenile form of the disease, survival ranges from several years after onset to the late teens, with rare cases living several decades. Due to the rarity of the adult form, little is known about the prognosis for this ALX variant.

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National Organization for Rare Disorders. P.O. Box 1968, 55 Kensonia Avenue, Danbury, CT 06813. (203) 744-0100 or (800) 999-NORD; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

United Leukodystrophy Foundation. 2304 Highland Drive, Sycamore, IL 60178. (815) 895-3211 or (800) 728-5483; Fax: (815) 895-2432. ulf@tbcnet.com. <http://www.ulf.org>.

Dawn J. Cardeiro, MS, CGC

Alpers' disease

Definition

Alpers' disease is an early-onset, progressive neurological degenerative disease that severely affects the brain and liver. In the familial (inherited) form of the disorder, it is transmitted as a recessive condition, which means that parents are unaffected, but both are carriers. Carrier parents have a 25% risk of having their biological child affected with Alpers' disease.

Description

Alpers' disease was first described by the late **neurologist** Alfons Maria Jakob (1884–1931). The disease was characterized and published by Bernard Jacob Alpers, Erna Christensen, and Knud Haraldsen Krabbe; thus, Alpers' disease is also known as Christensen's disease or Christensen-Krabbe disease. Additionally, the disease is known as progressive sclerosing poliodystrophy. Alpers' disease afflicts children and is eventually fatal. Degeneration in cognitive processes (reasoning ability) and muscular involvement caused by the disease is unrelenting and relatively rapid. Physically, children with Alpers' disease lose control of their muscle movements. The ramifications of this disorder can significantly affect the emotional state of the person with Alpers' disease, along with family members caring for them.

Demographics

Alpers' disease is a rare disorder. Due to complications related to the diagnosis of Alpers' disease, it is difficult to estimate how often it occurs in the population. Both genders are affected with equal frequency.

Causes and symptoms

Children with Alpers' disease usually develop symptoms between the ages of three months and five years old. Initially, the first symptom early in life is **seizures** (convulsions). These children tend to be hypotonic (unable to achieve normal muscle tone) and their limbs seem to be stiff. This is usually followed by the failure to reach cognitive and developmental milestones. **Mental retardation** is progressive in these children.

Among the most devastating features of this disorder is the progressive **dementia**. In children with Alpers' disease, mental deterioration can occur rapidly. The pathological nature of the defect involves an area of the brain called the cerebrum in which a specific part (the gray matter) is affected. Spastic quadriplegia (inability to use and control movements of the arms and legs) can develop in

Key Terms

Hypotonia Decreased muscle tone.

Mitochondrial DNA The genetic material found in mitochondria, the organelles that generate energy for the cell. Because reproduction is by cloning, mitochondrial DNA is usually passed along female lines.

Spastic quadriplegia Inability to use and control movements of the arms and legs.

the later stages of the disorder. Blindness is also observed, and this is usually due to a condition called optic atrophy. In optic atrophy, the optic nerve degenerates, resulting in the inability to process visual information from the eye to the brain.

The liver is also affected. Liver conditions that these children experience are jaundice or complete liver failure in more severe cases. Researchers at the National Institutes of Health (NIH) consider that children with Alpers' disease are often misdiagnosed as having childhood jaundice or liver failure. This is due to the problems associated with making a diagnosis in living patients.

Currently, the specific mechanism, whether genetic, environmental, or both, that causes this disease is unknown. Scientists assume that Alpers' disease is caused by an underlying metabolic defect. Mutations in the DNA of the mitochondria (DNA that is a separate genome from the nucleus) have been associated with this disorder. The mitochondria functions to produce energy to tissues and is particularly important for tissues such as the brain.

Diagnosis

Currently, the only way to arrive at a definitive diagnosis is by autopsy following the death of the child. A postmortem examination of the brain and liver is required.

Treatment team

Because children affected with Alpers' disease usually develop convulsions, they are first directed to a neurologist. An experienced neurologist is always necessary in order to get the appropriate palliative (supportive) care and treatment for these seizures. As the disease progresses, occupational therapists can provide aids for positioning and comfort. Due to the rapid nature of the disorder and the unavailability of treatment to slow the progression, children with Alpers' disease are usually unable to attend school. There are, however, support specialists and organizations that have experience with severe neurological disorders. The National Organization for Rare Disorder can help affected families find local support organizations. There are also organizations such as the Genetic Alliance that help identify support groups to allow families affected by genetic diseases to find other families with the same or related disorders. These organizations can be a tremendous help in alleviating the many emotional and situational burdens that arise by allowing family members to talk to other families that have experience with diseases such as Alpers' disease. Physical therapy can also be helpful to maintain range of motion in the child's arms and legs for as long as possible.

Treatment

There is no cure for Alpers' disease. Also, there is currently no treatment that will slow the progression of the disease. Therefore, treatment is aimed at symptoms such as the seizures. The neurologist must consider the choice of anticonvulsant carefully to avoid ones that may have an adverse effect on the liver.

Recovery and rehabilitation

As Alpers' disease is progressive and eventually fatal, emphasis is placed not upon recovery, but on maintaining functionality as long as possible. Several lifestyle adaptations must be addressed, as children with Alpers' disease eventually require full-time personal care. Depending on how severely and how rapidly the symptoms develop, families may require structural changes such as wheelchair access or other household modifications.

Clinical trials

As of February 2004, there are no ongoing **clinical trials** designed specifically to treat or study Alpers' diseases.

Prognosis

The prognosis for children with Alpers' disease is poor. Affected individuals typically die within the first decade of life, but in some cases of rapid progression, death can occur in as little as a few months after symptoms become apparent. Seizures can be particularly devastating, as they are often continuous and can lead to death. Other causes of death include complications related to liver disease or cardio-respiratory failure.

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ORGANIZATIONS

Genetic Alliance, Inc. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2369. (202) 966-5557; Fax: (202) 966-8553. info@geneticalliance.org. <http://www.geneticalliance.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605. (914) 428-7100 or (888) MODIMES; Fax: (914) 428-8203. askus@marchofdimes.com. <http://www.marchofdimes.com>.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). National Institutes of Health, Bldg. 31, Rm. 9A04, Bethesda, MD 20892-2560. (301) 496-3583. <http://www.niddk.nih.gov>.

National Organization for Rare Disorders (NORD). P.O. Box 1968, 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Bryan Richard Cobb, PhD

Alternating hemiplegia

Definition

Alternating hemiplegia is a very rare condition characterized by recurrent episodes of temporary paralysis.

Description

Alternating hemiplegia usually begins affecting a child before the age of four. Bouts of recurrent, temporary paralysis may involve the arms, legs, facial muscles, and/or eye muscles. The manifestations may range from numbness or tingling in the affected body part to complete paralysis. The episodes last between minutes and days, and are usually resolved by sleep. A variety of other neurological problems may also be present in children with alternating hemiplegia.

A less-severe variant of alternating hemiplegia is called "benign nocturnal alternating hemiplegia of childhood." In this variant, a child awakens from sleep to a state of paralysis that resolves completely over 2–15 minutes. Children with this variant do not suffer from other associated neurological problems. This particular condition is thought to be a variant of a migraine **headache**.

Key Terms

Dystonia Abnormal muscle movements and stiffening.

Hemiplegia Paralysis on one side of the body.

Migraine A type of chronic headache caused by a cascade of events in the brain, including initial dilatation or widening of blood vessels, followed by chemical release and then painful spasms of blood vessels in the brain.

Paralysis Loss of ability to move a part of the body.

Demographics

Alternating hemiplegia is quite rare, with fewer than 100 diagnosed cases in the United States, and fewer than 240 diagnosed patients worldwide.

Causes and symptoms

The underlying cause of alternating hemiplegia is unknown. Benign nocturnal alternating hemiplegia of childhood is thought to be a variant of migraine headache, and therefore may be caused by a similar mechanism (abnormal dilatation of blood vessels in the brain, followed by chemical release and then painful spasms of the blood vessels).

Individual episodes seem to occur spontaneously, although in some individuals they may be precipitated by stress, sleep deprivation, or viral illness.

Symptoms of alternating hemiplegia

Episodes of alternating hemiplegia come on suddenly during wakefulness, and can last between hours and days. Either or both sides of the body may become numb, tingly, or completely paralyzed. Limbs may be limp or stiff (dystonic). Facial and eye muscles are often affected, as well as the limbs. Children with alternating hemiplegia also

usually experience progressive difficulty with balance and walking, excess sweating, mental impairment, developmental delay, problems with body temperature, shortness of breath, and **seizures**. Although sleep can ameliorate the symptoms, the symptoms may recur upon awakening.

Symptoms of benign nocturnal alternating hemiplegia of childhood

Symptoms of benign nocturnal alternating hemiplegia of childhood may begin when the child is about two years of age. Boys appear to be more frequently affected than girls. Episodes may be preceded by several days by headache, abnormal irritability, and oppositional behavior. The actual episodes commence when a child is asleep, causing the child to awaken suddenly, screaming or crying and drooling. Although the child may appear to be awake, he or she usually does not respond normally to questions or commands. Usually only one side of the body appears limp and paralyzed. The episodes usually last about fifteen minutes, end with the child falling back into sleep, and are completely resolved when the child awakens again. Some children experience headache and vomiting with each episode, further underscoring the proposed link with migraine headache. Although children with this condition do not seem to exhibit any permanent effects of their hemiplegic episodes, and generally have normal intelligence, there does appear to be an increased risk of hyperactivity, irritability, and oppositional defiant disorder in children who experience episodes of benign nocturnal alternating hemiplegia of childhood.

Diagnosis

There are no available tests to definitively diagnose either form of alternating hemiplegia. These disorders are diagnosed by ruling out other possible reasons for a child's episodes and symptoms.

Treatment team

Children with the more benign form of alternating hemiplegia may not require an extensive treatment team, other than a **neurologist** to help in diagnosis. Children with the more severe form of alternating hemiplegia may require a neurologist, as well as other specialists to help with their progressive problems with walking, such as a physical and occupational therapist. Children with this disorder usually require a specialized educational setting.

Treatment

There is no cure for either form of alternating hemiplegia. A drug called flunarizine has been used to treat the more severe type of alternating hemiplegia, in an effort to decrease the frequency of hemiplegic episodes, as well as their duration and severity. Some researchers believe that decreasing the number and severity of attacks may improve the child's overall cognitive prognosis, by preventing damage to the brain.

Prognosis

The classic form of alternating hemiplegia has a poor prognosis, with progressively severe impairment of mobility and cognitive functioning, requiring long-term care. About half of all children with benign nocturnal alternating hemiplegia of childhood outgrow their episodes over time.

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ORGANIZATIONS

Alternating Hemiplegia of Childhood Foundation. Richard George, President. 11700 Merriman Road , Livonia, Michigan 48150. 888-557-5757. richard7@ameritech.net. <http://www.ahckids.org/index.htm>.

Rosalyn Carson-DeWitt, MD

Alzheimer disease

Definition

Alzheimer disease is a neurological disorder characterized by slow, progressive memory loss due to a gradual loss of brain cells. Alzheimer disease significantly affects cognitive (thought) capabilities and, eventually, affected individuals become incapacitated. Alzheimer-related issues can cause emotional and financial upheaval for both the individuals with the disease and their families. Alzheimer disease is the most common form of **dementia** (loss of intellectual function) and, according to the National Institutes of Health (NIH), it is the fourth leading cause of death in adults.

Key Terms

Amyloid plaques A waxy protein substance that forms clumps in brain tissues, leading to brain cell death.

Autosomal dominant disorder An inheritance pattern where an affected parent has a 50% chance of passing on a genetic mutation responsible for the disorder to their offspring in each pregnancy.

Dementia Deterioration or loss of intellectual faculties, reasoning power, and memory due to organic brain disease.

Neurofibrillary tangles An accumulation of twisted protein fragments inside nerve cells, and one of the characteristic structural abnormalities found in the brains of patients with Alzheimer disease.

Description

The condition was first described in 1906 by Alois Alzheimer, a German physician. Alzheimer characterized two abnormal structures in the brain of a woman with dementia that are now considered the hallmarks of the disease: amyloid plaques and neurofibrillary tangles. The nature of Alzheimer disease is progressive. Initially, dementia is manifested by barely noticeable memory deficits. Eventually, the memory loss becomes more severe until it is incapacitating. Other symptoms such as confusion, the inability to articulate words correctly, and hallucinations occur with varying degrees. Emotional problems such as easy agitation, poor judgment, and feelings of withdrawal are also common in the early stages. Affected individuals are also likely to develop **seizures**, hypertonicity (increased muscle movements), and incontinence. Without treatment or supervision, death often results from malnutrition or pneumonia. From the initial symptoms, disease progression can last up to 25 years, although typically the duration ranges from eight to 10 years.

Demographics

Dementia is thought to affect between 25–50% of individuals 85 years or older. The risk of developing Alzheimer disease increases with age and is independent of sex or geographical location (although there are environmental toxic agents that can impair various cognitive functions, including memory loss). A genetic association has been found for higher risk of developing Alzheimer disease in individuals with mutations in a particular gene who are also African American or Caribbean Hispanics. This association is greatest in individuals with a positive family history of dementia.

Approximately 10% of people 65 years or older are at risk for developing significant memory loss. More than half of these individuals (5% of all individuals 65 years or older) have Alzheimer disease. Approximately four in 10,000 individuals between the ages of 40 and 60 are at risk for having Alzheimer disease.

Causes and symptoms

Although there are several known causes of Alzheimer disease, about 75% of cases are sporadic and occur without a clear cause; this percentage represents people without a family history of the disorder. Scientists assume that these cases are due to a combination of unknown genetic predisposing factors and environmental exposures. Although various narcotics, therapeutic drugs, viruses, and toxins have been implicated in the etiology of the disease, there is currently no proof that they can cause Alzheimer disease.

Genetic basis for Alzheimer disease

Of all persons with Alzheimer disease, up to 25% of cases are thought to be part of a familial-based inheritance pattern and therefore are only determined based on family history or genetic test results. In general, these forms of Alzheimer disease are inherited as an autosomal dominant disorder, meaning that affected individuals have a 50% chance of passing on the mutated gene to their offspring in each pregnancy. There is a late-onset familial form (AD2), three early-onset familial forms (AD1, AD3, AD4), and a form of Alzheimer disease associated with Down syndrome.

Down syndrome and Alzheimer disease

Less than 1% of all cases of Alzheimer disease are due to a chromosomal defect called trisomy 21 (also known as Down syndrome). This occurs when there are three copies of genes found on chromosome 21, usually due to a person having an extra chromosome 21. These individuals usually develop Alzheimer disease after the age of 40. The APP gene, which encodes the amyloid precursor protein and is implicated in the pathogenesis of Alzheimer disease, is localized to chromosome 21; it is felt that people with Down syndrome overproduce this protein, resulting in its accumulation in the brain. The excess protein is thought to cause the disease.

Early-onset familial Alzheimer disease

A low percentage (2%) of Alzheimer cases results from a familial form of the disease in which there is an early onset of symptoms (AD1, AD3, and AD4), usually occurring before the age of 60. Age of onset usually occurs around 40–50 years, but can occur as early as 30 years.

The majority of these persons have family members that are also affected. The clinical manifestations are similar to the adult-onset form, with loss of memory and cognitive ability. In this form of Alzheimer disease, there are several chromosomal locations of genes implicated in causing the disease.

AD1 accounts for approximately 10–15% of early-onset Alzheimer disease and involves a protein called presenilin 1 that has a mutation in the gene that encodes it called PSEN1, which is found on chromosome 14. AD3 accounts for 20–70% of the early-onset familial form and is caused by mutations in APP found on chromosome 21, which encodes a protein called amyloid beta A4. AD4 is extremely rare and is caused by mutations in PSEN2, localized to chromosome 1, and encodes a protein called presenilin 2.

Late-onset familial Alzheimer disease

The late-onset familial form of Alzheimer disease (AD2) accounts for approximately 15–25% of all cases. These familial cases are seemingly indistinguishable from sporadic cases when observed clinically, but can be recognized based on molecular genetic testing. However, there is no clear chromosomal location for a gene directly responsible for the disease. Therefore, this complex type may involve many susceptibility genes. These familial cases are most likely due to multiple genes that make these individuals susceptible to developing the disease. For example, the APOE e4 gene on chromosome 19 associated with late-onset Alzheimer disease reduces the age in which symptoms develop by an unknown mechanism. There are many other candidate genes that are thought to modify Alzheimer disease risks and these genes, with various chromosomal locations, have been linked to the disease in different families.

Development (pathogenesis) of Alzheimer disease

Although scientists know how brain cells of persons with Alzheimer disease are affected, and additionally understand some of the genetic explanations of the disease, the precise cause of Alzheimer disease is still unclear. For example, it is known that accumulations of clumps of proteins called amyloid plaques outside brain cells and accumulation of altered proteins inside the cells called neurofibrillary tangles are characteristic of Alzheimer disease; however, it is unclear how these accumulated proteins cause brain cells to die.

According to the Alzheimer's Disease and Related Disorders Association, Inc., there are seven stages that characterize the disease:

- Stage 1: No decline in function is yet noted. This group includes individuals who may carry predictive gene mutations but have no symptoms, or those who will be affected by other unknown mechanisms.
- Stage 2: Normal function in general, although the person is aware of a subtle cognitive decline.
- Stage 3: Early Alzheimer disease. Persons experience difficulty in performing complex tasks that require cognitive skills.
- Stage 4: Mild Alzheimer disease. Persons require assistance with common tasks such as paying bills and balancing a checkbook.
- Stage 5: Moderate Alzheimer disease. Persons require assistance in making personal everyday decisions such as choosing appropriate clothing for the weather or ordering from a menu.
- Stage 6: Moderately severe Alzheimer disease. Persons require assistance dressing, bathing, and using the toilet. Urinary and bowel incontinence may be present.
- Stage 7: Severe Alzheimer disease. The vocabulary shrinks to only a few words; then little or no verbal communication is heard. The ability to walk is lost, followed by an inability to maintain a sitting posture in a chair. Eventually, the person experiences profound lack of purposeful muscle control, is totally dependent for care, and cannot smile or hold up his or her head.

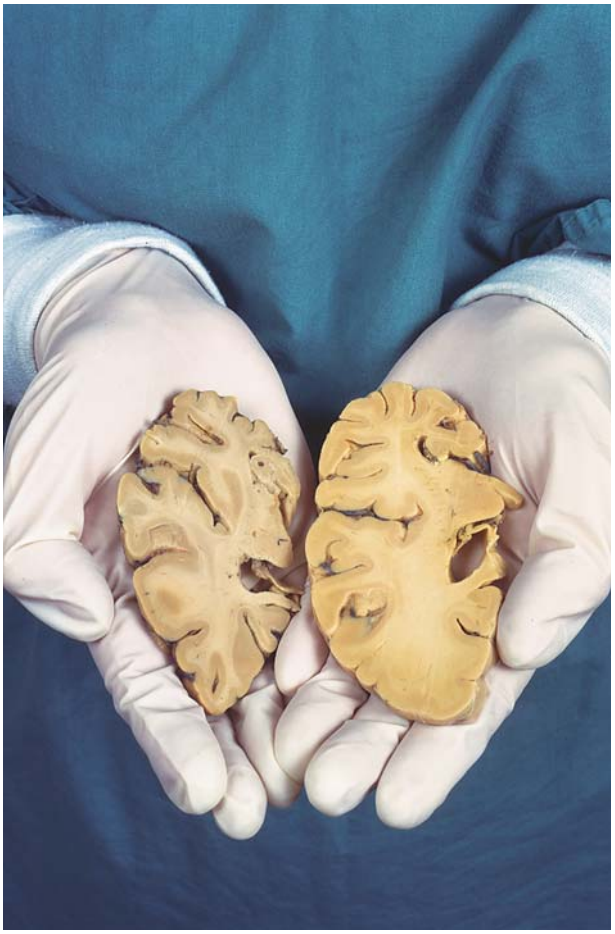
Diagnosis

Alzheimer disease is diagnosed clinically by a physician, postmortem by a histopathologist (a scientist who studies diseased tissues by their various staining patterns), or genetically by identifying mutations in genes associated with the disease.

The gold standard for diagnosis of Alzheimer disease is through autopsy examination by an experienced pathologist. Detection of amyloid plaques in the brain by histopathology is the most conclusive diagnostic tool. This is performed using antibodies that bind to the particular amyloid proteins and can be visualized by microscopic evaluation, as the antibodies are tagged with a fluorescent or colorimetric molecule. A positive result would involve a significantly greater number of plaques compared to age-matched controls. Other brain defects that characterize the disease, such as abnormal nerve cell configurations called intraneuronal neurofibrillary tangles, can also be detected by histopathology by the same methods. A clinical diagnosis by a physician accounts for 80–90% of patients diagnosed with Alzheimer disease.

Clinical diagnosis

A physician can use a number of different tests to assess memory skills, and, combined with any observed changes in the individual's behavior, they can help make a diagnosis of Alzheimer disease. Other tests that are important in diagnosing the disorder can involve laboratory tests that require blood and urine or imaging studies of the



The smaller, darker brain segment on the left is affected by Alzheimer disease; the segment on the right is from a healthy brain. *(Simon Fraser/MRC Unit, Newcastle General Hospital/Science Photo Library. Reproduced by permission.)*

brain. By using neuroimaging studies such as **magnetic resonance imaging (MRI)** scans, physicians have found that patients with Alzheimer disease often have diffuse atrophy (weakening or decrease in size) in a specific area of the brain called the cerebrum.

Genetic diagnosis

It has been shown that there is a significant association of a specific gene called APOE e4 with the development the early-onset form of the disease. There are three different types of Alzheimer disease that have been shown to be caused by mutations in three distinct genes known as APP, PSEN1, and PSEN2. However, determining the genotype (whether a patient carries this associated mutation) is not entirely conclusive. Currently, although APOE e4 mutation analysis can help in diagnosing a patient suspected of having Alzheimer disease, it is not used for predictive testing of these individuals.

Biochemical markers

Although there are no tests to definitively diagnose Alzheimer disease, there are useful biochemical markers that can help distinguish Alzheimer disease from other disorders that involve dementia, including dementia caused by vascular disorders, drugs, or thyroid disease. Fluid that is found in the brain and spinal cord called cerebrospinal fluid can be tested for levels of two proteins, Tau and Aβ42, in patients that develop symptoms of dementia. Aβ42 accumulation in the brain is associated with reduced levels in the cerebrospinal fluid. Accumulation of the Tau protein in the brain is associated with Alzheimer disease. Therefore, increased Tau protein levels and decreased Aβ42 in the cerebrospinal fluid can pinpoint which persons have Alzheimer disease, regardless of the cause or the age of onset.

The score for these tests is numerical and relies heavily on a reference range determined by a patient's age, sex, and the type of equipment used to perform the test. A positive result will only indicate that a patient is at high risk of having Alzheimer disease and requires further analysis for an accurate diagnosis. This test has yet to be widely performed and is, therefore, only available in certain reference laboratories.

Treatment team

Initially, a physician usually recommends counseling by a psychologist or a support group experienced with this disease. After the diagnosis, visits to the physician focus on treating mild behavioral changes such as **depression**. Eventually, treatment requires 24-hour supervision and nursing care. The caretakers are mostly nurses or professionals who are part of various assisted-living programs.

Treatment

Pharmacological treatment

Treatment of Alzheimer disease is mainly palliative (given for comfort) and focuses on mitigating symptoms. Each symptom is treated based on its severity and the other symptoms that are affecting the individual. Most affected individuals will eventually need professional care in assisted living or nursing homes. They require constant supervision as memory loss becomes incapacitating. There are several pharmacological interventions and treatment regimens that are suggested. Patients who have depression are treated with antidepressants. Tacrine is often prescribed to help with some of the behavioral problems and provides modest cognitive benefits in a small percentage of patients. Aricept, Galantamine, and Exelon are more recent drugs used for a similar purpose, and are not believed to cause liver toxicity; the liver must be monitored in those taking Tacrine. Non-steroidal anti-inflammatory drugs

(NSAIDs) are currently being investigated for their use in treating patients with Alzheimer disease.

Coping with the disorder

There are strategies to cope with this disorder and these should be considered in the beginning stages of the disease. Coping mechanisms depend on whether there are family members available for support. If an individual is without family members, relying on community support through neighbors or volunteers of Alzheimer disease organizations will be necessary.

Many precautions can be made early on to avoid difficult or life-threatening situations later, while maintaining everyday activities in the home environment. Dealing with a person with Alzheimer disease with patience is important. Daily tasks should be performed when the person with Alzheimer disease feels best. Informing neighbors of the person's condition is an important first step. Arranging for assistance, depending on the stage of the disorder, will become necessary. As the ability to drive may be compromised fairly early in the disorder, transportation may need to be arranged. There are local chapters of the Alzheimer's Association that offer help with transportation requirements.

In the early period of the disease when memory loss is minimal, it is helpful for family and friends to interact with the affected person, reminding him or her to take medication, eat, keep appointments, and so forth. Family and friends can help sustain the Alzheimer patient's daily living activities. Keeping records is also helpful, particularly if several people are overseeing the patient's care. Additionally, organizing the household so that it is easy to find important items is recommended.

Other helpful coping mechanisms include posting signs to remind patients of important phone numbers, to turn off appliances, and to lock doors. It is important that all electrical cords and appliances are arranged to minimize distraction, and to prevent danger of falling or misuse. Assistance in handling finances is usually necessary. Providing an extra house key for neighbors and setting up a schedule to check on persons with Alzheimer disease is very helpful for both the patient and the family. By utilizing these and other family, neighborhood, and community resources, many people with early Alzheimer disease are able to maintain a successful lifestyle in their home environment for months or years.

Recovery and rehabilitation

For a person with Alzheimer disease, emphasis is placed on maintaining cognitive and physical function for as long as possible. Currently, there is no cure for Alzheimer and, once the symptoms develop, patients do not recover. Instead, they progressively worsen, usually over a period of years. This has many psychosocial and financial ramifications for the patient and the patient's caretakers. Social service workers can help families plan for long-term care, as persons with Alzheimer disease most often eventually require 24-hour assistance with feeding, toileting, bathing, personal safety, and social interaction. Taking care of patients in the later stages can be financially and psychologically draining. Various support systems are available through community mental health centers and national support organizations.

Clinical trials

There are currently many **clinical trials** for the treatment or prevention of Alzheimer disease sponsored by the National Institutes of Health (NIH). Large multi-center clinical trials such as a Phase III clinical trail are aimed at determining whether anti-inflammatory drugs delay age-related cognitive decline. (Contact information: UCLA Neuropsychiatric Institute, Los Angeles, California, 90024. Recruiter: Andrea Kaplan, (310) 825-0545 or her email: akaplan@mednet.ucla.edu.) A Phase III clinical trial is also organized to test the drug Risperidone for the treatment of agitated behavior in Alzheimer's patients. (Contact information: Palo Alto Veterans Administration Health Care System, Menlo Park, California, 94025. Recruiter: Erin L. Cassidy, PhD, (650) 493-5000, ext.27013 or her email: ecassidy@stanford.edu.)

Other trials include:

- A study on Valproate to prevent cognitive and behavioral symptoms in patients. Contact information: Laura Jakimovich, RN, MS, (585) 760-6578 or her email: laura_jakimovich@urmc.rochester.edu.
- The drug Simvastatin, a cholesterol-lowering medication, is being studied to learn if it slows the progression of Alzheimer disease. Contact information: Stanford University, Palo Alto, California, 94304. Recruiter: Lisa M. Kinoshita, PhD, (650) 493-0571 or her email: lisakino@stanford.edu.
- A study of the efficacy and dose of the drug NS 2330 to improve cognition. Contact information: Peter Glassman, MD, PhD, (800) 344-4095, ext. 4776 or his email: pglassma@rdg.boehringer-ingelheim.com.
- A study of investigational medications for the treatment of Alzheimer patients. Contact information: Eli Lilly and Company, (877) 285-4559.

There are also many other studies that are investigating various other pharmacological agents such as vitamin E and other currently available drugs.

Prognosis

There is considerable variability in the rate of Alzheimer disease progression. The Alzheimer Disease Association claims that the time from the onset of clinical symptoms to death can range from three to 20 years, with an average duration of eight years. There are probably many environmental and genetic factors that play a role in the progression of the disease. The accumulation of damage and loss of brain cells eventually results in the failure of many different organ systems in the body. According to the National Institute of Neurological Disorders and Stroke, the most common cause of death is due to infection.

Special concerns

Alzheimer disease should be distinguished from other forms of dementia. In some cases, depression can result in dementia-like symptoms. Other examples include chronic drug use, chronic infections of the **central nervous system**, thyroid disease, and vitamin deficiencies. These causes of dementia can often be treated. It is, therefore, important to obtain an accurate diagnosis to avoid complications associated with the inappropriate treatment and long-term care of these patients. There are also several genetically based syndromes in which dementia plays a role.

Genetic counseling

Genetic counseling is important for family members biologically related to patients with Alzheimer disease because each first-degree relative has as much as a 20% lifetime risk of also being affected. The risk to immediate relatives increases as more family members develop the disease. In the early-onset form of the disease, the inheritance pattern is thought to be autosomal dominant. This means that a carrier (who will eventually be affected) has a 50% chance of passing on the mutated gene to his or her offspring.

The general consensus in the scientific and medical community is to not test children or adolescents in the absence of symptoms for adult-onset disorders. There are many problems associated with predictive testing of asymptomatic individuals who are not yet adults. Children who undergo predictive testing lose the choice later in life (when they are capable of understanding the full ramifications of the disease) to know or not to know this information. It is, therefore, an important consideration that involves ethical and psychological implications.

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Alzheimer's Association. 919 North Michigan Avenue, Suite 1000, Chicago, IL 60611-1676. (312) 335-8700 or (800) 272-3900; Fax: (312) 335-1110. info@alz.org. <http://www.alz.org>.

Alzheimer's Education and Referral Center. PO Box 8250, Silver Springs, MD 20907-8250. (800) 438-4380. adear@alzheimers.org. <http://www.alzheimers.org>.

National Institute on Aging. Building 31, Room 5C27, 31 Center Drive, MSC 2292, Bethesda, MD 20892. (301) 496-1752. <http://www.nia.nih.gov>.

Bryan Richard Cobb, PhD

Amantadine

Definition

Amantadine is a synthetic antiviral agent that also has strong antiparkinsonian properties. It is sold in the United States under the brand name Symmetrel, and is also available under its generic name.

Purpose

Amantadine is used to treat a group of side effects, called parkinsonian side effects, that include **tremors**, difficulty walking, and slack muscle tone. These side effects may occur in patients who are taking antipsychotic medications used to treat mental disorders such as **schizophrenia**. An unrelated use of amantadine is in the treatment of viral infections of some strains of influenza A.

Description

Some medicines, called antipsychotic drugs, that are used to treat schizophrenia and other mental disorders can cause side effects similar to the symptoms of **Parkinson's disease**. The patient does not have Parkinson's disease, but may experience shaking in muscles while at rest, difficulty with voluntary movements, and poor muscle tone. These symptoms are similar to the symptoms of Parkinson's disease.

One way to eliminate these undesirable side effects is to stop taking the antipsychotic medicine. Unfortunately, the symptoms of the original mental disorder usually come back; in most cases, simply stopping the antipsychotic medication is not a reasonable option. Some drugs such as amantadine that control the symptoms of Parkinson's disease also control the parkinsonian side effects of antipsychotic medicines.

Amantadine works by restoring the chemical balance between dopamine and acetylcholine, two neurotransmitter chemicals in the brain. Taking amantadine along with the antipsychotic medicine helps to control symptoms of the mental disorder, while reducing parkinsonian side effects. Amantadine is in the same family of drugs commonly known as anticholinergic drugs, including biperiden and trihexyphenidyl.

Recommended dosage

Amantadine is available in 100 mg tablets and capsules, as well as a syrup containing 50 mg of amantadine in each teaspoonful. For the treatment of drug-induced parkinsonian side effects, amantadine is usually given in a dose of 100 mg orally twice a day. Some patients may need a total daily dose as high as 300 mg. Patients who are taking other antiparkinsonian drugs at the same time may require lower daily doses of amantadine (e.g., 100 mg daily).

People with kidney disease or who are on hemodialysis must have their doses lowered. In these patients, doses may range from 100 mg daily to as little as 200 mg every seven days.

Key Terms

Acetylcholine A naturally occurring chemical in the body that transmits nerve impulses from cell to cell. It causes blood vessels to dilate, lowers blood pressure, and slows the heartbeat.

Anticholinergic Related to the ability of a drug to block the nervous system chemical acetylcholine.

Dopamine A chemical in brain tissue that serves to transmit nerve impulses (a neurotransmitter) and helps to regulate movement and emotions.

Neurotransmitter A chemical in the brain that transmits messages between neurons, or nerve cells.

Parkinsonian Related to symptoms associated with Parkinson's disease, a nervous system disorder characterized by abnormal muscle movement of the tongue, face, and neck; inability to walk or move quickly; walking in a shuffling manner; restlessness; and/or tremors.

Precautions

Amantadine increases the amount of the dopamine (a **central nervous system** stimulant) in the brain. Because of this, patients with a history of **epilepsy** or other seizure disorders should be carefully monitored while taking this drug. This is especially true in the elderly and in patients with kidney disease. Amantadine may cause **visual disturbances** and affect mental alertness and coordination. People should not operate dangerous machinery or motor vehicles while taking this drug.

Side effects

Five to 10% of patients taking amantadine may experience nervous system side effects, including:

- dizziness or lightheadedness
- insomnia

• nervousness or anxiety

• impaired concentration

One to 5% of patients taking amantadine may experience other nervous system side effects, including:

• irritability or agitation

• depression

• confusion

• lack of coordination

• sleepiness or nightmares

• fatigue

• headache

In addition, up to 1% of patients may experience hallucinations, euphoria (excitement), extreme forgetfulness, aggressive behavior, personality changes, or **seizures**. Seizures are the most serious of all the side effects associated with amantadine.

Gastrointestinal side effects may also occur in patients taking amantadine. Five to 10% of people taking this drug experience nausea and up to 5% have dry mouth, loss of appetite, constipation, and vomiting. In most situations, amantadine may be continued and these side effects treated symptomatically.

One to 5% of patients taking amantadine have also reported a bluish coloring of their skin (usually on the legs) that is associated with enlargement of the blood vessels (livedo reticularis). This side effect usually appears within one month to one year of starting the drug and subsides within weeks to months after the drug is discontinued. People who think they may be experiencing this or other side effects from any medication should tell their physician.

Interactions

Taking amantadine along with other drugs used to treat parkinsonian side effects may cause increased confusion or even hallucinations. The combination of amantadine and **central nervous system stimulants** (e.g., amphetamines or decongestants) may cause increased central nervous stimulation or increase the likelihood of seizures.

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Jack Raber, PharmD

Ambenonium *see* **Cholinergic stimulants**

Amnestic disorders

Definition

Amnestic disorders are conditions that cause memory loss.

Description

Memory is the ability to retain and recall new information. Memory can be subdivided into short-term memory, which involves holding onto information for a minute or less, and long-term memory, which involves holding onto information for over a minute. Long-term memory can be further subdivided into recent memory, which involves new learning, and remote memory, which involves old information. In general, amnestic disorders more frequently involve deficits in new learning or recent memory.

There are a number of terms that are crucial to the understanding of amnestic disorders. In order to retain information, an individual must be able to pay close enough attention to the information that is presented; this is referred to as registration. The process whereby memories are established is referred to as encoding or storage. Retaining information in the long-term memory requires passage of time during which memory is consolidated. When an individual's memory is tested, retrieval is the process whereby the individual recalls the information from memory. Working memory is the ability to manipulate information from short-term memory in order to perform some function. Amnestic disorders may affect any or all of these necessary steps.

The time period affecting memory is also described. Anterograde amnesia is more common. Anterograde amnesia begins at a certain point in time and continues to interfere with the establishment of memory from that point forward in time. Retrograde amnesia refers to a loss of memory for information that was learned prior to the onset of amnesia. Retrograde amnesia often occurs in conjunction with head injury, and may result in erasure of memory of events or information from some time period (ranging from seconds to months) prior to the head injury. Over the course of recovery and rehabilitation from a head

Key Terms

Acetylcholine A brain chemical or neurotransmitter that carries information throughout the nervous system.

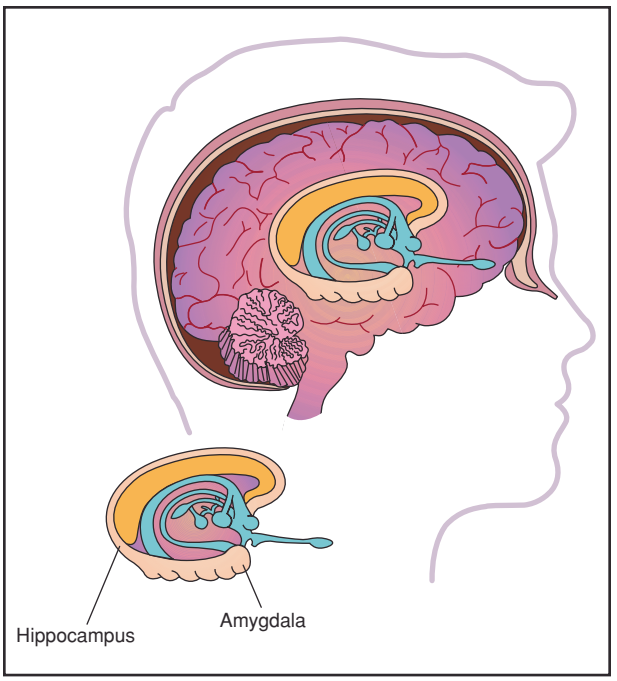
Anterograde Memory loss for information/events occurring after the onset of the amnestic disorder.

Delirium A condition characterized by waxing-and-waning episodes of confusion and agitation.

Dementia A chronic condition in which thinking and memory are progressively impaired. Other symptoms may also occur, including personality changes and depression.

Retrograde Memory loss for information/events prior to the onset of the amnestic disorder.

Transient ischemic attack (TIA) A stroke-like phenomenon in which a brief blockage of a brain blood vessel causes short-term neurological deficits that are completely resolved within 24 hours of their onset.



Memory loss may result from bilateral damage to the limbic system of the brain responsible for memory storage, processing, and recall. *(Illustration by Electronic Illustrators Group.)*

injury, memory may be restored or the period of amnesia may eventually shorten.

Demographics

About 7% of all individuals over the age of 65 have some form of **dementia** that involves some degree of amnesia, as do about 50% of all individuals over the age of 85.

Causes and symptoms

A number of brain disorders can result in amnestic disorders, including various types of dementia (such as **Alzheimer's disease**), **traumatic brain injury** (such as concussion), **stroke**, accidents that involve oxygen deprivation to the brain or interruption of blood flow to the brain (such as ruptured **aneurysms**), encephalitis, tumors in the thalamus and/or hypothalamus, Wernicke-Korsakoff syndrome (a sequelae of thiamine deficiency usually due to severe alcoholism), and **seizures**. Psychological disorders can also cause a type of amnesia called "psychogenic amnesia."

A curious condition called **transient global amnesia** causes **delirium** (a period of waxing and waning confusion and agitation), anterograde amnesia, and retrograde amnesia for events and information from the several hours prior to the onset of the attack. Transient global amnesia usually only lasts for several hours. Ultimately, the individual recovers completely, with no lasting memory deficit. The cause of transient global amnesia is poorly understood; researchers are suspicious that it may be due to either seizure activity in the brain or a brief blockage in a brain blood vessel, which causes a brief stroke-like event that completely resolves without permanent sequelae (similar to a **transient ischemic attack**).

Symptoms of amnestic disorders may include difficulty recalling remote events or information, and/or difficulty learning and then recalling new information. In some cases, the patient is fully aware of the memory impairment, and frustrated by it; in other cases, the patient may seem completely oblivious to the memory impairment or may even attempt to fill in the deficit in memory with confabulation. Depending on the underlying condition responsible for the amnesia, a number of other symptoms may be present as well.

Diagnosis

Diagnosis of amnestic disorders begins by establishing an individual's level of orientation to person, place, and time. Does he or she know who he or she is? Where he or she is? The day/date/time? An individual's ability to recall common current events (who is the president?) may reveal information about the memory deficit. A family member or close friend may be an invaluable part of the examination, in order to provide some background information on the onset and progression of the memory loss,

as well as information regarding the individual's original level of functioning.

A variety of memory tests can be utilized to assess an individual's ability to attend to information, utilize short-term memory, and store and retrieve information from long-term memory. Both verbal and visual memory should be tested. Verbal memory can be tested by working with an individual to memorize word lists, then testing recall after a certain amount of time has elapsed. Similarly, visual memory can be tested by asking an individual to locate several objects that were hidden in a room in the individual's presence.

Depending on what types of conditions are being considered, other tests may include blood tests, neuroimaging (**CT**, **MRI**, or **PET** scans of the brain), cerebrospinal fluid testing, and EEG testing.

Treatment team

A **neurologist** and/or psychiatrist may be involved in diagnosing and treating amnestic disorders. Depending on the underlying condition responsible for the memory deficit, other specialists may be involved as well. Occupational and speech and language therapists may be involved in rehabilitation programs for individuals who have amnestic disorders as part of their clinical picture.

Treatment

In some cases, treatment of the underlying disorder may help improve the accompanying amnesia. In mild cases of amnesia, rehabilitation may involve teaching memory techniques and encouraging the use of memory tools, such as association techniques, lists, notes, calendars, timers, etc. Memory exercises may be helpful. Recent treatments for Alzheimer's disease and other dementias have involved medications that interfere with the metabolism of the brain chemical (neurotransmitter) called acetylcholine, thus increasing the available quantity of acetylcholine. These drugs, such as donepezil and tacrine, seem to improve memory in patients with Alzheimer's disease. Research studies are attempting to explore whether these drugs may also help amnestic disorders that stem from other underlying conditions.

Prognosis

The prognosis is very dependent on the underlying condition that has caused the memory deficit, and on whether that condition has a tendency to progress or stabilize. Alzheimer's disease, for example, is relentlessly progressive, and therefore the memory deficits that accompany this condition can be expected to worsen considerably over time. Individuals who have memory deficits due to a brain tumor may have their symptoms improve after surgery to remove the tumor. Individuals with transient global amnesia can be expected to fully recover from their memory impairment within hours or days of its onset. In the case of some traumatic brain injuries, the amnesia may improve with time (as brain swelling decreases, for example), but there may always remain some degree of amnesia for the events just prior to the moment of the injury.

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Rosalyn Carson-DeWitt, MD

Amphetamine *see* **Central nervous system stimulants**

Amyotrophic lateral sclerosis

Definition

Amyotrophic lateral sclerosis (ALS) is a disease that breaks down tissues in the nervous system (a neurodegenerative disease) of unknown cause that affects the nerves responsible for movement. It is also known as motor neuron disease and Lou Gehrig's disease, after the baseball player whose career it ended.

Description

ALS is a disease of the motor neurons, those nerve cells reaching from the brain to the spinal cord (upper motor neurons) and the spinal cord to the peripheral nerves (lower motor neurons) that control muscle movement. In ALS, for unknown reasons, these neurons die, leading to a progressive loss of the ability to move virtually any of the muscles in the body. ALS affects "voluntary" muscles, those controlled by conscious thought, such as the arm, leg, and trunk muscles. ALS, in and of itself, does not affect sensation, thought processes, the heart muscle, or the "smooth" muscle of the digestive system, bladder, and other internal organs. Most people with ALS retain function of their eye muscles as well. However, various forms

Key Terms

Aspiration Inhalation of food or liquids into the lungs.

Bulbar muscles Muscles of the mouth and throat responsible for speech and swallowing.

Fasciculations Involuntary twitching of muscles.

Motor neuron A nerve cell that controls a muscle.

Riluzole (Rilutek) The first drug approved in the United States for the treatment of ALS.

Voluntary muscle A muscle under conscious control; contrasted with smooth muscle and heart muscle, which are not under voluntary control.

of ALS may be associated with a loss of intellectual function (**dementia**) or sensory symptoms.

"Amyotrophic" refers to the loss of muscle bulk, a cardinal sign of ALS. "Lateral" indicates one of the regions of the spinal cord affected, and "sclerosis" describes the hardened tissue that develops in place of healthy nerves. ALS affects approximately 30,000 people in the United States, with about 5,000 new cases each year. It usually begins between the ages of 40 and 70, although younger onset is possible. Men are slightly more likely to develop ALS than women.

ALS progresses rapidly in most cases. It is fatal within three years for 50% of all people affected, and within five years for 80%. Ten percent of people with ALS live beyond eight years.

Causes and symptoms

Causes

The symptoms of ALS are caused by the death of motor neurons in the spinal cord and brain. Normally, 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 die, the muscles they enervate cannot be moved as effectively, and weakness results. In addition, lack of stimulation leads to muscle wasting, or loss of bulk. Involvement of the upper motor neurons causes spasms and increased tone in the limbs, and abnormal reflexes. Involvement of the lower motor neurons causes muscle wasting and twitching (fasciculations).

Although many causes of motor neuron degeneration have been suggested for ALS, none has yet been proven responsible. Results of recent research have implicated toxic molecular fragments known as free radicals. Some evidence suggests that a cascade of events leads to excess free radical production inside motor neurons, leading to their death. Why free radicals should be produced in excess amounts is unclear, as is whether this excess is the cause or the effect of other degenerative processes. Additional agents within this toxic cascade may include excessive levels of a neurotransmitter known as glutamate, which may over-stimulate motor neurons, thereby increasing free-radical production, and a faulty detoxification enzyme known as SOD-1, for superoxide dismutase type 1. The actual pathway of destruction is not known, however, nor is the trigger for the rapid degeneration that marks ALS. Further research may show that other pathways are involved, perhaps ones even more important than this one. Autoimmune factors or premature aging may play some role, as could viral agents or environmental toxins.

Two major forms of ALS are known: familial and sporadic. Familial ALS accounts for about 10% of all ALS cases. As the name suggests, familial ALS is believed to be caused by the inheritance of one or more faulty genes. About 15% of families with this type of ALS have mutations in the gene for SOD-1. SOD-1 gene defects are dominant, meaning only one gene copy is needed to develop the disease. Therefore, a parent with the faulty gene has a 50% chance of passing the gene along to a child.

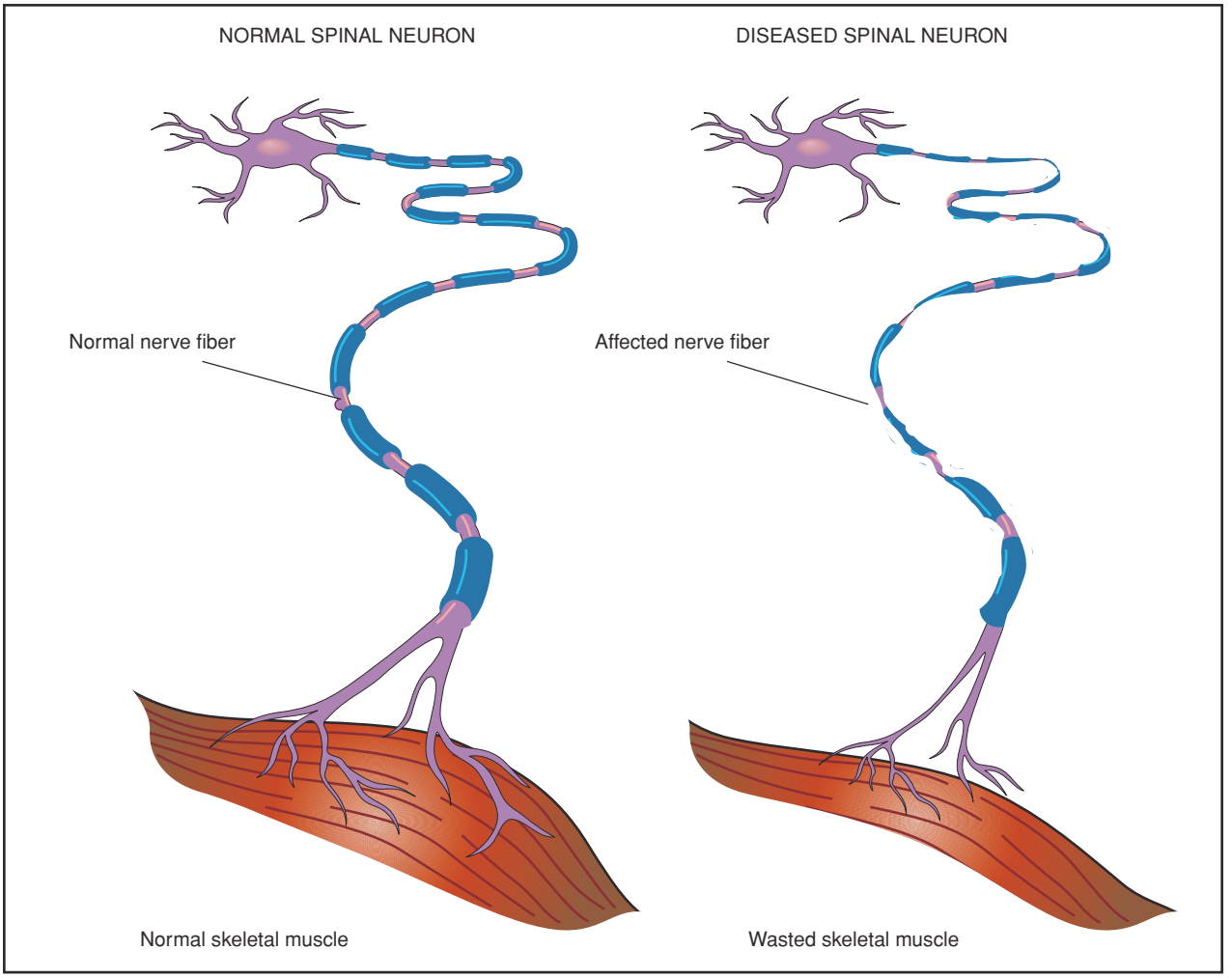
Sporadic ALS has no known cause. While many environmental toxins have been suggested as causes, to date no research has confirmed any of the candidates investigated, including aluminum and mercury and lead from dental fillings. As research progresses, it is likely that many cases of sporadic ALS will be shown to have a genetic basis as well.

A third type, called Western Pacific ALS, occurs in Guam and other Pacific islands. This form combines symptoms of both ALS and **Parkinson's disease**.

Symptoms

The earliest sign of ALS is most often weakness in the arms or legs, usually more pronounced on one side than the other at first. Loss of function is usually more rapid in the legs among people with familial ALS and in the arms among those with sporadic ALS. Leg weakness may first become apparent by an increased frequency of stumbling on uneven pavement, or an unexplained difficulty climbing stairs. Arm weakness may lead to difficulty grasping and holding a cup, for instance, or loss of dexterity in the fingers.

Less often, the earliest sign of ALS is weakness in the bulbar muscles, those muscles in the mouth and throat that control chewing, swallowing, and speaking. A person with bulbar weakness may become hoarse or tired after speaking at length, or speech may become slurred.



Amyotrophic lateral sclerosis (ALS) is caused by the degeneration and death of motor neurons in the spinal cord and brain. 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. *(Illustration by Electronic Illustrators Group.)*

In addition to weakness, the other cardinal signs of ALS are muscle wasting and persistent twitching (fasciculation). These are usually seen after weakness becomes obvious. Fasciculation is quite common in people without the disease, and is virtually never the first sign of ALS.

While initial weakness may be limited to one region, ALS almost always progresses rapidly to involve virtually all the voluntary muscle groups in the body. Later symptoms include loss of the ability to walk, to use the arms and hands, to speak clearly or at all, to swallow, and to hold the head up. Weakness of the respiratory muscles makes breathing and coughing difficult, and poor swallowing control increases the likelihood of inhaling food or saliva (aspiration). Aspiration increases the likelihood of lung infection, which is often the cause of death. With a ventilator and scrupulous bronchial hygiene, a person with ALS may live much longer than the average, although weakness and wasting will continue to erode any remaining functional abilities. Most people with ALS continue to retain function of the extraocular muscles that move their eyes, allowing some communication to take place with simple blinks or through use of a computer-assisted device.

Diagnosis

The diagnosis of ALS begins with a complete medical history and physical exam, plus a neurological examination to determine the distribution and extent of weakness. An electrical test of muscle function, called an electromyogram, or EMG, is an important part of the diagnostic process. Various other tests, including blood and urine tests, x rays, and CT scans, may be done to rule out other possible causes of the symptoms, such as tumors of

the skull base or high cervical spinal cord, thyroid disease, spinal arthritis, lead poisoning, or severe vitamin deficiency. ALS is rarely misdiagnosed following a careful review of all these factors.

Treatment

There is no cure for ALS, and no treatment that can significantly alter its course. There are many things which can be done, however, to help maintain quality of life and to retain functional ability even in the face of progressive weakness.

As of early 1998, only one drug had been approved for treatment of ALS. Riluzole (Rilutek) appears to provide on average a three-month increase in life expectancy when taken regularly early in the disease, and shows a significant slowing of the loss of muscle strength. Riluzole acts by decreasing glutamate release from nerve terminals. Experimental trials of nerve growth factor have not demonstrated any benefit. No other drug or vitamin currently available has been shown to have any effect on the course of ALS.

A physical therapist works with an affected person and family to implement **exercise** and stretching programs to maintain strength and range of motion, and to promote general health. Swimming may be a good choice for people with ALS, as it provides a low-impact workout to most muscle groups. One result of chronic inactivity is contracture, or muscle shortening. Contractures limit a person's range of motion, and are often painful. Regular stretching can prevent contracture. Several drugs are available to reduce cramping, a common complaint in ALS.

An occupational therapist can help design solutions to movement and coordination problems, and provide advice on adaptive devices and home modifications.

Speech and swallowing difficulties can be minimized or delayed through training provided by a speech-language pathologist. This specialist can also provide advice on communication aids, including computer-assisted devices and simpler word boards.

Nutritional advice can be provided by a nutritionist. A person with ALS often needs softer foods to prevent jaw exhaustion or choking. Later in the disease, nutrition may be provided by a gastrostomy tube inserted into the stomach.

Mechanical ventilation may be used when breathing becomes too difficult. Modern mechanical ventilators are small and portable, allowing a person with ALS to maintain the maximum level of function and mobility. Ventilation may be administered through a mouth or nose piece, or through a tracheostomy tube. This tube is inserted through a small hole made in the windpipe. In addition to providing direct access to the airway, the tube also decreases the risk aspiration. While many people with rapidly progressing ALS choose not to use ventilators for lengthy periods, they are increasingly being used to prolong life for a short time.

The progressive nature of ALS means that most persons will eventually require full-time nursing care. This care is often provided by a spouse or other family member. While the skills involved are not difficult to learn, the physical and emotional burden of care can be overwhelming. Caregivers need to recognize and provide for their own needs as well as those of people with ALS, to prevent **depression**, burnout, and bitterness.

Throughout the disease, a support group can provide important psychological aid to affected persons and their caregivers as they come to terms with the losses ALS inflicts. Support groups are sponsored by both the ALS Society and the Muscular Dystrophy Association.

Alternative treatment

Given the grave prognosis and absence of traditional medical treatments, it is not surprising that a large number of alternative treatments have been tried for ALS. Two studies published in 1988 suggested that amino-acid therapies may provide some improvement for some people with ALS. While individual reports claim benefits for megavitamin therapy, herbal medicine, and removal of dental fillings, for instance, no evidence suggests that these offer any more than a brief psychological boost, often followed by a more severe letdown when it becomes apparent the disease has continued unabated. However, once the causes of ALS are better understood, alternative therapies may be more intensively studied. For example, if damage by free radicals turns out to be the root of most of the symptoms, antioxidant vitamins and supplements may be used more routinely to slow the progression of ALS. Or, if environmental toxins are implicated, alternative therapies with the goal of detoxifying the body may be of some use.

Prognosis

ALS usually progresses rapidly, and leads to death from respiratory infection within three to five years in most cases. The slowest disease progression is seen in those who are young and have their first symptoms in the limbs. About 10% of people with ALS live longer than eight years.

Prevention

There is no known way to prevent ALS or to alter its course.

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ALS Association of America. 27001 Agoura Road, Suite 150, Calabasas Hills, CA 91301-5104. (800) 782-4747 (Information and Referral Service) or (818) 880-9007; Fax: (818) 880-9006. <http://www.alsa.org/als/>

American Academy of Family Physicians. 11400 Tomahawk Creek Parkway, Leawood, KS 66211-2672. (913) 906-6000. fp@aafp.org. <http://www.aafp.org/>.

American Academy of Neurology. 1080 Montreal Avenue, St. Paul, Minnesota 55116. (651) 695-1940; Fax: (651) 695-2791. info@aan.org. <http://www.aan.com/>.

American Medical Association, 515 N. State Street, Chicago, IL 60610. (312) 464-5000. <http://www.ama-assn.org/>.

Centers for Disease Control and Prevention. 1600 Clifton Road, Atlanta, GA 30333. (404) 639-3534 or (800) 311-3435. <http://www.cdc.gov/netinfo.htm>, <http://www.cdc.gov/ncidod/eid/vol7no1/brown.htm>.

Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718-3208. (520) 529-2000 or (800) 572-1717; Fax: (520) 529-5300. <www.mdausa.org>.

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American Academy of Family Physicians. <http://www.aafp.org/afp/990315ap/1489.html>.

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L. Fleming Fallon, Jr., MD, DrPH

Anatomical nomenclature

Over the centuries, anatomists developed a standard nomenclature, or method of naming anatomical structures. Terms such as "up" or "down" obviously have no meaning unless the orientation of the body is clear. When a body is lying on its back, the thorax and abdomen are at the same level. The upright sense of up and down is lost. Further, because anatomical studies and particularly embryological studies were often carried out in animals, the development of the nomenclature relative to comparative anatomy had an enormous impact on the development of human anatomical nomenclature. There were obvious difficulties in relating terms from quadrupeds (animals that walk on four legs) who have abdominal and thoracic regions at the same level as opposed to human bipeds in whom an upward and downward orientation might seem more obvious.

In order to standardize nomenclature, anatomical terms relate to the *standard anatomical position*. When the human body is in the standard anatomical position it is upright, erect on two legs, facing frontward, with the arms at the sides each rotated so that the palms of the hands turn forward.

In the standard anatomical position, *superior* means toward the head or the *cranial* end of the body.

The term *inferior* means toward the feet or the *caudal* end of the body.

The frontal surface of the body is the *anterior* or *ventral* surface of the body. Accordingly, the terms "anteriorly" and "ventrally" specify a position closer to—or toward—the frontal surface of the body. The back surface of the body is the *posterior* or *dorsal* surface and the terms "posteriorly" and "dorsally" specify a position closer to—or toward—the posterior surface of the body.

The terms *superficial* and *deep* relate to the distance from the exterior surface of the body. Cavities such as the thoracic cavity have internal and external regions that correspond to deep and superficial relationships in the midsagittal plane.

The bones of the skull are fused by sutures that form important anatomical landmarks. Sutures are joints that run jaggedly along the interface between the bones. At birth, the sutures are soft, broad, and cartilaginous. The sutures eventually fuse and become rigid and ossified near the end of puberty or early in adulthood.

The sagittal suture unties the parietal bones of the skull along the midline of the body. The suture is used as an anatomical landmark in anatomical nomenclature to establish what are termed *sagittal planes* of the body. The primary sagittal plane is the sagittal plane that runs through the length of the sagittal suture. Planes that are parallel to the sagittal plane, but that are offset from the midsagittal plane are termed *parasagittal planes*. Sagittal planes run anteriorly and posteriorly, are always at right angles to the coronal planes. The *medial plane* or *midsagittal plane* divides the body vertically into superficially symmetrical *right* and *left* halves.

The medial plane also establishes a centerline axis for the body. The terms *medial* and *lateral* relate positions relative to the medial axis. If a structure is medial to another structure, the medial structure is closer to the medial or center axis. If a structure is lateral to another structure, the lateral structure is farther way from the medial axis. For example, the lungs are lateral to the heart.

The coronal suture unites the frontal bone with the parietal bones. In anatomical nomenclature, the primary *coronal plane* designates the plane that runs through the length of the coronal suture. The primary coronal plane is also termed the *frontal plane* because it divides the body into frontal and back halves.

Planes that divide the body into superior and inferior portions, and that are at right angles to both the sagittal and coronal planes are termed transverse planes. Anatomical planes that are not parallel to sagittal, coronal, or transverse planes are termed oblique planes.

The body is also divided into several regional areas. The most superior area is the *cephalic region* that includes the head. The *thoracic region* is commonly known as the chest region. Although the *celiac region* more specifically refers to the center of the *abdominal region*, celiac is sometimes used to designate a wider area of abdominal structures. At the inferior end of the abdominal region lies the *pelvic region* or *pelvis*. The posterior or dorsal side of the body has its own special regions, named for the underlying vertebrae. From superior to inferior along the midline of the dorsal surface lie the *cervical, thoracic, lumbar*, and *sacral* regions. The buttocks are the most prominent feature of the *gluteal region*.

The term *upper limbs* or *upper extremities* refers to the arms. The term *lower limbs* or *lower extremities* refers to the legs.

The *proximal* end of an extremity is at the junction of the extremity (i.e., arm or leg) with the trunk of the body. The *distal* end of an extremity is the point on the extremity farthest away from the trunk (e.g., fingers and toes). Accordingly, if a structure is proximate to another structure it is closer to the trunk (e.g., the elbow is proximate to the wrist). If a structure is distal to another, it is farther from the trunk (e.g., the fingers are distal to the wrist).

Structures may also be described as being medial or lateral to the midline axis of each extremity. Within the upper limbs, the terms radial and ulnar may be used synonymous with lateral and medial. In the lower extremities, the terms fibular and tibial may be used as synonyms for lateral and medial.

Rotations of the extremities may de described as medial rotations (toward the midline) or lateral rotations (away from the midline).

Many structural relationships are described by combined anatomical terms (e.g., the eyes are anterio-medial to the ears).

There are also terms of movement that are standardized by anatomical nomenclature. Starting from the anatomical position, *abduction* indicates the movement of an arm or leg away from the midline or midsagittal plane. *Adduction* indicates movement of an extremity toward the midline.

The opening of the hands into the anatomical position is *supination* of the hands. Rotation so the dorsal side of the hands face forward is termed *pronation*.

The term *flexion* means movement toward the flexor or anterior surface. In contrast, *extension* may be generally regarded as movement toward the extensor or posterior surface. Flexion occurs when the arm brings the hand from the anatomical position toward the shoulder (a curl) or when the arm is raised over the head from the anatomical position. Extension returns the upper arm and or lower to the anatomical position. Because of the embryological rotation of the lower limbs that rotates the primitive dorsal

side to the adult form ventral side, flexion occurs as the thigh is raised anteriorly and superiorly toward the anterior portion of the pelvis. Extension occurs when the thigh is returned to anatomical position. Specifically, due to the embryological rotation, flexion of the lower leg occurs as the foot is raised toward the back of the thigh and extension of the lower leg occurs with the kicking motion that returns the lower leg to anatomical position.

The term *palmar surface* (palm side) is applied to the flexion side of the hand. The term *plantar surface* is applied to the bottom sole of the foot. From the anatomical position, extension occurs when the toes are curled back and the foot arches upward and flexion occurs as the foot is returned to anatomical position.

Rolling motions of the foot are described as *inversion* (rolling with the big toe initially lifting upward) and *eversion* (rolling with the big toe initially moving downward).

K. Lee Lerner

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 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.

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).

Key Terms

Alpha-fetoprotein (AFP) A chemical substance produced by the fetus and found in the fetal circulation.

Causes and symptoms

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**.

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.

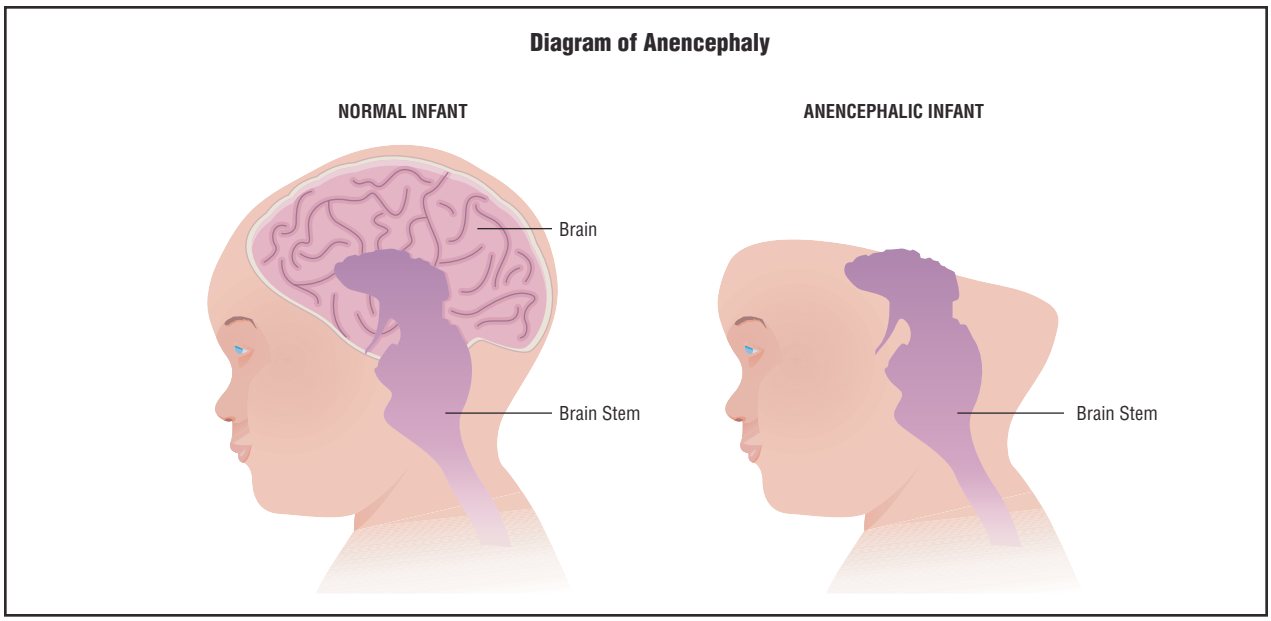
Diagnosis

Anencephaly is diagnosed by observation. Prenatal diagnosis may be made by ultrasound examination after 12–14 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.

There are no treatments for anencephaly. A pregnant woman or couple expecting an anencephalic baby will need a sensitive and supportive health care team, and perhaps some additional psychological support as they face the inevitable death of their infant, usually before or shortly after birth.

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



Infants born with anencephaly have either a severely underdeveloped brain or total brain absence. A portion of the brainstem usually protrudes through the skull, which also fails to develop properly. *(Gale Group.)*

the United States, all enriched cereal grain flours have been fortified with folic acid.

Clinical Trials

Research is primarily directed at understanding the underlying factors that affect early neurological development in the fetus.

Prognosis

Anencephaly is uniformly fatal at birth or soon thereafter.

Resources

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Sells, C. J., and J. G. Hall. "Neural Tube Defects." *Mental Retardation and Developmental Disabilities Research Reviews* 4, no. 4, 1998.

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>.

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Aneurysms

Definition

Cerebral aneurysm is the enlargement, distention, dilation, bulging, or ballooning of the wall of a cerebral artery or vein. Aneurysms affect arteries throughout the body, including blood vessels in the brain (intracerebral aneurysm). Ruptures of intracerebral aneurysm result in **stroke** (loss of blood supply to tissue) and bleeding into the subarachnoid space). The most common aneurysm is an abdominal aneurysm.

Description

Dilations, or ballooning, of blood vessels to form an aneurysm are particularly dangerous because they increase the chance of arterial rupture and subsequent bleeding into brain tissues (a hemorrhagic stroke). Rupture of an aneurysm can lead to the leakage of blood into the tissues and spaces surrounding the brain. This leaked blood then clots to form an intracranial hematoma. Aneurysms that rupture can result in severe disability or death.

Key Terms

Aneurysm A bulging, weakened area in a blood vessel.

Common complications of cerebral aneurysms that leak include **hydrocephalus** (the excessive accumulation of cerebrospinal fluid) and persistent spasms of blood vessels that adversely affect the maintenance of arterial blood pressure.

Once they rupture or bleed, aneurysms have a tendency toward recurrent bleeding episodes. This tendency to rebleed is particularly high in the first few days following the initial bleed. Intracerebral bleeds are often accompanied by increases in cerebrospinal fluid and an increased intracranial pressure (hydrocephalus).

Once they occur, aneurysms are dynamic and can increase in size over time. The increase in size is not always linear and can advance sporadically until they expand to a critical size. As they grow, aneurysms begin to put pressure on surrounding tissues. In addition, as they grow, aneurysms usually result in progressively more difficult problems.

The larger the size of an aneurysm, regardless of location, the greater the chance it will ultimately bleed. Cerebral aneurysm ruptures usually lead to subarachnoid hemorrhage (SAH).

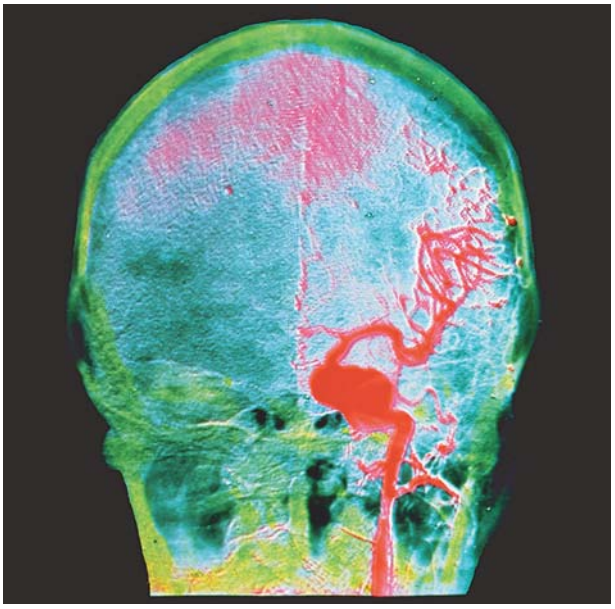
Demographics

Although more common in adults than children, cerebral aneurysms occur in all age groups. Cerebral aneurysms are more common—and the risk of aneurysm generally increases—with age.

Aneurysm sufferers are rarely young; the incidence of aneurysm is low in those under 20 years of age. In contrast, aneurysms are relatively common in people over 65 years of age. Risk indicators for some groups such as Caucasian males begin to increase at age 55. Some studies indicate that up to 5% of the population over 65 suffer some form of aneurysm.

Incidence of specific aneurysms varies, but in general within the United States they are occur less frequently in Caucasian women, and are relatively uncommon in African Americans.

Of those affected with an aneurysm anywhere in the body, the National Institute of Health (NIH) estimates that approximately 30,000 people in the United States will suffer an aneurysm rupture.



Arteriograph of the head from behind, showing an aneurysm, the balloon-like smooth swelling just below and to the right of center. *(CNRI/National Audubon Society Collection/Photo Researchers, Inc. Reproduced by permission.)*

Cigarette smoking and excess alcohol use substantially increase the risk of aneurysm rupture.

Causes and symptoms

An aneurysm may be a congenital defect in the structure of the muscular wall of affected blood vessels (e.g., the intima of an artery), or arise secondary to trauma, atherosclerosis, or high blood pressure. The defect results in an abnormal thinning of the arterial or venous wall that makes the wall subsequently susceptible to aneurysm.

Research data appears to show that some individuals have a basic genetic susceptibility or predisposition to aneurysms. The genetic inheritance patterns resemble characteristics linked to an autosomal dominant gene. Within some families, rates of aneurysms can run as high as five to 10 times those found in the general population.

Direct causes of intracerebral aneurysms include infection, trauma, or neoplastic disease. If infection is the cause, the infection may be from a remote site. For example, an aneurysm in the brain may result from the loosed embolus such as plaque, fatty deposit, clot, or clump of cells, originating at an infection in another part of the body. The embolus is transported to the site of the future cerebral aneurysm by the bloodstream and **cerebral circulation**. An aneurysm formed in this manner is termed a mycotic aneurysm.

Prior to rupture, the symptoms associated with an aneurysm depend upon its location, size, and rate of expansion. A static aneurysm that does not leak (bleed) or adversely affect cerebral circulation or neighboring tissue may be asymptomatic (without symptoms). In contrast, larger aneurysms or aneurysms with a rapid growth rate may produce pronounced symptoms such as swelling, loss of sensation, blurred vision, etc.

Just prior to an aneurysm rupture, patients typically experience some symptoms commonly associated with stroke. Depending on the size and location of the aneurysm about to rupture, a patient may suffer a severe **headache**, deterioration or disturbances of hearing, and disturbances of vision such as double vision, severe nausea and vomiting, and syncopal episodes (periodic **fainting** or loss of consciousness).

A severe headache that is unresponsive to standard analgesics is the most common sign of a leaking or bleeding aneurysm. Many patients experience a series of sentinel (warning) headaches if the aneurysm begins to leak prior to rupture. A fully ruptured aneurysm presents with a severe headache that is frequently accompanied by fainting or temporary (transient) loss of consciousness, often with severe nausea, vomiting, and rapidly developing stiff neck (nuchal rigidity).

Aneurysms normally rupture while the patient is active and awake.

Diagnosis

The severe headache that accompanies a cerebral aneurysm is often the principle complaint upon which the diagnosis of aneurysm begins to build.

Angiography provides the most definitive diagnosis of an intracerebral aneurysm by determining the specific site of the aneurysm. A computed tomography (**CT**) **scan** can also diagnose a bleeding cerebral aneurysm. Arteriography is an x ray of the carotid artery taken when a special dye is injected into the artery.

The presence of blood in the cerebrospinal fluid withdrawn during a lumbar puncture is also diagnostic evidence for blood leaking into the subarachnoid space.

Magnetic resonance imaging (MRI) studies can also be useful in accessing the extent of damage to surrounding tissues and are often used to study aneurysms prior to leakage or rupture. MRI uses magnetic fields to detect subtle changes in brain tissue content. The benefit of MRI over CT imaging is that MRI is better able to localize the exact anatomical position of an aneurysm. Other types of MRI scans are magnetic resonance angiography (MRA) and functional magnetic resonance imaging (fMRI). Neurosurgeons use MRA to detect stenosis (blockage) of the brain arteries inside the skull by mapping flowing blood. Functional MRI uses a magnet to pick up signals from oxygenated blood and can show brain activity through increases in local blood flow.

Duplex Doppler ultrasound and arteriography are two additional diagnostic imaging techniques used to decide if an individual would benefit from a surgical procedure called **carotid endarterectomy**. This surgery is used to remove fatty deposits from the carotid arteries and can help prevent stroke. Doppler ultrasound is a painless, noninvasive test in which sound waves bounce off the moving blood and the tissue in the artery and can be formed into an image.

Treatment team

Management and treatment of aneurysms require a multi-disciplinary team. Physicians are responsible for caring for general health and providing guidance aimed at preventing a stroke. Neurologists and neurosurgeons usually lead acute-care teams and direct patient care during hospitalization and recovery from surgery. Neuroradiologists help pinpoint the location and extent of aneurysms.

Treatment

Treatment for ruptures of cerebral aneurysms includes measures to stabilize the emergency by assuring cardiopulmonary functions (adequate heart rate and respiration) while simultaneously moving to decrease intracranial pressure and surgically clip (repair and seal) the ruptured cerebral aneurysm.

Surgery is often performed as soon as the patient is stabilized; ideally within 72 hours of the onset of rupture. The goal of surgery is to prevent rebleeding. Surgery is performed to expose the aneurysm and allow the placement of a clip across a strong portion of the vessel to obstruct the flow of blood through the weakened aneurysm. Repeat surgical procedures to seal an aneurysm are not uncommon.

Treatment of unruptured aneurysms is certainly less dramatic, but presents a more deliberate and complex path. Microcoil thrombosis or balloon embolization (the insertion via the arterial catheter of a balloon or other obstruction that blocks blood flow through the region of aneurysm) are alternatives to full surgical intervention.

Other nonsurgical interventions include rest, medications, and hypertensive-hypervolemic therapy to drive blood around obstructed vessels.

Treatment decisions are made between the treatment team and family members with regard to the best course of treatment and the probable outcomes for patients suffering a severe aneurysm rupture with extensive damage to surrounding brain tissue.

Asymptomatic aneurysms allow the treatment team to more fully evaluate surgical and nonsurgical options.

Recovery and rehabilitation

The recovery and rehabilitation of patients suffering a cerebral aneurysm depend on the location and size of the aneurysm. The course of recovery and rehabilitation is also heavily influenced by whether the aneurysm ruptures.

Key to recovery is the prevention of aneurysm rebleeding, the management of swelling in the **ventricular system** (hydrocephalus), **seizures**, cardiac arrhythmias, and vasospasm. The onset of vasospasm within the first two weeks of the initial bleeding incident is the major cause of death in those who survive the initial rupture of the aneurysm.

Ventricular drains are used to control the buildup of cerebrospinal fluid in the ventricular system.

Clinical trials

As of May 2004, current studies sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) include a study on the effect of the drug ProliNO on brain artery spasms after aneurysm rupture and a study of the role of genetics on the development of intracranial aneurysms (Familial Intracranial Aneurysm Study). Further information is available at <http://www.clinicaltrials.gov>.

Prognosis

The overall prognosis for a patient with a cerebral aneurysm depends on several factors including the size, location, and stability of the aneurysm. Facets of the patient's general health, neurological health, age, and familial history must also be evaluated in forming a prognosis.

Although each patient is different, and each aneurysm must be individually evaluated, in general, the prognosis for patients who have suffered a bleed is guarded at best, with mortality rates up 60% within a year of the initial bleeding incident. Approximately half of the survivors suffer some long-lasting disability. Patients with cerebral aneurysm can, however, fully recover with no long-lasting disorder.

Data regarding the prognosis for unruptured aneurysms is more tentative and not specific for cerebral aneurysms. Some long-term studies give evidence that only 10% of patients might suffer leakage or bleeding from their aneurysm over a period of 10 years and only about a quarter of patients would experience bleeding from the aneurysm over a period of 25 years.

Special concerns

Intracerebral aneurysms are sometimes associated with other diseases such as fibromuscular hyperplasia or other disorders such as high blood pressure (although aneurysms also occur in persons with normal blood pressure.

Other physiological stresses such as pregnancy have not been demonstrated to have a correlation to the rupture of cerebral aneurysm.

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ORGANIZATIONS

American Stroke Association: A Division of American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231-4596. (214) 706-5231 or (888) 4STROKE (478-7653). strokeassociation@heart.org. <http://www.strokeassociation.org/>.

Brain Aneurysm Foundation. 12 Clarendon Street, Boston, MA 02116. (617) 723-3870; Fax: (617) 723-8672. information@bafound.org. <http://www.bafound.org>.

National Stroke Association. 9707 East Easter Lane, Englewood, CO 80112-3747. (303) 649-9299 or (800) STROKES (787-6537); Fax: (303) 649-1328. info@stroke.org. <http//www.stroke.org/>.

Paul Arthur

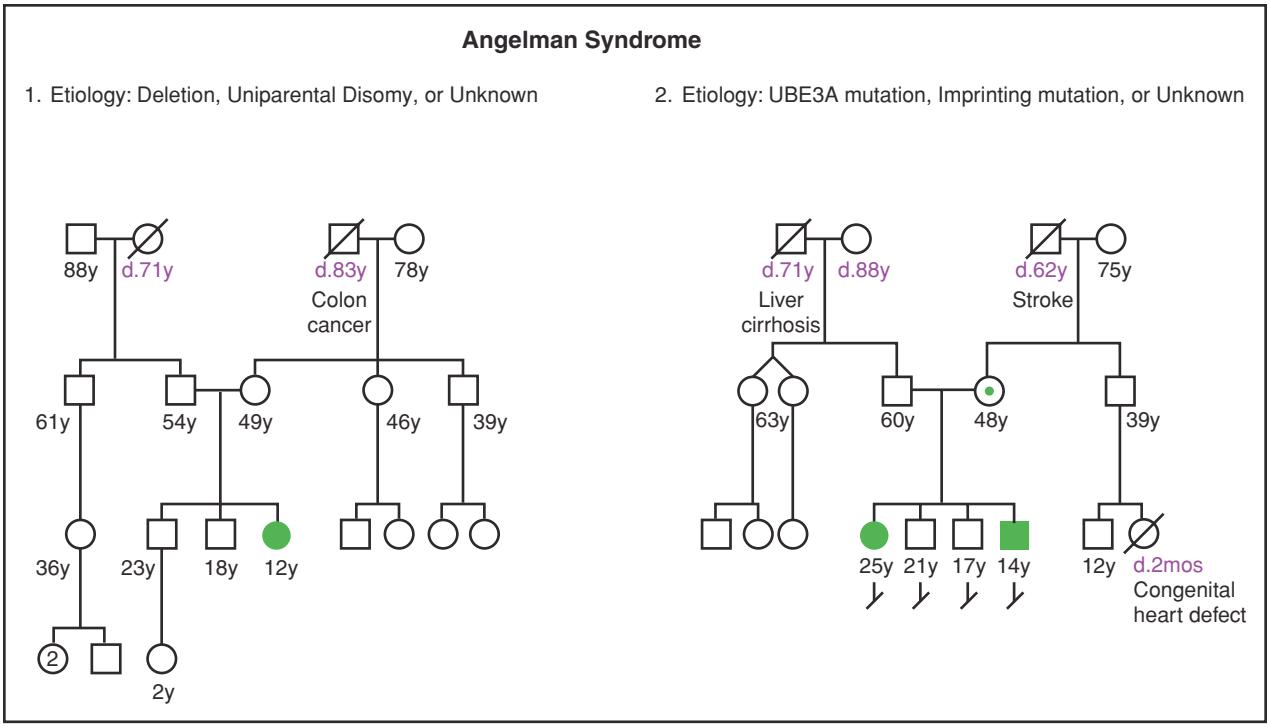
Angelman syndrome

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 retardation, AS is



See Symbol Guide for Pedigree Charts. *(Gale Group.)*

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. However, receptive language skills (listening to and understanding the speech of others) and non-verbal 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.

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.

Causes and symptoms

Most cases of AS have been traced to specific genetic defects on chromosomes received from the mother. 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.

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 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. These include DNA methylation studies, UBE3A mutation analysis, and fluorescent in situ hybridization (FISH).

Treatment team

Children with Angelman syndrome will need help from a variety of professionals, including a general pediatrician and pediatric **neurologist**. A child psychiatrist and/or psychologist may be helpful as well, particularly to help design and implement various behavioral plans. Physical, occupational, and speech and language therapists may help support specific deficits. A learning specialist may be consulted for help with an individualized educational plan.

Treatment

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.

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.

Special concerns

Educational concerns

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.

Legal issues

The most pressing long-term concern for patients with AS is working out a life plan for ongoing care, since many are likely to outlive their parents. The parents of a child diagnosed with AS should consult an estate planner, an attorney, and a certified public accountant (CPA) in order to draft a life plan and letter of intent. A letter of intent is not a legally binding document, but it gives the patient's siblings and other relatives or caregivers necessary information on providing for her in the future. The attorney can help the parents decide about such matters as guardianship as well as guide them through the legal process of appointing a guardian, which varies from state to state.

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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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Angiography

Definition

Angiography is the x-ray (radiographic) study of the blood vessels. An angiogram uses a radiopaque substance, or contrast medium, to make the blood vessels visible under x ray. The key ingredient in most radiographic contrast media is iodine.

Purpose

Angiography is used to detect abnormalities, including narrowing (stenosis) or blockages in the blood vessels (called occlusions) throughout the circulatory system and in some organs. The procedure is commonly used to identify atherosclerosis; to diagnose heart disease; to evaluate kidney function and detect kidney cysts or tumors; to map renal anatomy in transplant donors; to detect an aneurysm (an abnormal bulge of an artery that can rupture leading to hemorrhage), tumor, blood clot, or **arteriovenous malformations** (abnormal tangles of arteries and veins) in the brain; and to diagnose problems with the retina of the eye. It is also used to provide surgeons with an accurate vascular map of the heart prior to open-heart surgery, or of the brain prior to neurosurgery. Angiography may be used after penetrating trauma, like a gunshot or knife wound, to detect blood vessel injury. It may also be used to check the position of shunts and stents placed by physicians into blood vessels.

Precautions

Patients with kidney disease or injury may have further kidney damage from the contrast media used for angiography. Patients who have blood-clotting problems, have a known allergy to contrast media, or are allergic to iodine may not be suitable candidates for an angiography procedure. Newer types of contrast media classified as non-ionic are less toxic and cause fewer side effects than traditional ionic agents. Because x rays carry risks of ionizing **radiation** exposure to the fetus, pregnant women are also advised to avoid this procedure.

Description

Angiography requires the injection of a contrast medium that makes the blood vessels visible to x ray. The contrast medium is injected through a procedure known as arterial puncture. The puncture is usually made in the groin area, armpit, inside of the elbow, or neck.

Patients undergoing an angiogram are advised to stop eating and drinking eight hours prior to the procedure. They must remove all jewelry before the procedure and change into a hospital gown. If the arterial puncture is to be made in the armpit or groin area, shaving may be required. A sedative may be administered to relax the patient for the procedure. An intravenous (IV) line is also inserted into a vein in the patient's arm before the procedure begins, in case medication or blood products are required during the angiogram, or if complications arise.

Prior to the angiographic procedure, patients are briefed on the details of the test, the benefits and risks, and the possible complications involved, and asked to sign an informed consent form.

The site is cleaned with an antiseptic agent and injected with a local anesthetic. Then, a small incision is made in the skin to help the needle pass. A needle containing a solid inner core called a stylet is inserted through the incision and into the artery. When the radiologist has punctured the artery with the needle, the stylet is removed and replaced with another long wire called a guide wire. It is normal for blood to spurt out of the needle before the guide wire is inserted.

The guide wire is fed through the outer needle into the artery to the area that requires angiographic study. A fluoroscope displays a view of the patient's vascular system and is used to direct the guide wire to the correct location. Once it is in position, the needle is then removed, and a catheter is threaded over the length of the guide wire until it reaches the area of study. The guide wire is then removed, and the catheter is left in place in preparation for the injection of the contrast medium.

Depending on the type of angiographic procedure being performed, the contrast medium is either injected by hand with a syringe or is mechanically injected with an automatic injector, sometimes called a power injector, connected to the catheter. An automatic injector is used frequently because it is able to deliver a large volume of contrast medium very quickly to the angiographic site. Usually a small test injection is made by hand to confirm

A female patient undergoing a cerebral angiography. The arteries of her brain are seen in the angiograms (arterial x rays) on the monitors at the upper left; a radio-opaque dye has been injected into her arterial system. *(© Laurent. Photo Researchers. Reproduced by permission.)*

that the catheter is in the correct position. The patient is told that the injection will start, and is instructed to remain very still. The injection causes some mild to moderate discomfort. Possible side effects or reactions include **headache**, **dizziness**, irregular heartbeat, nausea, warmth, burning sensation, and chest **pain**, but they usually last only momentarily. To view the area of study from different angles or perspectives, the patient may be asked to change positions several times, and subsequent contrast medium injections may be administered. During any injection, the patient or the imaging equipment may move.

Throughout the injection procedure, radiographs (x-ray pictures) or fluoroscopic images are obtained. Because of the high pressure of arterial blood flow, the contrast medium dissipates through the patient's system quickly and becomes diluted, so images must be obtained in rapid succession. One or more automatic film changers may be used to capture the required radiographic images. In many imaging departments, angiographic images are captured digitally, negating the need for film changers. The ability to capture digital images also makes it possible to manipulate the information electronically, allowing for a procedure known as digital subtraction angiography (DSA). Because every image captured is comprised of tiny picture elements called pixels, computers can be used to manipulate the information in ways that enhance diagnostic information. One common approach is to electronically remove or (subtract) bony structures that otherwise would be superimposed over the vessels being studied, hence the name digital subtraction angiography.

Once the x rays are complete, the catheter is slowly and carefully removed from the patient. Manual pressure is applied to the site with a sandbag or other weight for 10–20 minutes to allow for clotting to take place and the arterial puncture to reseal itself. A pressure bandage is then applied, usually for 24 hours.

Key Terms

Arteriosclerosis A chronic condition characterized by thickening and hardening of the arteries and the build-up of plaque on the arterial walls. Arteriosclerosis can slow or impair blood circulation.

Carotid artery An artery located in the neck that supplies blood to the brain.

Catheter A long, thin, flexible tube used in angiography to inject contrast material into the arteries.

Cirrhosis A condition characterized by the destruction of healthy liver tissue. A cirrhotic liver is scarred and cannot function properly (i.e., breaks down the proteins in the bloodstream). Cirrhosis is associated with portal hypertension.

Embolism A blood clot, air bubble, or clot of foreign material that travels and blocks the flow of blood in an artery. When blood supply blocks a tissue or organ with an embolism, infarction (death of the tissue the artery feeds) occurs. Without immediate and appropriate treatment, an embolism can be fatal.

Femoral artery An artery located in the groin area that is the most frequently accessed site for arterial puncture in angiography.

Fluorescein dye An orange dye used to illuminate the blood vessels of the retina in fluorescein angiography.

Fluoroscope An imaging device that displays x rays of the body. Fluoroscopy allows the radiologist to visualize the guide wire and catheter moving through the patient's artery.

Guide wire A wire that is inserted into an artery to guide a catheter to a certain location in the body.

Ischemia A lack of normal blood supply to a organ or body part because of blockages or constriction of the blood vessels.

Necrosis Cellular or tissue death; skin necrosis may be caused by multiple, consecutive doses of radiation from fluoroscopic or x-ray procedures.

Plaque Fatty material that is deposited on the inside of the arterial wall.

Portal hypertension A condition caused by cirrhosis of the liver, characterized by impaired or reversed blood flow from the portal vein to the liver. The resulting pressure can cause an enlarged spleen and dilated, bleeding veins in the esophagus and stomach.

Portal vein thrombosis The development of a blood clot in the vein that brings blood into the liver. Untreated portal vein thrombosis causes portal hypertension.

Most angiograms follow the general procedures outlined above, but vary slightly depending on the area of the vascular system being studied. There is a variety of common angiographic procedures.

Cerebral angiography

Cerebral angiography is used to detect **aneurysms**, stenosis, blood clots, and other vascular irregularities in the brain. The catheter is inserted into the femoral or carotid artery and the injected contrast medium travels through the blood vessels in the brain. Patients frequently experience headache, warmth, or a burning sensation in the head or neck during the injection portion of the procedure. A cerebral angiogram takes two to four hours to complete.

Coronary angiography

Coronary angiography is administered by a cardiologist with training in radiology or, occasionally, by a radiologist. The arterial puncture is typically made in the femoral artery, and the cardiologist uses a guide wire and catheter to perform a contrast injection and x-ray series on the coronary arteries. The catheter may also be placed in the left ventricle to examine the mitral and aortic valves of the heart. If the cardiologist requires a view of the right ventricle of the heart or of the tricuspid or pulmonic valves, the catheter is inserted through a large vein and guided into the right ventricle. The catheter also serves the purpose of monitoring blood pressures in these different locations inside the heart. The angiographic procedure takes several hours, depending on the complexity of the procedure.

Pulmonary (lung) angiography

Pulmonary, or lung, angiography is performed to evaluate blood circulation to the lungs. It is also considered the most accurate diagnostic test for detecting a pulmonary embolism. The procedure differs from cerebral and coronary angiography in that the guide wire and catheter are inserted into a vein instead of an artery, and are guided up through the chambers of the heart and into the pulmonary artery. Throughout the procedure, the patient's **vital signs** are monitored to ensure that the catheter doesn't cause arrhythmias, or irregular heartbeats. The

contrast medium is then injected into the pulmonary artery where it circulates through the lungs' capillaries. The test typically takes up to 90 minutes and carries more risk than other angiography procedures.

Kidney (renal) angiography

Patients with chronic renal disease or injury can suffer further damage to their kidneys from the contrast medium used in a renal angiogram, yet they often require the test to evaluate kidney function. These patients should be well hydrated with an intravenous saline drip before the procedure, and may benefit from available medications (e.g., dopamine) that help to protect the kidney from further injury associated with contrast agents. During a renal angiogram, the guide wire and catheter are inserted into the femoral artery in the groin area and advanced through the abdominal aorta, the main artery in the abdomen, and into the renal arteries. The procedure takes approximately one hour.

Fluorescein angiography

Fluorescein angiography is used to diagnose retinal problems and circulatory disorders. It is typically conducted as an outpatient procedure. The patient's pupils are dilated with eye drops and he or she rests the chin and forehead against a bracing apparatus to keep it still. Sodium fluorescein dye is then injected with a syringe into a vein in the patient's arm. The dye travels through the patient's body and into the blood vessels of the eye. The procedure does not require x rays. Instead, a rapid series of close-up photographs of the patient's eyes are taken, one set immediately after the dye is injected, and a second set approximately 20 minutes later once the dye has moved through the patient's vascular system. The entire procedure takes up to one hour.

Celiac and mesenteric angiography

Celiac and mesenteric angiography involves radiographic exploration of the celiac and mesenteric arteries, arterial branches of the abdominal aorta that supply blood to the abdomen and digestive system. The test is commonly used to detect aneurysm, thrombosis, and signs of ischemia in the celiac and mesenteric arteries, and to locate the source of gastrointestinal bleeding. It is also used in the diagnosis of a number of conditions, including portal hypertension, and cirrhosis. The procedure can take up to three hours, depending on the number of blood vessels studied.

Splenoportography

A splenoportograph is a variation of an angiogram that involves the injection of contrast medium directly into the spleen to view the splenic and portal veins. It is used to diagnose blockages in the splenic vein and portal-vein thrombosis and to assess the patency and location of the vascular system prior to liver transplantation.

Most angiographic procedures are typically paid for by major medical insurance. Patients should check with their individual insurance plans to determine their coverage.

Computerized tomographic angiography (CTA), a new technique, is used in the evaluation of patients with intracranial aneurysms. CTA is particularly useful in delineating the relationship of vascular lesions with bony anatomy close to the skull base. While such lesions can be demonstrated with standard angiography, it often requires studying several projections of the two-dimensional films rendered with standard angiography. CTA is ideal for more anatomically complex skull-base lesions because it clearly demonstrates the exact relationship of the bony anatomy with the vascular pathology. This is not possible using standard angiographic techniques. Once the information has been captured a workstation is used to process and reconstruct images. The approach yields shaded surface displays of the actual vascular anatomy that are three dimensional and clearly show the relationship of the bony anatomy with the vascular pathology.

Angiography can also be performed using **magnetic resonance imaging** (**MRI**) scanners. The technique is called MRA (magnetic resonance angiography). A contrast medium is not usually used, but may be used in some body applications. The active ingredient in the contrast medium used for MRA is one of the rare earth elements, gadolinium. The contrast agent is injected into an arm vein, and images are acquired with careful attention being paid to the timing of the injection and selection of MRI specific imaging parameters. Once the information has been captured, a workstation is used to process and reconstruct the images. The post-processing capabilities associated with CTA and MRA yield three-dimensional representations of the vascular pathology being studied and can also be used to either enhance or subtract adjacent anatomical structures.

Aftercare

Because life-threatening internal bleeding is a possible complication of an arterial puncture, an overnight stay in the hospital is sometimes recommended following an angiographic procedure, particularly with cerebral and coronary angiography. If the procedure is performed on an outpatient basis, the patient is typically kept under close observation for a period of six to 12 hours before being released. If the arterial puncture was performed in the femoral artery, the patient is instructed to keep his or her leg straight and relatively immobile during the observation period. The patient's blood pressure and vital signs are monitored, and the puncture site observed closely. Pain medication may be prescribed if the patient is experiencing discomfort from the

puncture, and a cold pack is often applied to the site to reduce swelling. It is normal for the puncture site to be sore and bruised for several weeks. The patient may also develop a hematoma at the puncture site, a hard mass created by the blood vessels broken during the procedure. Hematomas should be watched carefully, as they may indicate continued bleeding of the arterial puncture site.

Angiography patients are also advised to have two to three days of rest after the procedure in order to avoid placing any undue stress on the arterial puncture site. Patients who experience continued bleeding or abnormal swelling of the puncture site, sudden dizziness, or chest pain in the days following an angiographic procedure should seek medical attention immediately.

Patients undergoing a fluorescein angiography should not drive or expose their eyes to direct sunlight for 12 hours following the procedure.

Risks

Because angiography involves puncturing an artery, internal bleeding or hemorrhage are possible complications of the test. As with any invasive procedure, infection of the puncture site or bloodstream is also a risk, but this is rare.

A **stroke** or heart attack may be triggered by an angiogram if blood clots or plaque on the inside of the arterial wall are dislodged by the catheter and form a blockage in the blood vessels or artery, or if the vessel undergoes temporary narrowing or spasm from irritation by the catheter. The heart may also become irritated by the movement of the catheter through its chambers during pulmonary and coronary angiographic procedures, and arrhythmias may develop.

Patients who develop an allergic reaction to the contrast medium used in angiography may experience a variety of symptoms, including swelling, difficulty breathing, heart failure, or a sudden drop in blood pressure. If the patient is aware of the allergy before the test is administered, certain medications (e.g., steroids) can be administered at that time to counteract the reaction.

Angiography involves minor exposure to radiation through the x rays and fluoroscopic guidance used in the procedure. Unless the patient is pregnant, or multiple radiological or fluoroscopic studies are required, the dose of radiation incurred during a single procedure poses little risk. However, multiple studies requiring fluoroscopic exposure that are conducted in a short time period have been known to cause skin necrosis in some individuals. This risk can be minimized by careful monitoring and documentation of cumulative radiation doses administered to these patients, particularly in those who have therapeutic procedures performed along with the diagnostic angiography.

Results

The results of an angiogram or arteriogram depend on the artery or organ system being examined. Generally, test results should display a normal and unimpeded flow of blood through the vascular system. Fluorescein angiography should result in no leakage of fluorescein dye through the retinal blood vessels.

Abnormal results of an angiogram may display a narrowed blood vessel with decreased arterial blood flow (ischemia) or an irregular arrangement or location of blood vessels. The results of an angiogram vary widely by the type of procedure performed, and should be interpreted by and explained to the patient by a trained radiologist.

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Angiomatosis *see* **von Hippel-Lindau disease**

Anosmia

Definition

The term anosmia means lack of the sense of smell. It may also refer to a decreased sense of smell. Ageusia, a companion word, refers to a lack of taste sensation. Patients who actually have anosmia may complain wrongly of ageusia, although they retain the ability to distinguish salt, sweet, sour, and bitter—humans' only taste sensations.

Description

Of the five senses, smell ranks fourth in importance for humans, although it is much more pronounced in other animals. Bloodhounds, for example, can smell an odor that is a thousand times weaker than one perceptible by humans. Taste, considered the fifth sense, is mostly the smell of food in the mouth. The sense of smell originates from the first cranial nerves (the olfactory nerves), which sit at the base of the brain's frontal lobes, right behind the eyes and above the nose. Inhaled airborne chemicals stimulate these nerves.

There are other aberrations of smell beside a decrease. Smells can be distorted, intensified, or hallucinated. These changes usually indicate a malfunction of the brain.

Key Terms

Allergen Any substance that irritates only those who are sensitive (allergic) to it.

Corticosteroids Cortisone, prednisone, and related drugs that reduce inflammation.

Rhinitis Inflammation and swelling of the nasal membranes.

Nasal polyps Drop-shaped overgrowths of the nasal membranes.

Causes and symptoms

The most common cause of anosmia is nasal occlusion caused by rhinitis (inflammation of the nasal membranes). If no air gets to the olfactory nerves, smell will not happen. In turn, rhinitis and nasal polyps (growths on nasal membranes) are caused by irritants such as allergens, infections, cigarette smoke, and other air pollutants. Tumors such as nasal polyps can also block the nasal passages and the olfactory nerves and cause anosmia. Head injury or, rarely, certain viral infections can damage or destroy the olfactory nerves.

Diagnosis

It is difficult to measure a loss of smell, and no one complains of loss of smell in just one nostril. So a physician usually begins by testing each nostril separately with a common, non-irritating odor such as perfume, lemon, vanilla, or coffee. Polyps and rhinitis are obvious causal agents a physician looks for. Imaging studies of the head may be necessary in order to detect brain injury, sinus infection, or tumor.

Treatment

Cessation of smoking is one step. Many smokers who quit discover new tastes so enthusiastically that they immediately gain weight. Attention to reducing exposure to other nasal irritants and treatment of respiratory allergies or chronic upper respiratory infections will be beneficial. Corticosteroids are particularly helpful.

Alternative treatment

Finding and treating the cause of the loss of smell is the first approach in naturopathic medicine. If rhinitis is the cause, treating acute rhinitis with herbal mast cell stabilizers and herbal decongestants can offer some relief as the body heals. If chronic rhinitis is present, this is often related to an environmental irritant or to food allergies. Removal of the causative factors is the first step to healing. Nasal steams with essential oils offer relief of the blockage and tonification of the membranes. Blockages can sometimes be resolved through naso-specific therapy—a way of realigning the nasal cavities. Polyp blockage can be addressed through botanical medicine treatment as well as hydrotherapy. Olfactory nerve damage may not be regenerable. Some olfactory aberrations, like intensified sense of smell, can be resolved using homeopathic medicine.

Prognosis

If nasal inflammation is the cause of anosmia, the chances of recovery are excellent. However, if nerve damage is the cause of the problem, the recovery of smell is much more difficult.

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Anoxia *see* **Hypoxia**

Anticholinergics

Definition

Anticholinergics are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. The nerve fibers of the parasympathetic system are responsible for the involuntary movements of smooth muscles present in the gastrointestinal tract, urinary tract, lungs, etc. Anticholinergics are divided into three categories in accordance with their specific targets in the central and/or **peripheral nervous system**: antimuscarinic agents, ganglionic blockers, and **neuromuscular blockers**.

Purpose

Anticholinergic drugs are used to treat a variety of disorders such as gastrointestinal cramps, urinary bladder spasm, asthma, motion sickness, muscular spasms, poisoning with certain toxic compounds, and as an aid to anesthesia.

Description

Antimuscarinic agents are so called because they block muscarine, a poisonous substance found in the *Amanita muscaria*, a nonedible mushroom species. Muscarine is a toxic compound that competes with acetylcholine for the same cholinoreceptors. Antimuscarinic agents are atropine, scopolamine, and ipratropium bromide. Atropine and scopolamine are alkaloids naturally occurring in *Atropa belladonna* and *Datura stramonium* plants, whereas ipratropium bromide is a derivative of atropine used to treat asthma.

Under the form of atropine sulfate, atropine is used in the treatment of gastrointestinal and bladder spasm, cardiac arrhythmias, and poisoning by cholinergic toxins such as organophosphates or muscarine. Atropine is used in ophthalmology as well when the measurement of eye refractive errors (i.e., cyclopegia) is required, due to its papillary dilation properties. Scopolamine shows an effect in the peripheral nervous system similar to those of atropine. However, scopolamine is a **central nervous system** (CNS) depressant and constitutes a highly effective treatment to prevent motion sickness, although at high doses it causes CNS excitement with side effects similar to those caused by high doses of atropine. Its use in ophthalmology is identical in purpose to that of atropine. The main use of ipratropium is for asthma treatment. Ipratropium is also administered to patients with chronic obstructive pulmonary disease.

Benapryzine, benzhexol, orphenadrine, and bornaprine are other examples of anticholinergic drugs used alone or in combination with other medications in **Parkinson's disease** to improve motor function. Disturbances in dopaminergic transmissions are associated with the symptoms observed in Parkinson's disease. The beneficial effects of anticholinergics in this disease are due to the resulting imbalance between dopamine and acetylcholine ratio in neurons (e.g., levels of acetylcholine lower than dopamine levels). These anticholinergic agents may interfere with mood and also decrease gastrointestinal movements, causing constipation; and the positive effects on motor functions vary among patients. Other classes of drugs available today that act on the pathways of dopamine and its receptors to treat Parkinson's disease, such as levodopa, tolcapone, and pramipexol, effectively increase the levels of dopamine at dopaminergic receptors in neurons.

Ganglionic blockers are anticholinergic agents that target nicotinic receptors in nerve cells of either sympathetic or parasympathetic systems. The most used ganglionic blockers are trimethaphan and mecamylamine. Trimethaphan is administered by intravenous infusion for the emergency short-term control of extreme high blood pressure caused by pulmonary edema, or in surgeries that require a controlled lower blood pressure, such as the repair of an aortic aneurysm. Mecamylamine is used to treat moderately severe and severe hypertension (high blood pressure), as the drug is easily absorbed when taken orally.

Neuromuscular anticholinergic agents act on motor-nerve cholinoreceptors. They prevent the transmission of signals from motor nerves to neuromuscular structures of the skeletal muscle. Neuromuscular blockers are very useful as muscle relaxants in several surgical procedures, either as an adjuvant to anesthesia or as a pre-anesthetic. Their main therapeutic use is in surgical procedures. Examples of the first group are mivacurium, tubocurarine,

Key Terms

Acetylcholine The neurotransmitter, or chemical that works in the brain to transmit nerve signals, involved in regulating muscles, memory, mood, and sleep.

Neuromuscular junction The junction between a nerve fiber and the muscle it supplies.

Neurotransmitter Chemicals that allow the movement of information from one neuron across the gap between the adjacent neuron.

Parasympathetic nervous system A branch of the autonomic nervous system that tends to induce secretion, increase the tone and contraction of smooth muscle, and cause dilation of blood vessels.

metocurine, doxacurium, and atracurium; the second group consists of rocuronium, vecuronium, pipercuronion, and pancuronium.

Precautions

Atropine should be avoided by persons suffering from hepatitis, glaucoma, gastrointestinal obstruction, decreased liver or kidney function, and allergy to anticholinergic agents. Scopolamine is not indicated in cases of glaucoma, asthma, severe colitis, genitourinary or gastrointestinal obstruction, and **myasthenia gravis**, as well as people with hypersensitivity to cholinergic blockers.

The prescription of ganglionic blockers to patients with kidney insufficiency, or coronary or cerebrovascular disorders requires special caution and should only be a choice when other agents cannot be used instead.

Side effects

Atropine may cause severe adverse effects with dose-dependent degrees of severity. Overdoses of atropine, for instance, may induce **delirium**, hallucinations, coma, circulatory and respiratory collapse, and death. Rapid heart rate, dilation of pupils and blurred vision, restlessness, burning **pain** in the throat, marked mouth dryness, and urinary retention are observed with higher doses, while lower dosages may result in decreased salivary, respiratory, and perspiration secretions. Sometimes surgeons administer atropine prior to surgery due to this antisecretory property. Scopolamine's main side effects are similar to those observed with atropine.

The adverse effects of ganglionic blockers include paralysis of gastrointestinal movements, nausea, gastritis, urinary retention, and blurred vision.

Neuromuscular blockers' adverse effects may include apnea (failure in breathing) due to paralysis of the diaphragm, hypotension (low blood pressure), tachycardia, post-surgery muscle pain, increased intraocular pressure, and malignant hyperthermia (uncontrolled high fever).

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Anticonvulsants

Definition

Anticonvulsants are a class of drugs indicated for the treatment of various types of **seizures** associated with seizure disorders such as **epilepsy**, a neurological dysfunction in which excessive surges of electrical energy are emitted in the brain, and other disorders.

Some anticonvulsants are indicated for other medical uses. Some **hydantoins**, such as phenytoin, are also used as skeletal muscle relaxants and antineuralgics in the treatment of neurogenic **pain**. Some anticonvulsants and **antiepileptic drugs** (AEDs) are used in psychiatry for the treatment of bipolar disorders (manic-depression).

Purpose

Although there is no cure for the disorder, anticonvulsants are often effective in controlling the seizures associated with epilepsy. The precise mechanisms by which many anticonvulsants work are unknown, and different sub-classes of anticonvulsants are thought to exert their therapeutic effects in diverse ways. Some anticonvulsants are thought to generally depress **central nervous system** (CNS) function. Others, such as GABA inhibitors, are thought to target specific neurochemical processes, suppress excess neuron function, and regulate electrochemical signals in the brain.

Description

There are several sub-classes and types of anticonvulsants. They are marketed in the United States under a variety of brand names.

- Barbiturates, including Mephobarbital (Mebaral), Pentobarbital (Nembutal), and **Phenobarbital** (Luminol, Solfoton).
- Benzodiazepines, including Chlorazepate (Tranxene), Clonazepam (Klonopin), and **Diazepam** (Valium).
- GABA Analogues, including **Gabapentin** (Neurontin) and **Tiagabine** (Gabitril).
- Hydantoins, including Ethotoin (Peganone), Fosphentyoin (Mesantoin), and Phenytoin (Dilantin).
- Oxazolidinediones, including Trimethadione (Tridione).
- Phenyltriazines, including **Lamotrigine** (Lamictal).

Key Terms

Bipolar disorder A psychiatric disorder marked by alternating episodes of mania and depression. Also called bipolar illness, manic-depressive illness.

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Neurogenic pain Pain originating in the nerves or nervous tissue and following the pathway of a nerve.

Seizure A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain, resulting in abnormal body movements or behaviors.

- Succinamides, including Ethosuximide (Zarontin), Methsuximide (Celontin), and Phensuximide (Milontin).
- Other anticonvulsants, including **Acetazolamide** (Diamox), **Carbamazepine** (Carbatrol, Tegretol), **Felbamate** (Felbatol), **Levetiracetam** (Keppra), Oxcarbazepine (Trileptal), **Primidone** (Mysoline), **Topiramate** (Topamax), Valproic acid (Depakene, Depakote), and **Zonisamide** (Zonegran).

A physician prescribes anticonvulsant medication, or a combination of anticonvulsant medications, according to seizure type and pattern in individual patients. Some anticonvulsant medications are not appropriate for pediatric patients under 16 years of age.

Recommended dosage

Anticonvulsants are available in oral suspension (syrup), injectable, capsule, tablet, and sprinkle forms, depending on the type of medication. Not all anticonvulsants will be available in all forms. Anticonvulsants are prescribed by physicians in varying daily dosages, depending on the age, weight, and other health concerns of the individual patient, as well as the severity and frequency of their seizures.

It is important to follow the prescribing physicians directions carefully as each individual anticonvulsant medication has its own recommended daily dosages and dose schedule. Some anticonvulsants are taken in a single daily dose; others are taken in divided, multiple daily doses. A double dose of any anticonvulsant medication should not be taken. If a dose is missed, it should be taken as soon as possible. However, if it is within four hours of the next scheduled dose, the missed dose should be skipped. Taking an anticonvulsant at regular intervals and at the same time each day enables consistent levels of the medication to be maintained in the bloodstream, and results in more effective seizure control.

In general, initiating any course of treatment which includes anticonvulsants requires a gradual dose-increasing regimen. Adults and children typically take a smaller daily dose for the first two weeks. Daily dosages of anticonvulsant medication may then be slowly titrated, or increased over time until adequate seizure control is achieved using the lowest dose possible.

When ending a course of treatment of anticonvulsant, physicians typically taper the patient's daily dose over a period of several weeks. Suddenly stopping treatment including anticonvulsants may cause seizures to return or occur with greater frequency. Patients taking anticonvulsants drugs for the treatment of pain or bipolar disorders may experience also have seizures, even if they have never had them before, if they suddenly stop taking the medication.

Precautions

Each anticonvulsant medication may have its own precautions, counter-indications, and side-effects. However, many are common to all anticonvulsant medications.

Consult the prescribing physician before taking any anticonvulsant with non-perscription medications. Patients should avoid alcohol and CNS depressants (medications that make one drowsy or tired, such as antihistimines, sleep medications, and some pain medications) while taking anticonvulants. Anticonvulsants can exacerbate the side effects of alcohol and other medications. Alcohol may also increase the risk or frequency of seizures.

Anticonvulsants may not be suitable for persons with a history of **stroke**, anemia, thyroid, liver, depressed kidney function, diabetes mellitus, severe gastro-intestional disorders, porphyria, **lupus**, some forms of mental illness, high blood presure, angina (chest pain), irregular heartbeats, and other heart problems.

Before beginning treatment with anticonvulsants, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are nursing, pregnant, or plan to become pregnant.

Physicians generally advise the use of effective birth control while taking many anticonvulsant medications. Patients taking anticonvulsants should be aware that many anticonvulsants may increase the risk of birth defects. Furthermore, many anticonvulsant medications are secreted in breast milk. Patients who become pregnant while taking any anticonvulsant should contact their physician immediately to discuss the risks and benefits of continuing treatment during pregnancy and while nursing.

Some anticonvulsants may be prescribed for children. However, children may experience increased side effects. Research indicates that some children who take high doses of some anticonvulsants (such as hydantoins) for an extended period of time may experience mild learning difficulties or not perform as well in school.

Side effects

In some patients, anticonvulsants may produce usually mild side effects. **Headache**, nausea, and unusual tiredness and weakness are the most frequently reported side effects of anticonvulsants. Other general side effects of anticonvulsants that do not usually require medical attention include:

- mild coordination problems
- mild dizziness
- abdominal pain or cramping
- sinus pain
- sleeplessness or nightmares
- change in appetite
- mild feelings of anxiety
- feeling of warmth
- tingling or prickly feeing on the skin, or in the toes and fingers
- mild tremors
- diarrhea or constipation
- heartburn or indigestion
- aching joints and muscles or chills
- unpleasant taste in mouth or dry mouth

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication. However, if any symptoms persist or become too uncomfortable, the perscribing physician should be consulted.

Other, uncommon side effects of anticonvulsants can be serious or may indicate an allergic reaction. A patient taking any anticonvulsant who experiencs one or more of the following symptoms should contact the prescribing physician immediately:

- rash or bluish, purplish, or white patches on the skin
- jaundice (yellowing of the skin and eyes)
- bloody nose or unusual bleeding
- hallucinations (seeing visions or hearing voices that are not present)
- sores in the mouth or around the eyes
- ringing or vibrations in the ears
- **depression** or suicidal thoughts
- mood or mental changes, including excessive fear, anxiety, hostility
- severe tremors
- prolonged numbness in the extremeties
- general loss of motor skills
- persistent lack of appetite
- altered vision
- frequent or burning urination
- difficulty breathing
- chest pain or irregular heartbeat
- faintness or loss of consciousness
- persistant, severe headaches
- persistant fever or pain.

Interactions

Anticonvulsants may have negative interactions with some antacids, anticoagulants, antihistimines, antidepressants, antibiotics, pain killers (including lidocaine) and monoamine oxidase inhibitors (MAOIs). Other medications such as amiodarone, diazoxide, phenybutazone, sulfonamides (sulfa drugs), corticosteroids, sucralfate, rifampin, and warfarin may also adversely react with anticonvulsants.

Some anticonvulsants should not be used in combination with other anticonvulsants. (For example, phenytoin (a hydantoin) when used with valproic acid, another anticonvulsant, may increase the seizure frequency). However, several anticonvulsant medications are indicated to be used in conjunction with or suppliment other anticonvulsants. If advised and carefully monitored by a physician, a course of treatment including multiple seizure prevention medications can be effective and safe.

Most anticonvulsants decrease the effectiveness of contraceptives that contain estrogens or progestins, including oral contraceptives (birth control pills), progesterone implants (Norplant), and progesterone injections (Depo-Provera).

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Key Terms

Absence seizures Also called a petit mal seizure, characterized by abrupt, short-term lack of conscious activity or other abnormal change in behavior.

Atonic seizure A seizure characterized by a sudden loss of muscle tone, causing the individual to fall to the floor.

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Febrile convulsion Seizures occurring mainly in children between three months and five years of age that are triggered by fever.

Partial seizure An episode of abnormal activity in a localized, specific part of the brain that causes changes in attention, movement, and/or behavior.

Status epilepticus A serious condition involving continuous seizures with no conscious intervals.

Tonic-clonic seizure A seizure involving the entire body characterized by unconsciousness, muscle contraction, and rigidity. Also called grand mal or generalized seizures.

Trigeminal neuralgia A disorder of the trigeminal nerve that causes severe facial pain.

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American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. <http://www.aesnet.org>.

Adrienne Wilmoth Lerner

Antiepileptic drugs

Definition

Antiepileptic drugs are all drugs used to treat or prevent convulsions, as in **epilepsy**.

Purpose

Antiepileptic drugs (AEDs) are designed to modify the structures and processes involved in the development of a seizure, including neurons, ion channels, receptors, glia, and inhibitory or excitatory synapses. These processes are modified to favor inhibition over excitation in order to stop or prevent seizure activity.

Description

The ideal AED would suppress all **seizures** without causing any unwanted side effects. Unfortunately, the drugs currently used not only fail to control seizure activity in some patients, but frequently cause side effects that range in severity from minimal impairment of the **central nervous system** (CNS) to death from aplastic anemia or liver (hepatic) failure.

Prior to 1993, the choice of an antiepileptic medication was limited to traditional drugs, as **phenobarbital**, **primidone**, phenytoin, **carbamazepine** and valproate. Although these drugs have the advantage of proven efficacy (effectiveness), many patients are left with refractory (break-through) seizures. Since 1993, many new medications have been approved by the United States Food and Drug Administration (FDA), expanding treatment options. The newer AEDs offer the potential advantages of fewer drug interactions, unique mechanisms of action, and a broader spectrum of activity.

The AEDs can be grouped according to their main mechanism of action, although many have several different actions and others work through unknown mechanisms. The main groups include sodium channel blockers, calcium current inhibitors, gamma-aminobutyric acid (GABA) enhancers, glutamate blockers, and drugs with unknown mechanisms of action.

Sodium Channel Blockade

Blocking the sodium channel in the cell membrane is the most common and the most well-characterized mechanism of currently available AEDs. AEDs that target these sodium channels prevent the return of the channels to the active state by stabilizing the inactive form. In doing so, repetitive firing of nerve impulses from the axon of the nerve is prevented. The blockade of sodium channels of

nerve axons causes stabilization of the neuronal membranes and limits the development of seizure activity. Sodium channel blocker drugs include: carbamazepine, phenytoin, fosphenytoin, oxcarbazepine, lamotrignine, and zonizamide.

Calcium Current Inhibitors

Calcium channels are small channels in the nerve cell that function as the "pacemakers" of normal rhythmic brain cell activity. Calcium current inhibitors are particularly useful for controlling absence seizures. The drug ethosuximide is a calcium current inhibitor.

GABA Reuptake Inhibitors

GABA reuptake inhibitors boost the levels of GABA, a neurotransmitter, in the brain. **Neurotransmitters** such as GABA are naturally occurring chemicals that transmit messages from one neuron (nerve cell) to another. When one neuron releases GABA, it normally binds to the next neuron, transmitting information and preventing the transmission of extra electrical activity. When levels of GABA are reduced, there may not be enough GABA to sufficiently bond to the neuron, leading to extra electrical activity in the brain and seizures. **Tiagabine** works to block GABA from being re-absorbed too quickly into the tissues, thereby increasing the amount available to bind to neurons.

GABA Receptor Agonist

GABA receptor agonists bind with certain cell-surface proteins and produce changes that mimic that action of GABA, thereby reducing excess electrical activity and seizures. Clonazepam, phenobarbital, and primidone are examples of GABA receptor agonist drugs. Some drugs such as valproate enhance the synthesis of GABA, in addition to other potential mechanisms of action, and thus prevent seizures.

Glutamate Blockers

Glutamate and aspartate are the two most important excitatory neurotransmitters in the brain. By blocking glutamate action, the excess electrical activity that causes seizures is controlled. **Topiramate** and **felbamate** are examples of glutamate blocker drugs, but their use is limited because they sometimes produce hallucinations and behavior changes.

Recommended dosage

Antiepileptic drugs are usually prescribed in an initial dose, then gradually increased over time until maximum seizure control is achieved with a minimum of side effects. Recommended dosages for specific antiepileptic drugs include:

- Carbamazepine: In generalized tonic-clonic seizures or partial seizures, by mouth, ADULT: initially 100 mg twice daily, increased gradually according to response to usual maintenance dose of 0.8–1.2 g; ELDERLY: reduce initial dose; CHILD: 10–20 mg/kg daily in divided doses. **Trigeminal neuralgia**, by mouth, ADULT: initially 100 mg 1–2 times daily increased gradually according to response; usual dose 200 mg 3–4 times daily with up to 1.6 g daily.
- Clonazepam: Epilepsy, by mouth, ADULT: initially 1 mg at night for 4 nights, increased gradually over 2–4 weeks to a usual maintenance dose of 4–8 mg daily in divided doses; ELDERLY: initial dose 500 micrograms increased as above; CHILD: up to 1 year initially 250 micrograms increased as above to 0.5–1 mg daily in divided doses; 1–5 years: initially 250 micrograms increased to 1–3 mg daily in divided doses; 5–12 years: initially 500 micrograms increased to 3–6 mg daily in divided doses.
- **Diazepam**: Emergency management of recurrent epileptic seizures, by slow intravenous injection (at rate of 5 mg/minute), ADULT: 10–20 mg, repeated if necessary after 30–60 minutes; may be followed by intravenous infusion to maximum 3 mg/kg over 24 hours; CHILD: 200 to 300 micrograms/kg (or 1 mg per year of age); by rectum as solution, ADULT and CHILD over 10 kg: 500 micrograms/kg; ELDERLY: 250 micrograms/kg; repeated if necessary every 12 hours. Febrile convulsions, by rectum as solution; CHILD over 10 kg: 500 micrograms/kg (maximum 10 mg), with dose repeated if necessary. Seizures associated with poisoning, by slow intravenous injection (at rate of 5 mg/minute), ADULT: 10–20 mg.
- Ethosuximide: Absence seizures, by mouth, ADULT and CHILD over 6 years: initially 500 mg daily, increased by 250 mg at intervals of 4–7 days to a usual dose of 1–1.5 g daily (occasionally, up to maximum of 2 g daily); CHILD under 6 years: initially 250 mg daily, increased gradually to usual dose of 20 mg/kg daily.
- Felbamate: By mouth, ADULT: 2400–4600 mg per day; CHILD: 40–60 mg/kg per day. Optimal individual maintenance doses will be determined by clinical response.
- Fosphenytoin: For emergency management of repeated seizures, by intravenous injection, 22.5 to 30 mg per kg. For nonemergent therapy, by intravenous injection, 15 to 30 mg per kg, followed by 6 to 12 mg per kg for maintenance therapy.
- **Lamotrigine**: ADULT: by mouth, if added to valproate monotherapy, 25 mg daily for two weeks, then 50 mg daily for two weeks, then titrate up to 150 mg twice daily. If added to carbamazepine, phenytoin, phenobarbital, or primidone, initial dose 50 mg twice daily, subsequent increases up to 100–200 mg twice daily.

CHILD, by mouth, if added to valproate monotherapy, initial dose 0.5 mg/kg/day, final maintenance dose of 1–5 mg/kg/day. If added to carbamazepine, phenytoin, phenobarbital, or primidone: initial doses 2 mg/kg/day, with subsequent increases to 5–15 mg/kg/day.

- Levetiracetam: ADULT: by mouth, 1000–3000 mg/day. CHILD: dosage range not established.
- Oxcarbazepine: ADULT: by mouth, 600–2400 mg per day; CHILD: by mouth, 10–30 mg/kg per day.
- Phenobarbital: Generalized tonic-clonic seizures, partial seizures, by mouth, ADULT: 60-180 mg at night; CHILD: up to 8 mg/kg daily. Febrile convulsions, by mouth, CHILD: up to 8 mg/kg daily. Neonatal seizures, by intravenous injection (dilute injection 1 in 10 with water for injections), NEWBORN: 5–10 mg/kg every 20–30 minutes up to plasma concentration of 40 mg/liter. By intravenous injection (dilute injection 1 in 10 with water for injections), ADULT: 10 mg/kg at a rate of not more than 100 mg/minute (up to maximum total dose of 1 g); CHILD: 5–10 mg/kg at a rate of not more than 30 mg/minute.
- Phenytoin sodium: Generalized tonic-clonic seizures, partial seizures, by mouth, ADULT: initially 3–4 mg/kg daily (as a single dose or in 2 divided doses), increased gradually by 25 mg at intervals of 2 weeks as necessary (with plasma-phenytoin concentration monitoring); usual dose 200–500 mg daily; CHILD: initially 5 mg/kg daily in 2 divided doses; usual dose range 4–8 mg/kg daily (maximum 300 mg).
- Primidone: ADULT: by mouth, 500–1250 mg per day. CHILD: by mouth, 5–20 mg/kg per day. Optimal individual maintenance doses will be determined by clinical response.
- Sodium valproate: Generalized tonic-clonic seizures, partial seizures, absence seizures, atonic seizures; myoclonic seizures, by mouth, ADULT: initially 600 mg daily in 2 divided doses, preferably after food, increased by 200 mg daily at 3-day intervals to maximum of 2.5 g daily in divided doses; usual maintenance dose 1–2 g daily (20–30 mg/kg daily); CHILD: up to 20 kg, initially 20 mg/kg daily in divided doses, may be increased provided plasma concentrations monitored; CHILD over 20 kg: initially 400 mg daily in divided doses, increased until control (usually in range of 20–30 mg/kg daily); maximum 35 mg/kg daily.
- Tiagabine: By mouth, suggested ADULT maintenance dose 32 to 56 mg/day. Dosage titrations of 4–8 mg/day weekly are suggested by the manufacturer.
- Topiramate: ADULT: by mouth, 400 mg per day. An initiation schedule, where the medication dose is increased by 50 mg/day each week, is recommended to reduce adverse effects; slower rates of initiation are used by some physicians.
- Zonisamide: ADULT: by mouth, 100–400 mg/day; CHILD dosage range not established.

Precautions

Withdrawal

Treatment is normally continued for a minimum of two years after the last seizure. Withdrawal should be extended over a period of several months, as abrupt withdrawal can lead to complications such as **status epilepticus**, a serious event where seizures occur rapidly and continuously. Many adult patients relapse once treatment is withdrawn and it may be justified to continue treatment indefinitely, particularly when the patient's livelihood or lifestyle can be endangered by recurrence of a seizure.

Pregnancy and Breast-feeding

Untreated epilepsy during pregnancy may cause harm to the fetus; there is, therefore, no justification for abrupt withdrawal of treatment. Withdrawal of therapy with antiepileptic medications may be an option if the patient has been seizure-free for at least two years. Resumption of treatment may be considered after the first trimester. If antiepileptics are continued in pregnancy, a single medication with the lowest effective dose is preferred, and blood levels of the medication should be monitored. There is an increased risk of birth defects with the use of AEDs, particularly carbamazepine, valproate, and phenytoin. However, if there is good seizure control, many physicians see no advantage in changing pregnant patients' AEDs. In view of the risks of neural tube and other defects, patients who may become pregnant should be informed of the risks and referred for advice, and pregnant patients should be offered counseling and screening. To counteract the risk of neural tube defects, adequate folic acid supplements are advised for women before and during pregnancy. In view of the risk of bleeding associated with carbamazepine, phenobarbital, and phenytoin, prophylactic phytomenadione (vitamin K1) is recommended for the mother before delivery and the newborn. Use of AEDs can often be continued during breastfeeding.

Driving

Regulations are in place in many countries that may restrict driving by patients with epilepsy. Further, AEDs may cause central nervous system **depression**, particularly in the early stages of treatment. Patients affected by adverse effects such as drowsiness or **dizziness** should not operate machinery or drive.

Side effects

The most common side effects of therapy with antiepileptic drugs are drowsiness and dizziness. Other drug-specific side effects include:

- Carbamazepine: Dizziness, double vision, nausea, loss of coordination, and blurred vision.
- Clonazepam: Sedation, **ataxia** (loss of coordination), hyperactivity, restlessness, irritability, depression, cardiovascular or respiratory depression. Children and infants may have excess saliva production. Occasionally, tonic seizures may be exacerbated.
- Diazepam: Drowsiness, dizziness, tiredness, weakness, dry mouth, diarrhea, upset stomach, changes in appetite, restlessness or excitement, constipation, difficulty urinating, frequent urination, blurred vision, changes in sex drive or ability.
- Ethosuximide: Drowsiness, upset stomach, vomiting, constipation, diarrhea, stomach **pain**, loss of taste and appetite, weight loss, irritability, mental confusion, depression, insomnia, nervousness, and **headache**.
- Felbamate: Insomnia, weight loss, nausea, decreased appetite, dizziness, **fatigue**, ataxia (loss of coordination), and lethargy.
- Fosphenytoin: Burning/tingling sensations, groin pain, itching, nausea, dizziness or drowsiness may occur. Serious side effects may occur: mental/mood changes, loss of coordination, rash, eye/vision problems.
- Lamotrigine: Rash is the main concern associated with this drug. Other commonly reported adverse reactions are headache, blood dyscrasias, ataxia (loss of coordination), double vision, psychosis, tremor, hypersensitivity reactions, and prolonged sleepiness or insomnia.
- Levetiracetam: Sleepiness, asthenia (loss of strength), dizziness, accidental injury, convulsion, infection, pain, pharyngitis, and a flu-like syndrome.
- Oxcarbazepine: Sleepiness, headache, dizziness, rash, low blood sodium level, weight gain, and hair loss.
- Phenobarbital: Thought and behavior alterations, sedation, psychomotor slowing, poor concentration, depression, irritability, ataxia (loss of coordination), and decreased libido.
- Phenytoin sodium: Ataxia (loss of coordination), abnormal rapid eye movements, drowsiness and lethargy, nausea and vomiting, rash, blood disorders, headaches, vitamin K and folate deficiencies, loss of libido, hormonal dysfunction, and bone marrow suppression.
- Primidone: Intense sedation, dizziness, and nausea at the onset of treatment.
- Sodium valproate: Nausea, vomiting, tremor, sedation, confusion or irritability, and weight gain, elevated blood sugar levels, and hair loss or curling of hair.
- Tiagabine: Dizziness, fatigue, depression, confusion, impaired concentration, speech or language problems, lack of energy, weakness, upset stomach, nervousness, tremor, and stomach pain.
- Topiramate: Dizziness, sleepiness, ataxia (loss of coordination), confusion, fatigue, decreased sensation in lower extremities, speech difficulties, double vision, impaired concentration, and nausea.
- Zonizamide: Dizziness, anorexia, headache, ataxia (loss of coordination), confusion, speech abnormalities, mental slowing, irritability, tremor, weight gain, excessive sleepiness, and fatigue.

Interactions

Antiepilectic drugs may be prescribed alone or in combination with other antiepileptic drugs. In general, drugs that cause central nervous system depression, including alcohol, should be used with caution by those taking antiepileptic medications. Many antiepileptic medications also reduce the effectiveness of oral contraceptives (birth control pills). Specific drug interventions include:

- Carbamazepine: Several drugs, such as macrolide antibiotics (erythromycin and clarithromycin), isoniazid, chloramphenicol, calcium channel blockers, cimetidine, and propoxyphene, inhibit liver enzyme function responsible for the metabolic breakdown of carbamazepine, thereby raising its levels in the blood. Phenobarbital, phenytoin, felbamate, and primidone decrease efficiency of carbamazepine. Toxic symptoms or breakthrough seizures may occur if the dose of carbamazepine is not adjusted. Grapefruit juice and St. John's wort can increase carbamazepine levels. Carbamazepine reduces the effectiveness of tricyclic antidepressants, oral contraceptives, cyclosporin A, and warfarin.
- Clonazepam: Clonazepam blood levels are decreased by coadministration of enzyme-inducing drugs. No significant clinical interactions have been reported.
- Diazepam: Diazepam may increase the effects of other drugs that cause drowsiness, including antidepressants, alcohol, antihistamines, sedatives, pain relievers, anxiety medicines, seizure medicines, and muscle relaxants. Antacids may decrease the effects of diazepam.
- Ethosuximide: Ethosuximide may increase the amount of other antiseizure medications in the blood. Such medications include phenytoin, mephenytoin, and ethotoin. These drugs must be monitored if they are used with ethosuximide to prevent the occurrence of dangerous side effects. Ethosuximide may decrease the level of primidone in the blood, which could lead to a loss of

seizure control. Valproic acid may increase or decrease ethosuximide levels and must be used with caution.

- Felbamate: Felbamate increases blood levels of phenytoin. Adjustments in dosage may be necessary. Its levels are increased by carbamazepine. Felbamate also increases levels of valproic acid in blood.
- Fosphenytoin: Fosphenytoin has no specific known interactions.
- Lamotrigine: Levels increase with concomitant use of valproate.
- Levetiracetam: No significant drug interactions have been identified.
- Oxcarbazepine: Interacts with oral contraceptives, thereby reducing their efficacy.
- Phenobarbital: Metabolism of phenobarbital is inhibited by phenytoin sodium, valproate, felbamate, and dextropropoxyphene. Enzyme inducers, such as rifampicin, decrease phenobarbital levels. Because of the potent induction of liver enzymes, phenobarbital increases the metabolism of estrogen, steroids, warfarin, carbamazepine, diazepam, clonazepam, and valproate.
- Phenytoin sodium: Among all AEDs, phenytoin sodium has one of the most problematic drug interaction profiles. Carbamazepine and phenobarbital have variable and unpredictable effects (i.e., increase or decrease) on phenytoin sodium levels. Valproate raises levels of phenytoin sodium by displacing phenytoin sodium from its protein-binding site and inhibiting its metabolism. Other drugs that significantly increase phenytoin sodium levels are isoniazid, cimetidine, chloramphenicol, dicumarol, and sulfonamides. Drugs that lower phenytoin sodium levels are vigabatrin and amiodarone. Phenytoin sodium itself is a strong inducer of liver enzymes and alters levels of other drugs. It decreases levels of carbamazepine, ethosuximide, felbamate, primidone, tiagabine, and phenobarbital. It inhibits dicumarol, warfarin, and corticosteroids; clotting factors and immunosuppression must be monitored and doses adjusted accordingly. Other drugs whose levels are reduced by phenytoin sodium and require monitoring and adjustment include furosemide, cyclosporin, folate, and praziquantel. Levels of chloramphenicol and quinidine are elevated by phenytoin sodium.
- Primidone: Primidone interacts with most other AEDs. **Acetazolamide**, carbamazepine, ethosuximide, and methsuximide may all decrease the effects of primidone, and larger primidone doses may be necessary. Phenytoin, ethotoin, mephenytoin, and isoniazid may increase blood levels of primidone, and an adjustment of primidone dosage may be necessary. Carbamazepine blood levels may be higher during therapy with primidone, and an adjustment of the carbamazepine dosage may also be necessary.
- Sodium valproate: Increases plasma levels of free fractions of phenytoin sodium, phenobarbital, carbamazepine epoxide, and lamotrigine. It decreases total phenytoin sodium level. The levels of sodium valproate are decreased by enzyme-inducing drugs and are increased by felbamate and clobazam.
- Tiagabine: Causes a small decrease in valproate levels. Hepatic-inducing drugs increase the clearance of tiagabine by two thirds. Drug plasma concentrations are not affected by valproate, cimetidine, or erythromycin.
- Topiramate: Enzyme-inducing drugs, such as phenytoin sodium or carbamazepine, decrease topiramate concentrations in the blood by approximately 50%. Topiramate generally does not affect the steady-state concentrations of the other drugs given in polytherapy, although phenytoin sodium levels may rise occasionally. Topiramate reduces ethyl estradiol levels by 30% and may inactivate the low-dose contraceptive pill. It may cause a mild reduction in digoxin levels.
- Zonisamide: Phenytoin sodium, carbamazepine, phenobarbital, and valproic acid reduce levels of zonizamide in the blood; however, zonizamide does not affect the levels of these drugs.

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ORGANIZATIONS

The Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org/

U.S. Food and Drug Administration. 5600 Fishers Lane, Rockville, MD 20857. (888) 463-6332. <http://www.fda.gov>.

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Antimigraine medications

Definition

Antimigraine medications are drugs that are given to lower the risk of a severe migraine attack or to reduce the severity of the **headache** once an attack begins.

Purpose

Treatment that is given to stop or ease the **pain** of a migraine headache after it has started is known as acute or abortive treatment.

Preventive treatment for migraine headaches is called migraine prophylaxis or prophylactic therapy. Prophylactic medications are taken when the patient is *not* having a headache. They have three purposes:

- lower the frequency and severity of the patient's headaches
- make acute migraines more responsive to abortive treatment
- improve the patient's overall quality of life

Not all patients with migraines need prophylactic treatment. Most doctors, however, recommend prophylactic medications in the following circumstances:

- The patient has two or more migraines per month, with disability lasting three or more days
- Acute treatment is contraindicated or is ineffective
- The patient has been using abortive medications more than twice a week
- The patient has a complex form of migraine such as hemiplegic or basilar migraine
- The patient is at risk of permanent neurologic injury from acute attacks

Description

Abortive medications

Abortive medications for migraine are prescribed according to the severity of the patient's headaches, the presence of nausea or vomiting, the patient's response to the drug, and the presence of such comorbid conditions as **depression** or **epilepsy**. With the exception of mild analgesics, however, these drugs cannot be used as preventive treatment; they are taken only when an acute attack begins. Abortive medications are categorized into four major groups.

SELECTIVE SEROTONIN RECEPTOR (5-HT1) AGONISTS Selective serotonin receptor agonists have been used to treat migraines since 1991. They work by activating serotonin receptors in the brain, which block an inflammatory process that affects the blood vessels in the head and leads to a leakage of blood plasma through the vessel walls. Some researchers think that the serotonin receptor agonists also reduce the pain of migraine by slowing down the firing of nerve cells in pain-sensitive parts of the head. These drugs, which are also known as triptans or 5-hydroxytryptamine 1B agonists, are effective in treating about 70% of migraine patients. Sumatriptan (Imitrex) is the prototype of this class of medications.

Second-generation triptans include such drugs as eletriptan (Relpax), naratriptan (Amerge), rizatriptan (Maxalt), almotriptan (Axert), frovatriptan (Frova), and zolmitriptan (Zomig). The second-generation triptans were developed to increase the speed of the drug's absorption through the digestive tract and thus relieve the patient's pain more rapidly. All the triptans are prescribed for moderately severe or severe migraines; one, sumatriptan, is available as a nasal spray or injection for patients with severe vomiting. One major drawback of the triptans, however, is that moderate-to-severe headache pain tends to recur within 24 hours of the first dose.

ERGOT ALKALOIDS Ergot alkaloids are an older group of drugs that include such compounds as ergotamine tartrate (Ergostat) and dihydroergotamine (DHE-45, Migranal). These drugs are derived from ergot, a compound produced by a fungus (*Claviceps purpurea*) that grows on rye plants. The medications work by causing the blood vessels in the head to constrict or narrow, which counteracts the dilation of the blood vessels that causes pain. Some medications in this group are combinations of ergotamine tartrate and caffeine (Cafergot, Ercaf); the caffeine intensifies the vasoconstrictive effect of the alkaloid. Like the triptans, the ergot alkaloids are used to treat moderate-to-severe migraines. They are not prescribed as frequently as they once were, however, because of the severity of their side effects and because they cannot be given to patients with coronary artery disease or other vascular disorders.

ANALGESICS Analgesics in general are medications given to relieve pain. These drugs are used to treat patients who have infrequent migraine headaches, or who cannot be treated with triptans. There are two main types of analgesics used as acute treatment for migraines, nonsteroidal anti-inflammatory drugs, or NSAIDs, and combination analgesics. NSAIDs include aspirin, naproxen (Naprosyn), diclofenac (Voltaren, Cataflam), ibuprofen (Advil, Motrin), flurbiprofen (Ansaid), ketorolac (Toradol), and ketoprofen (Orudis). Combination analgesics include butalbital plus acetaminophen (Fioricet), butalbital plus aspirin (Fiorinal), and isometheptene plus acetaminophen and **dichloralphenazone** (Midrin).

As of 2004, doctors disagree about the use of opioid (drugs that are or act like narcotics) analgesics to treat migraine pain. On the one hand, opioids are stronger

Key Terms

Analgesic A type of drug given to relieve pain.

Aneurysm A blood-filled sac formed by the dilation of a blood vessel, usually caused by a weakness in the vessel wall.

Anticonvulsant A type of drug given to prevent or relieve seizures. Anticonvulsants are also known as antiepileptics.

Antiemetic A type of drug given to stop vomiting.

Aura A group of visual or other sensations that precedes the onset of a migraine attack.

Basilar migraine A type of migraine with aura that involves the basilar artery at the base of the brain. It occurs most commonly in young women, and may include vision problems, confusion, and loss of consciousness as well as headache.

Comorbid A term used to refer to a disease or disorder that is not directly caused by another disorder but occurs at the same time.

Ergot A compound produced by a fungus that grows on rye plants. It is used in the production of some abortive antimigraine drugs.

Gangrene The death of tissue caused by loss of blood supply. Gangrene is a serious potential side effect of taking ergot alkaloids.

Hemiplegic migraine Migraine accompanied by temporary paralysis on one side of the body.

Papilledema Swelling of the optic disk inside the eye, often caused by increased pressure inside the head.

Primary headache A headache that is not caused by another disease or medical condition. Migraine headaches are one type of primary headache.

Prophylaxis A measure taken to prevent disease or an acute attack of a chronic disorder.

Rebound headache A type of primary headache caused by overuse of migraine medications or pain relievers. It is also known as analgesic abuse headache.

Serotonin syndrome A potentially fatal drug interaction caused by combining drugs that raise the level of serotonin in the patient's nervous system to dangerously high levels. The symptoms of serotonin syndrome include shivering, overreactive reflexes, nausea, low-grade fever, sweating, delirium, mental confusion, and coma.

Status migrainosus The medical term for an acute migraine headache that lasts 72 hours or longer.

Vasoconstrictive Causing a blood vessel to become narrower, thus decreasing blood flow.

painkillers than NSAIDs or butalbital. On the other hand, they often make the patient quite drowsy or sedated, and they have a high potential for overuse and dependence. Most doctors, however, consider opioids combined with other analgesics—for example, compounds such as oxycodone plus acetaminophen (Percocet) or aspirin with codeine—to be safe for patients with infrequent migraines who can rest if they feel drowsy. Some doctors will prescribe a synthetic opioid known as butorphanol in the form of a nasal spray (Stadol NS) for use as rescue therapy if the patient's usual abortive drug fails to stop an acute attack; this spray, however, is habit forming and is presently classified as a controlled drug.

ANTIEMETICS Antiemetics are medications given to stop vomiting. These may be beneficial if the patient's headaches are often accompanied by nausea and vomiting. The doctor may also prescribe them to enhance the absorption of other medications taken by mouth, because migraines cause the digestive tract to slow down. The most common antiemetics prescribed for migraine patients are droperidol (Inapsine), metoclopramide (Reglan), and prochlorperazine (Compazine). Prochlorperazine can be given intravenously, by rectal suppositories, or by intramuscular injection if the patient cannot take the drug by mouth.

Prophylactic medications

There are seven major categories of drugs given for migraine prophylaxis.

ANTICONVULSANTS **Anticonvulsants**, which are also called **antiepileptic drugs**, are considered first-line preventive treatment for migraine. These drugs work by enhancing the neurotransmission of gamma amino-butyric acid, or GABA. GABA is an amino acid that slows down or inhibits the transmission of nerve impulses in the **central nervous system**. Valproic acid (Depakote, divalproex sodium) is the most commonly used anticonvulsant in migraine treatment, and has been shown to reduce migraine frequency by 50%.

Other anticonvulsants that have been used in migraine prophylaxis are **gabapentin** (Neurontin) and **topiramate**

(Topamax). Both drugs are reported to be effective in 50–55% of migraine patients.

BETA-BLOCKERS Beta-blockers are widely prescribed as migraine prophylaxis; they are reported to help 50–70% of patients. The only beta-blockers that have been approved by the Food and Drug Administration (FDA) for migraine therapy, however, are propranolol (Inderal) and timolol (Blocadren). Other beta-blockers that have been used to treat migraines without FDA approval include nadolol (Corgard), atenolol (Tenormin), and metoprolol (Lopressor, Toprol-XL). It is thought that these drugs reduce the frequency of migraines by preventing the blood vessels in the head from dilating and by increasing the release of oxygen to the surrounding tissues. It takes about two months of treatment, however, for patients to benefit from beta-blockers.

CALCIUM CHANNEL BLOCKERS The most common drug in this category used in preventive treatment is verapamil (Calan, Covera, Verelan). Studies of the effectiveness of verapamil, however, have shown mixed results. It appears to be most useful in treating patients who cannot take beta-blockers or have been diagnosed with coexisting hypertension.

TRICYCLIC ANTIDEPRESSANTS (TCAS) The tricyclic antidepressants are another group of drugs used in migraine prophylaxis. Amitriptyline (Elavil) has been shown in well-conducted studies to benefit migraine patients, although doxepin (Sinequan), nortriptyline (Aventyl), and protriptyline (Vivactil, Triptil) have also been used for preventive treatment. TCAs are often given to patients who are suffering from insomnia or depression as well as migraine. Their chief drawback is their long-term side effects, particularly weight gain.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) These drugs are not as effective for migraine prophylaxis as the tricyclic antidepressants, but a few small-scale studies have shown that they benefit some patients. The SSRIs include such drugs as fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil).

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) Nonsteroidal anti-inflammatory medications can be used for migraine prophylaxis as well as abortive treatment; however, these drugs have a higher risk of adverse effects—particularly in the digestive tract—when they are used preventively.

SEROTONIN ANTAGONISTS Methysergide (Sansert) is a synthetic ergot alkaloid that has been used as prophylactic treatment; its primary disadvantage is the number and severity of possible side effects. Cyproheptadine (Periactin), an antihistamine, is sometimes used for migraine prophylaxis in children even though there is little evidence of its effectiveness.

Complementary and alternative medications (CAM)

There are two herbal preparations used as migraine preventives as of 2004. Feverfew (*Tanacetum parthenium*) is an herb related to the daisy that is traditionally used in England for migraine prophylaxis. Feverfew contains a compound called parthenolide, which is thought to counteract the inflammatory reaction in the cerebral blood vessels that precedes an acute migraine attack.

The second herb is butterbur root (*Petasites hybridus*), which is the active ingredient in Petadolex, a preparation that has been sold in Germany since the 1970s as a migraine preventive. Petadolex has been available in the United States since December 1998. Butterbur root contains compounds known as petasines, which relieve inflammation as well as counteract the spasmodic contraction of blood vessels that occurs during a migraine attack. Researchers reported in 2003 that Petadolex reduced the frequency of migraine attacks in subjects in a multicenter trial by 60%. The butterbur root preparation has fewer and milder side effects than conventional prophylactic drugs; it also appears to be safe for children and adolescents.

It should be noted that, contrary to the popular notion, herbals are drugs that can and do cause side effects; they are not the medical "free ride" many people seem to think they are. They should thus be used with care and caution and in consultation with a physician.

Recommended dosage

Abortive medications

Abortive medications are taken at the first sign of a migraine attack. About 20% of migraine patients have headaches preceded by an aura, or brief period of warning symptoms that may include seeing flashing or shimmering lights, temporary loss of vision, difficulty speaking, weakness in an arm or leg, or tingling sensations in the face or hands. Most patients with migraines, however, do not have auras but experience the headache pain as building gradually over an hour or two. Abortive medications include triptans, ergot alkaloids, NSAIDs, combination analgesics, and antiemetics.

TRIPTANS Sumatriptan is available as a nasal spray or injection as well as in tablet form; the other triptans are available only as tablets. (Sumatriptan should be injected only into the areas the manufacturer recommends; that is, injections into the arms are not recommended because they are much more painful than injections into thighs, the recommended site.) The patient may take 25–100 mg of sumatriptan by mouth at the beginning of an attack, with a second dose of up to 100 mg after two hours. Additional

doses may be taken at two-hour intervals, up to 300 mg daily. With the nasal spray, 5–20 mg may be inhaled into one nostril, with a second dose after two hours if the headache returns. Injections of sumatriptan contain 6 mg per dose and may be given twice, at least one hour apart. With zolmitriptan, the initial dose is 2.5–5 mg by mouth, with a second dose at any time after two hours following the first dose; the maximum daily dose is 10 mg. The initial dose of naratriptan is 2.5 mg, which can be repeated four hours after the first dose. Rizatriptan is taken by mouth in an initial dose of 5–10 mg, which may be repeated every two hours up to a maximum daily dose of 30 mg. Almotriptan is taken in an initial dose of 6.25–12.5 mg, which may be repeated only once. Frovatriptan is taken only once, in a dose of 2.5 mg at the beginning of the headache. Eletriptan is taken in an initial dose of 20–40 mg, which may be repeated once after two hours; the maximum daily dose is 80 mg.

ERGOT ALKALOIDS Ergotamine tartrate is taken by mouth in a 1 mg tablet at the beginning of the attack, with additional doses every 30 minutes as needed; total dosage must not exceed 6 mg per attack. Rectal suppositories containing 1–2 mg of the drug may be used at the onset of the headache and repeated every half hour, not to exceed 4 mg per attack. Dihydroergotamine mesylate (DHE-45) may be given by injection in an initial dose of 0.5–1 mg, to be repeated at hourly intervals up to a maximum dose of 3 mg. The drug may also be given intravenously for more rapid relief.

NSAIDS The patient may take an initial dose of 900–1,000 mg of aspirin, with the dose repeated every 1–2 hours as needed. Ibuprofen may be taken by mouth in an initial dose of 400–1,200 mg, to be repeated with a second dose of 400–800 mg in 1–2 hours. The maximum daily dose of ibuprofen is 3,200 mg. Naproxen may be taken in an initial dose of 825 mg, with additional doses of 550 mg after 1–2 hours as needed. Ketorolac may be taken in 10 mg doses every four hours, not to exceed 40 mg per day. Ketorolac should not be used for longer than five days.

COMBINATION ANALGESICS Fiorinal may be taken in an initial dose of 1–2 tablets by mouth every four hours as needed, up to six tablets per day. Midrin is taken in an initial dose of two capsules, then one capsule every hour until the headache is relieved; not to exceed five capsules in a 12-hour period.

ANTIEMETICS Droperidol is given by injection in a dose of 2.5–10 mg. Metoclopramide is given by mouth or by injection in a dose of 10–20 mg. Prochlorperazine may be taken by mouth in a dose of 5–10 mg every 4–6 hours; by injection in a dose of 5–10 mg every 3–4 hours up to a maximum dose of 40 mg per day; or by rectal suppositories in a dose of 25 mg twice a day.

Prophylactic medications

Dosages for these medications vary somewhat depending on the individual patient's response. The general principle of management is to begin with the lowest effective dose of the particular drug, increasing it gradually until the patient begins to benefit or until the maximal safe dose is reached.

ANTICONVULSANTS Valproic acid is given in an initial dose of 150–250 mg per day, gradually increasing to a maximum dose of 1,500 mg per day. Gabapentin is given in an initial dose of 300 mg per day, gradually increasing up to a maximum dose of 2,400 mg per day.

BETA-BLOCKERS Beta-blocker doses are as follows:

- propranolol: initial dose of 40 mg twice a day, up to a maximum of 320 mg per day
- timolol: 10 mg per day initially, maximum daily dose 30 mg
- nadolol: 20 mg four times per day initially, up to a maximum of 240 mg per day
- metoprolol: 50 mg twice a day initially, not to exceed 200 mg per day

CALCIUM CHANNEL BLOCKERS Verapamil is given in an initial dose of 40 mg three times a day; maximal daily dose is 480 mg.

TCAS Amitriptyline, doxepin, and nortriptyline are given by mouth at bedtime in an initial dose of 10–25 mg, with the dose increased by 10–25 mg every two weeks up to a maximum dose of 150–175 mg. Protriptyline is given in an initial dose of 15 mg, up to a maximum daily dose of 40 mg.

SSRIS Fluoxetine is taken on waking in an initial dose of 10 mg, which may be increased every two weeks up to a maximum daily dose of 60 mg. Sertraline may be given in an initial dose of 50 mg per day, increased at weekly intervals up to a daily dose of 200 mg. Paroxetine may be started at a dose of 10 mg per day and gradually increased up to a daily dose of 50 mg.

NSAIDS Naproxen may be taken in a dose of 275 mg three times daily or a dose of 550 mg twice daily.

SEROTONIN ANTAGONISTS Methysergide is given in a daily dose of 2 mg per day, gradually increasing to a maximum of 8 mg per day. Cyproheptadine is given in an initial dose of 2 mg, increasing every three days to a maintenance dose of 8–32 mg per day.

CAM preparations

The recommended dosage of feverfew as a migraine preventive is 125 mg daily of freeze-dried powdered leaf; patients should start out with a lower dose and work up gradually to 125 mg. The dried leaf is available in capsule

form. Petadolex is sold as soft gelatin 50-mg capsules. The recommended dose for migraine prophylaxis is 150 mg daily for adults and 50–100 mg daily for children and adolescents.

Precautions

Diagnosis

Migraine headaches are classified by the International Headache Society (IHS) as primary headaches, which means that they are not caused by other diseases or disorders. Severely painful headaches, however, are not necessarily migraines and may be caused by other conditions, some of them potentially life-threatening. Headaches caused by other disorders are known as secondary headaches. They may be associated with space-occupying brain tumors, meningitis, **stroke**, head trauma, pain referred from the neck or jaw, or a ruptured aneurysm inside the head. Patients with any of the following signs or symptoms should be carefully evaluated, including those who have been previously diagnosed with and treated for migraines:

- The patient is not responding to appropriate treatment for the headaches.
- The headache is severe and is sudden in onset. Although a small percentage of patients with migraines have what are called "crash" or "thunderclap" migraines, most migraine headaches build up slowly over a period of one or two hours.
- The headache differs from the usual pattern of the patient's migraines.
- The patient has described the present headache as "the worst ever."
- The patient has abnormal neurological signs or symptoms such as a swollen optic disk (papilledema), seeing double, loss of sensation, or alteration of consciousness.

Some patients may be suffering from another type of primary headache in addition to migraines. It is possible, for example, for people to have both chronic tension headaches and migraines, and each type may require separate treatment.

A third consideration is whether the patient has been diagnosed with any comorbid disorders. The doctor must take such conditions as hypertension, depression, epilepsy, heart problems, and other disorders into account when selecting antimigraine medications for the patient.

Patient education

Effective use of antimigraine drugs depends on good communication between the patient and the doctor. Migraine headaches vary considerably in their frequency, severity, and associated symptoms; in addition, people vary in their responses to a given medication. It may take some months of trial and error to work out the best treatment regimen for an individual patient with respect to the specific drugs used and their dosage levels. Patients should be advised to give each medication a fair trial (usually about two months) before deciding that the drug does not work for them. In addition, they should be told that some drugs—particularly the beta-blockers—must be taken for several months before the patient can expect to see results. Finally, patients who are taking abortive medications or opioid analgesics should be warned about the risks of dependence or rebound headaches from overuse of these drugs.

Rebound headaches

Rebound headaches are also known as analgesic abuse headaches. They result from overuse of abortive drugs, most commonly the ergot alkaloids. According to one survey of primary care physicians, about 20% of patients treated for migraine experience rebound headaches. These headaches have the following characteristics:

- They occur every day or almost every day.
- They are brought on by a very low level of physical or intellectual activity.
- The patient has been using abortive migraine medications more than two days a week.
- The patient has been using the medications above the recommended dosage level.
- The patient develops withdrawal symptoms if the medications are stopped abruptly.
- The headaches are accompanied by restlessness, depression, irritability, difficulty concentrating, or memory problems.

Status migrainosus

About 40% of all migraine attacks do not respond to treatment with triptans or any other medication. If the headache lasts longer than 72 hours (a condition known as status migrainosus), the patient may be given narcotic medications to bring on sleep and stop the attack. Patients with status migrainosus are often hospitalized because they are likely to be dehydrated from severe nausea and vomiting.

Special populations

CHILDREN Migraines in children are not unusual; a study published in 2003 reported that 10% of children between the ages of six and 20 suffer from migraines, and that they lose, on average, almost two more weeks of school each year than their classmates. Treatment of children's migraines, however, is complicated by the fact that

most effective medications—whether abortive or prophylactic—have not been adequately evaluated for use in children or are not recommended for children. As of late 2003, however, there have been few rigorous studies of antimigraine drugs in children; much more research is needed in this area. Cyproheptadine, which is the drug most often prescribed for children's migraines, is not always effective; preventive therapy with propranolol, one of the tricyclics, or an anticonvulsant medication appears to be safe as well as effective in children and adolescents.

PREGNANCY AND LACTATION Pregnancy and lactation complicate migraine treatment in that many antimigraine drugs should not be taken by pregnant or nursing women. These include the ergot alkaloids, anticonvulsants, tricyclic antidepressants, methysergide, and the SSRIs. In addition, NSAIDs should not be used during the last trimester of pregnancy.

OLDER ADULTS Some antimigraine medications are not recommended for patients over the age of 60–65, particularly the triptans and the ergot alkaloids. Older adults may also be more susceptible to the side effects of NSAIDs and TCAs.

Patient dissatisfaction

Antimigraine medications as a group have a high rate of reported patient complaints. One reason is the high cost of some of these drugs; another is dosing difficulties. One survey of migraine patients reported the following reasons for discontent with drug therapy: pain relief took too long (87%); pain was only partly relieved (84%); the medication sometimes failed to work (84%); headache returned within a day (71%); the drug had too many side effects (35%). Because of the limitations of antimigraine medications, many doctors advise their patients to supplement drug therapy with such other measures as adequate sleep and **exercise**, a low-fat diet, quitting smoking, stress management techniques, or cognitive-behavioral psychotherapy.

It is also worth noting that managed care (the health insurance industry) accounts for some patient dissatisfaction. Most health plans strictly limit coverage to an "average" number of doses of triptans per month. Patients who need more doses either must have their doctors try to get the insurance company to authorize them, or the patients must pay the full price of the extra medication themselves.

It is possible that new ways of thinking about migraine will lead to improved antimigraine medications in the future. Migraine headaches are no longer regarded as "just headaches," but as features of a largely inherited chronic disorder that increases the risk of long-term damage to the brain. The use of MRIs and other new imaging techniques may eventually answer some unresolved questions about effective migraine treatment.

Side effects

Abortive medications

In addition to the risk of rebound headaches, possible side effects of abortive medications include:

- Triptans: May cause tingling, numbness, sensations of heat or flushing, **dizziness**, drowsiness, or pain at the injection site.
- Ergot alkaloids: May cause nausea, vomiting, diarrhea, weakness, itching, cold skin, thirst, tingling sensations, and severe muscle cramps; also may cause severe rebound headaches. The most serious potential side effect of ergot alkaloids, however, is gangrene—the death of tissue in the fingers or toes due to constriction of the smaller blood vessels and loss of blood supply to the tissue.
- NSAIDs: May cause heartburn, nausea, and vomiting; may also cause drowsiness, dry mouth, or mild depression.
- Combination analgesics: Midrin has been reported to cause temporary dizziness and skin rashes. The most common side effects of Fioricet and Fiorinal include lightheadedness, nausea, and sleep disturbances. Also, the narcotics and barbiturates (Fiorinal) have the potential for drug abuse and dependence.
- Antiemetics: May cause anxiety, dizziness, low blood pressure, sedation, nausea, dry mouth, and restlessness.

Prophylactic medications

The following side effects have been reported for prophylactic medications:

- Anticonvulsants: Valproic acid may cause indigestion and vomiting, but hair loss, weight gain, tremor, hallucinations, and liver damage have also been reported. Gabapentin and topiramate are associated with drowsiness, dizziness, tingling sensations, diarrhea, altered taste, and **fatigue**.
- Beta-blockers: May cause dizziness, fatigue, nausea, memory problems, sexual dysfunction, bradycardia (slowed heartbeat), and hallucinations.
- Calcium channel blockers: May cause low blood pressure and constipation; in addition, the headaches may grow worse for the first few weeks of treatment.
- TCAs: May cause dry mouth, constipation, difficulty urinating, increased appetite, loss of sexual desire, heavy sweating, agitation, tremor, and **seizures**.
- SSRIs: May cause loss of appetite or sexual desire, anxiety, drowsiness, nausea, or flulike symptoms.
- NSAIDs: More likely to cause digestive problems when used for prophylaxis than when used for acute treatment.
- Serotonin antagonists: Methysergide has been reported to cause insomnia, abdominal pain, diarrhea, nausea,

heartburn, increased sensitivity to cold, and depression. Cyproheptadine may cause dry mouth, increased appetite, and weight gain.

CAM preparations

Feverfew should not be used by pregnant women because it may stimulate uterine contractions. It may also cause mild acid indigestion in some people. Patients who use fresh plant leaves rather than standardized preparations may experience mouth ulcers or temporary loss of taste. Also, patients who use fresh plant leaves cannot regulate their doses: one time they may get too much of the drug and another time not enough.

The side effects reported for preparations made from butterbur root are rare, but include an unpleasant taste in the mouth, belching, and a mild skin rash in some patients.

Interactions

Patients who are taking any antimigraine drug should make sure to give the doctor a list of all other medications that they take on a regular basis, including over-the-counter pain relievers, herbal preparations, and any special herbal or medicinal teas or extracts.

Abortive medications

The following interactions have been reported for abortive medications:

- Triptans: All the triptans narrow coronary arteries by 10–20% and will intensify the effects of other vasoconstrictive drugs, including the ergot alkaloids and drugs given for vascular disorders. With the exception of naratriptan, the triptans cannot be taken together with MAO inhibitor antidepressants because of the risk of a rapid and dangerous rise in blood pressure. Rizatriptan has been reported to interact with the beta-blocker propranolol.
- Ergot alkaloids: Cannot be taken together with the triptans. Ergot alkaloids should not be taken together with methysergide because of an additive effect. Should not be taken together with other vasoconstrictive drugs (including beta-blockers, some acid-reducing drugs, some antibiotics, and some antifungal drugs) because of the increased risk of gangrene.
- NSAIDs: These drugs tend to prolong bleeding time and should be used cautiously by patients taking blood-thinning medications. Alcoholic beverages increase the risk of gastric ulcers or bleeding from the use of NSAIDs. In addition, patients should not take more than one NSAID at a time.
- Combination analgesics: These drugs should not be used together with MAO inhibitors or other drugs that contain acetaminophen. They will intensify the actions of other drugs that may cause drowsiness, including alcohol, TCAs, antihistamines, sedatives, and muscle relaxants.
- Antiemetics: Should not be taken together with alcohol (intensifies central nervous system depression), tricyclic antidepressants (lowers blood pressure), or **phenobarbital**. Patients taking anticonvulsants may need to have their dosage increased if they are given an antiemetic.

Prophylactic medications

The following interactions have been reported for prophylactic medications:

- Anticonvulsants: Valproic acid will intensify the effects of other anticonvulsants, barbiturates, alcohol, and antidepressants. It interacts with aspirin and heparin to increase the risk of spontaneous bleeding. Gabapentin intensifies the effects of morphine, but is less effective when taken together with antacids.
- Beta-blockers: Antacids decrease the absorption of beta-blockers. Cimetidine is reported to intensify the actions of beta-blockers. Beta-blockers may interact with insulin or other diabetes medications to produce high blood sugar levels. They should not be taken together with MAO inhibitors because of the risks of severe high blood pressure. Cocaine also increases the risks of high blood pressure or other heart problems in patients taking beta-blockers.
- Calcium channel blockers: Verapamil may cause low blood pressure or dizziness if taken together with alcohol. It should not be taken with beta-blockers because of a risk of congestive heart failure or slowed heartbeat. Verapamil also intensifies the effects of cyclosporine and lithium.
- TCAs: Should not be taken together with barbiturates, alcohol, sleeping medicines, or sedatives because they intensify central nervous system depression. They may also intensify the effects of certain antibiotics and antifungal medications. They may interact with bupropion to produce seizures. TCAs should never be taken with MAO inhibitors or SSRIs because of the risk of serotonin syndrome, a potentially fatal condition marked by fever, rapid changes in blood pressure, sweating, hyperreactive reflexes, **delirium**, nausea, vomiting, and coma. Serotonin syndrome takes its name from the overly high levels of serotonin in the patient's nervous system that are produced by these drug combinations.
- SSRIs: Should never be taken together with other antidepressant medications because of the risk of serotonin syndrome. They may increase the patient's drowsiness if taken together with antihistamines, sleep medications, opioid analgesics, and muscle relaxants. Patients taking insulin or other diabetes medications may need to have their dosage adjusted if they are also taking an SSRI.

SSRIs should not be taken together with herbal preparations used as mild tranquilizers, particularly compounds containing valerian or St. John's wort.

- Serotonin antagonists: Methysergide should not be taken together with ergot alkaloids or triptans because it intensifies their vasoconstrictive action. Patients taking this drug should give up smoking for the same reason. In addition, methysergide has been reported to counteract the pain-relieving effectiveness of opioid analgesics.

CAM preparations

Feverfew should not be used with anticoagulants (blood thinners), as it intensifies their effects. It may also interfere with the body's absorption of iron. NSAIDs reduce the effectiveness of feverfew. No interactions with prescription drugs have been reported for butterbur root preparations.

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American Council for Headache Education (ACHE). 19 Mantua Road, Mt. Royal, NJ 08061. (856) 423-0258; Fax: (856) 423-0082. achehq@talley.com. <http://www.achenet.org>.

International Headache Society (IHS). Oakwood, 9 Willowmead Drive, Prestbury, Cheshire SK10 4BU, United Kingdom. +44 (0) 1625 828663; Fax: +44 (0) 1625 828494. rosemary@ihs.u-net.com. <http://216.25.100.131>.

National Headache Foundation. 820 North Orleans, Suite 217, Chicago, IL 60610. (773) 525-7357 or (888) NHF-5552. <http://www.headaches.org>.

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Rebecca Frey, PhD

Antiparkinson drugs

Definition

Antiparkinson drugs are medicines used to reduce the symptoms of **Parkinson's disease**.

Purpose

Parkinson's disease (PD) is a neurodegenerative disorder that affects movement. In PD, cells in a part of the brain called the substantia nigra die off. The normal function of these cells is to regulate the action of other cells in other brain regions by releasing a chemical called dopamine. When substantia nigra cells release dopamine, the dopamine attaches to dopamine receptors on the other cells, which influences them in various ways depending on the specific type of cell. The actions of these cells work in concert with other systems that influence movement. When all cells are working properly together, the end result is controlled, fluid movement.

When substantia nigra cells die off, however, as they do in PD, less dopamine is available for release. Consequently, the cells that depend on receiving dopamine are not properly regulated. The result is an imbalance in movement control that causes slowed movements, stiffness, and tremor—the classic signs of PD.

Antiparkinson drugs attempt to restore the balance through one of several mechanisms, depending on drug type. The most effective drugs, called dopaminergic drugs, replace dopamine, or mimic its action in the brain. Another group of drugs delays the breakdown of dopamine, thus increasing the level in the brain. Other drugs act on the other systems that influence movement, preventing them from being too active.

Key Terms

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

Dyskinesia Impaired ability to make voluntary movements.

Orthostatic hypotension A drop in blood pressure that causes faintness or dizziness and occurs when an individual rises to a standing position. Also known as postural hypotension.

Substantia nigra One of the movement control centers of the brain.

Description

Levodopa

Levodopa, also called L-dopa, is the most widely prescribed antiparkinson medication; almost all PD patients eventually receive levodopa. It is a chemical related to dopamine, and it is converted into dopamine within the brain. Dopamine itself cannot cross the barrier between the bloodstream and the brain, while levodopa can. This chemical form of dopamine works in the place of the natural dopamine that is lost due to the disease process.

Levodopa is chemically similar to amino acids, a type of molecule the body needs and absorbs from foods high in protein. In the digestive system, a carrier picks up the levodopa and transports it into the bloodstream. The same transport process occurs between blood and brain. Meals high in protein may interfere with absorption of levodopa from the digestive tract or from the blood into the brain. Patients may be advised to avoid high-protein meals too close to the time they take levodopa.

Once in the bloodstream, levodopa can be converted to dopamine. This is a problem because, as noted, dopamine cannot be taken into the brain. Additionally, dopamine in the periphery (that is, outside the brain) causes nausea, vomiting, and other adverse effects. To minimize these side effects, levodopa is always given with another drug that inhibits its conversion to dopamine in the periphery. In the United States, this drug is carbidopa. Levodopa and carbidopa are available in a single tablet, with doses adjusted for maximum benefit. However, it should be noted that peripheral dopamine is not always undesirable: it has important metabolic functions, including maintaining blood pressure.

Within the brain, levodopa is taken up by remaining substantia nigra cells, converted to dopamine, and released normally. The extra dopamine provided by the levodopa allows the brain to maintain normal movements, even in the face of dying substantia nigra cells. There are limitations because, as the disease progresses and more cells die, it becomes difficult for the few remaining cells to maintain normal function, even with extra dopamine.

Recommended dosage

Levodopa treatment is usually started when the patient's symptoms begin to interfere with daily living or the ability to work. Initial dosage is typically 200–600 mg of levodopa per day, taken in tablets with carbidopa. This amount of drug is contained in 2–6 tablets, which are taken at regular intervals during the day. The dose is adjusted to the point at which symptoms are well controlled. As the disease progresses, the dose is increased.

Precautions

Levodopa itself is not well tolerated, which is why it is combined with carbidopa. Carbidopa decreases peripheral metabolism of levodopa, which allows for lower doses of levodopa and less-severe side effects. The combination is a safe and well-tolerated medication for patients with

Parkinson's disease. Levodopa may cause **orthostatic hypotension**, or low blood pressure upon standing. Patients with low blood pressure or who are susceptible to orthostatic hypotension should be cautious when starting treatment or increasing the dose.

Levodopa can cause sudden and unexpected extreme drowsiness, which some physicians term "sleep attacks." Currently, no reliable predictive criteria have been developed to determine which patients are susceptible. Patients starting levodopa should be aware of this possibility, and discuss with their physician how best to modify their activities (such as driving) to guard against injury in the event of such an incident.

Patients who have had myocardial infarction (heart attack) or other heart abnormalities should be monitored carefully when beginning levodopa treatment.

Side effects

Early on in the disease, levodopa can cause nausea, vomiting, orthostatic hypotension, and drowsiness. Nausea and vomiting typically stop being problems within several months of treatment.

Long-term use of levodopa in PD often leads to dyskinesias, or unwanted and uncontrolled movements. Dyskinesias appear as writhing, shaking, or twitching movements that may involve a small or large part of the body. Early in the disease, lowering the dose of levopoda can help control dyskinesias, but later on, the lower dose leads to significant loss of movement. Balancing the control of symptoms with the control of dyskinesias is a difficult and frustrating challenge for both patient and physician.

Long-term levodopa use can also lead to psychotic symptoms, including hallucinations, vivid and disturbing dreams, paranoia, and confusion.

Interactions

Patients who are taking drugs called nonselective MAO (monoamine oxidase) inhibitors should discontinue these drugs at least two weeks before beginning levodopa. MAO inhibitors are used to treat **depression**. A selective MAO-B inhibitor, such as selegiline, may be taken, and indeed is often prescribed for use in Parkinson's disease.

Description

Dopamine agonists

Dopamine agonists are drugs that mimic the effect of dopamine by stimulating the same cells as dopamine. They have several theoretical advantages over levodopa in the treatment of PD: dopamine agonists do not require uptake and release by substantia nigra cells; they do not compete with amino acids for transport, and so high-protein meals are not a problem; and the effect of an individual dose lasts longer.

One of the most significant advantages of the dopamine agonists is their ability to delay the onset of dyskinesias when used instead of levodopa at the start of disease. Patients who take a dopamine agonist instead of levodopa for the first 1–2 years tend to develop dyskinesias many months later than those who begin on levodopa. On the other hand, dopamine agonists are not quite as effective as levodopa at controlling other PD symptoms, and may cause more confusion in elderly patients. For this reason, common advice for elderly patients is to begin on levodopa, with the expectation that dyskinesias are less likely to be a serious problem within the treatment timeframe, while younger patients should begin on a dopamine agonist to delay dyskinesias within a much longer timeframe of treatment.

Dopamine agonists prescribed for PD in the United States include pramipexole, ropinirole, pergolide, and bromocriptine. Approval of another, apomorphine, was expected in early 2004. Unlike the others, apomorphine is injected and has a very short duration of action. It is intended for intermittent (not continuous) use as a treatment for emergent symptoms while waiting for the effect of other medications to begin.

Recommended dosage

There are half a dozen dopamine agonists available in oral forms for treatment of PD. The individual dosage and schedule for each vary. In each case, a low dose is used to begin with, with a gradual adjustment over several weeks to achieve the optimum level of symptomatic benefit.

Precautions

Like levodopa, the dopamine agonists may cause sudden and unpredictable episodes of extreme drowsiness.

Side effects

Long-term use of dopamine agonists can cause nausea, vomiting, orthostatic hypotension, and psychotic symptoms, including hallucinations, vivid and disturbing dreams, paranoia, and confusion. While the risk for developing dyskinesias is lower with dopamine agonists, their long-term use does lead to this complication in many patients.

Description

COMT inhibitors

COMT (**Catechol-O-MethylTransferase**) **inhibitors** restrict the action of an enzyme that converts levodopa to dopamine in the periphery (outside the brain). This allows more of the levodopa to reach the brain. In this way, a

COMT inhibitor increases the effectiveness of a dose of levodopa. A COMT inhibitor cannot be used by itself, but must be administered with levodopa.

Recommended dosage

There are two COMT inhibitors approved for use in PD. Entacapone is dosed at 200 mg with each dose of levodopa. Tolcapone is dosed at either 100 or 200 mg three times per day.

Precautions

Tolcapone has been associated with liver damage in a small number of patients, which has led to death in three patients. Tolcapone is only approved for use by patients for whom other therapies are not providing adequate relief of symptoms.

COMT inhibitors increase the effectiveness of levodopa, as well as levodopa's side effects. Consequently, the same precautions apply for use of COMT inhibitors as for levodopa.

Side effects

COMT inhibitors can cause diarrhea. They also can increase the severity of levodopa's side effects, including orthostatic hypotension, hallucinations, and dyskinesias.

Description

MAO-B inhibitors

MAO-B inhibitors restrict the action of monoamine oxidase B, an enzyme that breaks down levodopa in the brain. Thus, an MAO-B inhibitor prolongs the effectiveness of dopamine, as well as a dose of levodopa. The only MAO-B inhibitor in widespread use for Parkinson's disease is selegiline, also called deprenyl.

Selegiline is often used in the early stages of PD, before other drugs, based on its mild symptomatic benefit. It is also often prescribed based on the possibility it may be neuroprotective—that is, it may help slow the death of neurons (brain cells) in the substantia nigra. While some experiments have suggested this may be true, others have shown no effect, and as of late 2003, there was no widespread consensus that selegiline had any effect in PD other than on symptoms.

Recommended dosage

Selegiline is usually prescribed at 5 mg twice daily.

Precautions

At doses higher than those used in PD, selegiline in combination with certain foods can lead to dangerously high blood pressure. These foods include aged cheeses, fermented beverages such as beer or wine, and smoked or pickled meats. This effect is also seen very rarely in patients taking the recommended dose for PD.

Selegiline should not be used with meperidine. Use with other narcotics should only be with the express approval of the patient's physician.

Side effects

Selegiline can cause side effects similar to levodopa, and when taken with levodopa, may worsen those effects. No reports of sudden drowsiness have been published for PD patients on selegiline alone.

Interactions

Interaction between selegiline and certain kinds of antidepressants is possible, and patients should consult with their physician before combining these two types of medications.

Description

Amantadine

Amantadine is prescribed for two different purposes in PD. It has a mild symptomatic effect in early PD, and is often prescribed before levodopa for that reason. It also reduces dyskinesias, and may be prescribed late in the disease once this symptom develops.

Recommended dosage

Amantadine is dosed at 200–300 mg per day.

Precautions

Patients with kidney disease or reduced kidney function require a much lower dose of amantadine.

Side effects

Amantadine can cause side effects similar to levodopa, including hallucinations, confusion, and orthostatic hypotension. Amantadine can also cause mottled skin and swelling in the peripheral tissues such as the legs.

Description

Anticholinergics

Anticholinergics were the first class of antiparkinson medications developed, but are used much less now than in the past, due to the availability of improved drugs. Anticholinergics suppress activity of the acetylcholine system in the brain, which is relatively overactive in PD. They are

Key Terms

Asthenia muscle weakness.

Cytomegalovirus (CMV) A type of virus that attacks and enlarges certain cells in the body. The virus also causes a disease in infants.

Herpes simplex A virus that causes sores on the lips (cold sores) or on the genitals (genital herpes).

HIV Acronym for human immunodeficiency virus, the virus that causes AIDS.

Parkinsonism A group of conditions that all have these typical symptoms in common: tremor, rigidity, slow movement, and poor balance and coordination.

Pregnancy category A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but no human studies, or adverse effects in animals, but not in well-controlled human studies. Category C: No adequate human or animal studies, or adverse fetal effects in animal studies, but no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk. Risks outweigh any benefits.

Prophylactic Guarding from or preventing the spread or occurrence of disease or infection.

Retrovirus A group of viruses that contain RNA and the enzyme reverse transcriptase. Many viruses in this family cause tumors. The virus that causes AIDS is a retrovirus.

Shingles An disease caused by an infection with the Herpes zoster virus, the same virus that causes chicken pox. Symptoms of shingles include pain and blisters along one nerve, usually on the face, chest, stomach, or back.

Virus A tiny, disease-causing structure that can reproduce only in living cells and causes a variety of infectious diseases.

mainly effective against tremor and rigidity, and less so against slowed movements.

Recommended dosage

Different anticholinergics are dosed at different levels and frequencies. A dose is chosen that maximizes benefits and minimizes side effects. The dose is gradually increased to avoid worsening side effects.

Side effects

Anticholinergics can cause significant confusion, **delirium**, and hallucinations, especially in older patients. For this reason, they are seldom used in this group. They can also cause constipation and urinary retention.

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ORGANIZATIONS

National Parkinson Foundation. 1501 N.W. 9th Avenue, Miami, FL 33136-1494. (800) 327-4545. mailbox@parkinson.org. <http://www.parkinson.org>.

Richard Robinson

Antiviral drugs

Definition

Antiviral drugs are medicines that cure or control virus infections.

Purpose

Antivirals are used to treat infections caused by viruses. Unlike antibacterial drugs, which may cover a wide range of pathogens, antiviral agents tend to be narrow in spectrum, and have limited efficacy.

Description

Exclusive of the antiretroviral agents used in HIV (**AIDS**) therapy, there are currently only 11 antiviral drugs available, covering four types of virus. Acyclovir (Zovirax), famciclovir (Famvir), and valacyclovir (Valtrex) are

effective against the herpes virus, including herpes zoster and herpes genitalis. They may also be of value in either conditions caused by herpes, such as chicken pox and **shingles**. These drugs are not curative, but may reduce the **pain** of a herpes outbreak and shorten the period of viral shedding.

Amantadine (Symmetrel), oseltamivir (Tamiflu), rimantidine (Flumadine), and zanamivir (Relenza) are useful in treatment of the influenza virus. Amantadine, rimantadine, and oseltamivir may be administered throughout the flu season as preventatives for patients who cannot take influenza virus vaccine.

Cidofovir (Vistide), foscarnet (Foscavir), and ganciclovir (Cytovene) have been beneficial in treatment of cytomegalovirus in immunosupressed patients, primarily HIV-positive patients and transplant recipients. Ribavirin (Virazole) is used to treat respiratory syncytial virus. In combination with **interferons**, ribavirin has shown some efficacy against hepatitis C, and there have been anecdotal reports of utility against other types of viral infections.

As a class, the antivirals are not curative, and must be used either prophylactically or early in the development of an infection. Their mechanism of action is typically to inactivate the enzymes needed for viral replication. This will reduce the rate of viral growth, but will not inactive the virus already present. Antiviral therapy must normally be initiated within 48 hours of the onset of an infection to provide any benefit. Drugs used for influenza may be used throughout the influenza season in high risk patients, or within 48 hours of exposure to a known carrier. Antiherpetic agents should be used at the first signs of an outbreak. Anti-cytomegaloviral drugs must routinely be used as part of a program of secondary prophylaxis (maintenance therapy following an initial response) in order to prevent reinfection in immunocompromised patients.

Recommended dosage

Dosage varies with the drug, patient age and condition, route of administration, and other factors. See specific references.

Precautions

Ganciclovir is available in intravenous injection, oral capsules, and intraoccular inserts. The capsules should be reserved for prophylactic use in organ transplant patients, or for HIV infected patients who cannot be treated with the intravenous drug. The toxicity profile of this drug when administered systemically includes granulocytopenia, anemia, and thrombocytopenia. The drug is in pregnancy category C, but has caused significant fetal abnormalities in animal studies including cleft palate and organ defects. Breast-feeding is not recommended.

Cidofovir causes renal toxicity in 53% of patients. Patients should be well hydrated, and renal function should be checked regularly. Other common adverse effects are nausea and vomiting in 65% or patients, asthenia in 46% and **headache** and diarrhea, both reported in 27% of cases. The drug is category C in pregnancy, due to fetal abnormalities in animal studies. Breast-feeding is not recommended.

Foscarnet is used in treatment of immunocompromised patients with cytomegalovirus infections and in acyclovir-resistant herpes simples virus. The primary hazard is renal toxicity. Alterations in electrolyte levels may cause **seizures**. Foscarnet is category C during pregnancy. The drug has caused skeletal abnormalities in developing fetuses. It is not known whether foscarnet is excreted in breast milk, however the drug does appear in breast milk in animal studies.

Valaciclovir is metabolized to acyclovir, so that the hazards of the two drugs are very similar. They are generally well tolerated, but nausea and headache are common adverse effects. They are both pregnancy category B. Although there have been no reports of fetal abnormalities attributable to either drug, the small number of reported cases makes it impossible to draw conclusions regarding safety in pregnancy. Acyclovir is found in breast milk, but no adverse effects have been reported in the newborn. Famciclovir is similar in actions and adverse effects.

Ribavirin is used by aerosol for treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). When administered orally, the drug has been used in adults to treat other viral diseases including acute and chronic hepatitis, herpes genitalis, measles, and Lassa fever, however there is relatively little information about these uses. In rare cases, initiation of ribavirin therapy has led to deterioration of respiratory function in infants. Careful monitoring is essential for safe use.

The anti-influenza drugs are generally well tolerated. Amantadine, which is also used for treatment of Parkinsonism, may show more frequent CNS effects, including sedation and **dizziness**. Rapid discontinuation of amantidine may cause an increase in Parkinsonian symptoms in patients using the drug for that purpose. All are schedule C for pregnancy. In animal studies, they have caused fetal malformations in doses several times higher than the normal human dose. Use caution in breast-feeding.

Interactions

Consult specific references for information on drug interactions.

Use particular caution in HIV-positive patients, since these patients are commonly on multi-drug regimens with

Key Terms

Amygdala An almond-shaped area of the brain involved with coordinating mood, feeling, instinct, and memory.

Buspirone An anxiolytic drug that does not affect GABA, but instead modifies serotonin neurotransmission. Unlike benzodiazepines, it may take 3–6 weeks for buspirone to reach maximal effectiveness. As a result, the drug is only used to treat generalized anxiety disorder.

Generalized anxiety disorder An anxiety disorder characterized by excessive worry or fear about a number of activities or events.

Neurotransmitter A chemical in the brain that transmits messages between neurons, or nerve cells.

Panic disorder A series of unexpected attacks, involving an intense, terrifying fear similar to that caused by a life-threatening danger.

Phobic disorder Persistent fear of social situations, objects, or specific situations.

Selective serotonin reuptake inhibitors (SSRIs) Prescription drugs used as antidepressants and anti-anxiety agents that enhance the actions of the neurotransmitter serotonin.

a high frequency of interactions. Ganciclovir should not be used with other drugs which cause hematologic toxicity, and cidofovir should not be used with other drugs that may cause kidney damage.

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Anxiolytics

Definition

Anxiolytics are prescription drugs used to treat and prevent anxiety disorders. Anxiety is an emotional state in which fear dominates a person's life. Drugs that are often prescribed to manage anxiety episodes are known as **benzodiazepines**. Probably the best-known example of a benzodiazepine is the anxiolytic **diazepam**. In the United States, diazepam is sold under the brand name Valium.

All together, there are six other anxiolytics approved for use in the United States. All of these medications are similar to diazepam in their chemical structures and the way they exert their beneficial anxiolytic effects. However, these drugs differ from one another in several important ways. Some drugs work faster than others, while other drugs continue their anxiolytic effects for longer periods of time. Additionally, some anxiolytics differ from one another in the way that they are eliminated from the body, and others are involved with more drug-to-drug interactions than others. In 2002, the two most commonly prescribed anxiolytics were the drugs lorazepam, sold under the trade name of Ativan, and alprazolam, sold under the brand name of Xanax.

Purpose

Diazepam and other anxiolytics reduce the frequency, severity, and duration of anxiety symptoms in individuals who have medical or psychiatric disorders associated with anxiety. Illnesses associated with anxiety symptoms include heart disease, gastrointestinal diseases, as well as diseases that affect the lungs and make breathing difficult. Anxiety may also occur in the absence of these diseases and is thought to involve abnormal function of several different **neurotransmitters** in a region of the brain known as the amygdala. The amygdala plays a critical role in assessing fear and responding to danger. Examples of common anxiety disorders include generalized anxiety disorder, panic disorder, and phobic disorders. Nearly 25% of the population will develop an anxiety disorder at some time during their life.

Description

Benzodiazepine anxiolytics like diazepam have similar chemical structures, including a benzene ring fused to a diazepine ring. This structure is important for anxiolytic activity. In the brain, anxiolytics are believed to enhance the actions of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. By enhancing GABA's inhibitory actions, brain cells are unable to be stimulated by excitatory neurotransmitters, and this inhibition alleviates symptoms of anxiety.

Although benzodiazepines like diazepam alleviate symptoms of anxiety in a manner similar to older anxiolytics like barbiturates, the distinctive feature that sets benzodiazepines apart from barbiturates is the wide margin of

safety associated with benzodiazepines. Unlike barbiturates, benzodiazepine anxiolytics have a wide margin of safety, meaning that the doses of benzodiazepines that cause life-threatening toxicities are considerably larger than the doses that are normally used for alleviating anxiety.

Diazepam and related anxiolytics are safe and effective medications for alleviating anxiety symptoms. Until the 1990s, these drugs were the mainstay of pharmacologic treatment for anxiety-related disorders. However, these anxiolytics do possess some unwanted properties. For example, the Drug Enforcement Administration (DEA) classifies diazepam and related anxiolytics as controlled substances because the drugs are sometimes abused, or used for recreational purposes due to their desirable anxiolytic effects. Additionally, physical dependence develops when these medications are used at high doses or for prolonged periods of time. This means that people experience unpleasant withdrawal symptoms if they abruptly stop taking their medication. Common withdrawal symptoms include anxiety, insomnia, restlessness, agitation, muscle tension, and irritability, although **seizures** and **depression** may sometimes occur. The unpleasant withdrawal effects that are experienced when discontinuing these medications cause people to continue using the drugs to avoid unpleasant effects. Because these drugs are sometimes used for non-medicinal purposes and are associated with unpleasant withdrawal symptoms, benzodiazepine anxiolytics are now typically prescribed only for short-term treatment of anxiety disorders, until other anxiolytics like buspirone or selective serotonin reuptake inhibitors (SSRIs) begin working.

Recommended dosage

The usual adult dosage of diazepam is 2–10 mg taken by mouth two to four times a day. In addition to oral tablets, diazepam is also available as an oral liquid or as an injection that can be given either intramuscularly or intravenously to individuals with severe anxiety symptoms.

Dosages for anxiolytics that are chemically related to diazepam vary. Examples include alprazolam given by mouth in dosages of 0.25–0.5 mg three times a day, or lorazepam taken by mouth in dosages of 0.5–2 mg two or three times a day.

The anxiolytic effects of diazepam occur in as little as 15 minutes, but only last for two or three hours. These features make diazepam an ideal drug for quickly eliminating acute anxiety attacks. On the other hand, lorazepam's anxiolytic effects are a little slower in onset but tend to persist for more than six hours. As a result, lorazepam may be better suited to prevent anxiety in people with generalized anxiety disorder.

Elderly patients may be more sensitive to the side effects of diazepam and related anxiolytics than younger adults. As a result, initial doses are usually reduced and increased slowly in the elderly to avoid excessive sedation and other unwanted side effects.

Precautions

Paradoxically, excitement, rage, anger, or hostility may occur in individuals taking anxiolytics for their calming effects. These reactions may occur secondarily to the relief of anxiety and usually occur within the first two weeks of therapy. If these reactions occur, anxiolytic therapy should be stopped.

Because suicidal tendencies may be present in patients who also have accompanying depressive disorders, only small amounts of anxiolytic agents should be dispensed at any given time to minimize the likelihood of intentional drug overdoses.

Side effects

Diazepam and related anxiolytics are often associated with drowsiness, sedation, confusion, and difficulty maintaining balance. These effects are more pronounced at the beginning of therapy and after dosage increases. People should avoid driving or performing tasks that require alertness until they know how the drugs will affect them.

When using anxiolytics like diazepam, **fainting** or **dizziness** sometimes occurs when a person stands up suddenly. Blurred vision may also occur.

When anxiolytics are used in high doses or taken with other drugs that depress the actions of the brain, such as alcohol or barbiturates, the normal breathing responses of the body may be interrupted and patients may stop breathing. For this reason, alcohol and other CNS depressants should be avoided in people taking diazepam and related anxiolytics. It is also best to avoid anxiolytics in those persons with a prior history of drug abuse or those who are suicidal.

Withdrawal symptoms will occur if patients stop taking anxiolytics suddenly. Patients should only discontinue using diazepam and related anxiolytics at the advice of their physician and the dosage of the drugs should be reduced slowly to avoid withdrawal effects.

Interactions

Diazepam will increase the drowsiness or sedative effects of other **central nervous system** depressants like alcohol or barbiturates. These combinations should be avoided.

Certain drugs, especially those eliminated by the liver, may interfere with the elimination of diazepam from the body. **Anticonvulsants**, antidepressants, numerous antibiotics, and cimetidine inhibit the elimination of most

anxiolytics from the body, causing higher blood levels and increased side effects.

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Aphasia

Definition

Aphasia is a communication disorder that occurs after language has been developed, usually in adulthood. Not simply a speech disorder, aphasia can affect the ability to comprehend the speech of others, as well as the ability to read and write. In most instances, intelligence per se is not affected.

Description

Aphasia has been known since the time of the ancient Greeks. However, it has been the focus of scientific study only since the mid-nineteenth century. Although aphasia can be caused by a head injury and neurologic conditions, its most common cause is **stroke**, a disruption of blood flow to the brain, which affects brain metabolism in localized areas of the brain. The onset of aphasia is usually abrupt, and occurs in individuals who have had no previous speech or language problems. Aphasia is at its most severe immediately after the event that causes it. Although its severity commonly diminishes over time through both natural, spontaneous recovery from brain damage and from clinical intervention, individuals who remain aphasic for two or three months after its onset are likely to have some residual aphasia for the rest of their lives. However, positive changes often continue to occur, largely with clinical intervention, for many years. The severity of aphasia is related to a number of factors, including the severity of the condition that brought it about, general overall health, age at onset, and numerous personal characteristics that relate to motivation.

Demographics

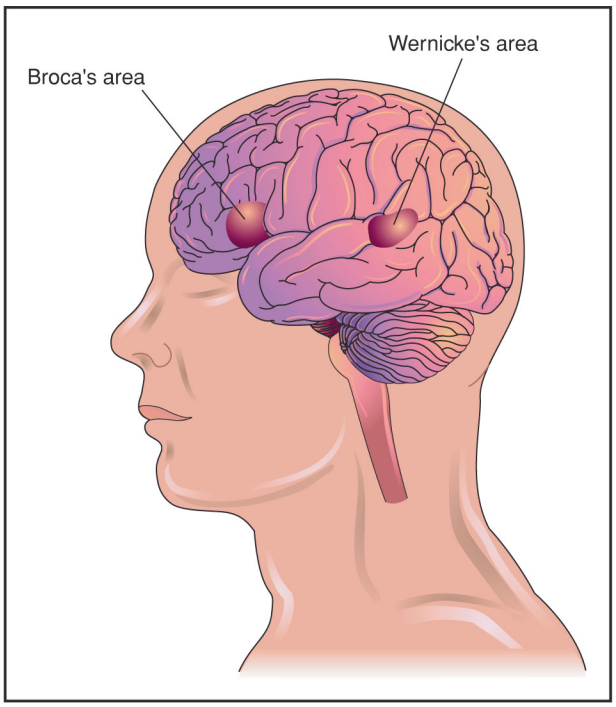
The National Aphasia Association estimates that approximately 25–40% of stroke survivors develop aphasia. There are approximately one million persons in the United States with aphasia, and roughly 100,000 new cases occur each year. There are more people with aphasia than with **Parkinson's disease**, **cerebral palsy**, or **muscular dystrophy**.

Causes and symptoms

Although aphasia occasionally results from damage to subcortical structures such as basal ganglia or the thalamus that has rich interconnections to the cerebral cortex, aphasia is most frequently caused by damage to the cerebral cortex of the brain's left hemisphere. This hemisphere plays a significant role in the processing of language skills. However, in about half of left-handed individuals (and a few right-handed persons), this pattern of dominance for language is reversed, making right-hemisphere damage the cause of aphasia in this small minority. Because the left side of the brain controls movement on the right side of the body (and vice versa), paralysis affecting the side of the body opposite the side of brain damage is a frequent co-existing problem. This condition is called hemiplegia and can affect walking, using one's arm, or both. If the arm used for writing is paralyzed, it poses an additional burden on the diminished writing abilities of some aphasic individuals. If paralysis affects the many muscles involved in speaking, such as the muscles of the tongue, this condition is called **dysarthria**. Dysarthria often co-occurs with aphasia.

There are a few more problems that can result from the same brain injury that produces aphasia, and complicate its presentation. Most notable among them are the problems collectively called **apraxia**, which influences one's ability to program movement. Apraxic difficulties make voluntary movements difficult and hard to initiate. Apraxia of speech results in difficulty initiating speech and in making speech sounds consistently. It frequently co-occurs with both dysarthria and aphasia. Finally, sensory problems such as visual field deficits (specifically, **hemianopsia**) and changes in (or absence of) sensation in arms, legs, and tongue commonly occur with aphasia.

There are neurological disorders other than aphasia that also manifest difficulty with language. This makes it important to note what aphasia is not. **Traumatic brain injury** and dementias such as **Alzheimer's disease** are excellent examples. Although brain injury is a cause of aphasia, most head injuries produce widespread brain damage and result in other neuropsychological and cognitive disorders. These disorders often create language that is disturbed in output and form, but are typically the linguistic consequences of cognitive disturbances. In Alzheimer's disease, the situation is much the same. Language spoken by individuals with Alzheimer's reflect their cognitive problems, and, as such, differ from the language retrieval problems typically designated as aphasia. In



Damage to these areas of the brain can cause types of aphasia. *(Illustration by Electronic Illustrators Group.)*

short, if the damage that results in language problems is general and produces additional intellectual problems, then aphasia is a correct diagnosis. In the absence of other significant intellectual problems, then the language disorder is probably localized to the brain's language processing areas and is properly termed aphasia.

Finally, aphasia is not conventionally used to refer to the developmental language learning problems encountered by some atypically developing children. However, when children who have been previously developing language normally have a stroke or some other type of localized brain damage, then the aphasia diagnosis is appropriate.

Aphasia manifests different language symptoms and syndromes as a result of where in the language-dominant hemisphere the damage has occurred. The advent of neuroimaging has improved the ability to localize the area of brain damage. Nevertheless, the different general patterns of language strengths and weaknesses, as well as unexpected dissociations in language function, can explain how normal language is processed in the brain, as well as provide insights into intervention for aphasia.

Aphasic individuals almost uniformly have some difficulty in using the substantive words of their native language. Most experts in aphasia recognize that aphasia varies along two major dimensions: auditory comprehension ability and fluency of speech output. In reality, aphasic behaviors vary greatly from individual to individual, and fluctuate in a given individual as a result of **fatigue** and other factors. In addition, largely in relationship to lesion size, aphasias differ in overall severity.

Nonfluent aphasia

Frontal cortex is responsible for shaping, initiating, and producing behaviors. Individuals with nonfluent aphasia characteristically have brain damage affecting Broca's area of the cortex and the frontal brain areas surrounding it. These areas are responsible for formulating sound, word, and sentence patterns. Damage to the anterior speech areas results in slow, labored speech with limited output and prosody and difficulty in producing grammatical sentences. Because the motor cortex is closely adjacent, nonfluent Broca's aphasia, by far the most common nonfluent variant, is quite likely to co-occur with motor problems.

Several additional characteristics of nonfluent aphasia can be noted: in nonfluent aphasia verbs and prepositions are disproportionately affected; speech errors occur mostly at the level of speech sounds, producing sound transpositions and inconsistencies; auditory comprehension is only minimally affected; reading abilities parallel comprehension, writing problems parallel speech output, but are sometimes further complicated by hemiplegia; finally, there is an inability to repeat what someone else says.

Fluent aphasia

Fluent aphasias occur when damage occurs in the posterior language areas of the brain, where sensory stimuli from hearing, sight, and bodily sensation converge. In fluent aphasia, the prosody and flow of speech is maintained; one typically must listen closely to recognize that the speech is not normal. Because this posterior damage is located far from the motor areas in the frontal lobes, individuals with fluent aphasia seldom have co-existing difficulty with the mechanics of speech, arm use, or walking. There are three major variants of fluent aphasia, each thought to occur as a function of disruption to different posterior brain regions.

WERNICKE'S APHASIA Wernicke's aphasia results from temporal lobe damage, where auditory input to the brain is received. The essential characteristic is that individuals with this disorder have disproportionate difficulty in understanding spoken and written language. They also have problems comprehending and monitoring their own speech. They are often verbose, and frequently use inappropriate and even jargon words when they speak. Reading and writing are impaired in similar ways to auditory comprehension and speech output. Their comprehension difficulties preclude their being able to repeat others' words.

ANOMIC APHASIA Most people, particularly as they grow older, have trouble with the names of persons and

things; all aphasic persons experience these difficulties. But when brain damage occurs in the area of the posterior brain where information from temporal, parietal, and occipital lobes converge, this problem of naming is much more pervasive than for normal and aphasic speakers alike. Most anomic aphasic individuals have excellent auditory comprehension and read well. But for most of them, writing mirrors speech, and individuals with anomic aphasia can take advantage of words provided by others. Hence, their repetition ability is good. Although anomic aphasia is classified as a fluent syndrome, frequent stops, starts, and word searches typically make speech choppy in between runs of fluency.

CONDUCTION APHASIA Individuals with conduction aphasia are thought to have a discrete brain lesion that disrupts the pathways that underlie the cortex and connect the anterior and posterior speech regions. These individuals have good comprehension, as well as high awareness of the errors that they make. Placement of their brain damage also suggests that there should be little interference with speech production, reading, and writing. However, damage to the neural links between posterior and anterior speech areas makes it quite difficult for these individuals to correct the errors they hear themselves making. Conduction aphasia also affects the ability to repeat the speech of others or to take advantage of the cues others provide. The speech of individuals with this problem includes many inappropriate words, typically involving inappropriate sequences of sounds.

UNUSUAL APHASIA SYNDROMES There are a few other rare aphasic syndromes (called "transcortical aphasias") and unique dissociations in aphasic patterns. The above aphasias represent the most common distinctive syndromes. However, they are estimated to account for only approximately 40% of individuals with aphasia.

MIXED AND GLOBAL APHASIA The remaining majority, about 60% of aphasic individuals, have aphasias that result from brain lesions involving both the anterior and posterior speech areas. Their aphasias, thus, affect both speech production and comprehension. They frequently have reading and writing disorders as well. Individuals with mixed and global aphasia are also very likely to have hemiplegia and dysarthria, as well as a variety of sensation losses. Depending upon the severity of these symptoms, people with mild-to-moderate symptomatology of this type are said to have mixed aphasia; global aphasia describes individuals with extensive difficulties in all language skills.

Diagnosis

As an aid to accurate diagosis immediately following stroke, it is important to differentiate aphasia from cognitive disorders such as confusion and disorientation. To this end, brief, but general testing of the language functions (naming, comprehension, reading, writing, and repetition) can be incorporated into broader testing that might determine other cognitive functions. Evaluators must remember that language is the medium though which most of these other functions are observed. Therefore, language should be assessed first; if extensive aphasia is present, then only cautious interpretations of other cognitive functions may be given. At present, there are few available objective and standardized measures for testing during the acute phases of disorders such as stroke.

A number of standardized measures are available that provide an inventory of aphasic symptoms. These tests are useful in providing baseline and follow-up assessments to measure progress in treatment, as well as to guide the treatment itself. A fairly general feature of aphasia tests is that individuals without aphasic symptoms should perform with almost no errors on them. Tests are available to measure the extent and severity of language impairments as well as to provide information about functional skills and outcomes. Finally, there are assessments designed specifically to look at quality of life with aphasia.

Treatment team

Because of the various other problems in addition to language that affect most individuals with aphasia, a multidisciplinary team is used in rehabilitation centers for the management of aphasia. Team members, as well as speech-language pathologists, typically include physical and occupational therapists, clinical neuropsychologists, nurses, and **social workers** who are guided by physiatrists and neurologists. Once discharged from rehabilitation centers, aphasic individuals often continue their treatment by speech-language pathologists in settings such as speech and hearing clinics. Self-help groups and support via the Internet are available as well.

Treatment

Most individuals with aphasia are hospitalized for some period of time for treatment of the condition that has resulted in aphasia. Assessment of the extent and type of language disorder is made during that time, as assessment of the ability to swallow (dysphagia). Early medical intervention is important for lessening the long-term effects of stroke.

Recovery and rehabilitation

To date, no pharmacological treatments for aphasia have proven effective, although a number of drugs (dopaminergic, cholinergic, and neurotrophic) continue to be investigated, usually in conjunction with behavioral treatments for aphasia. Various behavioral treatment approaches for aphasia exist. They are usually characterized

dichotomously as restorative (restitutive) or compensatory. The goal of restorative treatments is to reestablish disordered language skills. Goals for compensatory approaches are to develop and train alternative approaches to circumvent the language skills that have been affected by aphasia. Most clinicians use both approaches (often simultaneously) to aid in language recovery. Some examples of restorative approaches include practice of carefully selected syntactic structures, naming drills, or practice using self-selected communication needs such as using the telephone.

Compensatory approaches include training conversational partners to modify their own language and communication skills in ways that make it easier for the aphasic individual to communicate, or teaching aphasic individuals to use a relatively intact language skill such as writing or drawing to substitute for talking. Computerized approaches to both restitutive and compensatory aphasia treatment are increasing. Many clinics offer both individual treatment and group treatment, with the latter offering increased psychosocial support. Many clinics also incorporate family support groups.

Clinical trials

Randomized control trials (RCTs) are rare for the behavioral realm of treatments. Aphasia is no exception. To date, only four RCTs have been completed, with three of the four addressing to the efficacy of treatment. A far greater number of phases I and II studies exist, and investigate the value of language intervention, particularly post stroke. The largest testimony comes from single-case designs and qualitative case studies that agree that treatment has a positive influence on outcome. Only one meta-analysis of significant scope has been completed (Robey, 1998).

Prognosis

The traditional view is that most of the language gains made by aphasic individuals will occur in the first six months following injury, except in persons with global aphasia, who may begin the recovery process later, but are shown to make gains through one year. Significantly, it must be noted that most traditional treatment techniques have been validated using aphasic patients whose period of spontaneous recovery has passed. Some people with aphasia may be able to return to work, although the communicative demands of many occupations may affect employment.

As of the late 1990s, research has begun to focus on recovery across the remainder of the lifespan, and it has become apparent that aphasic individuals continue to make progress, often for years after the precipitating event. The factors that explain very late recovery are not clear and will require scientific observation and study.

Special concerns

Despite the prevalence of aphasia, the disorder is neither well recognized nor well understood. Aphasia's psychosocial and vocational consequences are overwhelmingly devastating, but community understanding is at best limited. Similarly, despite substantial evidence concerning the effectiveness of intervention, skepticism about the value of treatment remains. As a consequence of both of these factors, many aphasic individuals and their families are not well informed about either the disorder or what might be done to alleviate it.

Additionally, although a significant and growing number of individuals in the United States is bilingual, there is a surprising lack of research concerning the effects of speaking more than one language on recovery from aphasia. Finally, current funding for only very limited treatment for aphasia is available via third-party reimbursement.

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National Aphasia Association. 29 John Street, New York, NY 10038. (212) 267-2812 or (800) 922-4622. naa@aphasia.org. <http://www.aphasia.org>.

Audrey L. Holland, PhD

Apolipoprotein B deficiency *see* **Bassen-Kornzweig syndrome**

Apraxia

Definition

Apraxia is a neurological disorder. In general, the diagnostic term "apraxia" can be used to classify the inability of a person to perform voluntary and skillful movements of one or more body parts, even though there

is no evidence of underlying muscular paralysis, incoordination, or sensory deprivation. Additionally, motor performances in response to commands, imitation tasks, and use of familiar objects may be equally difficult but not attributable to **dementia** or confusion. These types of disturbances usually result from injuries, illnesses, or diseases of different regions of the brain normally responsible for regulating such abilities.

Description

The term apraxia is derived from the Greek word *praxis*, which refers to producing an action or movement. In 1861, Broca described in detail an 84-year-old man who suffered a sudden impairment of speech production, but preservation of oral musculature functions, overall language skills, and intelligence. Broca coined the term "aphemia" to classify the inability to articulate words in the presence of a good language foundation. In 1900, Leipmann reported a 48-year-old patient who was unable to execute various voluntary motor behaviors of the limbs and oral cavity, despite good muscle strength, intactness of certain automatic or previously well-rehearsed speech or bodily movements, and complete understanding of the intended acts. Liepmann popularized the diagnostic term "apraxia" to differentiate individuals with these types of select motor difficulties from those who struggle with movement disturbances because of weakness, paralysis, and incoordination of the muscles involved.

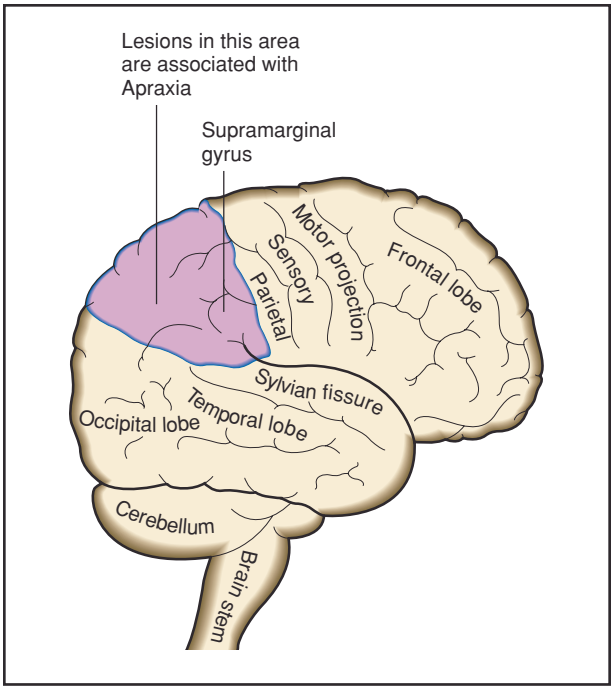
Demographics

There are no undisputed figures regarding the incidence of apraxia in the general population. However, because strokes are common causes, and African-American men are more susceptible to the development of this disease, by default this population may be at the greatest risk for this neurological disorder.

Causes and symptoms

Based on many additional case studies, Liepmann suggested that there are three major types of apraxia, each of which is caused by different sites of brain damage: ideational, ideo-motor, and kinetic.

Autopsy examinations and **magnetic resonance imaging (MRI)** scans have demonstrated that, in general, individuals with ideational, ideo-motor, and kinetic apraxias have pathologies involving either the back (parietal-occipital), middle (parietal), or front (frontal) lobes of the cerebral cortex, respectively. The individual with ideational apraxia cannot consistently produce complex serial actions, particularly with objects, due to disruptions at the conceptual stage of motor planning where the purpose and desire to perform specific movements are formulated. This individual may begin an act with a set purpose and start its performance, but then suddenly cease because the original goal is forgotten. The primary problem is failure to form concepts and/or inability to retain the conceptual plan for a sufficient period of time to allow the desired movements to be effectively programmed and executed. For example, if patients with ideational apraxia are requested to demonstrate proper use of a toothbrush, they might first brush their nails, then hesitate and brush their pants, and finally, with prompting, brush their teeth. Their actions will likely be slow and disorganized, appearing as though they have to think out each movement along the way.



The region of the brain affected by apraxia. *(Illustration by Electronic Illustrators Group.)*

Ideo-motor apraxia is characterized by derailments of bodily movement patterns, due to disturbances in the motor planning stages of a well-conceived behavioral act. Breakdowns most often occur during verbal commands to use objects rather than when the same objects are being used spontaneously. The patient with this disorder fails to translate the idea to perform specific movements into a coordinated and sequential scheme of muscle contractions to achieve the desired motor goal. If asked to demonstrate use of a pair of scissors, unlike ideational apraxics, individuals with ideo-motor apraxia will not make the mistake of using this tool as if it were a screwdriver. Rather, they might grasp the scissors with both hands and repetitively open and close the blades, or pick up the paper in one hand and the scissors in the other and rub them against one another with hesitant motions.

Kinetic apraxia is characterized by coarse, clumsy, groping, and mutilated movement patterns, especially on tasks that require simultaneous, sequential, and smooth contractions of separate muscle groups. These disturbances are usually proportional to the complexity of the task. The disorder does not involve ideation or concept formation, as the desired movement is almost always evident in the struggle. Typing, playing a musical instrument, and handwriting tasks are very difficult for the individual with kinetic apraxia. The problem is not with preliminary motor planning, as in ideo-motor apraxia. Instead, the kinetic apraxic suffers from disturbances in programming the motor plan into subunits of sequential muscle behaviors. Normally, such instructions are then conveyed directly to the primary motor system, which in turn initiates neural commands necessary to execute the intended act.

Apraxia of speech is a subtype of kinetic apraxia. This disorder is often observed following damage to the brain in an area named after Broca. Not infrequently, speech apraxia co-occurs with notable language disturbances, known as **aphasia**. Individuals with speech apraxia struggle with dysfluent articulation problems, as they grope to posture correctly sequential tongue, lip, and jaw movements during speech activities. Numerous, but variable articulatory errors occur, characterized by false starts, re-starts, sound substitutions, sound and word repetitions, and overall slow rate of speech. Multisyllabic words and complex word combinations are most vulnerable to these types of breakdowns.

Diagnosis

Testing for apraxia should employ basic screening tasks to identify individuals who do and do not require deeper testing for the differential diagnosis. Basic limb and orofacial praxis measures include the following commands:

- blow out a match
- protrude the tongue
- whistle
- salute
- wave goodbye
- brush the teeth
- flip a coin
- hammer a nail into wood
- cut paper with scissors
- tap the foot
- stand like a golfer
- jump up and down in place
- thread a needle
- tie a necktie
- recite isolated words, word sequences, and phrases

More detailed testing usually includes many additional tasks of increasing motor complexity.

Treatment team

Because the apraxias are neurological disorders, a clinical **neurologist** is often the team leader. A neurosurgeon may also be on the team, especially if the underlying cause requires surgical attention. Likewise, the primary medical care practitioner plays a very important role in taking care of the individual's overall health-related needs. The responsibilities of the nurse and clinical psychologist should not be underestimated, as many apraxic individuals experience the need for hospitalization, financial aid, social reintegration, and emotional and family counseling. Speech-language and occupational therapists are also key team members in those cases with clinically significant speech and/or limb-girdle movement abnormalities.

Treatment

Occupational therapists may employ exercises to rehabilitate proper use of eating utensils, health care and hygiene products, and self-dressing skills. The speech therapist focuses on retraining fluent and articulate movement patterns to improve overall speech intelligibility. Specific exercises may include tongue, lip, and jaw rate and rhythm activities, as well as combinations of complex sound and word productions.

Clinical trials

As of 2003, the National Institute of Neurological Disorders and Stroke (NINDS) sponsored two **clinical trials** that focused on patients with ideo-motor apraxia. These studies used different techniques to analyze brain activity as patients performed various movements and simple tasks.

The National Institute on Deafness and Other Communication Disorders (NIDCD) is also sponsoring a study. This clinical trial focuses on patients who experience speech and communication complications related to neurological illness.

Further information on these trials can be obtained by contacting the National Institutes of Health Patient Recruitment and Public Liaison Office.

Prognosis

The potential for significant improvements with treatments and self-healing (spontaneous recovery) are most likely in cases of mild apraxia with stable medical courses. For more severe cases, particularly those with progressive

or unstable neurological pathologies, the prognoses for notable gains with medical and behavioral interventions remain guarded at the outset. However, many such cases achieve sufficient gains to enable independent lifestyles.

Special concerns

People with apraxia who are elderly and/or who may also have co-morbid medical problems often require ongoing assistance with daily living activities. Nursing home facilities may be necessary for those individuals who do not have the opportunity or resources either to live by themselves or with family members, or to hire a home-based caregiver. Although apraxia most often afflicts adults, school-age children or adolescents with this disorder will require special education considerations and intensive academic and therapeutic programs.

Quality of life

Apraxia may be caused by very serious neurologic diseases or injuries. The quality of life of those afflicted with this disorder is usually influenced by its underlying cause. Many individuals have co-occurring physical, psychological, and intellectual disabilities, which complicate the differential diagnostic process and challenge the potential for meaningful rehabilitation and a fruitful quality of life. Others struggle with less intertwined functional disturbances. These individuals tend to lead more productive lives because they are not as severely impaired.

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National Institutes of Health Patient Recruitment and Public Liaison Office. 9000 Rockville Pike, Bethesda, MD 20892. (800) 411-1222. prpl@mail.cc.nih.gov. <http://www.nih.gov/>.

National Institute of Neurological Disorders and Stroke. P.O. Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

Wayne State University, Department of Otolaryngology, Head and Neck Surgery. 5E-UHC, 4201 St Antoine, Detroit, MI 48201. (313) 577-0804. <http://www.med.wayne.edu/otohns/index.htm>.

James Paul Dworkin, Ph.D.

Aprosodia *see* **Aphasia, Dysarthria**

Arachnoiditis

Definition

Arachnoiditis literally means "inflammation of the arachnoid," which is the middle of the three membranes (**meninges**) surrounding the brain and spinal cord. The term more generally refers to several rare neurologic disorders caused by inflammation of a portion of the arachnoid and subarachnoid space, affecting the neural tissue that lies beneath. Symptoms of arachnoiditis are quite variable, and may include anything from a skin rash to moderate or severe **pain**, to paralysis. The condition is often progressive, can only rarely be cured, and existing treatments vary in their effectiveness.

Description

Three membranes, including the dura mater, arachnoid, and pia mater, and a layer of cerebrospinal fluid (CSF) surround, protect, and cushion the brain and spinal cord. The pia mater adheres to the brain and spinal cord, and is separated from the arachnoid membrane by the subarachnoid space, which contains the circulating CSF. Arachnoiditis always involves inflammation in one or several restricted areas, but the entire membrane is never affected. Fibrous (scar) tissue growth along the affected section of the membrane usually occurs, projecting down through the subarachnoid space and encompassing neural tissue of the brain (cerebral arachnoiditis) and/or nerve roots of the spinal cord (spinal arachnoiditis). Nerve damage occurs through restricted blood flow (ischemia), compression from accumulated fluids (edema), and secondary effects of the inflammatory process itself.

Key Terms

Arachnoid One of the three membranes that sheath the spinal cord and brain; the arachnoid is the middle membrane. Also called the arachnoid mater.

Cerebrospinal fluid The clear, normally colorless fluid that fills the brain cavities (ventricles), the subarachnoid space around the brain, and the spinal cord, and acts as a shock absorber.

Epidural space The space immediately surrounding the outermost membrane (dura mater) of the spinal cord.

Meningitis An infection or inflammation of the membranes that cover the brain and spinal cord. It is usually caused by bacteria or a virus.

Subarachnoid space The space between two membranes surrounding the spinal cord and brain, the arachnoid and pia mater.

Other terms used less frequently for arachnoiditis include arachnitis, chronic adhesive arachnoiditis (CAA), and spinal fibrosis. Other conditions that may be associated with or mimic arachnoiditis include **syringomyelia** (cyst near the spinal cord), cauda equina (lower spinal cord) syndrome, and spinal tumor. Several different types of arachnoiditis have been described, including adhesive (fibrous attachments), ossifying (bony tissue growth), neoplastic (tumor growth), optochiasmatic (optic nerve and chiasm), and rhinosinusogenic (olfactory nerve and area above the sinuses).

Demographics

The true incidence of arachnoiditis is not known, but it is rare. It affects males and females equally, and seems to be less frequent in children than in adults. Rare cases of familial arachnoiditis have been documented, but no particular ethnic groups seem to be at higher risk.

Causes and symptoms

The causes of arachnoiditis are varied, but fall into the following four categories:

- trauma to the membrane due to spinal surgery (often multiple procedures), cranial or spinal injury, or needle insertion to remove CSF for testing
- external agents such as anesthesia, corticosteroids, medications, or medical dyes/chemicals injected near the spinal cord (epidural) or directly into the CSF
- infection of the arachnoid/CSF (meningitis)
- blood in the CSF caused by trauma, spontaneous bleeding, or infection

For reasons that are not entirely clear, different areas of the arachnoid have differing sensitivities to the causative agents. Spinal arachnoiditis due to infection most often occurs in the cervicothoracic (neck and upper back) region, while cases due to external agents most often occur in the lumbosacral (lower back) area. Likewise, spinal arachnoiditis of any type is more common than the cerebral/cranial variety.

Symptoms of cerebral arachnoiditis may include severe headaches, vision disturbances, **dizziness**, and nausea/vomiting. Vision disturbances are especially pronounced in optochiasmatic arachnoiditis. If inflammation and tissue growth in specific areas of the cranial arachnoid membrane divert or obstruct normal flow of the CSF, the result is **hydrocephalus** (increased fluid pressure within the brain).

Typical symptoms of spinal arachnoiditis include **back pain** that increases with activity, pain in one or both legs or feet, and sensory abnormalities of some type, usually involving decreased reflexes. Patients may also exhibit decreased range of motion of the trunk or legs, and urinary sphincter dysfunction (urgency, frequency, or incontinence). In more severe cases, partial or complete paralysis of the lower extremities may occur.

Diagnosis

The most reliable method of establishing the diagnosis of arachnoiditis is a positive computed tomography (CT) or **magnetic resonance imaging (MRI)** scan, combined with one or more of the symptoms. Testing for certain cell types and proteins in the CSF may prove helpful only in the early stages of the inflammation. On the other hand, imaging studies may be negative or equivocal early on, and only later be more definitive as inflammation and tissue growth becomes more pronounced. In some cases, a definitive diagnosis may not be possible.

Treatment team

A **neurologist** is the primary specialist involved in monitoring and treating arachnoiditis. Occupational/physical therapy (OT/PT) might also be suggested to assist with treatment for pain and adaptation to sensory deficits and/or muscular weakness in the back and lower limbs. A neurosurgeon performs any elected surgeries to address the various effects of the inflammation. Many individuals with chronic pain attend pain clinics staffed by physicians (usually anesthesiologists) and nurses who specialize in pain management. Neuropsychiatrists and neuropsychologists specialize in treating the psychological problems specific to individuals who have an underlying neurologic condition.

Treatment

Treatment for arachnoiditis is mostly done with medications, and is geared toward reducing the inflammation and alleviating pain. Medications may include both non-steroidal and steroidal anti-inflammatory drugs, along with non-narcotic and narcotic pain medications. Other possible treatments include epidural steroid injections, transcutaneous electrical nerve stimulation (TENS), topical analgesics, and alternative medical therapies.

Direct spinal cord stimulation is a newer pain management method that involves placement of tiny electrodes under the skin, directly on the affected nerve roots near the spine. Mild current application inhibits pain signals, and is provided by a small, battery-powered unit that is placed under the skin by a surgeon.

Surgery to remove fibrous or ossified tissue at the site of the inflammation is used only if more conservative methods do not provide sufficient relief. Surgical removal of a small portion of one or more vertebrae at the area of the nerve root is called a **laminectomy**. A neurosurgeon treats hydrocephalus by placing a shunt (plastic tube) from the brain to the abdominal cavity to relieve increased pressure. Microsurgical techniques to remove scar tissue from around the nerve roots themselves are a more recent development.

Prognosis

Given the lack of effective treatments for arachnoiditis, the prognosis in most instances is poor, with the neurologic symptoms remaining static or worsening over time. It is not uncommon for people who undergo surgery for the condition to improve at first, but eventually regress within several years.

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ORGANIZATIONS

American Paraplegia Society. 75-20 Astoria Boulevard, Jackson Heights, NY 11370-1177. (718) 803-3782. <http://www.apssci.org>.

American Syringomyelia Alliance Project, Inc. P.O. Box 1586, Longview, TX 75606-1586. 800-272-7282. <http://www.asap.org>.

NIH/NINDS Brain Resources and Information Network. PO Box 5801, Bethesda, MD 20824. (800) 352-9424. <http://www.ninds.nih.gov/>.

National Organization for Rare Disorders (NORD). 55 Kenosia Ave, PO Box 1968, Danbury, CT 06813-1968. (800) 999-6673; Fax: (203) 798-2291. <http://www.rarediseases.org>.

National Spinal Cord Injury Association. 6701 Democracy, Bethesda, MD 20817. (800) 962-9629. <http://www.spinalcord.org>.

Spinal Cord Society. 19051 County Hwy 1, Fergus Falls, MN 56537. (218) 739-5252.

Scott J. Polzin, MS, CGC

Arachnoid cysts

Definition

Arachnoid cysts are sacs that are filled with cerebrospinal fluid and form in the surface region of the brain around the cranial base, or on the arachnoid membrane (one of three membranes that covers the brain and spinal cord).

Description

An arachnoid cyst forms when the two lipid (fatty) layers of the arachnoid membrane split apart to form a cavity. Like most membranes, the arachnoid membrane is comprised of two layers (leaflets) of lipid molecules. The hydrophilic (water attracting) region of the lipids is oriented towards an environment rich in water. The hydrophobic (water repelling) portion of the lipids will spontaneously partition away from water, in the interior of the membrane. When an arachnoid cyst forms, the two leaflets of the membrane split apart. Cerebrospinal fluid then fills the cavity.

Arachnoid cysts can be classified according to their location and by the type of tissue making up the cyst wall (arachnoid connective tissue or glioependymal tissue). Cysts that are found in the area of the cerebrum and in the spinal cord tend to be composed of arachnoid tissue, while cysts found in the supracollicular or retrocerebellar regions of the brain tend to be composed of either arachnoid connective tissue or glioependymal tissue.

Key Terms

Arachnoid membrane A thin layer of tissue that is the middle layer of the three meninges surrounding the brain and spinal cord.

Cerebrospinal fluid The clear fluid that circulates through the brain and spinal cord.

Intracranial pressure The overall pressure within the skull.

The expansion of arachnoid cysts may occur when pulses of cerebrospinal fluid become trapped in the cyst cavity. The increasing volume of fluid causes the cyst to grow in size. However, the exact nature of cyst growth is not yet well understood. Arachnoid cysts tend to form on the left side of the brain, where the spinal canal intersects. Typically, a cyst makes up about one percent of the mass of the brain. Arachnoid cysts are also known as intracranial cysts.

Demographics

Infants are most susceptible to developing arachnoid cysts, although cyst formation can occur up through adolescence. Arachnoid cyst development in adults occurs much less frequently. Arachnoid cysts occur predominantly in males. The ratio of affected males to females is 4:1. The true rate of occurrence of arachnoid cysts is unknown, as many people with the disorder do not develop symptoms and the cyst remains undiagnosed.

Causes and symptoms

Arachnoid cysts arise mainly because of an abnormality occurring in development, sometimes as a result of a neonatal (newborn) infection. Other cysts are congenital (present at birth) and presumably result from abnormal formation of the subarachnoid space during embryological development. Cysts can also result from tumors, and complications of surgery or trauma (bleeding).

The symptoms of an arachnoid cyst are related to the size of the cyst and its location. For example, a small cyst may not cause any symptoms at all, and can be discovered accidentally during an unrelated examination. Large cysts can cause the head to change shape or to become enlarged (a phenomenon called macrocephaly). Symptoms associated with a larger cyst include headaches, **seizures**, accumulation of a pronounced amount of cerebrospinal fluid (**hydrocephalus**), increased pressure inside the cranial cavity, delay in mental and physical development, and altered behavior.

Other symptoms can include weakness or complete paralysis along one side of the body (hemiparesis), and the loss of control of muscles (**ataxia**).

Diagnosis

Arachnoid cysts are most commonly diagnosed followed a complaint of headaches, disruption of vision, or delayed development in a child. Even then, the discovery of a cyst is often incidental to another examination. The cysts can also be visualized using computerized tomography (CT) scanning, **magnetic resonance imaging (MRI)**, and cranial **ultrasonography**. Overall, MRI is the preferred diagnostic technique, although cranial ultrasonography is an especially useful technique for newborns.

Arachnoid cysts have also been documented in people who have maladies such as Cockayne syndrome and Menkes disease. However, it is unclear whether this association is typical (and so of diagnostic importance) or merely coincidental.

Treatment team

Treatment can involve medical specialists such as neurosurgeons, imaging technicians, as well as nursing and other care providers. Physical therapists are also often involved.

Treatment

Typically, treatment is for the symptoms caused by the presence of the cyst, rather than for the cyst itself. However, when symptoms warrant, surgery is performed to relieve symptoms of increased intracranial pressure caused by the accumulation of fluid within the arachnoid cyst. Often, a device (shunt) is implanted within the cyst that drains the fluid away from the cyst and into the ventricles of the brain, or into the peritoneum (abdominal space), thus relieving the pressure. An alternative surgery called endoscopic fenestration uses an endoscope (an operative tool with an attached camera) to cut a small hole in the cyst, allowing the fluid to escape into the normal cerebrospinal fluid pathway.

Recovery and rehabilitation

Recovery from either surgical treatment is usually rapid, with symptoms resolving quickly after the excess fluid is redirected, assuming no permanent neurological damage occurred prior to treatment. An active infant or young child often wears a protective helmet during the recovery phase. Physical and mental developmental milestones are usually monitored for infants and children. Follow-up monitoring of the implanted shunt and overall assessment of the cyst are normally required.

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.

Clinical trials

As of January 2004, the National Institute of Neurological Diseases and Stroke (NINDS) was recruiting patients for a study of **syringomyelia**. The malady arises when cerebrospinal fluid is blocked from its normal circulation, as by an arachnoid cyst. As well, NINDS and other agencies support research that seeks to understand the basis of arachnoid cyst formation.

Prognosis

While many arachnoid cysts cause no symptoms and require no treatment, others, if left untreated, can grow and cause pressure or severe bleeding within the brain (hemorrhage). The result can be permanent neurological damage. However, with treatment, the outlook for most persons with an arachnoid cyst is encouraging and permanent damage can be avoided.

Resources

BOOKS

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ORGANIZATIONS

National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders. 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Brian Douglas Hoyle, Ph.D.

Arnold-Chiari malformation

Definition

Arnold-Chiari malformation is a rare genetic disorder in which parts of the brain are formed abnormally. Malformations may occur in the lower portion of the brain (**cerebellum**) or in the brain stem.

Description

A German pathologist named Arnold-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 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.

A type II malformation is more severe than a type 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.

Demographics

Arnold-Chiari malformations are rare; no data has been collected to demonstrate the incidence of Arnold-Chiari malformations. However, it is known that 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.

Causes and symptoms

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.

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.

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

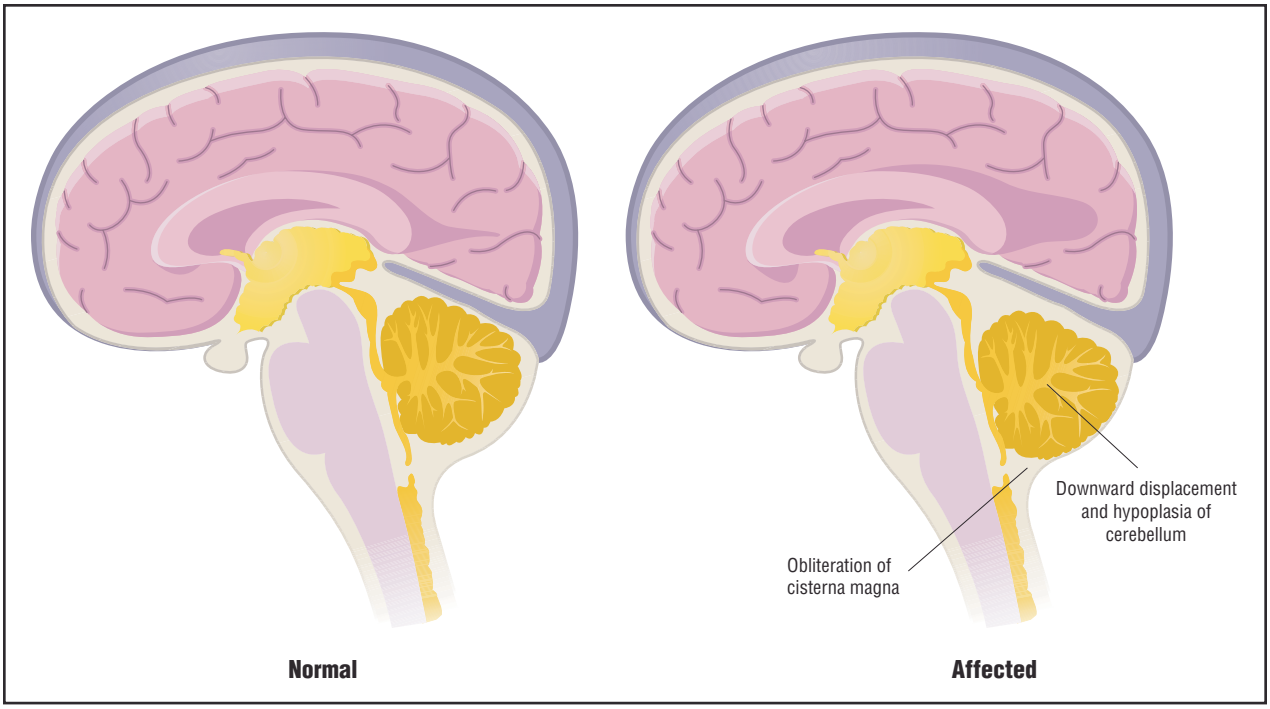
An Arnold-Chiari malformation is diagnosed with **magnetic resonance imaging (MRI)**. An MRI uses magnetism and radio waves to produce a picture of the brain and show the crowding of the space between the brain and spinal cord that occurs with Arnold-Chiari malformations. In addition to an MRI, patients will also have a thorough neurologic examination.

Treatment team

Individuals who begin to experience symptoms from an Arnold-Chiari malformation are usually first seen by their primary care physician, who may send them on to a **neurologist** for further evaluation. If the patient is deemed to require surgery, a neurosurgeon will be consulted.

Treatment

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.)*

Recover and Rehabilitation

Individuals who are recovering from surgery to repair an Arnold-Chiari malformation may require physical and/or occupational therapy as they try to regain strength and fine motor control in their arms and hands. A speech therapist may be helpful in improving both speech and swallowing.

Clinical Trials

The National Institutes of Health are undertaking several research studies exploring aspects of Arnold-Chiari malformations. Efforts are being made to delineate a possible genetic defect leading to such malformations; studies are further exploring the anatomy and physiology of the malformations; and comparisons of the efficacy of various surgical treatments are being made.

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
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Arteriovenous malformations

Definition

Arteriovenous malformations (AVMs) are blood vessel defects that occur before birth when the fetus is growing in the uterus (prenatal development). The blood vessels appear as a tangled mass of arteries and veins. They do not possess the capillary (very fine blood vessels) bed that normally exists in the common area where the arteries and

veins lie in close proximity (artery-vein interface). An arteriovenous malformation may hemorrhage, or bleed, leading to serious complications that can be life-threatening.

Key Terms

Aneurysm A weak point in a blood vessel where the pressure of the blood causes the vessel wall to bulge outwards.

Angiography A mapping of the brain's blood vessels, using x-ray imaging.

Capillary bed A dense network of tiny blood vessels that enables blood to fill a tissue or organ.

Hydrocephalus Swelling of the brain caused by an accumulation of fluid.

Lumbar puncture A diagnostic procedure in which a needle is inserted into the lower spine to withdraw a small amount of cerebrospinal fluid.

Saccular aneurysm A type of aneurysm that resembles a small sack of blood attached to the outer surface of a blood vessel by a thin neck.

Description

AVMs represent an abnormal interface between arteries and veins. Normally, arteries carry oxygenated blood to the body's tissues through progressively smaller blood vessels. The smallest are capillaries, which form a web of blood vessels (the capillary bed) through the body's tissues. The arterial blood moves through tissues by these tiny pathways, exchanging its load of oxygen and nutrients for carbon dioxide and other waste products produced by the body cells (cellular wastes). The blood is carried away by progressively larger blood vessels, the veins. AVMs lack a capillary bed, and arterial blood is moved (shunted) directly from the arteries into the veins.

AVMs can occur anywhere in the body and have been found in the arms, hands, legs, feet, lungs, heart, liver, and kidneys. However, 50% of these malformations are located in the brain, brainstem, and spinal cord. Owing to the possibility of hemorrhaging, such AVMs carry the risk of **stroke**, paralysis, and the loss of speech, memory, or vision. An AVM that hemorrhages can be fatal.

Approximately three of every 100,000 people have a cerebral (brain) AVM and roughly 40–80% of them will experience some bleeding from the abnormal blood vessels at some point. The annual risk of an AVM bleeding is estimated at about 1–4%. After age 55, the risk of bleeding decreases. Pre-existing high blood pressure or intense physical activity do not seem to be associated with AVM hemorrhage, but pregnancy and labor could cause a rupture or breaking open of a blood vessel. An AVM hemorrhage is not as dangerous as an aneurysmal rupture (an aneurysm is a swollen, blood-filled vessel where the pressure of the blood causes the wall to bulge outward). There is about a 10% fatality rate associated with AVM hemorrhage, compared to a 50% fatality rate for ruptured **aneurysms**.

Although AVMs are congenital defects, meaning a person is born with them, they are rarely discovered before age 20. A genetic link has been suggested for some AVMs, but studies have been inconclusive. The majority of AVMs are discovered in people ages 20–40. Medical researchers estimate that the malformations are created during days 45–60 of fetal development. Another theory suggests that AVMs are primitive structures that are left over after fetal blood-circulating systems developed.

However they form, AVMs have blood vessels that are abnormally fragile. The arteries that feed into the malformation are unusually swollen and thin walled. They lack the usual amount of smooth muscle tissue and elastin, a fibrous connective tissue. These blood vessels commonly accumulate deposits of calcium salts and hyaline. The venous part of the malformation receives blood directly from the artery. Without the intervening capillary bed, the veins receive blood at a higher pressure than they were designed to handle; this part of the malformation is also swollen (dilated) and thin walled. There is a measurable risk of an aneurysm forming near an AVM, increasing the threat of hemorrhage, brain damage, and death. Approximately 10–15% of AVMs are accompanied by saccular aneurysms, a type of aneurysm that looks like a small sac attached to the outer wall of the blood vessel.

Although the malformation itself lacks capillaries, there is often an abnormal proliferation of capillaries next to the defect. These blood vessels feed into the malformation, causing it to grow larger in some cases. As the AVM receives more blood through this "steal," adjacent brain tissue does not receive enough. These areas show abnormal nerve cell growth, cell death, and deposits of calcium (calcification). Nerve cells within the malformation may demonstrate abnormal growth and are believed to be nonfunctional. This may lead to progressive neurological deficits, or **seizures**, or both.

Causes and symptoms

About half of all patients with AVMs first come to medical attention because of hemorrhage; small AVMs are most likely to hemorrhage. If a hemorrhage occurs, it produces a sudden, severe **headache**. The headache may be focused in one specific area or it may be more general. It can also be mistaken for a migraine in some cases. The headache may be accompanied by other symptoms such as

vomiting, stiff neck, sleepiness, lethargy, confusion, irritability, or weakness anywhere in the body. Hemorrhaging from an AVM is generally less dangerous than hemorrhaging from an aneurysm, with a survival rate of 80–90%. Second or subsequent hemorrhages are more dangerous than first hemorrhages.

Almost half of AVM patients first present with seizures. A person may experience decreased, double, or blurred vision. About 25% of patients begin with a progressive neurological deficit such as loss of vision, weakness, or cognitive changes, depending on the exact location of the AVM. Larger AVMs are more likely to cause seizures and progressive deficits than smaller ones. Large AVMs exert pressure against brain tissue, cause abnormal development in the surrounding brain tissue, and slow down or block blood flow. **Hydrocephalus**, a swelling of brain tissue caused by accumulated fluids, may develop.

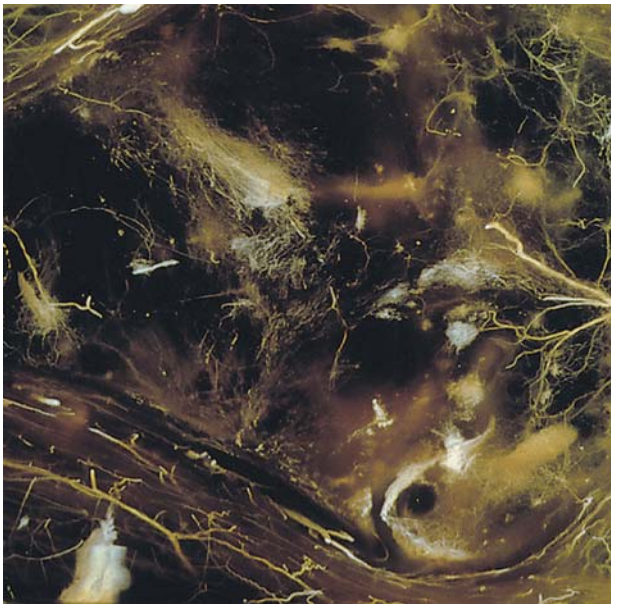
Additional warning signs of a bleeding AVM are impaired speech or smell, **fainting**, facial paralysis, drooping eyelid, **dizziness**, and ringing or buzzing in the ears.

About 65% of AVM patients have a mild learning disability present long before coming to medical attention for the AVM. There may also be a history of headaches or migraines.

Diagnosis

Based on the clinical symptoms such as severe headache or neurological problems, and after a complete neurologic exam, a computed tomography (CT) scan of the head will be done. In some cases, a whooshing sound from arteries in the neck or over the eye or jaw (called a bruit) can be heard with a stethoscope. The **CT scan** will reveal whether there has been bleeding in the brain and can identify AVMs larger than 1 in (2.5 cm). **Magnetic resonance imaging (MRI)** is also used to identify an AVM. A lumbar puncture, or spinal tap, may follow the **MRI** or CT scan. A lumbar puncture involves removing a small amount of cerebrospinal fluid from the lower part of the spine. Blood cells or blood breakdown products in the cerebrospinal fluid indicate bleeding.

To pinpoint where the blood is coming from, a cerebral **angiography** is done. This procedure uses x rays to map out the blood vessels in the brain, including the vessels that feed into the malformation. The information gained from angiography complements the MRI and helps distinguish the precise location of the AVM. During angiography, an anesthetic may be introduced into the AVM area to determine the precise function of the surrounding region. The patient will be given a variety of tests of language comprehension, speech production, sensation, and other tasks, depending on the precise location of the AVM. These results help determine the risk of treatment.



Arteriovenous malformations. *(Photograph by Patricia Barber. Custom Medical Stock Photo. Reproduced by permission.)*

Treatment team

The treatment team consists of a **neurologist**, neuroradiologist, **neuropsychologist**, neurosurgeon, and anesthesiologist.

Treatment

Neurosurgeons consider several factors before deciding on a treatment option. There is some debate over whether or not to treat AVMs that have not ruptured and are not causing any symptoms. The risks and benefits of proceeding with treatment need to be measured on an individual basis, taking into account factors such as the person's age and general health, as well as the AVM's size and location. In older patients at low risk for future hemorrhage, or for those in whom the AVM is located very close to critical brain areas, the doctor and patient may decide that treating symptoms alone is the best course. Antiseizure medications, **pain** relievers for headaches, and migraine medications may provide adequate symptom control for many patients.

To treat the AVM directly, several options are available. These treatment options may be used alone or in combination.

Surgery

Removing the AVM is the surest way of preventing it from causing future problems. Both small and large AVMs can be handled in surgery. Surgery is recommended for superficial AVMs (those close to the surface), but may be too

dangerous for deep or very large AVMs. In this procedure, a portion of the skull is opened to expose the AVM. The arteries and veins leading in and out are identified and closed off, and then the AVM itself is removed. Surgery requires general anesthesia and a longer period of recuperation than any other treatment option. It also carries the risk of intracranial bleeding during surgery, and interruption of blood supply to vital brain areas. The blood that no longer flows through the AVM is distributed elsewhere in the brain, and this increase in flow may be dangerous if it is too high for the vessels to handle.

Radiation

Radiation is particularly useful to treat small (under 1 in [2.5 cm]) malformations that are deep within the brain. Ionizing radiation is directed at the malformation, destroying the AVM without damaging the surrounding tissue. Radiation treatment is accomplished in a single session, and it is not necessary to open the skull. However, the radiation takes months to exert its complete effect, and success can only be measured over the course of the following two years. A year after the procedure, 50–75% of treated AVMs are completely blocked; two years after radiation treatment, the percentage increases to 85–95%.

Embolization

Embolization involves plugging up access to the malformation. This technique does not require opening the skull to expose the brain and can be used to treat deep AVMs. Using x-ray images as a guide, a catheter is threaded through the artery in the thigh (femoral artery) to the affected area. The patient remains awake during the procedure and medications can be administered to prevent discomfort. A device is inserted through the catheter into the AVM, and released there to block the blood supply to the malformation. The device may be metal spheres, an adhesive, a hardening polymer, or other such substance.

There may be a mild headache or nausea associated with the procedure, but patients may resume normal activities after leaving the hospital. At least two or three embolization procedures are usually necessary at intervals of 2–6 weeks. At least a three-day hospital stay is associated with each embolization. Embolization rarely provides complete blockage, and may be used prior to one or the other types of treatment.

Recovery and rehabilitation

Recovery and rehabilitation vary with each form of treatment. In general, successful treatment leads to reduction in the risk for cerebral hemorrhage and improvement of symptoms caused by the AVM. Surgical complications, including hemorrhage, infection, and treatment of too large an area, make recovery longer and more difficult, and may leave the patient with permanent neurologic deficits.

Clinical trials

Clinical trials of surgical techniques for treatment of AVMs are conducted in large medical centers.

Prognosis

Approximately 10% of AVM cases are fatal. Seizures and neurological changes may be permanent in another 10–30% cases of AVM rupture. If an AVM bleeds once, it is about 20% likely to bleed again in the next year. As time passes from the initial hemorrhage, the risk for further bleeding drops to about 3–4%. If the AVM has not bled, it is possible, but not guaranteed, that it never will. Untreated AVMs can grow larger over time and rarely go away by themselves. Once an AVM is removed and a person has recovered from the procedure, there should be no further symptoms associated with that malformation.

Resources

BOOKS

The Official Patient's Sourcebook on Arteriovenous Malformations: A Revised and Updated Directory for the Internet Age. San Diego: Icon Health Publications, 2002.

Steig, P., H. H. Batjer, and D. Samson. *Intracranial Arteriovenous Malformations.* New York: Macel Dekker, 2003.

Julia Barrett

Aspartame

Definition

Aspartame, an artificial sweetener that is used as a substitute for sugar in many foods and beverages, is considered by some scientists to be a neurotoxin, a substance that is detrimental to the nervous system. This allegation remains controversial.

Description

Aspartame was introduced as an artificial sweetener by the Monsanto Company in the 1970s. For much of the intervening time, individuals and special interest groups have maintained that aspartame damages the nervous system. Given the number and popularity of the items that are sweetened using aspartame (i.e., yogurts, soft drinks), the special interest groups assert that the general population is at risk for neurological damage caused by the ingestion of aspartame.

Key Terms

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

Fibromyalgia A condition characterized by aching and stiffness, fatigue, and sleep disturbance, as well as pain at various sites on the body.

Neurotoxin A poison that acts directly on the central nervous system.

Alleged harmful effects of aspartame ingestion include **seizures** and a change in the level of dopamine, a brain neurotransmitter. Symptoms associated with **lupus**, **multiple sclerosis**, and **Alzheimer's disease** have been claimed to result from an excess intake of aspartame. As well, aspartame consumption is claimed to increase the difficulty of diet-dependent diabetics in regulating their blood glucose level.

One peer-reviewed scientific study has documented an improvement in fibromyalgia symptoms (**pain** in the muscles, ligaments, and tendons) following the elimination of monosodium glutamate and aspartame from the diet. The influence of aspartame alone, however, was not assessed. Studies conducted prior to the marketing of aspartame and following its introduction have failed to demonstrate these claimed negative effects. The U.S. Food and Drug Administration (FDA) maintains that aspartame is not a health threat to the general population, although individuals who are sensitive to the compound can develop headaches and feel fatigued. Currently, there is no evidence directly linking aspartame with diseases such as lupus, multiple sclerosis, and Alzheimer's.

Demographics

As the association of aspartame with neurological disorders is not proven, statistics relating to how often and how many individuals suffer ill effects from aspartame are unavailable. If the claim of a general population effect is true, and that the effect is cumulative (builds up over time), then aspartame would affect older people more than younger people. There has been no evidence or suggestion of any gender, race, or cultural predilection to negative effects from aspartame.

If, however, only certain people are predisposed to be more sensitive to the presence of aspartame, then the demographics would include this subpopulation. The characteristics of such a group have not been defined.

Causes and symptoms

At elevated temperatures of about 90° Fahrenheit, a component of aspartame can convert to formaldehyde. High concentrations of formaldehyde can kill cells and tissues. Furthermore, formaldehyde can, in turn, be converted to formic acid, which can cause metabolic acidosis. Whether these changes are detrimental to the nervous system is not known.

One research paper published in 2001 reported one patient in whom aspartame exacerbated an ongoing migraine attack. Whether this occurrence is more widespread among the general public is unknown.

Diagnosis

Currently, any symptoms that are directly attributable to aspartame excess have not been conclusively identified. The suspected symptoms such as fibromyalgia and changes in dopamine levels are associated with other maladies including lupus, multiple sclerosis, or Alzheimer's disease. Factors that may trigger migraine **headache** vary among individuals, and physicians may suggest that those suffering from migraine lower their consumption of aspartame.

Treatment

Symptoms may disappear when the use of aspartame is discontinued.

Special concerns

Aspartame poisoning is a contentious issue. Scientific peer-reviewed papers have reported on research performed at companies that have a vested interest in sales of aspartame. While the quality of the scientific data contained in these studies may be sound, other scientists criticize that the evidence presented is difficult to evaluate in light of possible conflicting interests. By the same token, the claims made by special interest groups concerning the dangers of aspartame should be viewed cautiously, as little or no data is presented to support their claims.

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Key Terms

Autistic psychopathy Hans Asperger's original name for the condition now known as Asperger's disorder. It is still used occasionally as a synonym for the disorder.

DSM Abbreviation for the *Diagnostic and Statistical Manual of Mental Disorders,* a handbook for mental health professionals that includes lists of symptoms that indicate specific diagnoses. The text is periodically revised, and the latest version was published in 2000 and is called *DSM-IV-TR,* for Fourth Edition, Text Revised.

Gillberg's criteria A six-item checklist for AS developed by Christopher Gillberg, a Swedish researcher. It is widely used in Europe as a diagnostic tool.

High-functioning autism (HFA) A subcategory of autistic disorder consisting of children diagnosed with IQs of 70 or higher. Children with AS are often misdiagnosed as having HFA.

Nonverbal learning disability (NLD) A learning disability syndrome identified in 1989 that may overlap with some of the symptoms of AS.

Pervasive developmental disorders (PDDs) A category of childhood disorders that includes Asperger's syndrome and Rett's disorder. The PDDs are sometimes referred to collectively as autistic spectrum disorders.

Semantic-pragmatic disorder A term that refers to the difficulty that children with AS and some forms of autism have with pragmatic language skills. Pragmatic language skills include knowing the proper tone of voice for a given context, using humor appropriately, making eye contact with a conversation partner, maintaining the appropriate volume of one's voice, etc.

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Food and Drug Administration. 5600 Fishers Lane, CDER-HFD-210, Rockville, MD 20857. (301) 827-4573 or (888) 463-6332. <http://www.fda.gov>.

Brian Douglas Hoyle, PhD

Asperger's disorder

Definition

Asperger's disorder, which is also called Asperger's syndrome (AS) or autistic psychopathy, belongs to a group of childhood disorders known as pervasive developmental disorders (PDDs) or autistic spectrum disorders. The essential features of Asperger's disorder are severe social interaction impairment and restricted, repetitive patterns of behavior and activities. It is similar to **autism**, but children with Asperger's do not have the same difficulties in acquiring language that children with autism have.

In the mental health professional's diagnostic handbook, the *Diagnostic and Statistical Manual of Mental Disorders* fourth edition text revised, or *DSM-IV-TR*, Asperger's disorder is classified as a developmental disorder of childhood.

Description

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 *DSM-IV* (published in 1994) there was no officially agreed-upon definition of AS. In the words of ICD-10, the European equivalent of the *DSM-IV,* Asperger's is "a disorder of uncertain nosological validity." (Nosological refers to the classification of diseases.) There are three major reasons for this lack of clarity: differences between the diagnostic criteria used in Europe and those used in the United States; the fact that some of the diagnostic criteria depend on the observer's interpretation rather than objective measurements; and the fact that the clinical picture of Asperger's changes as the child grows older.

Asperger's disorder is one of the milder pervasive developmental disorders. 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 feed or dress themselves and take care of their

other daily needs. The distinguishing features of AS are problems with social interaction, particularly reciprocating and empathizing with the feelings of others; difficulties with nonverbal communication (such as 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 (for example, the parts of a clock or small machine, 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).

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, and nothing is known about the incidence of the disorder in different racial or ethnic groups.

With regard to gender differences, AS appears to be much more common in boys. Dr. Asperger's first patients were all boys, but girls have been diagnosed with AS since the 1980s. One Swedish study found the male/female ratio to be 4:1; however, the World Health Organization's ICD-10 classification gives the male to female ratio as 8 to 1.

Causes and symptoms

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 continues to be quite limited, however.

In addition, about 50% of AS patients have a history of oxygen deprivation during the birth process, which has led to the hypothesis that the disorder 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.

Research studies have made no connection between Asperger's disorder and childhood trauma, abuse or neglect.

In young children, the symptoms of AS typically include problems picking up social cues and understanding the basics of interacting with other children. The child may want friendships but find him- or herself unable to make friends.

Most children with Asperger's are diagnosed during the elementary school years because the symptoms of the disorder become more apparent at this point. They include:

- Poor pragmatic language skills. This phrase means that the child does not use the right tone or volume of voice for a specific context, and does not understand that using humorous or slang expressions also depends on social context.
- Problems with hand-eye coordination and other visual skills
- Problems making eye contact with others
- Learning difficulties, which may range from mild to severe
- Tendency to become absorbed in a particular topic and not know when others are bored with conversation about it. At this stage in their education, children with AS are likely to be labeled as "nerds."
- Repetitive behaviors. These include such behaviors as counting a group of coins or marbles over and over; reciting the same song or poem several times; buttoning and unbuttoning a jacket repeatedly; etc.

Adolescence is one of the most painful periods of life for young people with Asperger's, because social interactions are more complex in this age group and require more subtle social skills. Some boys with AS become frustrated trying to relate to their peers and may become aggressive. Both boys and girls with the disorder are often quite naive for their age and easily manipulated by "street-wise" classmates. They are also more vulnerable than most youngsters to peer pressure.

Little research has been done regarding adults with AS. Some have serious difficulties with social and occupational functioning, but others are able to finish their schooling, join the workforce, and marry and have families.

Diagnosis

Currently, 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 hyperactivity disorder** (ADHD), oppositional defiant disorder (ODD), or obsessive-compulsive disorder (OCD). Some researchers think that AS may overlap 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 higher than 70) autism" or HFA, and "schizoid personality disorder of childhood." Unlike schizoid personality disorder of childhood, AS is not an unchanging set of personality traits—AS 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 (scores on verbal sections of standardized intelligence tests) is usually higher than performance IQ (how well the child performs in school). The reverse is usually true for 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-TR *criteria for Asperger's disorder*

The *DSM-IV-TR* specifies the following 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 (facial expressions, for example); lack of age-appropriate peer relationships; failure to share enjoyment, interests, or accomplishment with others; lack of reciprocity (turn-taking) 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.

To establish the diagnosis, the child psychiatrist or psychologist would observe the child, and would interview parents, possibly teachers, and the affected child (depending on the child's age), and would gather a comprehensive medical and social history.

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's Syndrome, a detailed multi-item questionnaire developed in 1996.

Brain imaging findings

Current research has linked only a few structural abnormalities of the brain 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 (a part of the brain containing a sensory area associated with hearing). The first single photon emission tomography (SPECT) study of an AS patient found a lower-than-normal supply of blood to the left parietal area of the brain, an area associated with bodily sensations. Brain imaging studies on a larger sample of AS patients is the next stage of research.

Treatment team

The treatment team needed for a child with Asperger's syndrome will vary based on the specifics and the severity of the child's disabilities. Pediatricians, developmental pediatricians, neurologists, and child psychiatrists can all play a part in the diagnosis and the treatment planning for a child with Asperger's syndrome. Physical therapy, occupational therapy, speech and language therapy, individual and group behavioral therapy, and psychoeducational planning are all crucial to helping a child with Asperger's syndrome progress optimally.

Treatments

There is no cure for AS and no prescribed treatment regimen for all AS patients. Specific treatments are based on the individual's symptom pattern.

Medications

Many children with AS do not require any medication. For those who do, the drugs that are recommended most often include psychostimulants (methylphenidate, pemoline), clonidine, or one of the tricyclic antidepressants (TCAs) for hyperactivity or inattention; beta blockers, neuroleptics (antipsychotic medications), or lithium

(lithium carbonate) for anger or aggression; selective serotonin reuptake inhibitors (SSRIs) or TCAs for rituals (repetitive behaviors) and preoccupations; and SSRIs or TCAs for anxiety symptoms. One alternative herbal remedy that has been tried with AS patients is St. John's wort.

Psychotherapy

AS patients often benefit from individual psychotherapy, particularly during adolescence, in order to cope with depression and other painful feelings related to their social difficulties. Many children with AS are also helped by group therapy, which brings them together with others facing the same challenges. There are therapy groups for parents as well.

Therapists who are experienced in treating children with Asperger's disorder have found that the child should be allowed to proceed slowly in forming an emotional bond with the therapist. Too much emotional intensity at the beginning may be more than the child can handle. Behavioral approaches seem to work best with these children. Play therapy can be helpful in teaching the child to recognize social cues as well as lowering the level of emotional tension.

Adults with AS are most likely to benefit from individual therapy using a cognitive-behavioral approach, although many also attend group therapy. Some adults have been helped by working with speech therapists on their pragmatic language skills. A relatively new approach called behavioral coaching has been used to help adults with Asperger's learn to organize and set priorities for their daily activities.

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 are equipped to meet the special social needs of this group of children. Adults with AS appear to be at greater risk of depression than the general population. In addition, some researchers believe that people with AS have an increased risk of a psychotic episode (a period of time during which the affected person loses touch with reality) in adolescence or adult life.

Special concerns

Educational considerations

Most AS patients 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 AS children are dyslexic; others have difficulty with writing or mathematics. In some cases, AS children have been mistakenly put in special programs either for children with much lower levels of functioning, or for children with conduct disorders. AS children do best in structured learning situations in which they learn problem-solving and social 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. One approach that has been found helpful at the high-school level is to pair the adolescent with AS with a slightly older teenager who can serve as a mentor. The mentor can "clue in" the younger adolescent about the slang, dress code, cliques, and other "facts of life" at the local high school.

Employment

Adults with AS are productively employed in a wide variety of fields, including the learned professions. They do best, however, in jobs with regular routines or occupations that allow them to work in isolation. In large companies, employers or supervisors and workplace colleagues may need some information about AS in order to understand the new employee's "eccentricities."

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Autism Research Institute. 4182 Adams Avenue, San Diego, CA 92116.

Families of Adults Afflicted with Asperger's Syndrome (FAAAS). P.O. Box 514, Centerville, MA 02632. <www.faaas.org>.

National Association of Rare Disorders (NORD). P.O. Box 8923, New Fairfield, CT 06812-8923. (800) 999-NORD or (203) 746-6518.

Yale-LDA Social Learning Disabilities Project. Yale Child Study Center, New Haven, CT. The Project is looking for study subjects with PDDs between the ages of 8 and 24, including AS patients. Contact person: Sanno Zack at (203) 785-3488 or Sanno.Zack@yale.edu. <www.info.med.Yale.edu/chldstdy/autism>.

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American Academy of Child & Adolescent Psychiatry (AACAP). "Asperger's Disorder." AACAP Facts For Families Pamphlet #69. Washington, DC: American Academy of Child & Adolescent Psychiatry, 1999.

Rebecca Frey, Ph.D.

Assistive mobile devices

Definition

Assistive mobile devices are tools designed to improve the mobility and stability of persons who have difficulty moving independently.

Description

Assistive mobile devices include canes, crutches, walkers, and wheelchairs. The devices are used to allow a person to continue to be mobile; otherwise the person may have difficulty moving about independently. A large variety of medical conditions may lead to the need for a mobility aid. A partial list includes:

- **cerebral palsy**
- **multiple sclerosis**
- **stroke**
- brain or spinal cord injury
- **Parkinson's disease**
- diabetes
- arthritis
- **muscular dystrophies** (progressive muscle-weakening disorders)
- **ataxias** (group of disorders affecting balance and coordination)
- **amyotrophic lateral sclerosis** (ALS), also known as Lou Gehrig's disease, a progressive disease causing muscle weakness

Key Terms

Quadriplegia Permanent paralysis of the trunk, lower and upper limbs. It is caused by injury or disease affecting the spinal cord at the neck level.

- trauma of the lower extremities, such as sprain or fracture
- polio
- leg or hip **pain**

The choice of mobility aid will depend less on the patient's disease or disorder and more on the current level of mobility. Factors that affect mobility include leg strength, balance, endurance, **fatigue**, pain, generalized weakness, altered limb sensations, and limb coordination.

Types of Aids

Canes

A cane is appropriate for a person with good strength and endurance, whose balance is impaired either due to slowed movements, loss of isolated muscle control, or ataxia, or who has pain upon full weight bearing on one side. A cane is often used when the impairment is on one side, as from an ankle sprain or localized polio. The cane provides a third point of contact with the ground (along with the two legs), making a tripod that is far more stable than the two legs alone. The cane can support the weight, although prolonged weight bearing is uncomfortable on the wrists. Two canes may be used for extra stability. A cane typically has a rubber tip for traction, and may have a four-pronged base ("quad-cane") for even more stability. The cane and the favored leg move in unison to allow the cane to absorb the weight of the step.

Crutches

Crutches are used in pairs. The patient uses the crutches by gripping them and clasping them between the arm and the side of the chest, or the arms may slip through short tubular "cuffs" to reach the handgrips. The latter style is more commonly used for long-term disabilities such as cerebral palsy, while the former is often used for temporary fractures or sprains. In the case of a fracture or sprain, the goal is to keep weight off the injured limb during healing. Crutches allow the patient to use only a single foot, plus the two crutch tips, for the stable tripod stance. The patient's wrists support the weight, not the armpits. Cuffed crutches may be used when there is limited coordination in the legs, or when (as with polio) the

An occupational therapist assists a wheelchair-bound stroke patient. *(© Photo Reasearchers. Reproduced by permission.)*

legs are too weak to support the body's weight in full. The cuff transfers some of the bearing weight to the forearm, relieving the strain on the wrists.

Walkers

Walkers provide the maximum support and stability for a person who walks upright. The walker has four legs, or two legs plus two wheels, or four wheels. The walker's wide base of support provides great stability, important for those patients with balance problems. The frame supports the weight while the patient takes small steps forward. Following that, the patient lifts the walker and moves it forward, or rolls it forward (if it has wheels), and plants it again while taking another set of steps. Walkers move in front of the patient, but can still be useful for a person prone to fall backward. In this case, the height of the walker is lowered to ensure that weight is always tilted forward onto the walker. Wheeled walkers often have hand-operated brakes for greater safety, and may be equipped with a seat to allow the patient to sit down for short periods while ambulating.

Wheelchairs

Wheelchairs are designed for people who cannot support their weight on their legs, or for those whose balance is too impaired to stand. Wheelchairs may be short-term or long-term mobility aids, and may be used intermittently or all the time, depending on the requirements of the patient. There are several major designs for wheelchairs, including folding versus rigid, and manual versus powered. The technological developments in wheelchair design have made them extremely versatile and dependable, but at the same time have increased the cost of the more expensive models into the thousands of dollars. All wheelchairs have adjustable footrests to allow the legs to be held in a variety of positions.

The folding manual wheelchair is perhaps the most widely used style. Older folding chairs, still seen in airport

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."

terminals, hospitals, and school nursing offices, have the seat slung between the two sides. This is cheap and durable, but is not designed for maximum comfort or adaptability to the individual patient, and thus is rarely appropriate for long-term use.

More modern folding chairs provide a firm platform for a custom seat, allowing a choice of seating cushion. This is highly important for anyone who will spend long periods in the chair. Lack of proper seating leads to pressure sores, chafing, and skin breakdown. Choice of the right seat is one of the most important decisions in fitting the wheelchair. Seat styles include foam, air cushion, and other materials.

Rigid manual chairs are lighter than folding models, at the expense of some portability. Rigid chairs are also used by wheelchair athletes who compete in marathons and other events, attaining speeds of 30 miles per hour or more. These chairs are custom made for individual athletes, and have little in common with standard manual chairs. All manual chairs do share the same source of power—pushing either by the occupant or by an attendant. Frequent lubrication and maintenance maintains the chair in good shape to make this task as easy as possible.

Power wheelchairs use on-board batteries to drive the wheels, allowing independent mobility to those without enough upper body strength for a long trip in a manual chair. Power chairs are generally controlled by a joystick, although for quadriplegics or others who have lost sufficient arm control, a "sip-and-puff" mechanism is available, in which the patient's inhalations or exhalations into a straw control the direction and speed of the chair.

Resources

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Richard Robinson

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.

Children with A-T usually exhibit 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.

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.

Causes and symptoms

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.

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 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 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 team

The child's primary care physician will likely be the first person to begin evaluating the child for the presence of ataxia-telangiectasia. Other consulting physicians may include a **neurologist** (to help manage the neurologic complications), a pulmonologist and/or infectious disease specialist (to help manage the lung infections), and a hematologist/oncologist (to help manage lymphoma or leukemia). Physical therapists, occupational therapists, and speech and language therapists should also be consulted.

Treatment

There is no specific treatment for A-T because **gene therapy** is not yet an available option. Also, the disease is usually not diagnosed until the individual has developed health problems. Treatment is therefore focused on the observed conditions, especially if neoplasms 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. Although it is extremely rare, some patients with A-T may live into their 40s.

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ORGANIZATIONS

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A-T Medical Research Foundation. 5241 Round Meadow Rd., Hidden Hills, CA 91302. <http://pathnet.medsch.ucla.edu/people/faculty/gatti/gat-sign.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>.

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Ataxia

Definition

Ataxia, a medical term originated from the Greek language meaning "without order," refers to disturbances in the control of body posture, motor coordination, speech control, and eye movements. Several brain areas, including the **cerebellum** and the spinocerebellar tracts, substantia nigra, pons, and cerebral cortex control these functions. Injuries in one or more of these areas or in the spinal cord may lead to some form of ataxia. Birth trauma, medication toxicity, drug abuse, infections, tumors, degenerative disorders, head injury, **stroke**, or aneurysm, as well as hereditary neurological disorders also may cause ataxia. Many different types of inherited ataxias are presently known. Examples include **Machado-Joseph disease**, **ataxia-telangiectasia**, and **Friedreich ataxia**.

Description

Among children without inherited neurological disorders, important causes of ataxia are medication toxicity and post-infection inflammation of the brain. The later may happen as a complication of other viral diseases, such as measles, chicken pox, or influenza. While most people recover completely, some can have permanent neurological deficits.

Accidental ingestion of some drugs may cause ataxia, **seizures**, sensory neuropathies, or coma and death. The chronic administration of antihistamine medication and anticonvulsive drugs may cause ataxia in children, and should not be administered without instruction of a health-care provider. Ingestion of seafood contaminated with high levels of methyl-mercury also causes ataxia, as does accidental ingestion of solvents. Some drugs used in treating certain types of tumors, such as those in colorectal cancer, are especially neurotoxic and can induce temporary, but usually reversible ataxia. Alcoholism, metabolic disorders, and vitamin deficiencies may also lead to ataxia.

Demographics

Non-hereditary ataxia is known as sporadic or acquired ataxia. Approximately 150,000 people in the United States alone are presently affected by ataxia, either the acquired or hereditary form. Friedreich ataxia is the most common inherited ataxia, occurring in 1 out of 50,000 population.

Causes and symptoms

Ataxia may be a consequence of brain trauma, stroke, or aneurysm. Chronic and progressive ataxia is generally associated with either brain tumors or with one of the several types of inherited neurodegenerative disorders affecting one or more brain areas involved in movement and coordination control. Other neurodegenerative disorders, such as **Parkinson's disease** and **multiple sclerosis**, may present cerebellar and/or gait ataxia as one of the clinical signs. Another cause of either chronic or progressive

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.

Dystonia Painful involuntary muscle cramps or spasms.

Encephalitis Inflammation of the brain, usually caused by a virus. The inflammation may interfere with normal brain function and may cause seizures, sleepiness, confusion, personality changes, weakness in one or more parts of the body, and even coma.

Hypotonia Having reduced or diminished muscle tone or strength.

Microcephaly An abnormally small head.

Ophthalmoparesis Paralysis of one or more of the muscles of the eye.

ataxia is the congenital (present at birth) malformation of some structures of the **central nervous system**.

Hereditary ataxias are rare diseases, divided into two main categories according to the pattern of inheritance: autosomal dominant ataxias and autosomal recessive ataxias. Hereditary ataxias are additionally classified into types according to the affected structures and gene location of the defective chromosome. Autosomal dominant inheritance requires the presence of the mutation in only one of the two copies of a gene (maternal or paternal) to trigger the onset of the disease at some point in life, whereas autosomal recessive inheritance requires the inheritance of the mutation in both maternal and paternal genes. Other forms of hereditary ataxias are associated with metabolic disorders, such as the Maple Syrup Urine Disease, **Adrenoleukodystrophy**, and **Refsum disease**.

Autosomal Dominant Cerebellar Ataxias (ADCAs) are a group of ataxias divided into Types I, II, and III, according to the symptoms involved. Spinocerebellar ataxias (SCAs) Type 1, 2, 3, 4, 5, 6, 7, 10, and 11 belong to the ADCA group. Dominant Spinocerebellar Ataxias (SCAs) have several overlapping clinical signs, and a common feature to those belonging to the ADCA group is cerebellar ataxia, which manifests in difficulty walking and speaking. SCA1, 2, 3, and 4 may also involve partial paralysis of the eyes, slow eye movements, poor motor coordination, **dementia**, **peripheral neuropathy** (**pain**, numbness, or tingling sensation in the extremities of limbs and hands), optic neuropathy, and deafness. All of these symptoms are not necessarily present. SCA2 and SCA7 may also result in retinal damage, whereas those with SCA10 exhibit loss of muscle control and generalized seizures without other symptoms.

Inherited ataxias

SCA1 is caused by an abnormal gene expression located on chromosome 6. Genes consist of several different protein sequences, each coding (providing instructions) for one specific amino acid. A sequence error or abnormal repetition of a nucleotide (a building block of DNA and RNA) in a given gene impairs adequate protein synthesis or results in a wrong protein. In SCA1, abnormal amounts of the nucleotide CAG lead to symptoms such as eye-muscle dysfunction and increased tendon reflexes. The onset of symptoms usually occurs around the age of 30, or during the fourth decade of life. Increased amounts of CAG occur in each new generation, resulting in symptoms that usually appear earlier in life. SCA1 is also known as Spinocerebellar Atrophy I, **Olivopontocerebellar atrophy** I, and Menzel Type ataxia.

SCA2 is associated with abnormal gene expression on chromosome 12. Major symptoms include Parkisonism (**tremors** and **spasticity**), **myoclonus** (muscle spasms), Pons atrophy, and slowing of eye movement. SCA2 is subdivided in Episodic Ataxia Type 1 or EA1 (also named Paroxysmal and Myokymia syndrome) and Episodic Ataxia Type 2 or EA2. The onset of EA1 occurs in general around the five to six years of age, with muscles quickly becoming flaccid or rigid, tremors in the head or in the limbs, blurred vision, and/or vertigo. The severity of these episodes varies, and episodes usually last for about ten minutes, although in some cases they may last for as long as six hours. These episodes are generally triggered by stressful situations, anxiety, and abrupt movements, and also occur spontaneously due to a metabolic dysfunction. EA2 symptoms usually begin during school years or adolescence. The crisis starts with vertigo and ataxia, and is often associated with involuntary eye movements. This condition is treatable with daily administration of acetozolamide. When untreated, crisis may occur a few times per month, lasting from 1 to 24 hours. However, most affected individuals will experience a decrease in intensity and number of crises as they mature.

SCA3 ataxia is also known as Machado-Joseph disease and the gene affected is on chromosome 14. **Dystonia** (spasticity or involuntary and repetitive movements) or gait ataxia is usually the initial symptom in children. Gait ataxia is characterized by unstable walk and standing, which slowly progresses with the appearance of some of the other symptoms, such as abnormal hand movements, involuntary eye movements (i.e., nystagmus), muscular

wasting of hands, and loss of muscle tone in the face. SCA3 symptoms greatly vary among affected individuals as does the age of onset. Higher numbers of the CAG nucleotide repeats is associated with earlier onset and more severe symptoms. In addition, the number of CAG repeats tends to increase in each new generation, causing earlier onset and increased severity. There is no cure for Machado-Joseph disease.

SCA4 ataxia's genetic defect is located on chromosome 16, and results in major symptoms of cerebellar ataxia and sensory abnormalities. SCA4 may occur in two different forms, type I or type III. Both forms present symptoms 5–7 years earlier per generation. Symptoms usually become evident in type 1 from ages 19 to 59 years; from 45 to 72 years in type III. Difficulty walking, loss of muscle control, loss of fine-movement coordination of hands, and absence of tendon reflexes are the main symptoms observed in this progressive and crippling condition.

SCA5 ataxia is an extremely rare disorder linked to a defect on chromosome 11. Symptoms include mild ataxia and speech disorders. SCA5 ataxia was identified in one family descending from the paternal grandparents of Abraham Lincoln.

SCA6 ataxia is caused by a mutation on at chromosome 19. Clinical signs are varied, with some patients having limb and gait ataxia along with episodic headaches or nausea, and others having gait ataxia, speech difficulty, and abnormal eye movements. Initially, most patients only sense a momentary imbalance and mild vertigo when they make a quick movement or turn. After months or years, balance problems become more pronounced. The disease progresses over 20–30 years and eventually leads to severe disability. The age of onset ranges from 6 to 86 years. Periodic episodes of paralysis occur on one side of the body and last for days. Episodes may be triggered by head injuries and emotional stress. Some persons with SCA6 ataxia experience a more rapid progression and require wheelchair for support and mobility approximately 5 years after onset.

SCA7 ataxia is also known as olivopontocerebellar atrophy III, and results from a defect on chromosome 3. Symptoms of SCA7 ataxia occur earlier with each generation, and earlier onsets are associated with more severe symptoms. The onset of symptoms occurs in younger ages when the mutated copy of the gene is inherited from the paternal side. Ataxia, severe eye problems (retinal and macular degeneration), and early blue-yellow color blindness are typical clinical signs of the disease. Decreased vision occurs in over 80% of individuals with SCA7 ataxia, and almost one third of these persons eventually become blind. Hearing loss is also associated with SCA7 ataxia, and may slowly progress over decades. In more severe cases, usually associated with paternal inheritance of the defective gene, heart failure, liver disorders, muscle loss, and developmental delays can all occur. The degree of severity of SCA7 ataxia, the age of onset, and the rate of progression greatly vary both within and among families.

SCA10 ataxia is caused by an unstable protein repeat on chromosome 22. The main characteristics of SCA10 are generalized motor seizures, irregular eye movements, gait and limb ataxia, and speech difficulties. The age of onset ranges from 10 to 40 years. SCA11 ataxia is a very rare disease, mapped to chromosome 15. SCA11 progresses slowly over decades, with onset between adolescence and young adulthood. All individuals develop gait disorders, increased reflex action, eye disturbances and irregular movements, and speech difficulties.

Some inherited metabolic disorders cause progressive nerve degeneration with ataxia as one of its symptoms, as is the case with the group of diseases known as leukodistrophies. One famous example is Adrenoleukodystrophy (ALD), a rare autosomal dominant disease that causes progressive loss of the myelin sheath that covers the nerve fibers, along with progressive adrenal gland degeneration. ADL has two forms: the X-linked ADL (or X-ADL) and the non X-linked ADL (or ADL). The X-ADL is the more devastating form of the disease, with the onset of symptoms occurring between four and ten years of age. ADL (non X-linked) disease usually begins during adulthood, between 21 and 35 years of age and progresses slowly. In both forms of ADL, the loss of myelin by nerve fibers is due to an abnormal accumulation of saturated long fatty acid chains in the brain, because of a metabolic error involving a protein that transports fatty acids. The gene responsible for X-ADL was identified in 1993. The disorder was presented in the film *Lorenzo's Oil,* based on the story of Lorenzo Odone and his parents' quest to find a cure for the disease. Other X-ADL symptoms are seizures, speech and swallowing difficulties, gait and coordination ataxia, visual loss, progressive dementia, and loss of hearing that ends in deafness. As the mutation is inherited in the X chromosome, ADL is more severe in boys than in girls, because females have two X chromosomes, and the normal copy (or allele) of the affected gene will compensate for the dysfunctional one. Treatment with adrenal hormones can save the child's life and Lorenzo's oil, a mixture of oleic and euric acids, reduces or delays the onset of symptoms in carriers of the mutation without manifested symptoms. Oral intake of DHA (docosahexanoic acid) is prescribed for children and infants with X-ADL. As the neurological degeneration is progressive, prognosis is usually poor with patients dying within 10 years from the onset of symptoms.

Another metabolic disorder causing ataxia is the maple syrup urine disease or MSUD, an inherited disease caused by a metabolic disorder involving the breakdown

of certain amino acids by enzymes. MSUD may occur in three different forms: neonatal convulsive crisis (classical form); progressive **mental retardation** (intermediary form); or recurrent ataxia and **encephalopathy** (intermittent form). The disease was first discovered in the Mennonite Community of Lancaster, PA, where MSUD affects 1 out of 176 individuals, although it is rare in other populations. MSUD onset may occur between five months of age and the second year of life. During crisis, the urine presents an odor similar to maple syrup and the blood shows high levels of branched amino acids and ketoacids. Between crises, such concentrations are normal both in urine and blood. Severe crises with high concentrations of ketoacids may be life threatening, requiring dialysis. The standard treatment is protein restriction in the diet; but some patients who respond to the administration of thiamine during crises may benefit from the intake of thiamine on a daily basis.

Refsum disease is caused by a dysfunction in the metabolism of lipids that leads to high concentrations of phytanic acid in tissues and blood plasma. Phytanic acid is a component of chlorophyll, obtained through the diet. The enzyme phytanic acid hydrolase normally helps eliminate phytanic acid from the body. The inheritance is autosomal recessive, and the onset may occur between the first and the third decade of life. One of the first symptoms is night blindness, but the pace of progression varies among affected individuals. Other main symptoms are irregularities in the retina of the eye, bone and skin changes, and the abnormal gait, speech patterns, and muscle movements associated with cerebellar ataxia. Treatment involves dietary restrictions and blood transfusion exchanges aimed at halting the progression of the disease and resolving symptoms.

Friedreich ataxia is the most common form of hereditary ataxia, affecting 1 out of 50,000 individuals. Friedreich ataxia is a progressive disorder affecting the arms and legs, with progressive weakness, loss of deep tendon reflexes, and sensory loss. Diabetes and/or some forms of heart disease may also be present in people with Friedreich ataxia. Onset of symptoms usually occurs before 20 years of age. As symptoms of Friedreich ataxia are similar to those found in other juvenile ataxias, diagnosis requires genetic testing to conform.

Diagnosis

Genetic forms of ataxia must be distinguished from the acquired (non-genetic) ataxias. Diagnosis of inherited ataxias begins with the analysis of the clinical family history, physical examination, and neuro-imaging techniques such as **CT** or **MRI** scans. As similar symptoms are described in many different types of ataxia, genetic screening is the most reliable tool for diagnosis. Genetic tests for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, SCA17, episodic ataxia type 1, episodic ataxia type 2, DRPLA, Friedreich ataxia (FRDA), and Charlevoix-Saguenay ataxia are available.

Treatment team

Neurologists and geneticists are the front line treatment team for people with ataxia, along with specialized nurses and therapists. Both neurologists and geneticists usually participate in the diagnosis of the particular form of ataxia. Neurologists and other physicians provide treatment for the resulting symptoms. Genetic counseling and risk assessment of individuals without symptoms, but with a family history of the disease, is the task of the geneticist.

Treatment

Except for some acquired and reversible forms of ataxia as initially described, there is no cure or preventive treatment for the progressive forms of the disease, or for those ataxias resulting from accidental lesions of motor brain areas and/or the spinal cord. Antispasmodic and/or anticonvulsive medications, and analgesics for some painful neuropathies, may control and relieve the respective symptoms in some ataxia subtypes. Wheelchair, walking devices, and speech aids may be required in different stages of the progressive forms of ataxia.

Recovery and rehabilitation

Whether the ataxia is an acute condition that is likely to improve, or a progressive disease, therapy is aimed at maintaining the highest practical level of muscle function and coordination. Physical therapists provide strengthening exercises where muscle tissue integrity is likely to return or plateau, and range of motion exercises where muscle movement is limited. Gait training is also an important part of rehabilitation for persons with ataxia, as physical therapists help persons adapt to abnormal muscle movements, while safely maintaining posture and walking. As the disease progresses, the goals of therapy adapt to the person's changing abilities. Speech therapists help assess difficulties with speaking and eating, and offer strategies to compensate for them. Occupational therapists also make positional devices available to help maintain posture and comfort.

Clinical trials

Further basic research is needed before **clinical trials** become a possibility for this group of neurodegenerative diseases. Ongoing genetic and molecular research on the mechanisms involved in the disease will eventually yield enough data for the development of further diagnostic

markers and, hopefully, allow the design of experimental gene therapies to treat many of the inherited ataxias.

Prognosis

The prognosis for a person with ataxia depends upon the type and nature of the disease. Ataxia as a result of trauma or infection may be a temporary condition, or leave some degree of permanent disability. Hereditary ataxias are usually progressive syndromes, with symptoms becoming more disabling over varying periods of time.

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OTHER

Dystonia Medical Research Foundation. 1 East Wacker Drive, Suite 2430, Chicago, IL, 60601-1905. (312) 755-0198; Fax: (312) 803-0138. Dystonia@dystonia-foundation.org. <http://www.dystonia-foundation.org>.

International Joseph Disease Foundation, Inc. P.O. Box 994268, Redding, CA 96099-4268. (530) 246-4722. MJD@ijdf.net. <http://www.ijdf.net>.

National Ataxia Foundation (NAF). 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447-4752. (763) 553-0020; Fax: (763) 553-0167. Naf@ataxia.org. <http://www.ataxia.org>.

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National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD (6673); Fax: (203) 798-2291. Orphan@rarediseases.org. <http://www.rarediseases.org>.

Worldwide Education & Awareness for Movement Disorders (WE MOVE). 204 West 84th Street, New York, NY. (212) 875-8312 or (800) 437-MOV2 (6682). Fax: (212) 875-8389. Wemove@wemove.org. <http://www.wemove.org>.

Sandra Galeotti

Atomoxetine

Definition

Atomoxetine is a prescription drug that is used to treat symptoms of impulsivity, inattentiveness, and hyperactivity, which are hallmark features of **attention deficit hyperactivity disorder** (ADHD). In the United States, atomoxetine is sold under the brand name Strattera.

Purpose

Atomoxetine is the only nonstimulant drug that has proven effective for alleviating all three of the hallmark features of ADHD. The drug is frequently used along with other psychological, educational, or social therapies in ADHD management.

Description

Atomoxetine is a selective norepinephrine inhibitor. By enhancing the activities of norepinephrine in certain areas of the brain, atomoxetine reduces chemical imbalances that are believed to contribute to ADHD symptoms.

Although the exact way that atomoxetine works in the brain is not well understood, the drug is believed to correct chemical imbalances between dopamine and norepinephrine. These two naturally occurring chemicals are commonly referred to as **neurotransmitters**. Their function is to regulate transmission of impulses from one cell to another. Atomoxetine may restore normal attention spans, correct impulsiveness, and calm hyperactivity by counteracting the neurotransmission abnormalities that cause symptoms of ADHD.

Before atomoxetine was approved by the FDA in 2002, all the drugs previously approved for ADHD were stimulants. Stimulants such as amphetamines have the potential to be abused and are sometimes sold illegally. As a result, strict rules are in place to monitor dispensing of prescription stimulants, and patients must obtain new prescriptions from their doctors each month. Because atomoxetine is not a stimulant, it is easy for patients to obtain refills for their medication and fewer physician visits are required. Many patients prefer atomoxetine over stimulants for the convenience the drug offers.

Key Terms

Asthma A condition characterized by spasms of the lung's airways that causes breathing difficulties.

Attention deficit hyperactivity disorder (ADHD) A psychiatric disorder characterized by inattention, hyperactivity, and impulsiveness.

Dopamine A precursor to norepinephrine that is also a neurotransmitter in some regions of the brain.

Neurotransmitter A chemical in the brain that transmits messages between neurons or nerve cells.

Norepinephrine A hormone that controls blood pressure and heart rate. It is also a chemical found in the brain that is thought to play a role in ADHD.

Stimulant Any chemical or drug that has excitatory actions in the central nervous system.

Recommended dosage

In adults or children weighing more than 150 lb (70 kg), the initial dose of atomoxetine is typically 40 mg taken once a day. The dosage can be increased after three days to 80 mg. This can be given either as a single dose in the morning or divided evenly in the morning and late afternoon. If a higher dosage is needed, the dose can be increased after 2–4 weeks to a maximum of 100 mg per day. The dosage must be lowered in individuals that have liver disease, since atomoxetine is broken down by the liver.

Atomoxetine should be initiated at a total daily dose of 1 mg/lb (0.5 mg/kg) in children that weigh less than 150 lb (70 kg). After at least three days, the dose can be increased to 2.4 mg/lb (1.2 mg/kg). Children may either take the entire dose in the morning or may split the dose evenly in the morning and late afternoon.

Improvements in ADHD symptoms may be noticed within 24 hours of first taking atomoxetine, although 3–4 weeks may be required for full benefits to be seen.

Precautions

Atomoxetine may cause changes in heart rate or blood pressure. As a result, this drug may not be appropriate for patients that have high blood pressure, rapid heartbeats, heart disease, or a history of strokes. Patients should have their blood pressure and pulse rate monitored when they start therapy and any time their dosage is increased.

Because of the possibility of severe eye damage, patients with a history of narrow angle glaucoma should not take atomoxetine. Since the liver breaks down the drug, patients with a history of liver disease should only be prescribed a low dose.

Patients who take dietary supplements, herbal remedies, or drugs that are available without a prescription should consult with their doctor prior to taking atomoxetine. It is best to avoid atomoxetine while pregnant and breastfeeding since its effects have not been studied during pregnancy and it is not known whether the drug is excreted in breast milk.

The drug may cause **fatigue**, **dizziness**, and headaches. Patients with a history of low blood pressure may be especially susceptible to these effects. It is best to avoid driving or operating heavy machinery until it is clear whether the drug will alter reaction time or impair judgment.

Side effects

The most common side effects associated with atomoxetine in children and teens are upset stomach, nausea, vomiting, decreased appetite, dizziness, tiredness, and mood swings.

In adults, the effects of constipation, dry mouth, nausea, decreased appetite, dizziness, sleeping difficulties, sexual side effects, difficulty urinating, and menstrual cramps are commonly attributed to atomoxetine.

If patients experience swelling or hives, they should not continue taking atomoxetine since serious allergic reactions may occur.

Interactions

Atomoxetine should not be used with certain types of antidepressants known as monoamine oxidase (MAO) inhibitors since this combination may cause blood pressure and heart rates to increase sharply. Muscle stiffness, muscle spasms, and even death can occur as a result of this drug interaction.

Atomoxetine may also increase heart rate and blood pressure when combined with albuterol, a drug that is commonly used to treat asthma.

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Kelly Karpa, PhD, RPh

Attention deficit hyperactivity disorder

Definition

Attention deficit hyperactivity disorder (ADHD) is not a clinically definable illness or disease. Rather, as of December 2003, ADHD is a diagnosis that is made for children and adults who display certain behaviors over an extended period of time. The most common of these behavioral criteria are inattention, hyperactivity, and marked impulsiveness.

In the American description, there are three types of ADHD, depending on which diagnostic criteria have been met. These are: ADHD that is characterized by inattention, ADHD characterized by impulsive behavior, and ADHD that has both behaviors.

The European description of ADHD places the disorder in a subgroup of what are termed hyperkinetic disorders (hallmarks are inattention and over-activity).

Description

ADHD is also known as attention deficit disorder (ADD), attention deficit disorder with and without hyperactivity, hyperkinesis, hyperkinetic impulse disorder, hyperactive syndrome, hyperkinetic reaction of childhood, minimal brain damage, minimal brain dysfunction, and undifferentiated deficit disorder.

The term attention deficit is inexact, as the disorder is not thought to involve a lack of attention. Rather, there appears to be difficulty in regulating attention, so that attention is simultaneously given to many stimuli. The result is an unfocused reaction to the world. As well, people with ADHD can have difficulty in disregarding stimuli that are not relevant to the present task. They can also pay so much attention to one stimulus that they cannot absorb another stimulus that is more relevant at that particular time.

For many people with ADHD, life is a never-ending shift from one activity to another. Focus cannot be kept on any one topic long enough for a detailed assessment. The constant processing of information can also be distracting, making it difficult for an ADHD individual to direct his or her attention to someone who is talking to him or her. Personally, this struggle for focus can cause great chaos that can be disruptive and diminish self-esteem.

The neurological manifestations of ADHD are disturbances of what are known as executive functions. Specifically, the six executive functions that are affected include:

- the ability to organize thinking
- the ability to shift thought patterns
- short-term memory
- the ability to distinguish between emotional and logical responses
- the ability to make a reasoned decision
- the ability to set a goal and plan how to approach that goal

About half or more of those people with ADHD meet criteria set out by the American Psychiatric Association (*Diagnostic and Statistical Manual of Mental Disorders* [DSM-IV]) for at least one of the following other illnesses:

- learning disorder
- restless leg syndrome
- **depression**
- anxiety disorder
- antisocial behavior
- substance abuse
- obsessive-compulsive behavior

Key Terms

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

Executive functions A set of cognitive abilities that control and regulate other abilities and behaviors. Necessary for goal-directed behavior, they include the ability to initiate and stop actions, to monitor and change behavior as needed, and to plan future behavior when faced with novel tasks and situations.

Frontal cortex The part of the human brain associated with aggressiveness and impulse control. Abnormalities in the frontal cortex are associated with an increased risk of suicide.

Psychometric The development, administration, and interpretation of tests to measure mental or psychological abilities. Psychometric tests convert an individual's psychological traits and attributes into a numerical estimation or evaluation.

Demographics

ADHD is a common childhood disorder. It is estimated to affect 3–7% of all children in the United States, representing up to two million children. The percentage

may in fact be even higher, with up to 15% of boys in grades one through five being afflicted. On average, at least one child in each public and private classroom in the United States has ADHD. In countries such as Canada, New Zealand, and Germany, the prevalence rates are estimated to be 5–10% of the population.

The traditional view of ADHD is that boys are affected more often than girls. Community-based samples have found an incidence rate in boys that is double that of girls. In fact, statistics gathered from patient populations have reported male-to-female ratios of up to 4:1. However, as the understanding of ADHD has grown since the early 1990s and as the symptoms have been better recognized, the actual number of females who are affected by ADHD may be more similar to males than previously thought.

Causes and symptoms

The cause of ADHD is unknown. However, evidence is consistent with a biological cause rather than an environmental cause (e.g., home life). Not all children from dysfunctional homes or families have ADHD.

For many years, it was thought that ADHD developed following a physical blow to the head, or from an early childhood infection, leading to the terms "minimum brain damage" and "minimum brain dysfunction." However, these definitions apply to only a very small number of people diagnosed with ADHD, and so have been rejected as the main cause.

Another once-favored theory was that eating refined sugar or chemical additives in food produced hyperactivity and inattention. While sugar can produce changes in behavior, evidence does not support this proposed association. Indeed, in 1982, the results presented at a conference sponsored by the U.S. National Institutes of Health conclusively demonstrated that a sugar- and additive-restricted diet only benefits about 5% of children with ADHD, mostly young children and those with food allergies.

The biological roots of ADHD may involve certain areas of the brain, specifically the frontal cortex and nearby regions. One explanation is that the executive functions are controlled by the frontal lobes of the brain. **Magnetic resonance imaging (MRI)** examination of subjects who are exposed to a sensory cue has identified decreased activity of regions of the brain that are involved in tasks that require attention. Another MRI-based study published in November 2003 also implicates a region of the brain that controls impulsive behavior. Finally, a study conducted by the U.S. National Institute of Mental Health (NIMH) documented that the brains of children and adolescents with ADHD are 3–4% smaller than those of their ADHD-free counterparts. Additionally, the decreased brain size is not due to the use of drugs in ADHD treatment, the researchers concluded in a paper published in October 2002.

ADHD symptoms can sometimes be relieved by the use of stimulants that increase a chemical called dopamine. This chemical functions in the transmission of impulses from one neuron to another. Too little dopamine can produce decreased motivation and alertness. These observations led to the popular "dopamine hypothesis" for ADHD, which proposed that ADHD results from the inadequate supply of dopamine in the **central nervous system**.

The observations that ADHD runs in families (10–35% of children with ADHD have a direct relative with the disorder) point to an underlying genetic origin. Studies with twins have shown that the occurrence of ADHD in one twin is more likely to be mirrored in an identical twin (who has the same genetic make-up) than in a fraternal twin (whose genetic make-up is similar but not identical).

The genetic studies have implicated the binding, transport, and enzymatic conversion of dopamine. Two genes in particular have been implicated: a dopamine receptor (DRD) gene on chromosome 11 and the dopamine transporter gene (DAT1) on chromosome 5.

There may be environmental factors that influence the development of ADHD. Complications during pregnancy and birth, excessive use of marijuana, cocaine, and/or alcohol (especially by pregnant women), ingestion of lead-based paint, family or marital tension, and poverty have been associated with ADHD in some people. However, many other ADHD sufferers do not display any of these associations.

Heavy use of alcohol by a pregnant woman can lead to malformation of developing nerve cells in the fetus, which can result in a baby of lower than normal birth weight with impaired intelligence. This condition, called fetal alcohol syndrome, can also be evident as ADHD-like hyperactivity, inattention, and impulsive behavior.

Diagnosis

ADHD is sometimes difficult to diagnose. Unlike the flu or a limb fracture, ADHD lacks symptoms that can be detected in a physical examination or via a chemical test. Rather, the diagnosis of ADHD relies on the presence of a number of characteristic behaviors over an extended period of time. Often the specialist will observe the child during high-stimuli periods such as a birthday party and during quieter periods of focused concentration. Diagnosis uses the DSM-IV criteria, originally published in 1994, in combination with an interview and assessment of daily activity by a qualified clinician. (As of December 2003,

revised DSM criteria are pending. These revisions will reflect the increased awareness of the greater-than-perceived prevalence of ADHD in girls and women.)

The benchmarks for either inattention or for hyperactivity/impulsive behavior must be met. These benchmarks typically occur by the age of seven and are not exclusive to one particular social setting such as school. These benchmarks must have been present for an extended period of time, at least six months or more. There are nine separate criteria for each category. For diagnosis, six of the nine criteria must be met. Examples of diagnostic signs of inattention include difficulty in maintaining concentration on a task, failure to follow instructions, difficulty in organizing approaches to tasks, repeated misplacement of tools necessary for tasks, and tendency to become easily distracted. Examples of hyperactivity or impulsive behavior include fidgeting with hands or feet, restlessness, difficulty in being able to play quietly, excessive talk, and tendency to verbally or physically interrupt.

Because ADHD can be associated with the use of certain medications or supplements, diagnosis involves screening for the past or present use of medications such as anticonvulsant or antihypertensive agents, and caffeine-containing drugs.

Diagnosis of ADHD can also be complicated by the simultaneous presence of another illness. Diagnosis involves screening for bipolar disorder, depression, eating disorder, learning disability, panic disorder (including agoraphobia), sleep disorder, substance abuse, or Tourette's syndrome. Almost half of all children (mostly boys) with ADHD display what has been termed "oppositional defiant behavior." These children tend to be stubborn, temperamental, belligerent, and can lash out at others over a minor provocation. Without intervention, such children could progress to more serious difficulties such as destruction of property, theft, arson, and unsafe driving.

Other, nonclinical information such as legal infractions (arrests, tickets, vehicle accidents), school reports, and interviews with family members can be valuable, as ADHD can be perceived as antisocial, erratic, or uncommon behavior.

A complete physical examination is recommended as part of the diagnosis. The examination offers the clinician an opportunity to observe the behavior of the person. More specific tests can also be performed. Children can be assessed using the Conner's Parent and Teacher Rating Scale. Adolescent and adult assessment can utilize the Brown Attention Deficit Disorder Scale. Impulsive and inattentive behavior can be assessed using the Conner's Continuous Performance Test (CPT) or the Integrated Visual and Auditory CPT. Girls can be specifically assessed using the Nadeau/Quinn/Littman ADHD Self-Rating Scale.

Treatment team

The treatment team involves behavioral and medical specialists. Concerning behavior, teachers play a very important role. Their daily observation of the child and the use of standard evaluation tests can help in the diagnosis and treatment of ADHD. More specialized consultants within the school system, such as psychometrists, may also be available. Outside of the school setting, psychologists, **social workers**, and family therapists can also be involved in treatment.

The use of medications involves physicians, nurses, and pharmacists.

Treatment

Behavior treatment can consist of the monitoring of school performance and the use of standard evaluation tests. For older children, adolescents, and adults, support groups can be valuable. As well, ADHD patients can learn behavioral techniques that are useful in self-monitoring their behavior and making the appropriate modifications (such as a time out). Behavior treatment is useful in combination with drug therapy or as a stand-alone treatment in those cases in which the use of medication is not tolerated or is not preferred.

Medical treatment can consist of the use of drugs such as Ritalin that are intended to modify over-exuberant behavior, or other drugs that have differing targets of activity. Psychostimulant medications like Ritalin, Cylert, and Dexedrine increase brain activity by increasing the brain concentration of chemicals such as dopamine, which are involved in the transmission of impulses or by stimulating the receptors to which the chemicals bind. Psychostimulant medications can sometimes disrupt sleep, depress appetite, cause stomachaches and **headaches**, and trigger feelings of anger and anxiousness, particularly in people afflicted with psychiatric illnesses such as bipolar disorder or depression. For many people, the side effects are mild and can become even milder with long-term use of the drugs.

Antidepressant medications such as imipramine act by slowing down the absorption of chemicals that function in the transmission of impulses. Central alpha agonists are particularly used in the treatment of hyperactivity. By restricting the presence of neurotransmitter chemicals in the gap between neurons, drugs such as clonidine and guanfacine restrict the flow of information from one neuron to the next. There have been four reported cases of sudden death in people taking clonidine in combination with the drug methylphenidate (Ritalin), and reports of nonfatal heart disturbances in people taking clonidine alone.

Finally, medications known as selective norepinephrine reuptake inhibitors restrict the production of norepinephrine between neurons, which inhibits the sudden and often hyperactive "fight or flight" response.

A special education teacher helps a child with ADHD do his math assignment. *(© Photo Reasearchers. Reproduced by permission.)*

Recovery and rehabilitation

After a patient has been stabilized, typically using medication, follow-up visits to the physician are recommended every few months for the first year. Then, follow-ups every three or four months may be sufficient. The use of medications may continue for months or years.

Recovery and rehabilitation are not terms that apply to ADHD. Rather, a child with ADHD can be assisted to an optimum functionality. Assistance can take the form of special education in the case of those who prove too hyperactive to function in a normal classroom; the child may be seated in a quieter area of the class; or by using a system of rules and rewards for appropriate behavior. Children and adults can also learn strategies to maximize concentration (such as list making) and strategies to monitor and control their behavior.

Clinical trials

Beginning in 1996, the U.S. National Institute of Mental Health (NIMH) and the Department of Education began a clinical trial that included nearly 600 elementary school children ages seven to nine. The study, which compared the effects of medication alone, behavior management alone, or a combination of the two, found the combination to produce the most marked improvement in concentration and attention. Additionally, the involvement of teachers and other school personnel was more beneficial than if the child was examined only a few times a year by their family physician.

As of January 2004, a number of clinical studies were recruiting patients, including:

- Behavioral and functional neuroimaging study of inhibitory motor control. The basis of the inability to control behavior in ADHD was assessed using behavioral tests and the technique of **magnetic resonance imaging** (**MRI**).
- Brain imaging in children with ADHD. MRI was used to compare the connections between brain regions in children with and without ADHD.
- Brain imaging of childhood onset psychiatric disorders, endocrine disorders, and healthy children. MRI was used to investigate the structure and activity in the brains of healthy people and those with childhood onset psychiatric disorders, including ADHD.
- Genetic analysis of ADHD. Blood samples from a child with ADHD and his or her immediate family members were collected and analyzed to determine the genetic differences between ADHD and non-ADHD family members.
- Biological markers in ADHD. People with ADHD, their family members, and a control group of healthy people who had previously undergone magnetic resonance examination were assessed using psychiatric interviews, neuropsychological tests, and genetic analysis.
- Study of ADHD using transcranial magnetic stimulation. The technique, in which a magnetic signal is used to stimulate a region of the brain that controls several muscles, was used to investigate whether ADHD patients have a delayed maturation of areas of their nervous system responsible for such activity. Detectable differences could be useful in diagnosing ADHD.
- Clonidine in ADHD Children. The trial evaluated the benefits and side effects of two drugs (clonidine and methylphenidate) used individually or together to treat childhood ADHD.
- Nutrient intake in children with ADHD. The study determined if children with ADHD have a different eating pattern, such as intake of less food or a craving for carbohydrates, than children without ADHD. The information from the study would be used in probing the origins of ADHD and in devising treatment strategies.
- Preventing behavior problems in children with ADHD. The study was designed to gauge the effectiveness of a number of treatment combinations in preventing behavior that is characteristic of ADHD in children.
- Psychosocial treatment for ADHD Type I. The study focused on ADHD that is characterized by inattention. The aim of the study was to develop effective treatment strategies for Type I ADHD.

- Treatment of adolescents with comorbid alcohol use and ADHD. The effectiveness of a drug (bupropion) that is designed to be released at a constant rate over time was evaluated in the treatment of ADHD adolescents (14–18 years) who are also alcohol abusers.
- Behavioral treatment, drug treatment, and combined treatment for ADHD. The effectiveness of the three treatment approaches was compared, and the interactions between different levels of the behavioral and drug treatments were examined.
- Attention deficit disorder and exposure to lead. The effect of past exposure to lead was studied in children with ADHD.

Prognosis

The outlook for a patient with ADHD can be excellent, if the treatment regimen is followed and other existing conditions and disabilities have been identified and are treated. Methylphenidate, the major psychostimulant used in the treatment of ADHD, has been prescribed since the 1960s. The experience gained over this time has established the drug as being one of the safest pharmaceuticals for children. Indeed, intervention can be beneficial. Researchers from the Massachusetts General Hospital reported in 1999 that drug treatment of children diagnosed with ADHD could dramatically reduce the future risk of substance abuse.

Special concerns

The diagnosis of ADHD continues to be controversial. While some children do benefit from the use of medicines, other children who behave differently than is the norm may be needlessly medicated. The inattention, hyperactivity, and impulsive behavior that are the hallmarks of ADHD can be produced by many other conditions. The death of a parent, the discomfort of a chronic ear infection, and living in a dysfunctional household are all situations that can cause a child to become hyperactive, uncooperative, and distracted.

Evidence since the 1960s has led to the consensus that the medications used to treat ADHD, particularly methylphenidate (Ritalin), pose no long-term hazards. However, research published in December 2003 documented that rats exposed to the drug tended to avoid rewarding stimuli and instead became more anxious. More research on the effects of long-term drug treatment in ADHD is scheduled.

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Attention Deficit Disorder Association (ADDA). PO Box 543, Pottstown, PA 19464. (484) 945-2101; Fax: (610) 970-7520. mail@add.org. <http://www.add.org>.

Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD). 8181 Professional Place, Suite 150, Bethesda, MD 20785. (301) 306-7070 or (800) 233-4050; Fax: (301) 306-7090. <http://www.chadd.org>.

National Institute of Mental Health (NIMH). 6001 Executive Boulevard, Bethesda, MD 20892-9663. (301) 443-4513 or (866) 615-6464; Fax: (301) 443-4279. nimhinfor@nih.gov. <http://www.nimh.nih.gov>.

National Institute of Neurological Disorders and Stroke. 6001 Executive Boulevard, Bethesda, MD 20892-9663. (301) 446-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

Brian Douglas Hoyle

Autism

Definition

Autism is a behavior disorder, characterized by an impairment in social communication, social interaction, and social imagination. Those with autism often have a restricted range of interests and display repetitive behaviors

Key Terms

Cytogenetics The branch of biology that combines the study of genetic inheritance with the study of cell structure.

Fragile X syndrome A genetic condition related to the X chromosome that affects mental, physical, and sensory development. It is the most common form of inherited mental retardation.

Phenylketonuria A rare, inherited, metabolic disorder in which the enzyme necessary to break down and use phenylalanine, an amino acid necessary for normal growth and development, is lacking. As a result, phenylalanine builds up in the body causing mental retardation and other neurological problems.

Schizophrenia A severe mental illness in which a person has difficulty distinguishing what is real from what is not real. It is often characterized by hallucinations, delusions, and withdrawal from people and social activities.

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).

Tuberous sclerosis A genetic condition that affects many organ systems including the brain, skin, heart, eyes, and lungs. Benign (non-cancerous) growths or tumors called hamartomas form in various parts of the body, disrupting their normal function.

and mannerisms, along with altered reactions to the everyday environment.

Description

In 1943, the American physician Leo Kanner published his seminal paper, in which he described 11 children who were socially isolated, with "autistic disturbances of affective contact," impaired communication, and behavioral inflexibility. He coined the term "infantile autism" and discussed the causes in terms of biological processes, although at that time, most scientific attention was focused on analytical theories of the disorder. Kanner's paper did not initially receive much scientific credit, and children with autistic symptoms continued to be incorrectly diagnosed with childhood **schizophrenia**. His choice of the term "autism" may have created some confusion, because the word was first used to describe a mental state of fantastical, self-centered thought processes, similar to the symptoms of schizophrenia.

During the development of the disorder, the first year of life is usually marked with no clear discriminating features. Between two and three years of age, children show impairment in language development, especially comprehension; unusual language usage; poor response to name calling; deficient non-verbal communication; minimal recognition or responsiveness to other people's happiness or distress; and limited variety of imaginative play or pretence, and especially social imagination.

During school age, children's abnormalities in language development (including muteness or the use of odd or inappropriate words), their social withdrawal, inability to join in with the play of other children, or inappropriate attempts at joint play often alert teachers and others to the possibility of an autistic type disorder. The manifestations of autism can also change with time during childhood, depending on other developmental impairments, personality, and the addition of medical or mental health problems.

Demographics

Autism is a disorder that affects predominantly males (four times as many males as females have autism). According to studies, autism is increasing in the pediatric population. In 1966, 4–5 babies per 10,000 births developed autism, while in 2003, two studies showed that between 14–39 babies per 10,000 develop the disorder. Although there is no question that more clinical cases are being detected, the increase in prevalence of autism is in dispute as diagnostic practices have changed over the years and this heightened awareness has changed the evaluation of previously unrecognized cases.

Causes and symptoms

Although autism is behaviorally defined, it is now well recognized to be the endpoint of several organic causes. These include prenatal problems such as rubella (measles) infection, untreated metabolic disorders, and anticonvulsant medication taken during pregnancy, as well as postnatal infections such as encephalitis. A specific medical cause is found in only a minority of people with autism (6–10%, depending on the study). **Epilepsy** occurs more commonly than usual in patients with this disorder

Three autistic children in a classroom. *(© Andy Levin/Photo Researchers, Inc. Reproduced by permission.)*

and was one of the early indications that this was a neurobiological problem and not one caused by parental behavior or the environment.

In most people with autism, genetic factors play a key role. Multiple genes are likely to be involved, and studies have identified possible candidate genes on chromosomes 2, 7, 16, and 19. Autism has been associated with some genetic abnormalities, especially on chromosome 15, and it is also found associated with the "fragile X syndrome." Despite the fact autism is now agreed to be a neurobiological disorder, results from structural brain scans have not shown consistent features that point to a diagnosis of autism.

Symptoms of autism usually appear during the first three years of childhood and continue throughout life. Some common symptoms are:

- absence or impairment of imaginative and social play
- impaired ability to make friends with peers
- impaired ability to initiate or sustain a conversation with others
- stereotyped, repetitive, or unusual use of language
- restricted patterns of interests that are abnormal in intensity or focus
- apparently inflexible adherence to specific routines or rituals
- preoccupation with parts of objects

Children with some symptoms of autism, but not a sufficient number to be diagnosed with the classical form of the disorder, often receive the diagnosis of pervasive developmental disorder, not otherwise specified (PDD-NOS). People with autistic behavior, but also have well-developed language skills, are often diagnosed with Asperger syndrome. Children who appear normal in their first several years, then lose skills and begin showing autistic behavior, may be diagnosed with childhood disintegrative disorder (CDD). Girls with **Rett syndrome**, a

sex-linked genetic disorder characterized by inadequate brain growth, **seizures**, and other neurological problems, may also show autistic behavior. PDD-NOS, Asperger syndrome, CDD, and Rett syndrome are referred to as autism spectrum disorders.

Diagnosis

Currently, there are no objective medical tests for the diagnosis of autism and no reproducible genetic or biological markers for the disorder. The diagnosis is made with a multidisciplinary approach involving a developmental pediatrician, psychologist, speech and language professional, audiologist, and special educator.

Using a standardized rating scale, the specialist closely observes and evaluates the child's language and social behavior. A structured interview is also used to elicit information from parents about the child's behavior and early development. Reviewing family videotapes, photos, and baby albums may help parents recall when each behavior first occurred and when the child reached certain developmental milestones. The specialists may also test for certain genetic and neurological problems.

Treatment team

The treatment of childhood autism traditionally falls within the competence of the psychiatrist and the psychologist and involves the application of various methods of individual therapy. Speech therapists can work with children to help them develop social and language skills because children learn most effectively and rapidly when very young.

Moreover, occupational therapists and physiotherapists are important professionals in the development and life quality improvement for patients and parents. The treatment involves a therapist's work with the child and with the caregivers, who work with the child at home under the therapist's direction. Basic medical assistance is provided by the pediatrician and other physicians.

Treatment

No definitive treatment regimes have thus far been developed for this serious disturbance and therapy is generally merely supportive. Some attempts have been made to support such therapy with psychiatry and psychology, as well as high doses of vitamin B6, vitamin E, and magnesium. Various psychoactive drugs have also been tried, as well as a group of medications called H2 blockers. A "hugging machine" has been built to support therapy by the holding method. This device makes it possible for children with autism to overcome their fear of touch (tactile stimuli).

An alternative treatment approach has been attempted using secretin, which is a hormone secreted by cells in the digestive tract to help control digestion. The history of the application of secretin in the treatment of childhood autism dates back to 1996, when, by coincidence, a significant improvement in mental condition was noticed in a child with autism who had received secretin for diagnostic purposes. When it was administrated, one of the chief symptoms of autism, the avoidance of eye contact, was 75% reduced. Some additional children with autism also showed limited improvement after treatment with secretin. On January 5, 2004, results of a clinical trial revealed that the hormone was of little value in improving the socialization of young children with autism. Nevertheless, many parents and physicians continue to advocate development of the drug and further study.

Recovery and rehabilitation

A wide variety of long-term interventions have been advocated for children with autism. These include applied behavioral analysis, use of pictures for expressive communication (as in the picture exchange communication system), and intensive **exercise** programs. Therapists working in schools now recognize the holistic learning needs of the child, including personal and emotional growth as well as opportunities to broaden their experiences, regardless of whether measurable developmental progress is made.

Clinical trials

As of early 2004, there were numerous open **clinical trials** for autism, including:

- drug treatment for autism at the National Institute of Mental Health (NIMH)
- synthetic human secretin in children with autism, sponsored by Repligen Corporation
- improving attention skills of children with autism at the National Institute of Child Health and Human Development (NICHD) in collaboration with the National Institute of Mental Health (NIMH)
- study of fluoxetine in adults with autistic disorder
- a controlled study of olanzapine in children with autism, sponsored by the FDA Office of Orphan Products Development
- randomized study of fluoxetine in children and adolescents with autism, sponsored by the FDA Office of Orphan Products Development and Mount Sinai Medical Center
- valproate response in aggressive autistic adolescents at the NICHD and the NIMH

• brain imaging of childhood onset psychiatric disorders, endocrine disorders, and healthy children at the NIMH

Prognosis

Among individuals suffering with autism, 75% have a poor outcome and 25% show significant improvement. Acquisition of language before the age of six years old, IQ levels above 50, and having a special skill, such as expertise in computers, predict good outcome. For people with severe autism, independent living and social functioning are unlikely. For those with higher functioning autism, the jobs acquired are often below their education level. The social interactions of most adults with autism are limited or modified.

Special concerns

Most scientists concur that autism has a strong biological basis, with evidence continuing to accumulate for an underlying genetic cause that results in abnormal brain development. Future genetic and brain-imaging studies will undoubtedly contribute to a greater understanding of the disorder's etiology and pathophysiology. The combination of continually evolving methodological and technological advances will, hopefully, bring science closer to the goal of better and earlier intervention in autism.

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Cure Autism Now (CAN) Foundation. 5455 Wilshire Blvd. Suite 715, Los Angeles, CA 90036-4234. (323) 549-0500 or (888) 828-8476; Fax: (323) 549-0547. info@cureautismnow.org. <http://www.cureautismnow.org/>.

National Institute of Child Health and Human Development (NICHD). 9000 Rockville Pike Bldg. 31, Rm. 2A32, Bethesda, MD 20892-2425. (301) 496-5133. NICHDClearinghouse@mail.nih.gov. <http://www.nichd.nih.gov/>.

National Institute of Mental Health (NIMH). 6001 Executive Boulevard, Room 8184, MSC 9663, Bethesda, MD 20892-9663. (301) 443-4513; Fax: (301) 443-4279. nimhinfo@nih.gov. <http://www.nimh.nih.gov/>.

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Autonomic dysfunction

Definition

Dysfunction of the autonomic nervous system (ANS) is known as dysautonomia. The autonomic nervous system regulates unconscious body functions, including heart rate, blood pressure, temperature regulation, gastrointestinal secretion, and metabolic and endocrine responses to stress such as the "fight or flight" syndrome. As regulating these functions involves various and multiple organ systems, dysfunctions of the autonomic nervous systems encompass various and multiple disorders.

Description

The autonomic nervous system consists of three subsystems: the sympathetic nervous system, the parasympathetic nervous system and the enteric nervous system. The ANS regulates the activities of cardiac muscle, smooth muscle, endocrine glands, and exocrine glands. The autonomic nervous system functions involuntarily (reflexively) in an automatic manner without conscious control.

In contrast to the somatic nervous system that always acts to excite muscles groups, the autonomic nervous systems can act to excite or inhibit innervated tissue. The ANS achieves this ability to excite or inhibit activity via a dual innervation of target tissues and organs. Most target organs and tissues are innervated by neural fibers from both the parasympathetic and sympathetic systems. The systems can act to stimulate organs and tissues in opposite ways (antagonistic). For example, parasympathetic stimulation acts to decrease heart rate. In contrast, sympathetic stimulation results in increased heart rate. The systems can also act in concert to stimulate activity. The autonomic nervous system achieves this control via two divisions: the sympathetic nervous system and the parasympathetic nervous system. Dysfunctions of the autonomic nervous system are recognized by the symptoms that result from failure of the sympathetic or parasympathetic components of the ANS.

Primary dysautonomias include **multiple system atrophy** (MSA) and familial dysautonomia. The dysfunction can be extensive and manifest as a general autonomic failure or can be confined to a more localized reflex dysfunction.

With multiple system atrophy, a generalized autonomic failure, male patients experience urinary retention or incontinence and impotence (an inability to achieve or maintain a penile erection). Both males and females experience **ataxia** (lack of muscle coordination) and a dramatic decline in blood pressure when they attempt to stand (**orthostatic hypotension**). Symptoms similar to **Parkinson's disease** may develop, such as slow movement, **tremors**, and stiff muscles. **Visual disturbances**, sleep disturbances, and decreased sweating may also occur.

Persons with autonomic dysfunction who do not exhibit the classical symptoms of orthostatic hypotension may exhibit a less dramatic dysfunction termed orthostatic intolerance. These patients experience a milder fall in blood pressure when attempting to stand. However, because the patients have an increased heart rate when standing, they are described as having postural tachycardia syndrome (POTS).

Although not as prevalent in the general population as hypertension, orthostatic intolerance is the second most common disorder of blood pressure regulation and is the most prevalent autonomic dysfunction. Orthostatic hypotension and orthostatic intolerance can result in a wide array of disabilities. Common orthostatic intolerance syndromes include: hyperadrenergic orthostatic hypotension (partial dysautonomia); orthostatic tachycardia syndrome (sympathicotonic orthostatic hypotension); postural orthostatic tachycardia syndrome (mitral valve prolapse syndrome); postural tachycardia syndrome (soldier's heart); hyperadrenergic postural hypotension (vasoregulatory asthenia); sympathotonic orthostatic hypotension (neurocirculatory asthenia); hyperdynamic beta-adrenergic state (irritable heart syndrome); and idiopathic hypovolemia (orthostatic anemia).

Key Terms

Dysarthria A group of speech disorders caused by disturbances in the strength or coordination of the muscles of the speech mechanism as a result of damage to the brain or nerves.

Dysautonomia A disorder or dysfunction of the autonomic nervous system.

Orthostatic hypotension A sudden fall in blood pressure that occurs when standing.

Parasympathetic nervous system A branch of the autonomic nervous system that tends to induce secretion, increase the tone and contraction of smooth muscle, and cause dilation of blood vessels.

Stridor A high-pitched sound made when breathing caused by the narrowing of the airway.

Sympathetic nervous system A branch of the autonomic nervous system that regulates involuntary reactions to stress such as increased heart and breathing rates, blood vessel contraction, and reduction in digestive secretions.

Demographics

Milder forms of autonomic dysfunction such as orthostatic intolerance affect an estimated 500,000 people in the United States. Orthostatic intolerance more frequently affects women; female-to-male ratio is at least 4:1. It is most common in people less than 35 years of age. More severe forms of dysautonomia such as multiple system atrophy often occur later in life (average age of onset 60 years) and affect men four times as often as women.

Causes and symptoms

Symptoms of the autonomic dysfunction of orthostatic intolerance include lightheadedness, palpitations, weakness, and tremors when attempting to assume an upright posture. Less frequently, patients experience visual disturbances, throbbing headaches, and often complain of **fatigue** and poor concentration. Some patients report **fainting** when attempting to stand.

The cause of lightheadedness, fainting, and similar symptoms is a lack of adequate blood pressure in the cerebral circulatory system.

In addition to orthostatic hypotension and Parkinson-type symptoms, persons with multiple systems atrophy may have difficulty articulating speech, **sleep apnea** and snoring, **pain** in the back of the neck, and fatigue. Eventually, cognitive (mental reasoning) ability declines in about 20% of cases. Multiple systems atrophy occurs sporadically and the cause is unknown.

Diagnosis

Diagnosis of orthostatic intolerance is made when a patient experiences a decrease of blood pressure (not exceeding 20/10 mmHg) when attempting to stand and a heart rate increase of less than 30 beats per minute.

Diagnosis of other types of dysautonomia is difficult, as the disorders are varied and mimic other diseases of the nervous system. As Parkinsonism is the most frequent motor deficit seen in multiple systems atrophy, it is often misdiagnosed as Parkinson's disease. **Magnetic resonance imaging (MRI)** of the brain can sometimes detect abnormalities of striatum, **cerebellum**, and brainstem associated with multiple systems atrophy. But in up to 20% of MSA patients, MRI of the brain is normal. A test with the drug clonidine has also been used to differentiate Parkinson's disease from multiple systems atrophy, as certain hormone levels in the blood will increase in persons with Parkinson's disease after clonidine administration, but not in persons with multiple systems atrophy. Symptoms such as severe **dysarthria** (difficulty articulating speech) and stridor (noisy inspiration) alert the physician to the possibility of multiple systems atrophy, as they occur in the disorder, but are rare in Parkinson's disease.

Treatment team

Caring for a person with a disorder of the autonomic nervous system requires a network of health professionals, community resources, and friends or family members. A **neurologist** usually makes the diagnosis, and the neurologist and primary physician coordinate ongoing treatment and symptom relief. Physical, occupational, speech, and respiratory therapists provide specialized care, as do nurses. Social service and mental health consultants organize support services.

Treatment

At present there is no cure for severe autonomic dysfunction. Treatment is centered on the remediation of symptoms, patient support, and the treatment of underlying diseases and disorders in cases of secondary autonomic dysfunction. In many cases, cure or an improvement in the underlying disease or disorder improves the patient prognosis with regard to remediation of autonomic dysfunction symptoms

With regard to orthostatic hypotension, drug treatment includes fludrocortisone, ephedrine, or midodrine. Medications are accompanied by postural relief such as elevation of the bed at the head and by dietary modifications to provide some relief for the symptoms of **dizziness** and tunnel vision.

In multiple systems atrophy, anti-Parkinson medications such as Sinemet often help with some of the symptoms of muscle rigidity and tremor, and create an overall feeling of well-being. Medications used in the treatment of orthostatic hypotension tend to not perform as well in this group; although they elevate the blood pressure while standing, they decrease the blood pressure while reclining.

Recovery and rehabilitation

Recovery from some dysautonomias can be complicated by secondary conditions such as alcoholism, diabetes, or Parkinson's disease. Some conditions improve with treatment of the underlying disease, while only halting of the progression of symptoms is accomplished in others. Some mild dysautonomias stabilize and, with treatment, cause few limitations to daily activities.

Overall, as there are no cures for most severe or progressive dysautonomias, the emphasis is instead placed upon maintaining mobility and function for as long as possible. Aids for walking and reaching, positioning devices, and strategies for maintaining posture, balance, and blood pressure while rising can be provided by physical and occupational therapists. Speech and nutritional therapists can devise diets and safe strategies for eating, and recommend tube feedings if necessary.

Clinical trials

As of mid-2004, the Mount Sinai Medical Center in New York was recruiting participants for a study related to a new drug for the treatment of multiple systems atrophy. Persons interested in participating in the study (Droxidopa in Treating Patients With Neurogenic Hypotension) should contact the study recruiting coordinator Horacio Kaufmann at telephone: (212) 241-7315. Additional trials for the study and treatment of multiple systems atrophy and other dysautonomias can be found at the National Institutes of Health website for **clinical trials**: <http://www.clinicaltrials.gov>.

Prognosis

The prognosis for persons suffering autonomic dysfunction is variable and depends on specific dysfunction and on the severity of the dysfunction. Autonomic dysfunctions can present as acute and reversible syndromes,

or can present in more chronic and progressive forms. Persons with orthostatic intolerance can usually maintain a normal lifespan and active lifestyle with treatment and minimal coping measures, while persons with multiple systems atrophy usually have a lifespan of about 5–7 years after diagnosis.

Resources

BOOKS

Goldstein, David S., and Linda J. Smith. *The NDRF Handbook for Patients with Dysautonomias.* Malden, MA: Blackwell Futura Media, 2002.

OTHER

"Disorders of the Autonomic Nervous System." *National Dysautonomia Research Foundation.* May 16, 2004 (May 22, 2004). <http://www.ndrf.org/autonomic_disorders.htm>.

"NINDS Dysautonomia Information Page." *National Institute of Neurological Disorders and Stroke.* May 16, 2004 (May 22, 2004). <http://www.ninds.nih.gov/health_and_medical/disorders/dysauto_doc.htm>.

ORGANIZATIONS

Dysautonomia Foundation. 633 Third Avenue, 12th Floor, New York, NY 10017-6706. (212) 949-6644; Fax: (212) 682-7625. info@familialdysautonomia.org. <http://www.familialdysautonomia.org>.

Familial Dysautonomia Hope Foundation, Inc. (FD Hope). 1170 Green Knolls Drive, Buffalo Grove, IL 60089. (828) 466-1678. info@fdhope.org. <http://www.fdhope.org>.

National Dysautonomia Research Foundation. 1407 West 4th Street, Red Wing, MN 55066-2108. (651) 267-0525; Fax: (651) 267-0524. ndrf@ndrf.org. <http://www.ndrf.org>.

National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Shy-Drager/Multiple System Atrophy Support Group, Inc. 2004 Howard Lane, Austin, TX 78728. (866) 737-4999 or (800) 999-NORD; Fax: (512) 251-3315. Don.Summers@shy-drager.com. <http://www.shy-drager.com>.

Paul Arthur

B

Back pain

Definition

Back **pain** may occur in the upper, middle, or lower back; it is most often experienced in the lower back. It may originate from the bones and ligaments forming the spine, the muscles and tendons supporting the back, the nerves that exit the spinal column, or even the internal organs.

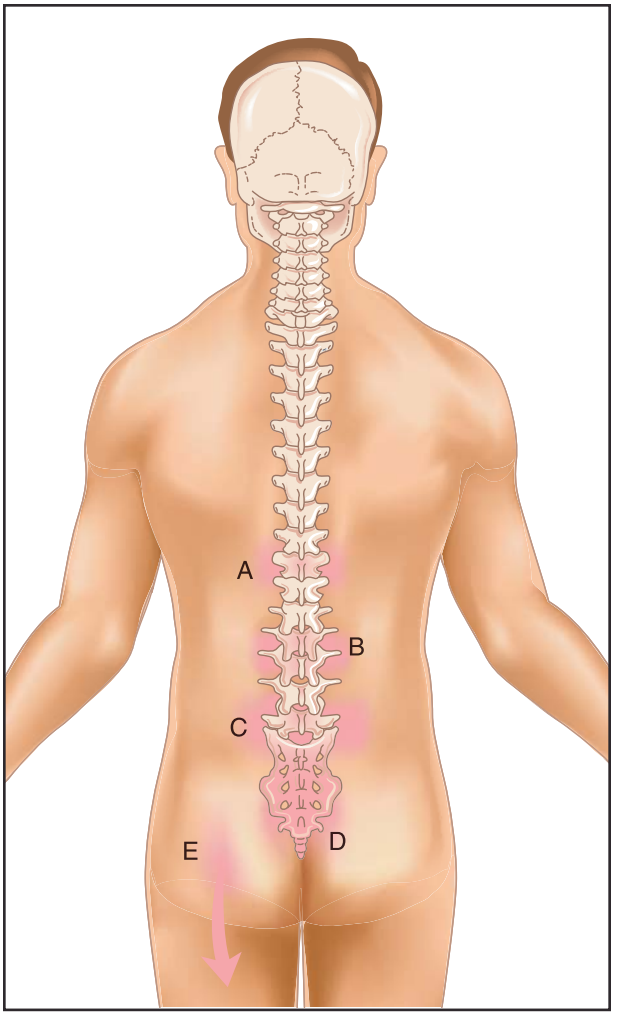
Description

Back pain can range from mild, annoying discomfort to excruciating agony. Depending on how long it lasts, it can be described as acute or chronic. Acute back pain comes on suddenly but lasts only briefly, and is often intense. While chronic back pain is typically not as severe as acute back pain, it persists for a longer period and may recur frequently. The duration of acute back pain is a few days to a few weeks, with improvement during that time, whereas chronic back pain lasts for more than three months and often gets progressively worse.

The back is composed of bones, muscles, ligaments, tendons, and other tissues that make up the posterior, or back half, of the trunk extending from the neck to the pelvis. Running through and supporting the back is the spinal column, which forms a cage-like structure enclosing the spinal cord. Nerve signals directing movement travel from the brain to the limbs, while nerve signals transmitting pain and other sensations travel from the limbs to the brain. All nerve signals pass through the spinal cord. If the individual vertebrae stacked together to form the spinal column slide out of place, which is referred to as spondylolisthesis, pain may result as the bones rub against each other or as nerves entering the spinal cord are compressed.

Demographics

Lower back pain affects approximately four out of five adults at least once during their lifetime, often interfering with work, recreation, or household chores and



Sites of low back pain. Pain anywhere along the spine (A) can be caused by osteoarthritis. Pain along one or the other side of the spine may be (B) a kidney infection. Trauma to back muscles, joints, or disks (C) causes low back pain. Damage to the coccyx (D) can occur during a fall. Sciatica (E) can cause pain to run from the back and buttocks area down a leg. *(Illustration by Electronic Illustrators Group.)*

other routine activities. It is one of the most common conditions for which Americans seek medical attention, and it is second only to **headache** as the most common neurological condition in the United States. According to the National Institute for Occupational Safety and Health, back pain related to work is one of the most-often diagnosed occupational disorders.

Health care dollars spent on the diagnosis and treatment of low back pain are estimated to be at least $50 billion annually, with additional costs related to disability and delay in return to work.

Back pain strikes equal numbers of men and women, and it typically begins between the fourth and sixth decades. The likelihood of disc disease and spinal degeneration, both prominent causes of back pain, increases with age. A sedentary lifestyle increases vulnerability to back pain, especially when coupled with obesity or sporadic bursts of overexertion.

Because of their greater flexibility and lack of age-related degeneration, children and teenagers are much less prone than adults to develop medically significant back pain.

Causes and symptoms

The spinal column is composed of 24–25 movable bones, or vertebrae, held together by ligaments and separated by intervertebral discs that act as shock absorbers. Although this structure allows great flexibility and range of movement, it also affords many opportunities for injury. Compounding the potential for injury is that the human spine bears weight in the upright position and must therefore counteract gravity. Stresses on the muscles and ligaments that support the spine can cause acute pain or chronic injury.

With normal aging, the fluid cushioning the intervertebral discs tends to dry up, making them more brittle and less protective of the vertebrae. The normal wear and tear of daily activities can eventually erode the vertebral edges, undermining stability and putting pressure on nerves that enter and exit the spinal column to control movement and sensation of the arms and legs.

Heavy physical labor accelerates these processes, but lack of physical activity allows the muscles to lose tone, offering less protection to the spine as it twists and turns. Consequently, regardless of activity levels, back pain becomes more common with increasing age. Bone density and muscle flexibility and strength also tend to decrease with age, further increasing the chance of painful injury.

Obesity increases both the weight that the spine must support and the pressure on the discs, thereby elevating the risk of back pain and injury. Physically demanding sports can also damage the back, especially in the case of "weekend warriors" who overexert themselves on occasion while generally maintaining a low level of physical fitness. Even simple movements like bending over may trigger muscle spasms in individuals with chronic pain.

Injuries unrelated to activity may include motor vehicle accidents or falls that subject the spine and its supporting structures to direct impact or unusual torque. These injuries and those related to overexertion may result in painful sprain, strain, or spasm in the back muscles or ligaments.

Excessive strain or compression of the spine may cause **disc herniation**, in which the disc bulges or even ruptures. The bulging disc or its fragments may be displaced outward, putting pressure on nerve roots entering or exiting the spine and thereby causing pain. Most disc herniations occur in the lumbar or lower part of the spinal column, especially between the fourth and fifth lumbar vertebrae (L4 and L5, respectively) and between the fifth lumbar and first sacral vertebrae (L5 and S1, respectively).

Activities involving hyperextension of the back, such as gymnastics, may result in spondylosis, or disruption of the joint between adjacent vertebrae. A more extreme form of spondylosis is spondylolisthesis, or slippage of one vertebra relative to its neighbor. Impact or excessive mechanical force to the spine may cause spinal fracture. After repeated back injuries, buildup of scar tissue eventually weakens the back and can increase the risk of more serious injury.

Diseases of the bone, such as endocrine conditions or metastatic cancer spreading from the lung, breast, prostate, or other primary site, may cause fractures or other painful conditions in the spinal column. Fractures occurring without apparent traumatic injury, especially in a debilitated or chronically ill person, may be a warning of cancer or other underlying bone disease such as osteoporosis. Osteoporosis is a metabolic bone disease in which progressive decreases in bone strength and density makes the bones brittle, porous, and easily broken.

Other diseases causing back pain include arthritis, which erodes the joints, myopathies and inflammatory conditions, which involve the muscles, and neuropathy, which affects the nerves. Back pain is common in diabetes because this disease may be complicated by **myopathy** (though this is rare) or neuropathy, both of which create gait disturbances that, in turn, cause back pain. In women, fibromyalgia is a fairly common chronic condition associated with musculoskeletal pain, **fatigue**, morning stiffness, and other nonspecific symptoms.

Conditions affecting the spine include spinal degeneration from disc wear and tear, which can narrow the spinal canal and cause back stiffness and pain, especially

Key Terms

Cordotomy Surgery to relieve pain by destroying bundles of nerve fibers on one or both sides of the spinal cord.

Discectomy Surgery to relieve pressure on a nerve root caused by a bulging disc or bone spur.

Discography A test in which dye is injected into a disc space thought to be causing back pain, allowing the surgeon to confirm that an operation on that disc will be likely to relieve pain.

Dorsal root entry zone operation (DREZ) Surgery to relieve pain by severing spinal neurons.

Endorphins Naturally occurring pain relievers produced by the brain.

Fibromyalgia A fairly common chronic condition associated with musculoskeletal pain, fatigue, morning stiffness, and other nonspecific symptoms.

Foraminotomy Surgery to enlarge the bony hole, or foramen, where a nerve root enters or exits the spinal canal.

Intervertebral discs Gelatinous structures separating the spinal vertebrae and acting as shock absorbers.

Kyphosis (dowager's hump) A pronounced rounding of the normal forward curve of the upper back.

Lordosis (swayback) An exaggeration of the normal backward arch in the lower back.

Myelography A test in which dye is injected into the spinal canal and the patient is then tilted in different directions on a special table, allowing dye to outline the spinal cord and nerve roots and to show areas of compression.

Rhizotomy Surgery to relieve pain by cutting the nerve root near its point of entry to the spinal cord.

Sciatica A common form of nerve pain related to compression of fibers from one or more of the lower spinal nerve roots, characterized by burning low back pain radiating to the buttock and back of the leg to below the knee or even to the foot.

Scoliosis An asymmetric curvature of the spine to one side.

Spinal degeneration Wear and tear on the intervertebral discs, which can narrow the spinal canal and cause back stiffness and pain.

Spinal fusion A surgical procedure that stabilizes the spine and prevents painful movements, but with resulting loss of flexibility.

Spinal laminectomy (spinal decompression) Surgical removal of a piece of the bony roof of the spinal canal known as the lamina to increase the size of the spinal canal and reduce pressure on the spinal cord and nerve roots.

Spinal stenosis A narrowing of the spinal canal which is present from birth.

Spondylitis Inflammation of the spinal joints, characterized by chronic back pain and stiffness.

Spondylolisthesis A more extreme form of spondylosis, with slippage of one vertebra relative to its neighbor.

Spondylosis Disruption of the joint between adjacent vertebrae.

Thermography A test using infrared sensing devices to measure differences in temperature in body regions thought to be the source of pain.

Transcutaneous electrical nerve stimulation (TENS) A battery-powered device generating weak electrical impulses applied along the course of nerves to block pain signals traveling to the brain.

Traction Spinal stretching using weights applied to the spine, once thought to decrease pressure on the nerve roots but now seldom used.

upon awakening or after prolonged walking or standing. Spinal stenosis is a narrowing of the spinal canal, a condition that is present from birth. Both conditions increase the likelihood of back pain from disc disease. Spondylitis, or inflammation of the spinal joints, is characterized by chronic back pain and stiffness.

Anatomical abnormalities of the skeleton subject the vertebrae and supporting structures to increased strain, and often manifest as back pain. Scoliosis is an asymmetric curvature of the spine to one side. Kyphosis, or dowager's hump, refers to a pronounced rounding of the normal forward curve of the upper back, whereas lordosis (swayback) is an exaggeration of the normal backward arch in the lower back.

Lifestyle and general medical factors contributing to back pain include smoking, pregnancy, inherited disorders

affecting the spine or limbs, poor posture, inappropriate posture for the activity being performed, and poor sleeping position. Psychological stress is a common but often unrecognized source of back pain. Injuries, arthritis, or other conditions affecting the feet, ankles, knees, or hips may result in abnormal walking patterns that exacerbate or cause back pain.

Apart from all the musculoskeletal structures and nerves, the internal organs can also be a source of pain felt in the back. Kidney stones, urinary tract infections, blood clots, stomach ulcers, and diseases of the pancreas can all be experienced as back pain. Fever or other bodily symptoms suggesting infection or involvement of internal organs should prompt a medical evaluation.

The discomfort of back pain may range from the dull ache of muscle soreness, to shooting or stabbing pain if a muscle acutely goes into spasm, to a toothache-like sensation along the course of a spinal nerve. Surprisingly, the severity of the pain may not be correlated with the severity of injury. In uncomplicated back strain, acute muscle spasm can cause agonizing back pain that prevents the person from standing up straight. On the other hand, a massive disc herniation may not produce pain or any other symptoms.

Depending on its source, back pain is usually aggravated by certain movements, although prolonged sitting or standing may also make it worse. Associated symptoms may include limited flexibility and range of motion, difficulty straightening up, or weakness in the arms or legs.

When back pain is caused by **nerve compression**, pain may travel, or radiate, from the back to peripheral areas, usually following the course of the nerve as it supplies the arm or leg. There may be numbness, sensitivity to touch, or "pins and needles" (tingling sensations) along the same distribution. Pain originating from an internal organ may also radiate to an area of the back supplied by the same nerve root as that organ.

Sciatica is a common form of nerve pain related to compression of fibers from one or more of the lower spinal nerve roots, characterized by burning low back pain radiating to the buttock and back of the leg to below the knee or even to the foot. In more severe cases, there may be numbness or tingling in the same regions, as well as weakness. Typically, sciatic pain is caused by a herniated or ruptured disc, but it may also rarely be caused by a tumor or cyst.

Worrisome symptoms associated with back pain that warrant immediate medical attention include loss of control of bowel or bladder, change in bowel and bladder habits, or profound or progressive weakness or sensory loss. Any of these may signal compression of one or more nerve roots, or even of the spinal cord itself, which may result in irreversible paralysis if not treated promptly.

Low back pain is unusual in children, unless caused by motor vehicle accidents and other traumatic injuries. One notable exception is back strain and muscle fatigue caused by carrying an overloaded backpack. According to the U.S. Consumer Product Safety Commission, more than 13,260 injuries caused by backpacks were treated at medical offices, clinics, and emergency rooms in 2000.

Persistent back pain in a young child should raise suspicions of a serious problem such as a tumor or infection of the spine, meriting further evaluation and treatment. Teenagers indulging in extreme sports may subject themselves to compression fractures, stress injuries, spondylosis, and rarely, disc herniation.

Diagnosis

According to the *Clinical Practice Guideline for Understanding Acute Low Back Problems*, published in 1994 by the Department of Health and Human Services Agency for Health Care Policy and Research, the precise cause of back pain is seldom determined, despite the advent of sophisticated diagnostic techniques. Although x rays and other imaging tests typically fail to disclose the reason for back pain, they may be important in ruling out serious conditions demanding specific treatment.

As with most other neurologic conditions, the cornerstone of diagnosis is the history, or analysis, of the patient's complaints, and the physical and neurologic examination. Additional diagnostic testing is needed in only about 1% of individuals with acute back pain. If symptoms do not improve in four to six weeks, further testing may be indicated.

The history focuses on a description of the pain and other symptoms, the circumstances in which the pain first occurred, and conditions that tend to make it better or worse, as well as any injuries and a general medical history. The physical examination should begin with a general medical examination and should include finding areas of back tenderness, testing spinal range of motion and flexibility, and measuring strength, sensation, and reflexes in the legs.

Specialized maneuvers include the straight leg-raising test. While the patient is lying flat on the back, pain in the low back or leg caused by raising a straight leg off the examining table suggests sciatica.

If there is suspicion of a serious cause for back pain, imaging or other tests may be done right away. Reasons for immediate testing include sudden back pain after a fall, suggesting fracture; back pain at night, suggesting a tumor, fever, or other signs of back infection; or loss of bowel or bladder control or progressive leg weakness, suggesting compression of the spinal cord or nerve roots.

Cancer patients who develop back pain should have testing to determine if cancer has spread to the spine, which can lead to spinal cord compression and permanent paralysis if not treated promptly. Children with back pain unrelated to backpacks or sports injuries should also be tested sooner rather than later.

X rays are typically performed first as they are readily available and do a good job of visualizing bony structures, fractures, and deformities. However, they do not usually detect injuries of the muscles or other soft tissues. If x rays are negative and the doctor suspects a tumor, infection, or fracture not easily seen on x ray, bone scans may be helpful. In this test, injecting a low-dose radioactive medication into a vein allows the doctor to study bone structure and function using a special scanning camera.

Because **magnetic resonance imaging (MRI)** provides sharp, clear images of bones, discs, nerves, and soft tissues, it is the best test to show disc herniation and nerve compression. This test uses magnetic signals in water rather than x rays, and therefore poses no risk to the patient other than that associated with a contrast dye, which is not needed in most cases. Although the MRI may show disc bulging, this does not necessarily mean that the disc bulge is causing the back pain or that it needs to be treated. In about half of people without back pain, the MRI shows disc bulges. On the other hand, a bulging disc directly compressing a spinal nerve is more significant and may be causing pain and associated symptoms.

Computed tomography (CT) scan of the spine uses a computer to reconstruct cross-sectional x-ray images. A **CT scan** is good at visualizing bone problems like spinal stenosis, but it is not as sensitive as the MRI in diagnosing soft tissue injuries, and it has the added disadvantage of considerable x-ray exposure.

Because they are painful and carry a small risk of injury to the patient, certain tests are only done in patients who are about to have surgery so that the surgeon can plan the operation better. In myelography, dye is injected into the spinal canal and the patient is then tilted in different directions on a special table, allowing dye to outline the spinal cord and nerve roots and to show areas of compression. In discography, dye is injected into a disc space thought to be causing the pain, allowing the surgeon to confirm that an operation on that disc will likely relieve pain.

If there is evidence of nerve root compression on CT, MRI, history, or physical examination, **electromyography** (EMG), nerve conduction velocity (NCV), and evoked potential (EP) studies help determine the motor and sensory function of the involved nerve(s). These tests are also useful in diagnosing myopathy or neuropathy. During the EMG, fine needles inserted into the muscle determine how rapidly and forcefully the muscle contracts when stimulated. By applying a series of weak electrical shocks over areas supplied by a particular nerve, the NCV helps determine sensory function. Both tests are helpful in pinpointing specific patterns of nerve involvement.

In special cases, thermography and ultrasound imaging may provide additional information. Thermography uses infrared sensing devices to measure differences in temperature in body regions thought to be the source of pain. Ultrasound uses high-frequency sound waves to show tears in ligaments, muscles, tendons, and other soft tissues.

Treatment team

Internists and general practitioners are often the first to see patients with back pain. Depending on the cause and severity of pain, neurologists, orthopedists, physical medicine specialists, pain management specialists, psychologists, psychiatrists, and other medical specialists may offer evaluation and treatment. Physical therapists, chiropractors, acupuncturists, vocational rehabilitation counselors, and radiology technicians may all become involved in management.

Treatment

Most cases of acute musculoskeletal back pain respond in a few days or weeks to limited rest, combined with appropriate **exercise** and education on correct movement patterns to avoid further injury. However, many cases resolve on their own without any treatment during a similar time period.

Although acute back pain was previously treated with complete, prolonged bed rest, this is no longer recommended because it leads to muscular deconditioning and loss of bone calcium, which can make the situation worse. Other complications of bed rest may include **depression** and blood clots in the legs. In 1996, a Finnish study showed that an exercise program to improve back mobility, coupled with resumption of normal activities and avoidance of rest during the day, allowed better back range of motion by the seventh day than did a program of strict bed rest.

Current wisdom is to limit bed rest for low back pain to one day, beginning immediately after injury or acute onset of pain, followed by resuming activities as soon as possible. While resting or sleeping, the best positions are on one side with a pillow between the knees, or on the back with a pillow under the knees.

Exercise speeds up recovery, reduces the risk of future back injuries, and releases the body's natural pain relievers known as endorphins. Doctors may suggest specific back exercises; aerobic exercises that improve conditioning without undue stress on the back include walking, stationary bicycle, and swimming or water aerobics. Any

exercise program should be started slowly and built up gradually. Discomfort during exercise is not unusual, especially when starting out. However, patients experiencing pain of moderate or greater severity or lasting more than 15 minutes during exercise should stop exercising and inform their physician.

Local application of an ice pack or heat to the painful area, or use of muscle balms containing menthol, eucalyptus, or camphor may reduce inflammation, feel soothing, and facilitate exercise. Cold packs are recommended within the first 48 hours after back pain begins, with use of hot packs subsequently.

For back pain following an injury, physical therapy may offer strengthening programs and education in posture, movement patterns, and lifting techniques that protect the back to avoid further injury. Exercises designed to increase flexibility, tone, and strength help to replace fluid into dehydrated discs. Ultrasound, moist heat application, hydrotherapy involving pools or spas, or massage of painful areas may relieve pain and spasm, increase local circulation, and improve mobility.

Transcutaneous electrical nerve stimulation (TENS) uses a battery-powered device generating weak electrical impulses applied along the course of affected nerves to block pain signals traveling to the brain. This technique may also stimulate production of endorphins, or naturally occurring pain relievers, by the brain.

Although traction, or spinal stretching using weights applied to the spine, was once thought to decrease pressure on the nerve roots, this treatment has not been proven to be effective and is now seldom used.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may relieve pain by reducing inflammation. These include naproxen (Aleve) and ibuprofen (Nuprin, Motrin IB, and Advil). Because these drugs may cause gastrointestinal bleeding, patients with ulcers, bleeding disorders, or other gastrointestinal conditions should avoid them. Other side effects may include kidney damage, and salt and fluid retention leading to high blood pressure.

COX-2 inhibitors are a more recently developed class of prescription drugs that reduce pain and inflammation with fewer gastrointestinal effects than the NSAIDs. These include celecoxib (Celebrex) and rofecoxib (Vioxx).

For severe back pain caused by inflammation of nerve roots or other structures, steroids may be injected directly into the inflamed area, often combined with local anesthetic. These can be epidural injections targeting the nerve roots, or trigger point injections into tender areas of muscle.

Other medications that may be indicated include analgesics or pain relievers such as aspirin or acetaminophen (Tylenol), muscle relaxants, antidepressants, or **antiepileptic drugs**. Muscle relaxants such as cyclobenzaprine (Flexeril), carisoprodol (Soma), and methocarbamol (Robaxin) may relieve painful spasms, but may also cause drowsiness and should not be used when working, driving, or operating heavy equipment.

Some antidepressants, especially when given in low doses, act as pain relievers in addition to reducing symptoms of depression and insomnia. Among these medications are tricyclic antidepressants such as amitriptyline and desipramine; and newer antidepressants such as the selective serotonin reuptake inhibitors (SSRI)s are being tested for their ability to relieve pain. However, a review of studies published in November 2003 suggests that the tricyclic antidepressants, but not the SSRIs, reduce pain symptoms. Although antiepileptic drugs are primarily used to treat **seizures**, they have a stabilizing effect on nerve cells that makes them effective for certain types of nerve pain.

For severe pain, opioids and narcotics such as oxycodone-release (Oxycontin), acetaminophen with codeine (Tylenol with codeine), and meperidine (Demerol) may be prescribed. However, they may be addicting and associated with troublesome side effects including constipation, impaired judgment and reaction time, and sleepiness. Therefore, these drugs should only be used under a doctor's supervision, only when other medications are ineffective, and only for limited periods. Some pain management specialists believe that habitual use of these drugs may worsen depression and even increase pain.

In some patients, spinal manipulation, also known as osteopathic manipulative therapy or chiropractic, may correct patterns of spinal imbalance that impedes recovery. It may be helpful during the first month of low back pain, but it should be avoided in patients with previous back surgery, back injury related to underlying disease, and back malformations. Before proceeding with chiropractic, it may be wise to get clearance from a medical doctor.

Acupuncture is an alternative medicine technique in which trained practitioners place very-fine needles at precisely specified body locations to relieve pain. Insertion of these needles is thought to unblock the body's normal flow of energy and to release peptides, which are naturally occurring pain relievers. Clinical studies are underway to compare how effective acupuncture is relative to standard treatments for low back pain.

Biofeedback is a treatment recommended by some pain specialists, in conjunction with other treatments. By placing electrodes on the skin and connecting them to a biofeedback machine, the patient learns to modify the response to pain by controlling muscle tension, heart rate, and skin temperature. Meditation or other relaxation techniques may enhance the response to biofeedback training.

Patients who do not respond to the above treatments may be candidates for back surgery if there is a clear abnormality in structure that could be corrected surgically. Although surgery is typically a last resort, it may be done on an urgent basis if the spinal cord or nerve roots are being compromised.

Discectomy is a surgical procedure to relieve pressure on a nerve root caused by a bulging disc or bone spur, whereas foraminotomy enlarges the bony hole, or foramen, where a nerve root enters or exits the spinal canal. In spinal **laminectomy**, or spinal decompression, a piece of the bony roof of the spinal canal known as the lamina is removed on one or both sides to increase the size of the spinal canal and reduce pressure on the spinal cord and nerve roots.

Spinal fusion stabilizes the spine and prevents painful movements, but with resulting loss of flexibility. The spinal discs between two or more vertebrae are removed, and the neighboring vertebrae are joined together with bone grafts and/or metal devices attached by screws. To allow the bone grafts to grow and fuse the vertebrae together, a long recovery period is needed. The Food and Drug Administration (FDA) has approved the intervertebral body fusion device, the anterior spinal implant, and the posterior spinal implant for use in this type of procedure.

To relieve severe chronic pain, spinal cord stimulation devices may be surgically implanted. These devices discharge electrical impulses to stimulate the spinal cord and to block the perception of pain. Other procedures used as a last resort cut nerve fibers to relieve pain, but patients may find the resultant altered sensations more troubling than the pain itself. Rhizotomy involves cutting the nerve root near its point of entry to the spinal cord. Cordotomy destroys bundles of nerve fibers on one or both sides of the spinal cord, and dorsal root entry zone (DREZ) operation severs spinal neurons.

Clinical trials

The National Institute of Neurological Disorders and Stroke (NINDS) and other institutes at the National Institutes of Health (NIH) fund, support, and conduct general pain research, as well as studies of new treatments for pain and nerve damage associated with back pain and other conditions.

Ongoing studies are comparing the effects of different drugs; different treatment approaches such as standard care, chiropractic, or acupuncture; and surgery versus nonsurgical treatments. Treatments under investigation include acupuncture and yoga in chronic low back pain, low-dose **radiation** to decrease postsurgical scarring around the spinal cord, and artificial spinal disc replacement surgery.

Studies that are currently recruiting patients include magnets in the treatment of sciatica and a comparison of nortriptyline and MS Contin in sciatica. Contact information for both trials is (800) 411-1222, or prpl@mail.cc.nih.gov.

Prognosis

In about 90% of people, back pain resolves within one month without treatment. Although most people with acute low back pain improve within a few days, others take much longer to recover or develop more serious conditions, especially if left untreated. Fractures, tumors, severe disc herniations, or other spinal conditions compromising nerve roots, spinal cord, or spinal stability may lead to progressive neurologic deterioration if not treated promptly.

Special concerns

Although back pain is usually not a cause for serious concern, it can interfere with work and activities and may even be disabling. Adopting lifestyle habits to prevent back pain and injury are therefore worthwhile, beginning at an early age. These include weight control and nutritionally sound diet, regular exercise, stretching before strenuous exercise, stopping smoking, good posture, and reducing emotional stress contributing to muscle tension.

In the workplace, at home, and while driving, supportive seats can reduce stress and fatigue. Other ergonomically designed furniture, tools, workstations, and living space help protect the body from injury.

Sleeping on the side with knees bent and cradling a pillow, or on the back with a pillow under bent knees, reduces back strain. Proper lifting techniques include bending at the knees rather than the waist, holding the weight close to the body rather than at arm's length, exhaling while lifting a heavy load, not twisting while lifting, and not attempting to lift a load that is too heavy. Frequent stretch breaks while sitting, standing, or working in one position for long periods will reduce muscle fatigue and back discomfort. Wearing comfortable, supportive, low-heeled shoes helps prevent falls and cushions the weight load on the spine during standing and walking.

Children using backpacks should be taught proper lifting techniques, should reduce the amount of books or supplies carried, or should switch to a wheeled carrier.

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National Institute Of Neurological Disorders and Stroke. NIH Neurological Institute. PO Box 5801, Bethesda, MD 20824. (800) 352-9424. (March 18, 2004.) <http://www.ninds.nih.gov/health_and_medical/disorders/backpain_doc.htm>.

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Laurie Barclay

Bassen-Kornzweig syndrome

Definition

Bassen-Kornzweig syndrome is a rare genetic disorder that is characterized by an inability to properly absorb dietary fats, resulting in neurological abnormalities, degeneration of the retina of the eye, a typical red blood cell abnormality ("burr-cell" malformation), and failure to thrive (grow and gain weight) during infancy.

Description

Bassen-Kornzweig syndrome is inherited as an autosomal recessive disorder, which means that parents of affected individuals are themselves unaffected carriers, and that they have a 25% risk of having an affected child in each pregnancy. Alternate names for this disorder include abetalipoproteinemia, acanthocytosis, and apolipoprotein B deficiency. Affected individuals can have severe, irreversible neurological impairments, especially if untreated. Psychological counseling for parents and family members is often helpful. There are support groups that are useful in learning more about other families with affected individuals and how they manage in terms of coping mechanisms, responses to treatment, as well as practical considerations such as lifestyle changes. As the recurrence risk for this disorder is high, genetic counseling is recommended. In some families, prenatal diagnosis is possible.

Demographics

For unclear reasons, males are affected with Bassen-Kornzweig syndrome with greater frequency (70%) than girls, which is uncharacteristic in most autosomal recessive conditions. A majority of the originally described patients (including the first case of an 18-year old girl in 1950) were of Jewish descent. Bassen-Kornzweig syndrome is a rare disorder; estimations of how often it occurs are limited because the responsible genetic mutations were only recently identified and there is more than one gene that contributes to the disorder.

Causes and symptoms

Mutations in two genes have been shown to cause Bassen-Kornzweig syndrome: apolipoprotein B (APOB) and microsomal triglyceride transfer protein (MTP). These proteins are an important part of fat-containing molecules called lipoproteins in the blood. Several of these lipoproteins, such as low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL), are found in either very low concentrations or are completely absent in the blood. These lipoproteins function to transport fat and are important in fat metabolism. Not having these important lipoproteins can result in malabsorption (poor absorption) of fats, and excessive and wasteful fat excretion in the bile called steatorrhea.

MTP is a gene that encodes a protein responsible for transporting triglycerides, cholesteryl esters, and components of the cell's surface called phospholipids. Biochemical studies revealed that in biopsies from patients that lack lipoproteins (abetalipoproteinemia) and controls, MTP enzyme activity was only detected in control samples. MTP is expressed in the lumen of the liver and intestine and is not only important for transport of lipoproteins, but also for their assembly.

The body requires fats for healthy nerves and muscles. The symptoms that develop in Bassen-Kornzweig syndrome affect a person's sensory perception, coordinating muscle movements, blood chemistry, and vision. People with Bassen-Kornzweig can develop problems related to sensing temperature and touch, particularly on the

Key Terms

Autosomal recessive disorder A genetic disorder that is inherited from parents that are both carriers, but do not have the disorder. Parents with an affected recessive gene have a 25% chance of passing on the disorder to their offspring with each pregnancy.

Lipoproteins Compounds of protein that carry fats and fat-like substances such as cholesterol in the blood.

Malabsorption The inability to adequately or efficiently absorb nutrients from the intestinal tract.

Retinitis pigmentosa A family of genetically linked retinal diseases that causes progressive deterioration of peripheral vision and eventually blindness.

hands and feet, a condition called hypesthesia. The inability to produce lipoproteins leads to several symptoms that can adversely affect infants, who show signs of failure to grow and gain weight, and have fatty, foul-smelling stools that appear to be pale and frothy. A protruding abdomen can often be observed. Brain involvement can be significant, leading to developmental motor delay. Muscle coordination becomes compromised, usually after the child reaches 10 years old. Children with Bassen-Kornzweig syndrome also can have slurred speech that is likely to be secondary to the neurological impairment. Abnormal curvature of the spine, progressively diminished visual abilities, and balance difficulties can also be symptoms experienced by these patients. Finally, affected individuals can develop poor eyesight due to retinitis pigmentosa, along with cataracts and difficulty maintaining eye control.

In Bassen-Kornzweig syndrome, lacking the appropriate concentration of lipoproteins due to defective intestinal absorption of lipids can result in low serum cholesterol levels. Low levels of LDL have also been observed in patients with **AIDS**, certain types of leukemia, and disorders that involve enlargement of the spleen (Gaucher's disease) and should, therefore, not be confused with Bassen-Kornzweig syndrome.

Diagnosis

The initial observations that leads a physician to suspect a fat digestion problem is that affected babies have severe stomach problems with a high level of fats detected in the stool; the stool is often pale and foul smelling. One of the first medical tests usually performed on infants with failure to thrive is a complete blood count (CBC), which shows abnormal, thorny-shaped red blood cells (acanthocytes) that can be visualized using a microscope. A lipid profile demonstrates low levels of total cholesterol and low concentrations of VLDL and LDL in the blood. Apolipoprotein B can be completely absent or detected in reduced amounts in the blood. Due to the inability to digest fats, loss of fat-soluble vitamins such as vitamin A, D, E, or K occurs and can result in a deficiency. An examination by an ophthalmologist might show retinal degeneration leading to visual loss. A **neurologist** might find nerve demyelination (degeneration of the protective layer of the nerve) by performing nerve conduction studies or an EMG. Loss of peripheral nerves can be associated with **ataxia** (abnormal muscle coordination).

Treatment team

In addition to consistent evaluation by an experienced neurologist, it is important to consult with a nutritionist regarding the appropriate dietary restriction, as this can influence the development and well being of an affected individual. There is also a requirement for large doses of fat-soluble vitamin supplements because there is an inability to digest fat from the diet; the body does not retain these vitamins. Because the child with Bassen-Kornzweig syndrome often suffers from **hypotonia** and ataxia, an experienced physical therapist can often help develop strategies to treat the associated symptoms.

Treatment

Persons with Bassen-Kornzweig syndrome are treated primarily to lessen symptoms. The most formidable approach to treatment is dietary restriction and supplementation with the appropriate vitamins (D, E, A, and K) as well as with fats that can be broken down more easily. Supplementation with fat-soluble vitamins may slow the progression of the retinal degeneration. As these patients can develop **movement disorders** such as **tremors**, **chorea** (uncontrollable shaking), difficulty talking (**dysarthria**), and difficulty with tasks that require coordination, speech and occupational therapy is recommended and can be helpful.

Recovery and rehabilitation

Due to the nature of Bassen-Kornzweig syndrome and the biochemical defects, treatment is based solely on monitoring the diet and treating symptoms as well as any biochemical abnormalities that might develop. Currently, there is no cure.

Clinical trials

The National Heart, Lung, and Blood Institute (NHLBI) and the National Institutes of Health (NIH) are sponsoring a clinical trial to investigate circulating lipoproteins in the blood in order to better understand fat metabolism and the role it plays in heart disease. As part of the ongoing studies, healthy patients will receive injections of controlled doses of isolated and purified lipoproteins, along with a specially formulated diet. Patients will have blood drawn and a urinalysis and be monitored during the study. Contact information: National Heart, Lung and Blood Institute (NHLBI), 9000 Rockville Pike, Bethesda, Maryland, 20892; Patient Recruitment and Public Liaison Office (800) 411-1222; e-mail: prpl@mail.cc.nih.gov.

Prognosis

The prognosis depends on the severity of the neurological impairments, which can vary from patient to patient. There have been cases of severe, progressive neurological damage occurring before the person reaches age 30. Neurological damage is irreversible. The visual problems can also be progressive and the extent of retinal degeneration and visual loss can be variable. Mental deterioration can also sometimes occur.

Special concerns

An important consideration for these patients is dietary restriction. Due to the inability to digest dietary fats, the diet of persons with Bassen-Kornzweig syndrome should contain no more than five ounces of lean meat, fish, or chicken per day. This will help mitigate unpleasant intestinal symptoms. Certain high fat foods should be avoided, or foods that contain long-chain triglycerides (fat-containing molecules that are more difficult to breakdown). However, because the body needs some fats, as fat is important for many components of cells and tissues including cell membranes, medium chain triglycerides can be taken to supplement the diet.

All dietary restrictions should be carefully considered by a nutritionist and a physician, and the patient should be monitored for symptoms and responses to such treatments. Failure to supplement with vitamins such as vitamin E can lead to a vitamin deficiency. Vitamin E deficiency is associated with poor transmission of nerve impulses, hypotonia (weak muscles), and retinal degeneration leading to blindness. For these reasons, it is important to supplement with the appropriate vitamins at a dose recommended by a physician.

Resources

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ORGANIZATIONS

Abetalipoproteinemia Support Group. 14252 Culver drive #543, Irvine, CA 92604. abetalipoproteinemia@yahoogroups.com. <http://groups.yahoo.com/group/Abetalipoproteinemia>.

CLIMB (Children Living with Inherited Metabolic Diseases). The Quadrangle, Crewe Hall, Weston Road, Crewe, Cheshire, CW1-6UR, United Kingdom. (127) 0 2-50221. Lesley@climb.org.uk. <http://www.CLIMB.org.uk>.

Foundation Fighting Blindness. Executive Plaza 1, 11350 McCormick Road, Suite 800, Hunt Valley, MD 21031-1014. (410) 785-1414 or (888) 394-3937. jchader@blindness.org. <http://www.blindness.org>.

Retinitis Pigmentosa International. 23241 Ventura Boulevard, Suite 117, Woodland Hills, CA 91364. (818) 992-0500. <http://groups.yahoo.com/group/Abetalipoproteinemia>.

Bryan Richard Cobb, PhD

Batten disease

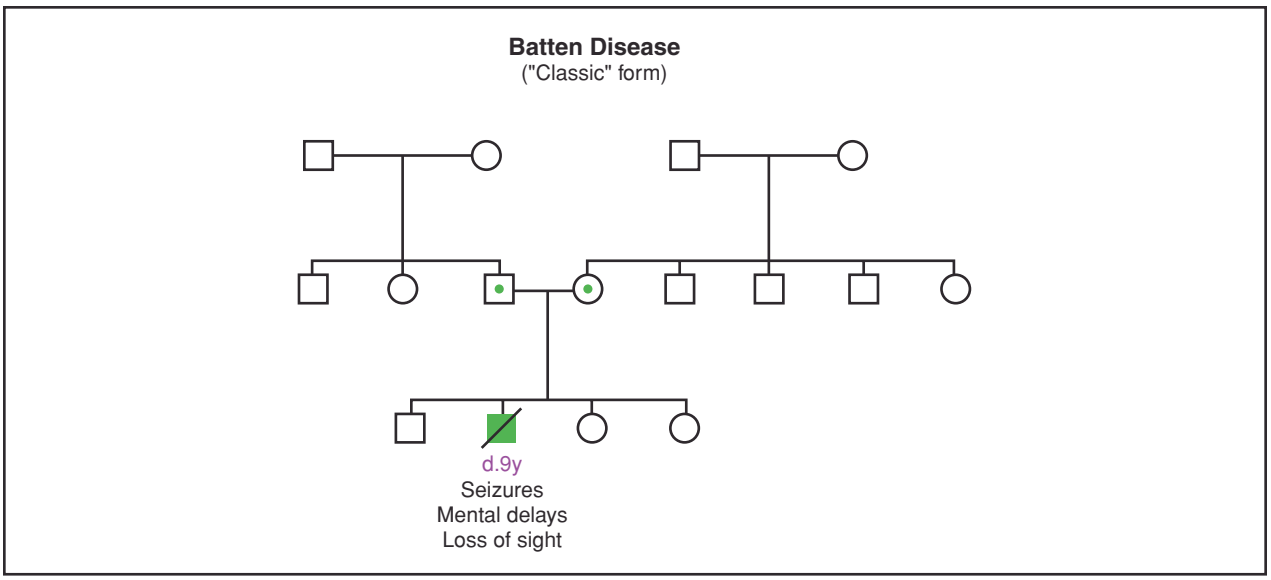
Definition

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.

Description

Batten disease was named after the British pediatrician who first described it in 1903. The 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



See Symbol Guide for Pedigree Charts. *(Gale Group.)*

(or NCLs). The disease 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.

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.

Causes and symptoms

Batten disease 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.

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, which further detect various eye problems common in childhood NCLs
- brain scans, which spot changes in the brain's appearance

Treatment team

Patients suspected of having Batten disease will be diagnosed and then treated by an ophthalmologist and neurologist. Physical and occupational therapists will be consulted to help the patient maintain optimal functioning.

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.

Treatment

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.

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

Batten 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. contact cca@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
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Behçet disease

Definition

Behçet disease (BD), also known as Behçet syndrome, is a chronic form of **vasculitis** (inflammation of the blood vessels) involving four primary symptoms: oral and genital ulcers, ocular inflammation, and arthritis.

Description

Behçet disease was first described in the 1930s by Turkish dermatologist Hulusi Behçet. His observations of the three classic symptoms (oral and genital ulcers and eye inflammation) now define this complex condition. BD also has a unique ability to affect all sizes of blood vessels, including arteries and veins. Symptoms related to vasculitis, such as inflammation of joints, gastrointestinal areas, or the **central nervous system**, are also common.

Demographics

Incidence of BD is very rare in the United States with approximately five in 100,000 people developing the syndrome. In Middle Eastern and Asian countries between Iran and Japan (known as the "Old Silk Route"), BD is quite prevalent. Incidence in these countries is double that of the United States.

More than twice as many females are diagnosed with BD than males in the United States. However, in Middle Eastern and Asian areas, significantly more men are affected than females.

Causes and symptoms

Behçet disease is caused by an autoimmune response that triggers inflammation of the blood vessels. Researchers have discovered a gene, HLA-B51, which predisposes an individual to BD. However, not all individuals with this gene develop the disease. The specific event leading to onset of BD is not known, but there are speculations that it may be related to the following:

Key Terms

Neuopathy Disease or disorder, especially a degenerative one, that affects the nervous system.

Vasculitis Inflammation of the blood vessels.

- herpes simplex virus infections
- frequent infections of *Streptococcus* bacteria
- environmental factors

The four primary symptoms of BD are recurring complications that rarely present simultaneously. These include:

- Oral ulcers (aphthous ulcers). Usually the first sign of disease, these sores resemble common canker sores, but are present in greater number, larger size, and occur more frequently. They may be painful and persist for up to two weeks.
- Genital ulcers. Similar in appearance to oral ulcers, genital sores typically occur on the scrotum in males and in the vulva in females. These ulcers are painful.
- Ocular inflammation (uveitis). May affect the front of or behind the eye, or both together. Inflammation of the middle eye area leads to blurred vision, light sensitivity, and possibly loss of sight.
- Arthritis. Temporary inflammation of the joints develops intermittently.

A large number of secondary symptoms are also associated with BD. These affect the following areas:

- Skin. Acne-like outbreaks of red skin sores develop on the legs and parts of the upper body.
- Vascular system. Formation of blood clots may lead to **aneurysms** or inflammation of veins (thrombosis). This is more frequent in men.
- Gastrointestinal system. Less often, patients may develop ulcers along the digestive tract.
- Central nervous system. Inflammation of the blood vessels in the brain can result in a variety of conditions such as **headache**, confusion, **stroke**, or seizures.

Diagnosis

Behçet disease is diagnosed based on a set of guidelines established by an international group of physicians. A physician observes clinical signs and symptoms during patient examination. The most recent and accepted guidelines for a positive diagnosis include the presence of recurring oral ulcers (three or more times in one year) and at least two of four secondary symptoms, including recurring genital ulcers, uveitis, skin lesions, a positive pathergy test.

A pathergy test is a skin-prick test to see if a red bump will form at the injection site. If there is a reaction, the test is positive. This test may be given to patients suspected of BD, but it is not an indicator for the disease. Only a small percentage of patients diagnosed with BD actually test positive.

Treatment team

Patients diagnosed with Behçet disease require a diverse treatment team due to the variety of symptoms and complications. The primary specialist is usually a physician who specializes in arthritis (rheumatologist). In addition, the team includes a dermatologist (skin), an ophthalmologist (eyes), a gynecologist or urologist (genital), a gastroenterologist (digestive system), and a **neurologist** (nervous system).

Treatment

Treatment is focused on the symptoms. Several medications are available to minimize discomfort caused by these symptoms.

Most treatment efforts attempt to reduce **pain** and inflammation. Corticosteroids such as Prednisone are prescribed since they are effective at regulating inflammatory responses. These may be administered as injections, pills, or creams. Immunosuppresant drugs such as cyclosporine, azathioprine or cyclophosphamide help suppress the immune system's response to a less-active state. Both corticosteroids and immunosuppresants can have serious side effects. Patients must be closely monitored by a physician while using these medications.

The use of interferon alpha 2a and 2b has been an effective treatment for ulcers and arthritis in patients who were less responsive to standard treatment regimens. Thalidomide has also shown potential as a treatment for BD. A complication of thalidomide is neuropathy. Thalidomide should not be used by women since it causes severe birth defects in fetuses.

Recovery and rehabilitation

Unlike most diseases, BD has symptoms that periodically flare up and then disappear for a period of time. As a result, patients may have long intervals with no complications. After treatment for active symptoms, patients usually require rest due to **fatigue**. Moderate **exercise** is also recommended to improve circulation and muscle strength.

Clinical trials

As of early 2004, the National Eye Institute was sponsoring two studies and recruiting patients with Behçet disease.

"Evaluation and Treatment of Patients with Inflammatory Eye Diseases" (study number 000204) evaluates patients with inflammatory eye diseases and the success of current therapies. "Biological Markers in Retinal Vasculitis" (study number 030068) is attempting to isolate biological markers related to primary retinal vasculitis by evaluating patients with differing initial causes of the disease.

Additional information on either of these studies can be found at the National Eye Institute (NEI), Patient Recruitment and Public Liaison Office, 9000 Rockville Pike, Bethesda, Maryland, 20892, (800) 411-1222, TTY (866) 411-1010.

Prognosis

For most patients, the prognosis of Behçet disease is good. Individuals typically experience periods of active symptoms followed by periods of remission in which there are no symptoms. The length of these intervals varies, with ulcerous outbreaks lasting a few weeks and other symptoms occurring for longer durations. With proper treatments and medication, patients can continue to lead active lifestyles in most cases.

Development of vascular or neurological complications often indicates a poorer prognosis. Blindness due to ocular inflammation is also prevalent in patients with BD.

Special concerns

In cases in which a patient becomes visually impaired, major lifestyle changes take place. The patient will have to learn adaptive behaviors and new forms of communication. Leader dog assistance or additional caregiver support are also considerations.

Resources

BOOKS

Lee, Sungnack. *Behçet's Disease: A Guide to Its Clinical Understanding.* New York: Springer Verlag, 2001.

Zeis, Joanne. *Essential Guide to Behçet's Disease.* Uxbridge, MA: Central Vision Press, 2003.

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Lee, Sungnack. "Behçet Disease." *EMedicine.* February 18, 2004 (May 17, 2004). <http://www.emedicine.com/derm/topic49.htm>.

"Types of Vasculitis: Behçet's Disease." *The Johns Hopkins Vasculitis Center Website*. The Johns Hopkins University. 2002 (May 17, 2004). <http://vasculitis.med.jhu.edu/typesof/behcets.html>.

ORGANIZATIONS

American Behçet's Disease Association. P.O. Box 19952, Amarillo, TX 79114. (800) 724-2387. jbadillo@behcets.com. <http://www.behcets.com>.

Behçets Organisation Worldwide. P.O. Box 27, Watchet, Somerset TA23 0YJ, United Kingdom. information@behcetsuk.org. <http://behcets.org>.

National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse. 1AMS Circle, Bethesda, MD 20892. (301) 495-4484 or (877) 226-4267; Fax: (301) 718-6366. niamsinfo@mail.nih.gov. <http://www.niams.nih.gov>.

Stacey L. Chamberlin

Bell's palsy

Definition

Bell's palsy describes the acute onset of an unexplained weakness or paralysis of the muscles on one side of the face. Afflicted individuals may be unable to close the eye on the affected side of the face, and may also experience tearing, drooling, and hypersensitive hearing on the same side. The onset can be quite sudden, sometimes occurring overnight. The weakness and paralysis resolve completely in the majority of cases. Although it cannot be considered a serious condition from a health standpoint, it can cause extreme stress, embarrassment, and inconvenience for those affected.

Description

Bell's palsy has been described as a diagnosis of exclusion because several other disorders exhibit similar symptoms. Facial palsies have been linked to conditions such as **Lyme disease**, ear infection, meningitis, syphilis, German measles (rubella), mumps, chicken pox (varicella), and infection with Epstein-Barr virus (e.g., infectious mononucleosis). True Bell's palsy is an idiopathic facial palsy, meaning the root cause cannot be identified. Although Bell's palsy is not life-threatening, it can present symptoms similar to serious conditions such as **stroke**, ruptured aneurysm, or tumors.

Demographics

Every year, approximately 40,000–65,000 Americans are stricken with Bell's palsy. Worldwide, there is an annual incidence of 20–30 cases per 100,000 individuals. An

Key Terms

Antiviral A drug that prevents viruses from replicating and therefore spreading infection.

Computed tomography (CT) Cross-sectional x rays of the body are compiled to create a three-dimensional image of the body's internal structures.

Electromyography A recording of the electrical activity generated in the muscle.

Facial nerve A cranial nerve that controls the muscles in the face.

Magnetic resonance imaging (MRI) This imaging technique uses a large circular magnet and radio waves to generate signals from atoms in the body. These signals are used to construct images of internal structures.

Nerve conduction velocity A recording of how well a nerve conducts electrical impulses.

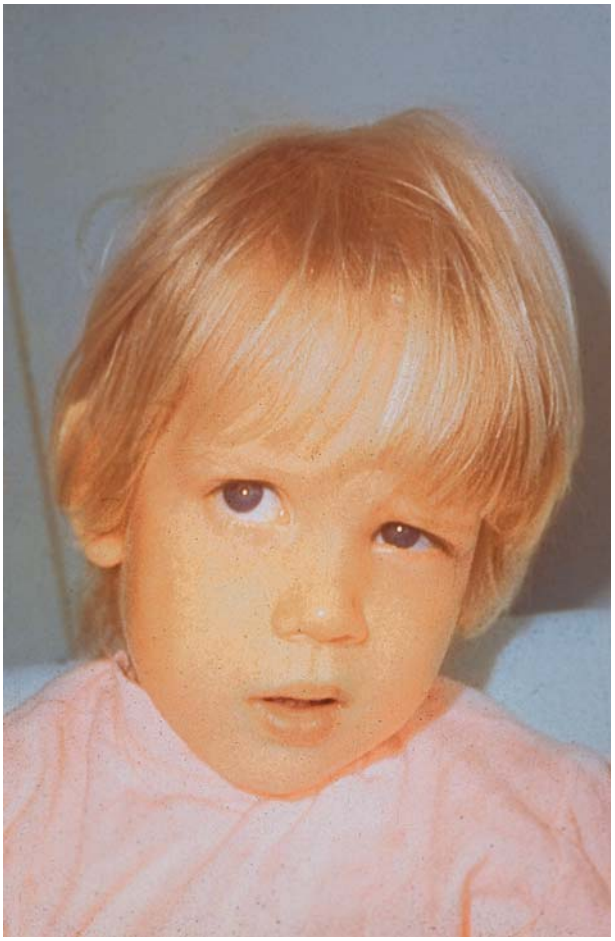
Steroid A drug used to reduce swelling and fluid accumulation.

individual can be affected at any age, but young and middle-aged adults are the most likely to be affected. It is unusual to see Bell's palsy in people less than 10 years old. Bell's palsy can affect either side of the face. Gender does not seem to factor into risk, though pregnant women and individuals with diabetes, influenza, a cold, or an upper respiratory infection seem to be at a greater risk.

In the large majority of cases (80–85%), the facial weakness or paralysis is temporary. However, individuals who experience complete paralysis seem to have a poorer recovery rate with only 60% returning to normal. Approximately 4–6% of all Bell's palsy cases result in permanent facial deformity, and another 10–15% experience permanent problems with spasms, twitching, or contracted muscles. Between 2% and 7.3% of individuals who have had Bell's palsy could experience a recurrence: on average, the first recurrence happens 9.8 years after the first episode; the second, 6.7 years later. One recurrence is very infrequent, and a second is extremely rare.

Causes and symptoms

The symptoms of Bell's palsy arise from an inflammation of the seventh cranial nerve, otherwise called the facial nerve. Each side of the face has a facial nerve that controls the muscles on that side of the face. Inflammation leads to the interference with conduction of nerve signals, and that in turn results in the loss of muscle control and tone.



This boy's facial paralysis was caused by a tick-borne meningopadiculitis. *(Photo Researchers, Inc. Reproduced by permission.)*

Why the facial nerve becomes inflamed in Bell's palsy is a matter of considerable debate. Some evidence implicates the herpes simplex virus (HSV), which is responsible for cold sores and fever blisters. HSV infection has been suggested in up to 70% of Bell's palsy cases. Most people harbor this virus, although they may not exhibit symptoms. A number of other conditions have also been associated with the development of Bell's palsy, including facial or head injuries, **headache**, repeated middle ear infections, high blood pressure, diabetes, sarcoidosis, tumors, influenza, and other viral infections, as well as Lyme disease.

The major symptom of Bell's palsy is one-sided facial weakness or paralysis. Muscle control is either inadequate or completely missing. Patients frequently have difficulty shutting the affected eye and may not be able to close it at all.

Other symptoms can include **pain** in the jaw or behind the ear on the affected side, ringing in the ear,

headache, decreased sense of taste, hypersensitivity to sound on the affected side, difficulty with speech, **dizziness**, and problems eating and drinking.

Diagnosis

Although Bell's palsy is not life-threatening, it has similar symptoms to serious conditions such as stroke. The fact that Bell's palsy is a diagnosis of exclusion becomes apparent in the course of the medical examination—it is imperative to rule out other disorders. Disorders that need to be excluded include demyelinating disease (e.g., **multiple sclerosis**), stroke, tumors, bacterial or viral infection, and bone fracture. Therefore, emergency medical attention is a wise and necessary precaution.

During the evaluation, the affected individual is asked about recent illnesses, accidents, infections, and any other symptoms. A visual exam of the ears, throat, and sinus is done, and hearing is tested. The extent of the symptoms is assessed by grading the symmetry of the face at rest and during voluntary movements such as wrinkling the forehead, puckering the lips, and closing the affected eye. Involuntary movements are assessed in combination with the voluntary movements. Neurologic exam is done to rule out involvement of other parts of the nervous system.

Blood tests and sometimes a cerebrospinal fluid (CSF) analysis may be needed. The results of these tests help determine the presence of a bacterial or viral infection or an inflammatory disease. Electrophysiological tests such as **electromyography** and **nerve conduction study**, in which a muscle or nerve is artificially stimulated, may be used to assess the condition of facial muscles and the facial nerve. Radiological tests may also be included, such as an x ray, **magnetic resonance imaging (MRI)**, and computed tomography (CT).

Once all other possibilities are exhausted, a diagnosis of Bell's palsy is made. During the next few weeks, the patient is carefully assessed. If facial movement, even a small amount, has not returned within 3–4 months, the diagnosis of Bell's palsy may need to be reevaluated.

Treatment team

The patient's primary care provider may be the initial contact; further consultation may be obtained from a **neurologist** and/or an ophthalmologist. Physical therapists may help with pain issues and regaining function.

Treatment

Many doctors prescribe an antiviral drug and/or a steroid for Bell's palsy, but there is some controversy about whether these drugs actually help. The consensus opinion seems to be that, although drugs might not be necessary, they are not dangerous, and they may help in some cases. If drugs are used, they need to be taken as soon as possible following the onset of symptoms. The use of **antiviral drugs** such as acyclovir, famciclovir, or valacyclovir is recommended to destroy actively replicating herpes viruses. Steroids such as prednisone are thought to be useful in reducing inflammation and swelling.

In the past, surgery was performed to relieve the compression on the nerve. However, this treatment option is now used very infrequently because its benefits are uncertain, and it carries the risk of permanent nerve damage.

The need to protect the affected eye is universally promoted. Since the individual may not be able to lower the affected eyelid, the eye may become dry, particularly at night. Excessive dryness can damage the cornea. Daytime treatment includes artificial tears and may include an eye patch or other protective measures. Nighttime treatment involves a more intense effort at keeping the eye protected. Eye lubricants or viscous ointments, along with taping the eye shut, are frequently recommended.

In cases of permanent nerve damage, cosmetic treatment options such as therapeutic injections of **botulism** toxin or surgery may be sought or suggested.

Prognosis

Most individuals with Bell's palsy begin to notice improvement in their condition within 2–3 weeks of the symptoms' onset. At least 80% of them will be fully recovered within three months. Among the other 20% of afflicted individuals, symptoms may take longer to resolve or they may be permanent. Individuals suffering permanent nerve damage may not regain control of the muscles on the affected side of the face. These muscles may remain weak or paralyzed. As the nerve recovers, muscles may experience involuntary facial twitches or spasms that accompany normal facial expressions.

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ORGANIZATIONS

Bell's Palsy Research Foundation. 9121 E. Tanque Verde, Suite 105-286, Tucson, AZ 85749. (520) 749-4614.

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Benign essential blepharospasm *see* **Blepharospasm**

Benign focal amyotrophy *see* **Monomelic amyotrophy**

Benign intracranial hypertension *see* **Pseudotumor cerebri**

Benign positional vertigo

Definition

Benign positional vertigo (BPV) is the most common cause of **dizziness** due to an impairment of the balance center in the ear.

Description

BPV was first described by Adler in 1987. Dix and Hallpike named the disorder benign paroxysmal positional vertigo. The disorder can also be called canalithiasis or positional vertigo or "top shelf vertigo" (affected persons tip their heads back to look up when having an attack).

The internal ear consists of sacs, ducts, and bone. The internal portion of the ear can be divided into the bony labyrinth and membranous labyrinth. The bony labyrinth is a cave-like area composed of three parts: the cochlea, vestibule, and semicircular canals. The shell-shaped cochlea is the organ for hearing. The vestibule is a small oval chamber that contains two structures, the utricle and the saccule, responsible for balance. A membrane within the utricle and saccule normally contains particles called otoliths (calcium carbonate particles). The semicircular canals that occupy three planes in space contain the semicircular ducts for fluid (endolymph) flow.

The Canalolithiasis Theory, the most widely accepted explanation for the cause of BPV, explains the actual mechanism that causes BPV. The theory is that otoliths can become displaced from the utricle and enter a portion of the semicircular ducts. Changing head position can cause free otoliths to gravitate longitudinally through the canal. The endolymph fluid contained in the semicircular canal will flow abnormally, causing stimulation of special sensors (hair cells) of the affected posterior semicircular canal duct. This stimulation causes vertigo or dizziness.

Demographics

In the United States, the number of new cases (incidence) is 64 cases per 100,000 populations per year. The incidence is greater in patients older than 40 years, and women are affected twice more often than men. Several studies indicate that an average age of onset in the mid-50s. Approximately 20% of all falls by the elderly, resulting in hospitalization for serious injuries, are due to vertigo (dizziness). No information is available concerning predilection to race. Approximately 25–40% of patients with BPV express dizziness as their chief complaint. The incidence among the elderly is estimated to be about 8%.

Causes and symptoms

The most common cause of BPV is head trauma (21% of cases) with a secondary concussion. The force of head trauma is thought to displace otolith particles in the semicircular canal. Approximately 39% of cases do not have a cause (idiopathic), and 29% of patients with BPV usually present with an existing ear disease. Other common causes include alcoholism, **central nervous system** (CNS) disease (approximately 11%), major surgery, and chronic ear infections such as chronic otitis media (approximately 9% of cases).

The severity of cases varies. Some patients may experience nausea and vomiting even with the slightest head movement, whereas some patients may be minimally bothered by the dizziness. As the name implies, symptoms of BPV are typically dependent on head position. Head movement, rolling in bed, leaning forward or backward, or changing posture can cause an attack. The symptoms start abruptly and disappear with 20–30 seconds.

Diagnosis

In addition to a detailed history, the physical examination is important for detection of characteristic physical signs such as nystagmus (involuntary rhythmic oscillation of the eyes). The examination is also necessary to exclude other neurological diseases that may mimic benign positional vertigo. A physician familiar with the condition may perform the Hallpike test. Also, in patients with vertigo, hearing tests are generally necessary. Further testing may be necessary to evaluation other conditions that can cause vertigo or dizziness.

Treatment team

The treatment team can consist of an emergency room physician, ear, nose, and throat (ENT) specialist-surgeon, **neurologist**, and audiologist. A primary care practitioner can initiate symptomatic management. Patients typically require follow-up care and monitoring. Surgical candidates require specialty care from an ENT surgeon, as well as and a surgical team in a hospital that is equipped for such an intervention.

Treatment

There are three types of treatment given to patients with BPV: medical care, surgery, and home treatment. Medical care (office treatment) consists of either the Semont maneuver (also referred to as the Liberaroty maneuver) or the Epley maneuver, named after their

Key Terms

Sensorium The place in the brain where external expressions are localized and processed before being perceived.

inventors. The Semont maneuver (a series of head-turning exercises) involves a rapid shift from lying on one side to lying on the opposite side. The Epley maneuver involves sequentially moving the head in four different positions and waiting for 30 seconds on each turn. These maneuvers are effective in approximately 80% of patients who are diagnosed with BPV, although symptoms may reoccur after initial improvement in a substantial percentage of patients. If office medical treatment fails, patients can continue treatment at home with the Brandt-Daroff Exercises, which are difficult to perform, but effective in 95% of cases. These exercises are time consuming and done in three sets per day for two weeks. Medical treatment with medications is not recommended since they do not help relieve symptoms.

A surgical procedure called posterior canal plugging can be utilized in patients who had no response to any other form of treatment. With this procedure, there is a small risk of hearing deficit (usually less than 20%), but it is effective in most patients. The posterior semicircular canal is excised, exposing the membranous labyrinth with floating otoliths. The canal is patched off with tissue so otolith particles cannot move into the canal to stimulate the hair cells within this area. The canal is sealed and the incision sutured. Typically, the patient will stay in the hospital overnight and return one week later for suture removal.

Recovery and rehabilitation

Recovery and rehabilitation is favorable. Most patients recover well with head-tilting exercises. Patients who have recurrence of symptoms will undergo further exercises or surgical correction, which is successful for resolution of symptoms in more than 90% of surgical candidates.

Clinical trials

A large study is currently active concerning the treatment of BPV in family practice at McMaster University Department of Family Medicine in Hamilton, Ontario, Canada. Contact is Shawn Ling at (905) 521-2100 ext. 75451; fax: (905) 521-5010; e-mail: lingfpu@yahoo.ca. **Clinical trials** as of 2001 reported good results using the Epley canalith repositioning maneuver. In 86 patients studied, 70% had resolution of symptoms within two days after treatment.

Prognosis

The overall prognosis for patients who suffer from BPV is good. Spontaneous remission can occur within six weeks, but some cases never remit. Once treated, the recurrence rate is between 5% and 15%.

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ORGANIZATIONS

American Hearing Research Association Foundation. 8 South Michigan Avenue, Suite 814, Chicago, IL 60603-4539. (312) 726-9670; Fax: (312) 726-9695.

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Benzodiazepines

Definition

Benzodiazepines are medicines that help relieve nervousness, tension, and other symptoms by slowing the **central nervous system**.

Purpose

Benzodiazepines are a type of antianxiety drugs. While anxiety is a normal response to stressful situations, some people have unusually high levels of anxiety that can interfere with everyday life. For these people, benzodiazepines can help bring their feelings under control. The

medicine can also relieve troubling symptoms of anxiety, such as pounding heartbeat, breathing problems, irritability, nausea, and faintness.

Physicians may sometimes prescribe these drugs for other conditions, such as muscle spasms, **epilepsy** and other seizure disorders, phobias, panic disorder, withdrawal from alcohol, and sleeping problems. However, this medicine should not be used every day for sleep problems that last more than a few days. If used this way, the drug loses its effectiveness within a few weeks.

Benzodiazepines should not be used to relieve the nervousness and tension of normal everyday life.

Description

The family of antianxiety drugs known as benzodiazepines includes alprazolam (Xanax), chlordiazepoxide (Librium), **diazepam** (Valium), and lorazepam (Ativan). These medicines take effect fairly quickly, starting to work within an hour after they are taken. Benzodiazepines are available only with a physician's prescription and are available in tablet, capsule, liquid, or injectable forms.

Recommended dosage

The recommended dosage depends on the type of benzodiazepine, its strength, and the condition for which it is being taken. Doses may be different for different people. Check with the physician who prescribed the drug or the pharmacist who filled the prescription for the correct dosage.

Always take benzodiazepines exactly as directed. Never take larger or more frequent doses, and do not take the drug for longer than directed. If the medicine does not seem to be working, check with the physician who prescribed it. Do not increase the dose or stop taking the medicine unless the physician says to do so. Stopping the drug suddenly may cause withdrawal symptoms, especially if it has been taken in large doses or over a long period. People who are taking the medicine for seizure disorders may have **seizures** if they stop taking it suddenly. If it is necessary to stop taking the medicine, check with a physician for directions on how to stop. The physician may recommend tapering down gradually to reduce the chance of withdrawal symptoms or other problems.

Precautions

Seeing a physician regularly while taking benzodiazepines is important, especially during the first few months of treatment. The physician will check to make sure the medicine is working as it should and will note unwanted side effects.

People who take benzodiazepines to relieve nervousness, tension, or symptoms of panic disorder should check with their physicians every two to three months to make sure they still need to keep taking the medicine.

Patients who are taking benzodiazepines for sleep problems should check with their physicians if they are not sleeping better within 7-10 days. Sleep problems that last longer than this may be a sign of another medical problem.

People who take this medicine to help them sleep may have trouble sleeping when they stop taking the medicine. This effect should last only a few nights.

Some people, especially older people, feel drowsy, dizzy, lightheaded, or less alert when using benzodiazepines. The drugs may also cause clumsiness or unsteadiness. When the medicine is taken at bedtime, these effects may even occur the next morning. Anyone who takes these drugs should not drive, use machines, or do anything else that might be dangerous until they have found out how the drugs affect them.

Benzodiazepines may also cause behavior changes in some people, similar to those seen in people who act differently when they drink alcohol. More extreme changes, such as confusion, agitation, and **hallucinations**, also are possible. Anyone who starts having strange or unusual thoughts or behavior while taking this medicine should get in touch with his or her physician.

Because benzodiazepines work on the central nervous system, they may add to the effects of alcohol and other drugs that slow down the central nervous system, such as antihistamines, cold medicine, allergy medicine, sleep aids, medicine for seizures, tranquilizers, some **pain** relievers, and muscle relaxants. They may also add to the effects of anesthetics, including those used for dental procedures. These effects may last several days after treatment with benzodiazepines ends. The combined effects of benzodiazepines and alcohol or other CNS depressants (drugs that slow the central nervous system) can be very dangerous, leading to unconsciousness or, rarely, even death. Anyone taking benzodiazepines should not drink alcohol and should check with his or her physician before using any CNS depressants. Taking an overdose of benzodiazepines can also cause unconsciousness and possibly death. Anyone who shows signs of an overdose or of the effects of combining benzodiazepines with alcohol or other drugs should get immediate emergency help. Warning signs include slurred speech or confusion, severe drowsiness, staggering, and profound weakness.

Some benzodiazepines may change the results of certain medical tests. Before having medical tests, anyone taking this medicine should alert the health care professional in charge.

Children are generally more sensitive than adults to the effects of benzodiazepines. This sensitivity may increase the chance of side effects.

Key Terms

Anxiety Worry or tension in response to real or imagined stress, danger, or dreaded situations. Physical reactions, such as fast pulse, sweating, trembling, fatigue, and weakness may accompany anxiety.

Asthma A disease in which the air passages of the lungs become inflamed and narrowed.

Bronchitis Inflammation of the air passages of the lungs.

Central nervous system The brain, spinal cord, and the nerves throughout the body.

Chronic A word used to describe a long-lasting condition. Chronic conditions often develop gradually and involve slow changes.

Emphysema An irreversible lung disease in which breathing becomes increasingly difficult.

Epilepsy A brain disorder with symptoms that include seizures.

Glaucoma A condition in which pressure in the eye is abnormally high. If not treated, glaucoma may lead to blindness.

Myasthenia gravis A chronic disease with symptoms that include muscle weakness and sometimes paralysis.

Panic disorder A disorder in which people have sudden and intense attacks of anxiety in certain situations. Symptoms such as shortness of breath, sweating, dizziness, chest pain, and extreme fear often accompany the attacks.

Phobia An intense, abnormal, or illogical fear of something specific, such as heights or open spaces.

Porphyria A disorder in which porphyrins build up in the blood and urine.

Porphyrin A type of pigment found in living things.

Seizure A sudden attack, spasm, or convulsion.

Sleep apnea A condition in which a person temporarily stops breathing during sleep.

Withdrawal symptoms A group of physical or mental symptoms that may occur when a person suddenly stops using a drug to which he or she has become dependent.

Older people are more sensitive than younger adults to the effects of this medicine and may be at greater risk for side effects. Older people who take these drugs to help them sleep may be drowsy during the day. Older people also increase their risk of falling and injuring themselves when they take these drugs.

Special conditions

People with certain medical conditions or who are taking certain other medicines can have problems if they take benzodiazepines. Before taking these drugs, be sure to let the physician know about any of these conditions:

ALLERGIES Anyone who has had unusual reactions to benzodiazepines or other mood-altering drugs in the past should let his or her physician know before taking the drugs again. The physician should also be told about any allergies to foods, dyes, preservatives, or other substances.

PREGNANCY Some benzodiazepines increase the likelihood of birth defects. Using these medicines during pregnancy may also cause the baby to become dependent on them and to have withdrawal symptoms after birth. When taken late in pregnancy or around the time of labor and delivery, these drugs can cause other problems in the newborn baby, such as weakness, breathing problems, slow heartbeat, and body temperature problems.

Women who are pregnant or who may become pregnant should not use benzodiazepines unless their anxiety is so severe that it threatens their pregnancy. Any woman who must take this medicine while pregnant should be sure to thoroughly discuss its risks and benefits with her physician.

BREAST-FEEDING Benzodiazepines may pass into breast milk and cause problems in babies whose mothers take the medicine. These problems include drowsiness, breathing problems, and slow heartbeat. Women who are breast-feeding their babies should not use this medicine without checking with their physicians.

OTHER MEDICAL CONDITIONS Before using benzodiazepines, people with any of these medical problems should make sure their physicians are aware of their conditions:

- current or past drug or alcohol abuse
- **depression**
- severe mental illness
- epilepsy or other seizure disorders
- **swallowing disorders**
- chronic lung disease such as emphysema, asthma, or chronic bronchitis

- kidney disease
- liver disease
- brain disease
- glaucoma
- hyperactivity
- **myasthenia gravis**
- porphyria
- **sleep apnea**

USE OF CERTAIN MEDICINES Taking benzodiazepines with certain other drugs may affect the way the drugs work or may increase the chance of side effects.

Side effects

The most common side effects are **dizziness**, lightheadedness, drowsiness, clumsiness, unsteadiness, and slurred speech. These problems usually go away as the body adjusts to the drug and do not require medical treatment unless they persist or they interfere with normal activities.

More serious side effects are not common, but may occur. If any of the following side effects occur, check with the physician who prescribed the medicine as soon as possible:

- behavior changes
- memory problems
- difficulty concentrating
- confusion
- depression
- seizures (convulsions)
- hallucinations
- sleep problems
- increased nervousness, excitability, or irritability
- involuntary movements of the body, including the eyes
- low blood pressure
- unusual weakness or tiredness
- skin rash or itching
- unusual bleeding or bruising
- yellow skin or eyes
- sore throat
- sores in the mouth or throat
- fever and chills.

Patients who take benzodiazepines for a long time or at high doses may notice side effects for several weeks after they stop taking the drug. They should check with their physicians if these or other troublesome symptoms occur:

- irritability
- nervousness
- sleep problems.

Other rare side effects may occur. Anyone who has unusual symptoms during or after treatment with benzodiazepines should get in touch with his or her physician.

Interactions

Benzodiazepines may interact with a variety of other medicines. When this happens, the effects of one or both of the drugs may change or the risk of side effects may be greater. Anyone who takes benzodiazepines should let the physician know all other medicines he or she is taking. Among the drugs that may interact with benzodiazepines are:

- central nervous system (CNS) depressants such as medicine for allergies, colds, hay fever, and asthma
- sedatives
- tranquilizers
- prescription pain medicine
- muscle relaxants
- medicine for seizures
- sleep aids
- barbiturates
- anesthetics

Medicines other than those listed above may interact with benzodiazepines. Be sure to check with a physician or pharmacist before combining benzodiazepines with any other prescription or nonprescription (over-the-counter) medicine.

Resources

OTHER

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Nancy Ross-Flanigan

Beriberi

Definition

Beriberi is a condition caused by severe prolonged deficiency of vitamin B1 (also known as thiamine). Beriberi refers to a constellation of heart, gastrointestinal, and nervous system problems from thiamine deficiency.

Description

Thiamine is found in a variety of foods, particularly whole grains, legumes, and pork. Thiamine serves as a coenzyme in the chemical pathway responsible for the metabolism of carbohydrates. Thiamine deficiency interferes with the metabolism of glucose and the production of energy.

Four major types of beriberi exist: wet beriberi, which affects primarily the cardiovascular system; dry beriberi, which affects primarily the nervous system; shoshin, which is a rapidly evolving and frequently fatal form of cardiovascular beriberi; and infantile beriberi, which tends to strike babies between the ages of one and four months who are breastfed by mothers who are severely thiamine deficient.

Demographics

Because so many foods in the United States and other western countries are vitamin enriched, beriberi is extremely rare. In developed countries, beriberi is primarily a complication of malnutrition secondary to alcoholism or gastrointestinal disorders. Because alcoholism affects more males than females, rates of beriberi in developed countries are higher among males. The syndrome of symptoms caused by thiamine deficiency in alcoholism is called Wernicke-Korsakoff syndrome.

In developing countries, where diets are more limited, beriberi is endemic. In some areas of Asia, people subsist on polished rice, in which the outer, more nutritious husk is removed. The rates of beriberi in these areas are quite high. In certain parts of Indonesia, the prevalence of beriberi among low-income families is as high as 66%. The majority of patients with beriberi are infants (ages 1–4 months) and adults.

Causes and symptoms

Symptoms of beriberi are caused by abnormal metabolism of carbohydrates throughout the body, resulting in a decreased production of energy, and particular injury to the heart muscle and the nervous system.

Symptoms of dry beriberi include:

- numbness, tingling, burning **pain** in extremities
- pain and cramping in the leg muscles
- difficulty with speech
- problems walking
- disturbed sense of balance

Symptoms of wet beriberi include:

- fast heart rate
- swollen feet and legs
- enlarged heart
- enlarged, tender liver
- shortness of breath
- congestion in the lungs

Symptoms of shoshin beriberi are the same as those of wet beriberi, but the onset is sudden, the progression is rapid, and the risk of death is very high.

Symptoms of infantile beriberi include:

- restlessness
- difficulty sleeping
- diarrhea
- swollen arms and legs
- muscle wasting in arms and legs
- silent cry
- heart failure

Symptoms may coexist with other disorders due to thiamine deficiency such as Wernicke-Korsakoff **encephalopathy**. In such cases, confusion, memory loss, difficulty with eye movements, and even coma may occur.

Diagnosis

The first step to diagnosis includes taking a careful history to uncover a possible underlying cause for thiamine deficiency. Physical examination will demonstrate some of the expected signs of beriberi, such as swelling, decreased reflexes, decreased sensation, problems with walking or balance, etc.

Laboratory testing to demonstrate thiamine deficiency includes measurements of thiamine in the blood; tests of the activity of thiamine in whole blood or red blood cells (called transketolase activity), both before and after the administration of thiamine; measurements of the chemicals lactate and pyruvate in the blood (these will be increased in beriberi); and measurements of the amount of thiamine passed into the urine (this will be decreased in beriberi).

In some cases, the diagnosis of beriberi is made only after thiamine supplementation results in a resolution of the patient's symptoms.

Treatment team

Depending on how a patient enters the health care system, an emergency room physician, internal medicine physician, family practitioner, **neurologist**, gastroenterologist, or cardiologist may treat a patient for beriberi. A nutritionist should be consulted to develop a nutritional plan. If alcoholism is an underlying problem, the patient

may need to enter an alcohol rehabilitation program. Physical therapy may help patients recover from the neurological complications of beriberi.

Treatment

When a patient has serious symptoms of thiamine deficiency, supplementation is usually started by giving thiamine through an IV or by intramuscular shots. Because magnesium is required for the proper functioning of thiamine, magnesium is usually administered through injections as well. After several days of this therapy, a multivitamin containing 5–10 times the usually recommended daily allowance of all the water-soluble vitamins, including thiamine, should be given for several weeks. Ultimately, the patient will be advised to follow a lifelong regimen of nutritious eating, with the regular diet supplying 1–2 times the recommended daily allowance of the water-soluble vitamins, including thiamine.

Recovery and rehabilitation

Recovery from the cardiovascular effects of beriberi is nearly always complete. Some of the neurological problems, however, may remain even after thiamine supplementation has been accomplished.

Prognosis

The longer a patient lives with a thiamine deficiency, the more severe the symptoms of beriberi. If untreated, beriberi is fatal. When treated with thiamine supplementation and a healthy diet, most of the symptoms of beriberi can be resolved.

Special concerns

Although beriberi is readily avoided with a healthy diet or successfully treated with thiamine supplementation and the initiation of a healthy diet, this is not always possible in developing countries where resources are scarce.

Resources

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Rosalyn Carson-DeWitt, MD

Bernhardt-Roth syndrome *see* **Meralgia paresthetica**

Binswanger disease

Definition

Binswanger disease is a rare form of progressive **dementia** that develops after age 60 and involves degeneration of the brain's white matter.

Description

Also known as subcortical arteriosclerotic **encephalopathy**, Binswanger disease is a form of subcortical dementia. Dementia is a general term used to describe a generalized deterioration of thinking and reasoning skills. In the case of Binswanger disease, the deterioration is due to physiological problems (i.e., organic factors). While many dementias result from damage to cortical areas of the brain, some diseases, including Binswanger disease, **Alzheimer's disease**, **Parkinson's disease**, **Huntington disease**, and dementia associated with **AIDS**, result from damage to subcortical areas of the brain (specifically, to subcortical connections).

Alternate names for Binswanger disease include Binswanger-type **multi-infarct dementia**, Binswanger encephalopathy, and Binswanger-type vascular dementia.

As with other individuals suffering subcortical dementia, people with Binswanger experience difficulties in maintaining attention to tasks and show depressed levels of motivation often accompanied by mood swings or apathy.

Demographics

Although Binswanger disease may occur in younger groups, the symptoms usually become pronounced in patients over 60 years of age.

Causes and symptoms

The exact cause of Binswanger disease is unknown, however, lesions in cerebrovascular tissue located in the inner white matter of the brain cause most of the symptoms. Prominent symptoms include rapid mood changes, loss of the ability to focus on tasks, a deterioration in thought processes (e.g., loss of memory and cognition), and mood changes.

Key Terms

Dementia Usually a long-lasting (chronic), often progressive, deterioration of the ability to think and reason due to an organic cause (an underlying illness or disorder).

Subcortical The neural centers located below (inferior to) the cerebral cortex.

Individuals with Binswanger disease may also have elevated blood pressure or suffer from **stroke**. Binswanger disease is found to be associated with blood (hematological) abnormalities with regard to the types and numbers of cells present, diseases of large blood vessels (especially in the upper chest and neck regions), and diseases of the heart. Abnormal electrical disturbances in the brain may cause **seizures**.

Binswanger's symptoms may be elusive in both appearance and degree. Not all people experience all the symptoms normally associated with the disease, and patients may experience symptoms for a period of time, followed by brief periods in which they are relatively symptom free.

As with other dementias, patients often present evidence of forgetfulness, memory loss, confusion and/or confabulation of events in terms of time and space (e.g., having a memory of two events that occur on different days as a combined memory of one event).

People with Binswanger disease often suffer **depression** and withdraw from family, friends, and co-workers (social withdrawal). Although clinical depression is a psychiatric term and requires a separate diagnosis, Binswanger patients suffering depression show a marked loss of interest in activities they once found pleasurable.

As the dementia progresses, people with Binswanger disease may initially lose the ability to perform tasks involving fine motor coordination, such as tying shoes or writing by hand, followed by a loss of broader function. Loss of bladder control (urinary incontinence) may develop, as well as generalized clumsiness or difficulty in walking. Later, patients often develop a blank-like stare and may have difficulty speaking or swallowing.

Diagnosis

Binswanger disease is identified by detection and characterization of lesions in the cerebrovascular tissue located in the inner white matter of the brain, which are usually visible on computed tomography (**CT**) **scan** or **magnetic resonance imaging (MRI)**.

A tentative diagnosis of Binswanger disease is made upon an evaluation of patient history and symptoms. A definitive diagnosis is made upon autopsy that reveals lesions in cerebrovascular tissue lying in the subcortical regions of the brain. Lesions are not always confined to subcortical areas and additional lesions also may extend into cortical areas.

Treatment team

The treatment team for patients suffering from dementia, either cortical or subcortical, usually includes physicians, nurses, and physical, speech, and occupational therapists.

The diagnosis of Binswanger disease is often made by a **neurologist**. Physical therapists evaluate deficits in strength, movement, and gait, and supervise exercises to improve these deficits. Speech-language pathologists evaluate deficits in the ability to eat and speak, and provide adaptive strategies to minimize their effects. Occupational therapists evaluate a person's ability to maintain posture and focus while executing normal activities of daily living (such as reaching for and using a toothbrush) and devise strategic movements and equipment to adapt to deficits.

An expanded network of professionals, including mental health counselors and social service workers, may be beneficial. Caregivers are often required for personal care during the late stages of the disease.

Treatment

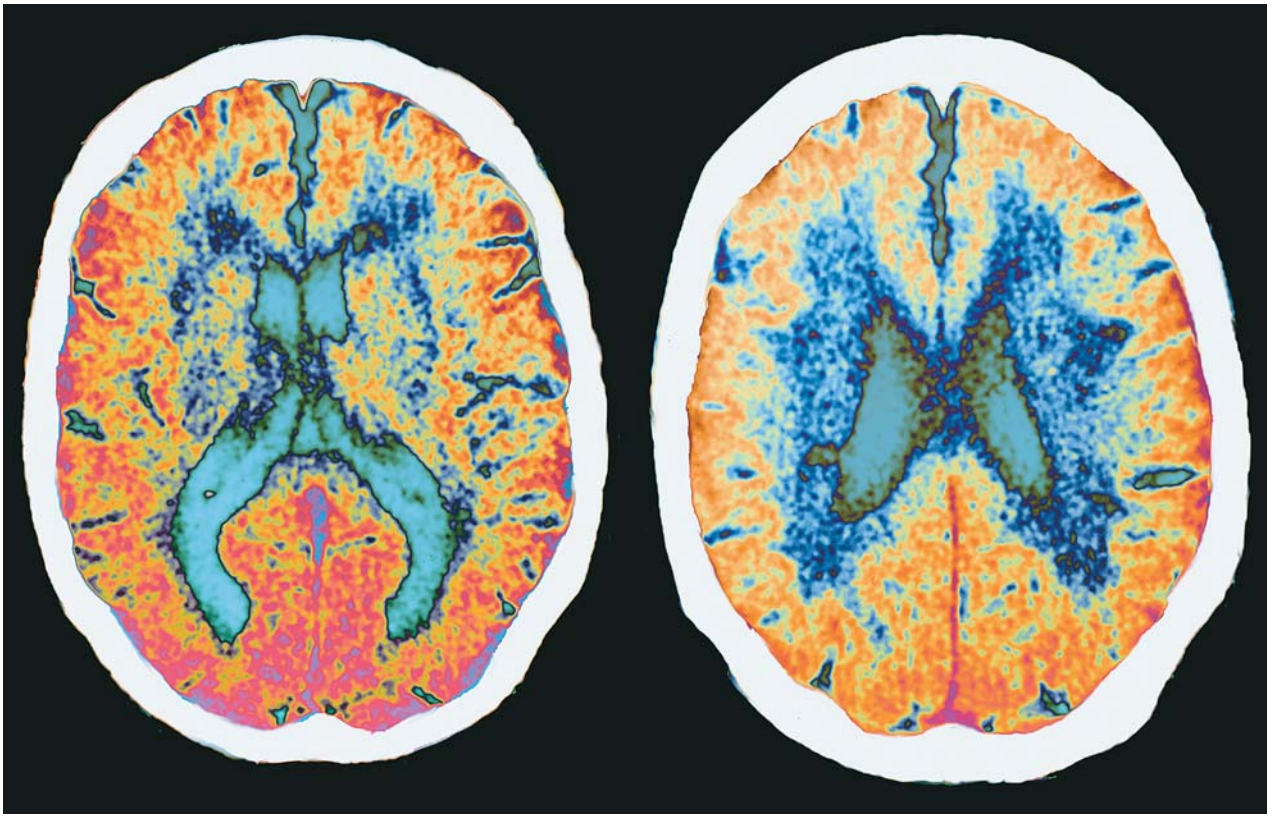
There is no known cure or specific treatment for Binswanger disease. Patients are treated symptomatically, i.e., treated for the symptoms such as high blood pressure, seizures, or heart disease often associated with Binswanger disease.

In most cases, specialized treatment plans include medications to control mood swings and depression, blood pressure (both elevated and low), seizures, and rhythm irregularities in the heart. Treatment is designed to reduce the adverse effects of these associated conditions.

Recovery and rehabilitation

Although currently no cure exists for dementias such as the Binswanger type, the goal of therapy is to maintain the highest state of physical health by managing the symptoms, along with maintaining the highest possible state of functional activity and well being. In addition to physical and occupational therapy, treatment for mood swings or depression helps the person with Binswanger disease to remain active, socially engaged, and mobile for as long as possible.

When the disease progresses and mobility, along with mental ability, decreases, the person with Binswanger or



CT scans of a patient with Binswanger disease. The CT scans show the presence of periventricular white matter hypodensities. *(Phototake, Inc. All rights reserved.)*

other dementias will likely require a nurturing environment that provides for medical care and safety. Whether at home or in a care facility, personal care assistance may be necessary for many or all hours of the day.

Many communities have adult daycare centers with targeted, stimulating activities for persons with dementia in the early stages. Long-term care facilities that specialize in dementia can provide an environment that fosters mobility in a soothing environment, where staff provides cues to orient the person with dementia to memories and surroundings.

Clinical trials

Research on a wide range of neurological diseases, including dementias, is conducted by agencies of the National Institutes of Health such as the National Institute of Neurological Disorders and Stroke (NINDS), and other institutes and research organizations such as the National Institute on Aging and the National Institute of Mental Health. As of November 2003, scientists at the National Institute of Neurological Disorders and Stroke are reevaluating the definitions for many forms of dementia, including Binswanger disease.

Prognosis

Because there is no known specific cure for Binswanger disease, in most cases the disease follows a slowly progressing course during which a patient may suffer progressive strokes interspersed with periods of partial recovery. Once symptoms become visible (manifest), persons with Binswanger disease often die within five years of the onset of the disease.

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Alzheimer's Association. 919 North Michigan Avenue, Suite 1100, Chicago, IL 60611-1676. (312) 335-8700 or (800)

272-3900; Fax: (312) 335-1110. info@alz.org. <http://www.alz.org>.

Alzheimer's Disease Education and Referral Center (ADEAR). P.O. Box 8250, Silver Spring, MD 20907-8250. (301) 495-3311 or (800) 438-4380; Fax: (301) 495-3334. adear@alzheimers.org. <http://www.alzheimers.org>.

Family Caregiver Alliance. 690 Market Street / Suite 600, San Francisco, CA 94104. (415) 434-3388 or (800) 445-8106; Fax: (415) 434-3508. info@caregiver.org. <http://www.caregiver.org>.

National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health. P.O. Box 5801, Bethesda, MD 20824; (301) 496-5751 or (800) 352-9424; TTY (301) 468-5981. braininfo@ninds.nih.gov. <http://www.ninds.nih.gov/>.

National Organization for Rare Disorders (NORD). 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Paul Arthur

Biopsy

Definition

A biopsy is the removal of a small portion of tissue from the body for microscopic examination.

Description

When a physician diagnoses the nature of an ailment, various examinations provide information that is vital to accurately determining the nature of the problem. Blood and urine samples can be examined to determine the amounts of various compounds. As useful as this information can be, it reveals little about the state of tissues. In diseases such as cancer, knowledge of the affected tissue is crucial for diagnosis and the formulation of treatment strategies.

Examination of tissues can be accomplished without obtaining a sample, using techniques like ultrasound and **magnetic resonance imaging (MRI)**. However, the information gained may not be detailed enough for a definitive diagnosis. For example, a physician may be interested in the activity of a particular enzyme in the tissue, as a marker of a disease process, or the presence of a toxin. For such determinations, a tissue sample that can be analyzed in the laboratory is needed.

Similarly, for certain diseases and conditions that involve nerve abnormalities, the ability to directly examine nerves can be advantageous in diagnosis and treatment. For instance, direct microscopic examination of a nerve sample can reveal whether or not the protective myelin sheath that surrounds a nerve is intact or is in the process of degrading. Obtaining a nerve via a biopsy is a valuable aid to these examinations.

Muscle biopsies can serve a similar purpose, since maladies that affect the structure and/or functioning of nerves will ultimately affect the muscles into which the nerve passes. The loss of muscle function or strength can be the direct consequence of nerve damage.

Biopsy

A biopsy describes the procedure that is used to obtain a very small piece of the target tissue. For some tissues, like the lining of the cheek, cells can be obtained just by scrapping the tissue surface. Other samples are collected using forceps that are positioned at the end of an optical device called an endoscope. The physician can view the tissue surface (such as the wall of the large intestine) through the endoscope and use the forceps to pluck tissue from the desired region of the surface. In other cases, the tissue sample needs to be collected as a "plug," using a large hypodermic needle. Examples of the latter include liver or kidney biopsy samples. Samples of muscles and nerves can also be obtained by cutting out a small piece of the target once an incision has been made.

When a biopsy is obtained using a needle, the retrieval of a sample relies on the design of the needle and the energy of its insertion into the tissue. The needle used is a hollow tube with a sharp point capable of puncturing tissue. As the needle is driven deeper into a tissue following puncture, tissue will accumulate in the hollow tube. When the needle is withdrawn from the tissue, the plug of tissue remains in the needle tube and can be retrieved for analysis.

Many biopsy samples are examined using a light microscope to look for abnormalities in the tissues cells. This examination can involve the staining of the sample to specifically detect target molecules. As well, samples can be used for various biochemical tests, and even to test for the presence and activity of particular genes.

A biopsy can remove the entire target region (excisional biopsy) or can remove just a small portion of the target region (incisional biopsy). The latter can be done in three different ways, depending on the sample. A shave biopsy slices off surface tissue. Samples collected by piercing the tissue with a needle represent a punch biopsy. Finally, in fine needle aspiration, a needle is inserted and tissue is subsequently withdrawn into the needle using a syringe.

Muscle biopsy

A muscle biopsy can represent the punch type, in which a plug of tissue is obtained using an inserted needle. Or, in an open biopsy procedure, a small incision is made and a piece of tissue is removed. This biopsy is done for a

Key Terms

Excisional biopsy Removal of an entire lesion for microscopic examination.

Incisional biopsy Removal of a small part of a sample tissue area for microscopic examination.

variety of reasons: to distinguish between nerve and muscle disorders, to identify specific muscular disorders such as **muscular dystrophy**, to probe muscle metabolic activities, and to detect muscle infections such as trichinosis and toxoplasmosis. Biopsy of a muscle necessarily involves nerves, as muscle is highly infused by nerves. The small amount of muscle that is extracted during a muscle biopsy does not damage nerves to such an extent that muscle function is affected.

Brain biopsy

A brain biopsy is performed following the drilling of a hole in the skull, through which the biopsy needle is subsequently introduced. An MRI or computed tomography (**CT**) **scan** is performed prior to the procedure in order to identify the area where the biopsy will be performed. As of the mid-1990s, the patient's head is no longer immobilized during the procedure by a frame device. Instead, the precise location is located by a computer-guided system that is designed to avoid damage to other regions of the brain. In contrast to a skin biopsy, for example, where the sample scraping may affect few nerves, a brain biopsy is a delicate and potentially problematic procedure. Rarely, nerve damage may result, and the puncture site may form scar tissue, causing **seizures**.

Nerve biopsy

Nerves such as the sural nerve in the ankle and the superficial radial nerve in the wrist are most often used for a nerve biopsy. A nerve biopsy is performed to detect nerve-damaging conditions, including leprosy, necrotizing **vasculitis** (an inflammation of the blood vessels), other nerve inflammation, and damage or loss of the nerve's protective myelin sheath (demyelination). A nerve biopsy can also be done to try to identify nerve abnormalities that are generically called neuropathies, or to confirm a specific diagnosis relating to a nerve. An example is the progressive wasting away of muscle tissue in the feet and legs that is known as Charcot-Marie-Tooth disease.

When a nerve biopsy is performed, local anesthetic is used. Then a small incision is made and a small piece of the target nerve is removed. Usually, a biopsy of the adjacent muscle is done at the same time. The biopsy procedure carries minimal risks, including allergic reaction to the anesthetic, infection, and permanent numbness. A small degree of persistent numbness is to be expected, however, because a portion of nerve has been removed. As a nerve biopsy is generally performed in the ankle or wrist, the numbness is typically not debilitating and is seldom recognized during normal activities.

Biopsy sample processing and examination

Biopsy specimens are often sliced into thin slices, stained, mounted on a glass slide, and examined using a light microscope. Newer sample preparation techniques involve the rapid freezing of the sample and slicing of the still-frozen material. The latter technique has the advantage of avoiding the removal of water, which can alter the structure of the tissue cells. Microscopic examination focuses on the general appearance of the cells, including their structure, presence of abnormalities, and specific molecules that have been revealed by the use of specialized stains or antibodies. This interpretation can be subjective, and relies on the expertise of the experienced examiner.

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American Academy of Neurology. 1080 Montreal Avenue, Saint Paul, MN 55116. (651) 695-2717 or (800) 879-1960; Fax: (651) 695-2791. memberservices@aan.com. <http://www.aan.com>.

Brian Douglas Hoyle, PhD

Blepharospasm

Definition

Blepharospasm is an involuntary closure of the eyelids.

Description

"Blepharo" refers to the eyelids, and "spasm" to involuntary muscle contraction. In blepharospasm, the eyelids close involuntarily due to an unknown cause within the brain. Blepharospasm is a form of **dystonia**, a disorder characterized by sustained muscle contraction. The most common form of blepharospasm is called "benign essential blepharospasm," meaning it is not life threatening and is not due to some other identifiable disorder. A condition called **hemifacial spasm** causes similar symptoms, but affects only one side of the face, and is caused by an irritation of the facial nerve outside of the brain.

Demographics

Blepharospasm is estimated to affect approximately 15,000 people in the United States. Onset is most commonly between the ages of 40 and 60, but can begin in childhood or old age. Women are affected approximately twice as often as men.

Causes and symptoms

The cause of benign essential blepharospasm is unknown. Evidence suggests it may be genetic in some cases, although genes have not been identified. A person with blepharospasm often has dystonia in another region of the body such as the mouth or the hands (i.e., writer's cramp). Other forms of dystonia or tremor may affect other family members. Blepharospasm is not caused by a problem with the eyes themselves, but rather with the brain regions controlling the muscles of the eyelids.

Secondary blepharospasm occurs due to some identifiable cause. The most-common cause of secondary blepharospasm is a reaction to antipsychotic medications, and is called tardive dystonia. Damage to the brain, either through **stroke**, **multiple sclerosis**, or trauma, may also cause blepharospasm.

Blepharospasm often begins with increased frequency of blinking, which may be accompanied by a feeling of irritation in the eyes or "dry eye." It progresses to intermittent, and then sustained, forceful closure of the eyelids. Symptoms are usually worse when the patient is tired, under stress, or exposed to bright light. Symptoms may become severe enough to interfere with activities of daily living, and can render the patient functionally blind.

Diagnosis

Blepharospasm is diagnosed by a careful clinical exam. A detailed medical history is taken to determine exposure to drugs or other possible causative agents, and a family history is used to determine if other family members are affected by other forms of dystonia or tremor.

Key Terms

Dystonia Painful involuntary muscle cramps or spasms.

Treatment team

The treatment team consists of a **neurologist** and possibly a neurosurgeon.

Treatment

The most effective treatment for blepharospasm is injection of **botulinum toxin** (BTX) into the muscles controlling the eyelids. BTX temporarily prevents the muscles from contracting, allowing patient to keep their eyes open. BTX is a safe and effective treatment for this condition. Usually the effects are seen within several days of injection, have their maximum effect for 6–8 weeks, and last between 12 and 16 weeks, at which time reinjection is performed. Side effects of BTX injection include mild discomfort at the injection site(s), and occasional double vision or inability to lift the eyelids due to local spread of the toxin to other muscles. Dry eyes or excessive tearing may also occur. Development of resistance to BTX injections is possible if the patient's immune system creates antibodies against the toxin. While this has not been reported in blepharospasm as the injected dose is very low, it has occurred in other conditions in which the doses are higher.

Oral medications are rarely effective for blepharospasm. Among the most widely used are **anticholinergics** (trihexyphenidyl, benztropine), baclofen, and **benzodiazepines** (**diazepam**, clonazepam). Surgery is an option for patients who do not respond to BTX injections. The surgical procedures are performed to remove part of the overactive muscles, or to sever the nerve leading to them, or both. Unfortunately, surgery is rarely completely successful, and there is a high rate of recurrence of blepharospasm.

Clinical trials

There are no current **clinical trials** for blepharospasm since effective treatment is available.

Prognosis

Blepharospasm is a chronic condition, which tends to worsen over time. Many patients with blepharospasm develop other dystonias in other body regions.

Resources

WEBSITES

Benign Essential Blepharospasm Research Foundation. (April 19, 2004.) <http://www.blepharospasm.org/>.

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Richard Robinson

Bloch-Sulzberger syndrome *see* **Incontinentia pigmenti**

Blood-brain barrier *see* **Cerebral circulation**

Bodywork therapies

Definition

Bodywork therapies is a general term that refers to a group of body-based approaches to treatment that emphasize manipulation and realignment of the body's structure in order to improve its function as well as the client's mental outlook. These therapies typically combine a relatively passive phase, in which the client receives deep-tissue bodywork or postural correction from an experienced instructor or practitioner, and a more active period of movement education, in which the client practices sitting, standing, and moving about with better alignment of the body and greater ease of motion.

Bodywork should not be equated with massage simply speaking. Massage therapy is one form of bodywork, but in massage therapy, the practitioner uses oil or lotion to reduce the friction between his or her hands and the client's skin. In most forms of body work, little if any lubrication is used, as the goal of this type of hands-on treatment is to warm, relax, and stretch the fascia (a band or sheath of connective tissue that covers, supports, or connects the muscles and the internal organs) and underlying layers of tissue.

Purpose

The purpose of bodywork therapy is the correction of problems in the client's overall posture, connective tissue, and/or musculature in order to bring about greater ease of movement, less discomfort, and a higher level of energy in daily activity. Some forms of bodywork have as a secondary purpose the healing or prevention of repetitive stress injuries, particularly for people whose occupations require intensive use of specific parts of the body (e.g., dancers, musicians, professional athletes, opera singers, etc.). Bodywork may also heal or prevent specific musculoskeletal problems, such as lower **back pain** or neck **pain**.

Bodywork therapies are holistic in that they stress increased self-awareness and intelligent use of one's body as one of the goals of treatment. Some of these therapies use verbal discussion, visualization, or guided imagery along with movement education to help clients break old patterns of moving and feeling. Although most bodywork therapists do not address mental disorders directly in their work with clients, they are often knowledgeable about the applications of bodywork to such specific emotions as depession, anger, or fear.

Although some bodywork therapies, such as Rolfing or Hellerwork, offer programs structured around a specific number or sequence of lessons, all therapies of this type emphasize individualized treatment and respect for the uniqueness of each individual's body. Bodywork instructors or practitioners typically work with clients on a one-to-one basis, as distinct from a group or classroom approach.

Precautions

Persons who are seriously ill, acutely feverish, or suffering from a contagious infection should wait until they have recovered before beginning a course of bodywork. As a rule, types of bodywork that involve intensive manipulation or stretching of the deeper layers of body tissue are not suitable for persons who have undergone recent surgery or have recently suffered severe injury. In the case of Tragerwork, shiatsu, and trigger point therapy, clients should inform the therapist of any open wounds, bruises, or fractures so that the affected part of the body can be avoided during treatment. Craniosacral therapy, the Feldenkrais method, and the Alexander technique involve gentle touch and do not require any special precautions.

Persons who are recovering from abuse or receiving treatment for any post-traumatic syndrome or dissociative disorder should consult their therapist before undertaking bodywork. Although bodywork is frequently recommended as an adjunctive treatment for these disorders, it can also trigger flashbacks if the bodywork therapist touches a part of the patient's body associated with the abuse or trauma. Many bodywork therapists, however, are well informed about post-traumatic symptoms and disorders, and able to adjust their treatments accordingly.

Description

The following are brief descriptions of some of the more popular bodywork therapies.

Alexander technique

The Alexander technique was developed by an Australian actor named F. Matthias Alexander (1869-1955), who had voice problems that were not helped by any available medical treatments. Alexander decided to set up a number of mirrors so that he could watch himself during

Key Terms

Bodywork Any technique involving hands-on massage or manipulation of the body.

Endorphins A group of peptide compounds released by the body in response to stress or traumatic injury. Endorphins react with opiate receptors in the brain to reduce or relieve pain sensations. Shiatsu is thought to work by stimulating the release of endorphins.

Fascia (plural, fasciae) A band or sheath of connective tissue that covers, supports, or connects the muscles and the internal organs.

Ki The Japanese spelling of qi, the traditional Chinese term for vital energy or the life force.

Meridians In traditional Chinese medicine, a network of pathways or channels that convey qi (also sometimes spelled "ki"), or vital energy, through the body.

Movement education A term that refers to the active phase of bodywork, in which clients learn to move with greater freedom and to maintain the proper alignment of their bodies.

Repetitive stress injury (RSI) A type of injury to the musculoskeletal and nervous systems associated with occupational strain or overuse of a specific part of the body. Bodywork therapies are often recommended to people suffering from RSIs.

Somatic education A term used in both Hellerwork and the Feldenkrais method to describe the integration of bodywork with self-awareness, intelligence, and imagination.

Structural integration The term used to describe the method and philosophy of life associated with Rolfing. Its fundamental concept is the vertical line.

Tsubo In shiatsu, a center of high energy located along one of the body's meridians. Stimulation of the tsubos during a shiatsu treatment is thought to rebalance the flow of vital energy in the body.

a performance from different angles. He found that he was holding his head and neck too far forward, and that these unconscious patterns were the source of the tension in his body that was harming his voice. He then developed a method for teaching others to observe the patterns of tension and stress in their posture and movement, and to correct these patterns with a combination of hands-on guidance and visualization exercises. As of 2002, the Alexander technique is included in the curricula of the Juilliard School of Music and many other drama and music schools around the world, because performing artists are particularly vulnerable to repetitive stress injuries if they hold or move their bodies incorrectly.

In an Alexander technique session, the client works one-on-one with an instructor who uses verbal explanations as well as guided movement. The sessions are usually referred to as "explorations" and last about 30 minutes. Although most clients see positive changes after only two or three sessions, teachers of the technique recommend a course of 20–30 sessions so that new movement skills can be learned and changes maintained.

Rolfing

Rolfing, which is also called Rolf therapy or structural integration, is a holistic system of bodywork that uses deep manipulation of the body's soft tissue to realign and balance the body's myofascial (muscular and connective tissue) structure. It was developed by Ida Rolf (1896-1979), a biochemist who became interested in the structure of the human body after an accident damaged her health. She studied with an osteopath as well as with practitioners of other forms of alternative medicine, and developed her own technique of body movement that she called structural integration. Rolfing is an approach that seeks to counteract the effects of gravity, which tends to pull the body out of alignment over time and cause the connective tissues to stiffen and contract.

Rolfing treatment begins with the so-called "Basic Ten," a series of ten sessions each lasting 60–90 minutes, spaced a week or longer apart. After a period of integration, the client may undertake advanced treatment sessions. "Tune-up" sessions are recommended every six months. In Rolfing sessions, the practitioner uses his or her fingers, hands, knuckles, or elbows to rework the connective tissue over the client's entire body. The deep tissues are worked until they become pliable, which allows the muscles to lengthen and return to their proper alignment. Rolfing treatments are done on a massage table, with the client wearing only undergarments.

Hellerwork

Hellerwork is a bodywork therapy developed by Joseph Heller, a former NASA engineer who became a certified Rolfer in 1972 and started his own version of structural integration, called Hellerwork, in 1979. Heller describes his program as "a powerful system of somatic

education and structural bodywork" based on a series of eleven sessions. Hellerwork is somewhat similar to Rolfing in that it begins with manipulation of the deep tissues of the body. Heller, however, decided that physical realignment of the body by itself is insufficient, so he extended his system to include movement education and "self-awareness facilitated through dialogue."

The bodywork aspect of Hellerwork is intended to release the tension that exists in the fascia, which is the sheath or layer of connective tissue that covers, supports, or connects the muscles and internal organs of the body. Fascia is flexible and moist in its normal state, but the effects of gravity and ongoing physical stresses lead to misalignments that cause the fascia to become stiff and rigid. The first hour of a Hellerwork session is devoted to deep connective tissue bodywork in which the Hellerwork practitioner uses his or her hands to release tension in the client's fascia. The bodywork is followed by movement education, which includes the use of video feedback to help clients learn movement patterns that will help to keep their bodies in proper alignment. The third component of Hellerwork is verbal dialogue, which is intended to help clients become more aware of the relationships between their emotions and attitudes and their body.

Tragerwork

Trager psychophysical integration, which is often called simply Tragerwork, was developed by Milton Trager (1908-1977), a man who was born with a spinal deformity and earned a medical degree in his middle age after working out an approach to healing chronic pain. Tragerwork is based on the theory that many illnesses are caused by tension patterns that are held in the unconscious mind as much as in the tissues of the body; clients are advised to think of Tragerwork sessions as "learning experiences" rather than "treatments." Tragerwork sessions are divided into bodywork, which is referred to as tablework, and an **exercise** period. Trager practitioners use their hands during tablework to perform a variety of gentle motions—rocking, shaking, vibrating, and gentle stretching—intended to help the client release their patterns of tension by experiencing how it feels to move freely and effortlessly on one's own. Following the tablework, clients are taught how to perform simple dance-like exercises called Mentastics, for practice at home. Tragerwork sessions take between 60–90 minutes, while clients are advised to spend 10–15 minutes three times a day doing the Mentastics exercises.

Feldenkrais method

The Feldenkrais method, like Hellerwork, refers to its approach as "somatic education." Developed by Moshe Feldenkrais (1904-1984), a scientist and engineer who was also a judo instructor, the Feldenkrais method consists of two major applications—Awareness Through Movement (ATM) lessons, a set of verbally directed exercise lessons intended to engage the client's intelligence as well as physical perception; and Functional Integration (FI), in which a Feldenkrais practitioner works with the client one-on-one, guiding him or her through a series of movements that alter habitual patterns and convey new learning directly to the neuromuscular system. Functional Integration is done with the client fully clothed, lying or sitting on a low padded table.

Perhaps the most distinctive feature of the Feldenkrais method is its emphasis on new patterns of thinking, attention, cognition, and imagination as byproducts of new patterns of physical movement. It is the most intellectually oriented of the various bodywork therapies, and has been described by one observer as "an unusual melding of motor development, biomechanics, psychology, and martial arts." The Feldenkrais method is the form of bodywork that has been most extensively studied by mainstream medical researchers.

Trigger point therapy

Trigger point therapy, which is sometimes called myotherapy, is a treatment for pain relief in the musculoskeletal system based on the application of pressure to trigger points in the client's body. Trigger points are defined as hypersensitive spots or areas in the muscles that cause pain when subjected to stress, whether the stress is an occupational injury, a disease, or emotional stress. Trigger points are not necessarily in the same location where the client feels pain.

Myotherapy is a two-step process. In the first step, the therapist locates the client's trigger points and applies pressure to them. This step relieves pain and also relaxes the muscles associated with it. In the second part of the therapy session, the client learns a series of exercises that progressively stretch the muscles that have been relaxed by the therapist's pressure. Most clients need fewer than 10 sessions to benefit from myotherapy. One distinctive feature of trigger point therapy is that clients are asked to bring a relative or trusted friend to learn the pressure technique and the client's personal trigger points. This "buddy system" helps the client to maintain the benefits of the therapy in the event of a relapse.

Shiatsu

Shiatsu is the oldest form of bodywork therapy, having been practiced for centuries in Japan as part of traditional medical practice. As of 2002, it is also the type of bodywork most commonly requested by clients in Western countries as well as in East Asia. The word *shiatsu* itself is a combination of two Japanese words that mean "pressure" and "finger." Shiatsu resembles **acupuncture** in its

use of the basic concepts of ki, the vital energy that flows throughout the body, and the meridians, or 12 major pathways that channel ki to the various organs of the body. In Asian terms, shiatsu works by unblocking and rebalancing the distribution of ki in the body. In the categories of Western medicine, shiatsu may stimulate the release of endorphins, which are chemical compounds that block the receptors in the brain that perceive pain.

A shiatsu treatment begins with the practitioner's assessment of the client's basic state of health, including posture, vocal tone, complexion color, and condition of hair. This evaluation is used together with ongoing information about the client's energy level gained through the actual bodywork. The shiatsu practitioner works with the client lying fully clothed on a futon. The practitioner seeks out the meridians in the client's body through finger pressure, and stimulates points along the meridians known as tsubos. The tsubos are centers of high energy where the ki tends to collect. Pressure on the tsubos results in a release of energy that rebalances the energy level throughout the body.

Craniosacral therapy

Craniosacral therapy, or CST, is a form of treatment that originated with William Sutherland, an American osteopath of the 1930s who theorized that the manipulative techniques that osteopaths were taught could be applied to the skull. Sutherland knew from his medical training that the skull is not a single piece of bone, but consists of several bones that meet at seams; and that the cerebrospinal fluid that bathes the brain and spinal cord has a natural rise-and-fall rhythm. Sutherland experimented with gentle manipulation of the skull in order to correct imbalances in the distribution of the cerebrospinal fluid. Contemporary craniosacral therapists practice manipulation not only of the skull, but of the meningeal membranes that cover the brain and the spinal cord, and sometimes of the facial bones. Many practitioners of CST are also osteopaths, or DOs.

In CST, the patient lies on a massage table while the therapist gently palpates, or presses, the skull and spine. If the practitioner is also an osteopath, he or she will take a complete medical history as well. The therapist also "listens" to the cranial rhythmic impulse, or rhythmic pulsation of the cerebrospinal fluid, with his or her hands. Interruptions of the normal flow by abnormalities caused by tension or by injuries are diagnostic clues to the practitioner. Once he or she has identified the cause of the abnormal rhythm, the skull and spinal column are gently manipulated to restore the natural rhythm of the cranial impulse. Craniosacral therapy appears to be particularly useful in treating physical disorders of the head, including migraine headaches, ringing in the ears, sinus problems, and injuries of the head, neck, and spine. In addition, patients rarely require extended periods of CST treatments.

Preparation

Bodywork usually requires little preparation on the client's or patient's part, except for partial undressing for Rolfing, trigger point therapy, and Hellerwork.

Aftercare

Aftercare for shiatsu, trigger point therapy, and craniosacral therapy involves a brief period of rest after the treatment.

Some bodywork approaches involve various types of long-term aftercare. Rolfing clients return for advanced treatments or tune-ups after a period of integrating the changes in their bodies resulting from the Basic Ten sessions. Tragerwork clients are taught Mentastics exercises to be done at home. The Alexander technique and the Feldenkrais approach assume that clients will continue to practice their movement and postural changes for the rest of their lives. Trigger point therapy clients are asked to involve friends or relatives who can help them maintain the benefits of the therapy after the treatment sessions are over.

Risks

The deep tissue massage and manipulation in Rolfing and Hellerwork are uncomfortable for many people, particularly the first few sessions. There are, however, no serious risks of physical injury from any form of bodywork that is administered by a trained practitioner of the specific treatment. As mentioned, however, bodywork therapies that involve intensive manipulation or stretching of the deeper layers of body tissue are not suitable for persons who have undergone recent surgery or have recently suffered severe injury.

Normal results

Normal results from bodywork include deep relaxation, improved posture, greater ease and spontaneity of movement, greater range of motion for certain joints, greater understanding of the structures and functions of the body and their relationship to emotions, and release of negative emotions.

Many persons also report healing or improvement of specific conditions, including migraine headaches, repetitive stress injuries, osteoarthritis, insomnia, sprains and bruises, sports injuries, stress-related illnesses, **sciatica**, postpregnancy problems, menstrual cramps, temporomandibular joint disorders, lower back pain, **whiplash** injuries, disorders of the immune system, asthma, **depression**, digestive problems, chronic **fatigue**, and

painful scar tissue. The Alexander technique has been reported to ease the process of childbirth by improving the mother's postural alignment prior to delivery.

Some studies of the Feldenkrais method have found that its positive effects on subjects' self-esteem, mood, and anxiety sympoms are more significant than its effects on body function.

Abnormal results

Abnormal results from bodywork therapies would include serious physical injury or trauma-based psychological reactions.

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Bonnie Prudden Pain Erasure Clinic and School for Physical Fitness and Myotherapy. P.O. Box 65240. Tucson, AZ 85728. (520) 529-3979. Fax: (520) 529-6679. <www.bonnieprudden.com>.

Cranial Academy. 3500 DePauw Boulevard, Indianapolis, IN 46268. (317) 879-0713.

Craniosacral Therapy Association of the United Kingdom. Monomark House, 27 Old Gloucester Street, London, WC1N 3XX. Telephone: 07000-784-735. <www.craniosacral.co.uk/>.

Feldenkrais Guild of North America. 3611 S.W. Hood Avenue, Suite 100, Portland, OR 97201. (800) 775-2118 or (503) 221-6612. Fax: (503) 221-6616. <www.feldenkrais.com>.

The Guild for Structural Integration. 209 Canyon Blvd. P.O. Box 1868. Boulder, CO 80306-1868. (303) 449-5903. (800) 530-8875. <www.rolfguild.org>.

Hellerwork. 406 Berry St. Mt. Shasta, CA 96067. (530) 926-2500. <www.hellerwork.com>.

International School of Shiatsu. 10 South Clinton Street, Doylestown, PA 18901. (215) 340-9918. Fax: (215) 340-9181. <www.shiatsubo.com>.

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The Trager Institute. 21 Locust Avenue, Mill Valley, CA 94941-2806. (415) 388-2688. Fax: (415) 388-2710. <www.trager.com>.

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National Certification Board for Therapeutic Massage and Bodywork. 8201 Greensboro Drive, Suite 300. McLean, VA 22102. (703) 610-9015.

NIH National Center for Complementary and Alternative Medicine (NCCAM) Clearinghouse. P. O. Box 8218, Silver Spring, MD 20907-8218. TTY/TDY: (888) 644-6226; Fax: (301) 495-4957. Web site: <http://www.nccam.nih.gov>.

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Botulinum toxin

Definition

Botulinum toxin is the purified form of a poison created by the bacterium *Clostridium botulinum*. These bacteria grow in improperly canned food and cause **botulism** poisoning. Minute amounts of the purified form can be injected into muscles to prevent them from contracting; it is used in this way to treat a wide variety of disorders and cosmetic conditions.

Purpose

Botulinum toxin was developed to treat strabismus (cross-eye or lazy eye), and was shortly thereafter discovered to be highly effective for many forms of **dystonia**. **Spasticity** can also be effectively treated with botulinum toxin. Injected into selected small muscles of the face, it can reduce wrinkling. Other conditions treated with botulinum toxin include:

- achalasia
- anismus
- **back pain**
- bruxism
- excess saliva production

- eyelid spasm
- **headache**
- **hemifacial spasm**
- hyperhidrosis
- **migraine**
- palatal **myoclonus**
- spastic bladder
- **stuttering**
- tics
- **tremor**
- uncontrollable eye blinking
- vaginismus

It is important to note that as of early 2004, the only Food and Drug Administration-approved uses for botulinum toxin are for certain forms of dystonia, hemifacial spasm, strabismus, **blepharospasm** (eyelid spasms), and certain types of facial wrinkles. While there is general recognition that certain other conditions can be effectively treated with botulinum toxin, other uses, including for headache or migraine, are considered experimental.

Key Terms

Achalasia An esophageal disease of unknown cause, in which the lower sphincter or muscle is unable to relax normally, resulting in obstruction, either partial or complete.

Bruxism Habitual clenching and grinding of the teeth, especially during sleep.

Hyperhidrosis Excessive sweating. Hyperhidrosis can be caused by heat, overactive thyroid glands, strong emotion, menopause, or infection.

Migraine A throbbing headache that usually affects only one side of the head. Nausea, vomiting, increased sensitivity to light, and other symptoms often accompany a migraine.

Stuttering Speech disorder characterized by speech that has more dysfluencies than is considered average.

Tic A brief and intermittent involuntary movement or sound.

Tremor Involuntary shakiness or trembling.

Vaginismus An involuntary spasm of the muscles surrounding the vagina, making penetration painful or impossible.

Description

A solution of botulinum toxin is injected into the overactive muscle. The toxin is taken up by nerve endings at the junction between nerve and muscle. Once inside the cell, the toxin divides a protein. The normal job of this protein is to help the nerve release a chemical, a neurotransmitter, which stimulates the muscle to contract. When botulinum toxin divides the protein, the nerve cannot release the neurotransmitter, and the muscle cannot contract as forcefully.

The effects of botulinum toxin begin to be felt several days after the injection. They reach their peak usually within two weeks, and then gradually fade over the next 2–3 months. Since the effects of the toxin disappear after several months, reinjection is necessary for continued muscle relaxation.

Recommended dosage

In the United States, purified botulinum toxin is available in two commercial forms: Botox and MyoBloc. The recommended doses of the two products are quite different, owing to the differing potencies of the two products. The size of the muscle and the degree of weakening desired also affect the dose injected. For Botox, the maximum recommended dose for adults is 400–600 units in any three-month period, while for MyoBloc it is 10,000–15,000 units. The maximum dosage may be reached in the treatment of spasticity or cervical dystonia, while much smaller amounts are used in the treatment of facial lines, strabismus, and hemifacial spasm.

Precautions

When injected by a trained physician, botulinum toxin is very safe. The toxin remains mainly in the muscle injected, spreading only slightly to surrounding muscles or beyond. Botulism poisoning, which occurs after ingesting large amounts of the toxin, is due to the effects of the poison on the breathing muscles. In medical use, far less toxin is injected, and care is taken to avoid any chance of spread to muscles needed for breathing. Injection into the shoulders or neck may weaken muscles used for swallowing, which patients need to be aware of. Some patients may need to change to a softer diet to make swallowing easier during the peak effect of their treatment.

Repeated injections of large amounts of botulinum toxin can lead to immune system resistance. While this is not a dangerous condition, it makes further treatment ineffective.

Patients with neuromuscular disease should not receive treatment with botulinum toxin without careful consultation with a **neurologist** familiar with its effects.

Side effects

Botulinum toxin can cause a mild flu-like syndrome for several days after injection. Injection of too much toxin causes excess weakness, which may make it difficult to carry on normal activities of daily living. In some patients, toxin injection may cause blurred vision and dry mouth. This is more common in patients receiving MyoBloc than with Botox.

Interactions

Patients taking aminoglycoside antibiotics may be cautioned against treatment with botulinum toxin. These antibiotics include gentamicin, kanamycin, and tobramycin, among others.

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Richard Robinson

Botulism

Definition

Botulism is a neuroparalytic disease caused by the potent toxin of the *Clostridium botulinum* bacterium. There are three main types of botulism: foodborne botulism, infant botulism, and wound botulism.

Description

Botulism was first identified in Wildbad, Germany, in 1793, when six people died after consuming a locally produced blood sausage. In 1829, Jutinius Kerner, a health official, described 230 cases of sausage poisoning. Thereafter, the illness became known as "botulism," which is derived from the Latin "botulus," meaning sausage. In 1897, E. Van Ermengem identified the bacterium and its toxin while investigating an outbreak of the disease among musicians in Elezells, Belgium.

C. botulinum is a spore-forming, anaerobic, gram-positive bacilli found globally in soil and honey. The toxin has recently gain notoriety. It is a potential bioterrorism agent, and it is used as a beauty aid to eliminate frown lines.

Clinically, food-borne botulism is dominated by neurological symptoms, including dry mouth, blurred vision and diplopia, caused by the blockade of neuromuscular junctions.

In wound botulism the neurologic findings are similar to the food-borne illness, but the gastrointestinal symptoms are absent. Infants suffering from the intestinal colonization of spores of *C. botulinum* suffer first from constipation, and later develop neurological paralysis, which can lead to respiratory distress.

There are seven distinct neurotoxic serotypes, all of which are closely related to the tetanus toxin. Types A and B are most commonly implicated, but types E and, more rarely, F have been associated with human disease.

Demographics

Botulism is rare, but its incidence does vary by geographic region. The food-borne version remains highest among people who can their own foods. In 1995, only 24 cases of food-borne botulism were reported to the Centers for Disease Control and Prevention.

About 90% of global cases of infant botulism are diagnosed in the US, where the annual incidence is about 2 per 100,000 live births. It is the most common form of human botulism in the United States, with over 1,400 cases diagnosed between 1976 and 1996.

Between 1943 and 1985, 33 cases of wound botulism were diagnosed in the United States, mainly associated with deep and avascular wounds. However, between 1986 and 1996, 78 cases of wound botulism were diagnosed, many the result of illicit drug use, occurring at injection sites or at nasal or sinus sites associated with chronic cocaine snorting.

Causes and symptoms

Botulism is caused by the protein toxin released by the microorganism *C. botulinum*. After the toxin is absorbed into the bloodstream, it irreversibly binds to the acetylcholine receptors on the motor nerve terminals at neuromuscular junctions. After the toxin is internalized, it cleaves the apparatus in the neuron that is responsible for acetylcholine release, making the neuron unresponsive to action potentials. The blockade is irreversible and may last for months, until new nerve buds grow.

FOOD-BORNE BOTULISM The symptoms can range from mild to life threatening, depending on the toxin dose. Generally, symptoms appear within 36 hours of consuming food containing the toxin. Paralysis is symmetric and

Key Terms

Acetylcholine A chemical called a neurotransmitter that functions primarily to mediate activity of the nervous system and skeletal muscles.

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.

Anaerobic Pertaining to an organism that grows and thrives in an oxygen-free environment.

Bacillus A rod-shaped bacterium, such as the diphtheria bacterium.

Congenital myopathy Any abnormal condition or disease of muscle tissue that is present at birth; it is characterized by muscle weakness and wasting.

Diplopia A term used to describe double vision.

Dysarthria Slurred speech.

Dysphagia Difficulty in swallowing.

ELISA protocols ELISA is an acronym for "enzyme-linked immunosorbent assay"; it is a highly sensitive technique for detecting and measuring antigens or antibodies in a solution.

Gram-positive Refers to a bacteria that takes on a purplish color when exposed to the Gram stain. Common examples of gram-positive bacteria include several species of streptococci, staphylococci, and clostridia.

Guillain-Barré syndrome Progressive and usually reversible paralysis or weakness of multiple muscles usually starting in the lower extremities and often ascending to the muscles involved in respiration. The syndrome is due to inflammation and loss of the myelin covering of the nerve fibers, often associated with an acute infection. Also called acute idiopathic polyneuritis.

Myasthenia gravis A chronic, autoimmune, neuromuscular disease with symptoms that include muscle weakness and sometimes paralysis.

Polymerase chain reaction (PCR) A process by which numerous copies of DNA or a gene can be made within a few hours. PCR is used to evaluate false-negative results to the ELISA and Western blot tests for HIV and to make prenatal diagnoses of genetic disorders.

Reye syndrome A serious, life-threatening illness in children, usually developing after a bout of flu or chicken pox, and often associated with the use of aspirin. Symptoms include uncontrollable vomiting, often with lethargy, memory loss, disorientation, or delirium. Swelling of the brain may cause seizures, coma, and in severe cases, death.

Sepsis A severe systemic infection in which bacteria have entered the bloodstream or body tissues.

Spore A dormant form assumed by some bacteria, such as anthrax, that enable the bacterium to survive high temperatures, dryness, and lack of nourishment for long periods of time. Under proper conditions, the spore may revert to the actively multiplying form of the bacteria. Also refers to the small, thick-walled reproductive structure of a fungus.

descending. The first symptoms to appear include dysphagia, **dysarthria**, and diplopia, a reflection of cranial nerve involvement. Neck and limb weakness, nausea, vomiting, and **dizziness** follow. Respiratory muscle paralysis can lead to ventilatory failure and death unless support is provided.

WOUND BOTULISM The in vivo production of toxin by *C. botulinum* spores, leads to the neurologic symptoms seen in food-borne botulism. Gastrointestinal symptoms are absent.

INFANT BOTULISM Peak incidence occurs between 2 and 3 months of age. *C. botulinum* spores colonize the gastrointestinal tract and produce the toxin. Most infants show signs of constipation, followed by neuromuscular weakness that results in decreased sucking, lack of muscle tone and characteristic "floppy head." Symptoms may range from mild to severe, and may lead to respiratory failure.

Diagnosis

Physicians should consider a diagnosis of botulism in a patient who presents with neuromuscular impairment, but remains mentally alert. The disease is often mistaken for other more common conditions, including **stroke**, encephalitis, **Guillain-Barré syndrome**, **myasthenia gravis**, tick paralysis, chemical or mushroom poisoning, and adverse reactions to antibiotics or other medication. Sepsis, electrolyte imbalances, **Reye syndrome**, congenital **myopathy**, Werdnig-Hoffman disease and **Leigh disease** should be considered in infants.

A definitive diagnosis can be made by detecting the toxin in serum samples, or isolating *C. botulinum* from

stool or wound specimens. Toxins can be detected with a mouse neutralization assay, or using PCR or ELISA protocols.

Treatment

Because of the threat of respiratory complications, patients should be hospitalized immediately and closely monitored. Mechanical ventilation should begin when the vital capacity falls below 30% of predicted. Trivalent (types A, B and E) equine antitoxin should be administered as soon as botulism is suspected to slow the progression of the illness and limit the duration of respiratory failure in critical cases. Caution should be exercised as approximately 9% of patients experience a hypersensitivity reaction. Due to the high incidence of side effects and anaphylaxis, infants should not receive equine antitoxin.

In 2003, the FDA approved an intravenously administered human botulism immune globulin for types A and B infant botulism.

Patients suffering from wound botulism should receive equine antitoxin and antibiotics such as penicillin.

Clinical Trials

As of early 2004, there was one open clinical trial for infant botulism at the National Institutes of Health (NIH), to assess the safety and efficacy of human botulism immune globulin.

Prognosis

Prompt diagnosis and treatment coupled with improved respiratory care have decreased mortality from food-borne botulism. Severe cases often call for prolonged respiratory support. The case-fatality rate is 7.5%, although mortality is greater in patients older than 60 years. Infant botulism has an excellent prognosis, although relapse can occur following hospital discharge. The case-fatality rate for infant botulism is 2%. Because toxin binding is irreversible, acetylocholine release and strength return only after the nerve terminals sprout new endings.

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Hannah M. Hoag, MSc

Braces *see* **Assistive mobile devices**

Brachial plexitis neuritis *see* **Parsonage-Turner syndrome**

Brachial plexus injuries

Definition

Brachial plexus injuries affect the nerves that originate from the spinal cord behind the head and neck (cervical nerves).

Description

The brachial plexus are nerves that leave the cervical vertebrae (but originate in the brain) and extend to peripheral structures (muscles/organs) to transmit motor and sensory nerve impulses. The brachial plexus consists of several cervical nerve roots, which include: C4, sending fibers to the shoulder and trapezius muscle; C5, sending fibers to the deltoid muscle and sides of upper arm or distal radius and involved with shoulders abduction; C6, involved with elbow flexion and fibers in the biceps and lateral forearm and thumb; C7, fibers to the triceps muscle, index and middle finger tips and involved with elbow extension; and C8, involved with extension of thumb and 4th and 5th fingers. Injury to the brachial plexus can involve avulsion injuries (nerve torn from attachment to the spinal cord), which are the most serious type of injury; neuroma injuries, due to injury causing scar formation tissue, which compresses nerves; rupture injuries, nerve is torn, but not at the spinal cord; and stretch injuries, nerve is damaged, but not torn.

Sports related injuries to the the cervical spine are common, especially injury to cervical vertebra 5 (C5) and

Key Terms

Axonotmesis Loss of the protective sheet of tissue that covers the axon (the part of the nerve cell which carries a transmission).

Biceps muscle Muscle in the arm which helps to flex the arm.

Breech presentation Buttocks presentation during delivery.

Deltoid muscle A muscle near the clavicle bone which is responsible for arm movement.

Dysesthesias A burning pain sensation.

Elbow extension Movement away from the body at a jointed point.

Erb point A point 2–3 centimeters above the clavicle.

Flail To swing freely.

Lateral flexion To flex toward a side.

Paresthesias Abnormality of sensation (e.g., numbness, burning, tingling).

Pronation The motion of the forearm to turn the palm downwards.

Shoulder dystocia Difficult shoulder delivery.

Trapezius muscle Muscle in the scapula, which helps in elevation of the scapula.

Vertex presentation Head presentation during delivery.

C6. Erb described this condition with paralysis in 1874. Other names for the disorder include "burner" or "stinger" syndrome and cervical nerve pinch syndrome. Traumatic sports injury to the brachial plexus is characterized by a classical symptom—burning sensation that radiates down an upper extremity. The sensation may be short lived (2 minutes) or in chronic cases may last as long as two weeks. There are three common mechanisms that cause BPI, which include: direct impact to Erb point resulting in brachial plexus compression; traction caused by lateral flexion opposite from affected side; and **nerve compression** caused by hyperextension of the neck.

Obstetrical brachial plexus paralysis (OBPP) refers to injury to all or part of the brachial plexus during delivery. The condition was first described by Smellie in 1764 who described bilateral (both arms) paralysis in the newborn. Klumpke described paralysis (of the lower plexus) in 1885. Erb described paralysis of the upper brachial plexus (upper C5-C6 nerve damage) in 1874. Lower brachial plexus injuries are called Klumpke palsies and upper brachial plexus injury are termed Erb palsies. Injury is rare but is more prevalent in neonates born by cesarean delivery.

Demographics

In the United States a true measurement of new and existing cases is undetermined largely due to the significant underreporting of injuries. Approximately 5% of all peripheral nerve injuries results from trauma to the brachial plexus. Research studies conducted on college football players reported approximately 45% to 65% experience BPI during their collegiate careers. Additionally, it is estimated that there is an 87% recurrence rate. Estimates in other countries are not possible due to significant underreporting.

The incidence (number of new cases) of OBPP ranges from 0.2–4% of live births globally. The World Health Organization estimates the worldwide incidence is approximately 1–2%. In the United States it is rare and the incidence is 0.2% of live births. Every year 1–2 babies per 1000 live births are affected by obstetrical brachial nerve injury.

Causes and symptoms

BPI typically occurs as a result of a blow to the head, shoulder, and/or Erb point in an athlete during a contact sport. There are two grades of BPI. Grade 1 occurs when there is an interruption of nerve function due to demyelination. Muscle weakness is often detected soon after injury. Grade 2 describes more extensive damage to deeper and vital nerve areas (axons). Muscle weakness is often present and if persistent could mean a higher-grade lesion. Further tests for grade 2 BPI are indicated to fully assess the extent of nerve degeneration.

The causes of OBPP include shoulder dystocia, large birth weight, and breech delivery (vertex presentation accounts for 94–97% of cases). Maternal diabetes (mother has diabetes) is associated as a risk factor. Mothers who have had several children who were recorded to be large babies have an increased risk for delivering neonates with OBPP.

Commonly, affected athletes complain and describe burning and/or numbness in the neck, shoulder, or upper extremity (affected arm). Symptoms typically occur after

a blow to the head or shoulder. These symptoms include burning sensation in the neck, **pain** in the neck, (also called **dysesthesias**), and a feeling of weakness or "heaviness" in the affected arm. Bilateral (on both arms) numbness possibly indicates a more severe form of cervical cord injury. Symptoms can last from a few seconds to weeks.

Infants affected by OBPI may present with flail arms at birth. The affected arm may be internally rotated and pronated and devoid of elbow and shoulder movement (Erb palsy). If brachial plexus paralysis is present the entire hand and arm is flail with no movement ability.

The symptoms of OBPP can be grouped according to Sunderland's classification, which was proposed in 1951. A first-degree injury (also called neuropraxia or "stretch injuries") involves nerve injury that can completely resolve within 12 weeks. A second-degree injury results in severe trauma and nerve compression, but essential nerve elements are still intact and complete recovery is expected. A third-degree nerve injury is more severe, and essential nerve structures have been damaged as well as possible muscle damage. Some nerves and muscles may be permanently damaged. A fourth-degree injury results from extensive nerve damage that affects muscles, and typically it requires corrective surgical repair. The most severe form of obstetrical brachial plexus injury is fifth-degree injury, which is complete transaction of the nerve (the nerve is completely cut).

Diagnosis

A careful history, physical examination, and testing are essential for diagnosis. The clinician must suspect cervical fracture and/or **spinal cord injury** in an athlete presenting with altered consciousness. If the patient is awake and alert a complete neurological examination is indicated. The patient's mental status should be immediately assessed. Cervical nerve root assessment for detection of motor and sensory deficits is essential. A special test called the Spurling test is performed. During the Spurling test, the cervical spine is extended and head rotated toward the affected shoulder while loading axial weight. The purpose of manipulating the neck in this fashion is to reproduce the symptoms of the BPI. A positive Spurling test will reproduce symptoms. Clinical examination on-site at the time of injury typically includes; grip strength, identification of specific symptoms, duration of symptoms; assessment of motor impairment; assessment of cervical range of motion (only if no cervical fracture is present). Lab tests are generally not required and imaging studies are routinely limited to radiographic (x-ray) studies, taken from different views. Higher resolution studies such as **MRI** and **CT scans** can be utilized in cases where cervical spine or cervical nerve root damage is suspected. Use of a special test to detect the extent of muscle damage (**electromyography**) can help to localize lesions and confirm the diagnosis. No specific lab tests are useful in the diagnostic process.

For infants with BPI due to delivery complications an assessment scale called the Active Movement Scale (7-point scale) can determine impairment from no contraction to full motion in the absence of or against gravity. This scale can help to assess arm movement impairment caused by nerve damage. The extent of nerve damage can be classified according to Sunderland. Typically, a lack of clinical evidence of elbow flexion by the 3rd or 4th month of life is indication for surgical repair of damaged nerves.

Treatment team

The treatment team for sports-related BPI typically includes the immediate responders (coach, team physician). Further consults from a comprehensive team can include a primary care practitioner, **neurologist**, physical therapist, and possibly a medical pain specialist.

For patients with OBPP a complete team of special nursing care and specialists is usually indicated. For surgical candidates, a specialist in neurosurgery or an orthopedic spine surgeon is essential. The pediatrician and pediatric neurologist play a vital role in assessment and provide information to parents. Long-term rehabilitation may be necessary in severe cases.

Treatment

On-site treatment for sports-related BPI typically includes mobilization and icing of the affected region. Treatment of BPI can be divided into three phases: the acute phase, recovery phase, and maintenance phases. Treatment during the acute phase typically involves physical therapy and medical issues (i.e., further imaging studies). Surgery may be required. During the recovery phases, physical therapy continues and the patient is monitored to continue follow-up care. During the maintenance phase of treatment physical therapy continues. The goal for medication is to prevent complications and help alleviate pain. Typically analgesics such as the anti-inflammatory type or an opiate narcotic are recommended. Analgesia may also help the affected person to cope better with physical therapy sessions. Typical opiate-narcotics include Lortab, Norcet, or Vicodin. Nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., Motrin, Ibuprin) have both anti-inflammatory and analgesic effects.

For infants with OBPI medical treatment initially focuses on protection of ligaments, joints, and tendons from stress. Physical therapy may be indicated for movement exercises. Surgical intervention may be necessary if patients do not show recovery of neurological function by

four months of age. Some controversy exists in the United States, with some surgeons advocating surgery on patients younger than 4 months.

Recovery and rehabilitation

Rehabilitation for BPI primarily entails physical therapy (PT) during the entire treatment course (acute, recovery, and maintenance treatment phases). The focus of PT during the acute phases primarily involves early mobilization and icing. Patients attempt to improve cervical range of motion to strengthen cervical muscles. During the recovery phases, special PT programs attempt to strengthen cervical muscles to a level of performance prior to injury. Special focus on muscles supporting the injured brachial plexus nerve (i.e., cervical and shoulder regions) is emphasized. Treatment for the maintenance phases primarily focuses on continuation of cervical muscle strength and conditioning. Clinical findings during examination and testing are key factors for determining return to play and recovery. A full recovery of affected muscle is necessary to prevent recurrence of burner syndrome and further injury. An athlete in a contact sport, who has fully recovered, is capable of supporting his or her weight at the neck leaning at a 45 degree angle. Some athletes may have some asymmetry of affected muscles that persists, and care should be taken as the athlete returns to contact sport participation.

Most infants with OBPI spontaneously recover (92-95% of reported cases) because the nerve injury is usually minor. Initial rehabilitation can include physical therapy to maintain passive range of movement. Surgery may be necessary for severe cases that require special postoperative care, monitoring, and physical therapy. Recovery for children with OBPP depends on the severity of nerve injury. Recovery after surgery is variable given that results depend on extent of damage to nerves and successful repair if surgery is indicated.

Prognosis

Prognosis for sports-related BPI is generally good. Some athletes develop a chronic complicated condition with symptoms called chronic burner syndrome. Most cases of nerve injury in infants are self-limiting and spontaneously resolve. Severe cases may require surgery. Surgical candidates typically have severe nerve injury and must undergo microsurgery to repair nerve damage.

Special concerns

In sports-related injury medical/legal problems can exist because cervical spine injury is sometimes not considered the cause of symptoms. Overlooking BPI can result in further damage to peripheral nerves.

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Laith Farid Gulli, M.D.
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Brain aneurysm *see* **Aneurysm**

Brain biopsy *see* **Biopsy**

Brain injury *see* **Traumatic brain injury, Spinal cord injury**

Brain surgery *see* **Craniotomy**

Brain tumors *see* **Brain and spinal tumors**

Brain anatomy

Definition

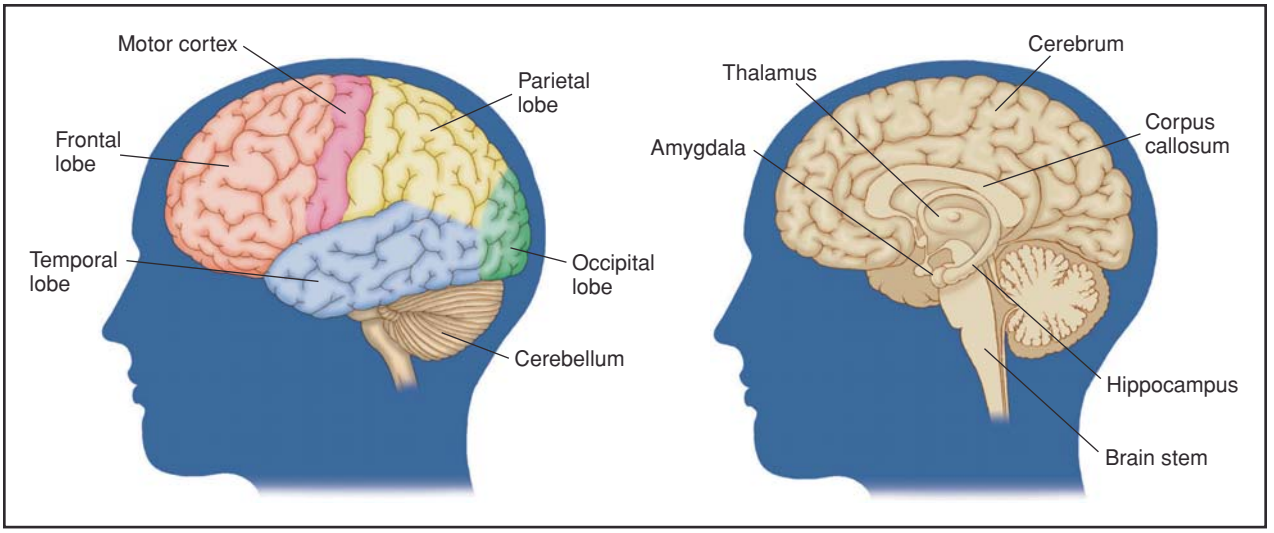
The brain is a large mass of soft nervous tissue made up of both neurons and supporting glial cells lying within the cranium of the skull. The brain contains both gray and white matter. Gray matter is primarily nerve cell bodies, whereas white matter contains myelinated nerve cell processes, giving it a white appearance. White matter is mostly found in the cortex (shell) of the cerebral hemispheres. The brain has a highly complex appearance, with convolutions referred to as gyri and valleys referred to as sulci. These convolutions create a greater surface area within the same size skull.

Description

Central nervous system

The **central nervous system** is made up of the brain and spinal cord. The major divisions of the human brain are the brainstem, **cerebellum**, **diencephalon**, and cerebral hemispheres. The **meninges** cover and protect the brain and spinal cord.

BRAINSTEM The brainstem, made up of the midbrain, pons, and medulla, sits at the base of the brain. The brainstem is involved in sensory input and motor output. Sensory input enters the brainstem from the head, neck, and face area, while motor output from the brainstem controls muscle movements in these areas as well. The brainstem also receives sensory input from specialized cranial



Anatomy of the brain. The exterior view on the left shows the lobes, and the interior view on the right shows other major areas and structures. *(Illustration by Frank Forney.)*

nerves for olfaction (smell), vision, hearing, gustation (taste), and balance. The brainstem contains ascending and descending nerve pathways that carry sensory input and motor output information to and from higher brain regions, like a relay center. Ascending nerve pathways bring information through the brainstem into the rest of the brain, and descending nerve pathways send information back that coordinates many activities, including motor function. The brainstem also plays a role in vital functions such as cardiovascular and respiratory activity and consciousness.

The medulla is a structure in the brainstem closest to the spinal cord. It is vaguely scoop shaped, with longitudinal grooves indicating the presence of many nerve tracts. It is responsible for maintaining vital body functions such as breathing and heart rate.

The pons is named after the Latin word for bridge. In appearance, the pons seems to be a bridge connecting the two hemispheres, but in reality the connection is indirect through a complicated nerve pathway. The pons is involved in motor control, sensory analysis, and levels of consciousness and sleep. Some structures within the pons are linked to the cerebellum, involving them in movement and posture.

The midbrain, also called the mesencephalon, is the smallest and most anterior part of the brainstem with a tubular appearance. It is involved in functions such as vision, hearing, movement of the eyes, and body motor function. The anterior part of the midbrain contains the cerebral peduncle, a large bundle of axons traveling from the cerebral cortex through the brainstem. These nerve fibers (along with other structures) are important for voluntary motor function.

CEREBELLUM The cerebellum, or "little brain," wraps around the brainstem. It is similar to the cerebrum in that it has two hemispheres with a highly folded surface (cortex). The cerebellum is involved in regulation and coordination of movement, posture, balance, and also some cognitive function.

DIENCEPHALON The diencephalon, or "between brain," lies between the cerebral hemispheres and the midbrain. It is formed by the thalamus and hypothalamus, and has connections to the limbic system and cerebral hemispheres.

The thalamus is a large body of gray matter at the top of the diencephalon, positioned deep within the forebrain. The thalamus has sensory and motor functions. Almost all sensory information enters this structure, where it is relayed to the cortex. Axons, or nerve endings, from every sensory system except olfaction come together (synapse) here as the last relay site before the information reaches the cerebral cortex. The synapse is the junction where nerve endings meet and communicate with each other using chemical messengers that cross the junction.

The hypothalamus is a part of the diencephalon lying next to the thalamus. The hypothalamus is involved in homeostasis, emotional responses, coordinating drive-related behavior such as thirst and hunger, circadian rhythms, control of the autonomic nervous system, and control of the pituitary gland.

MENINGES AND VENTRICULAR SYSTEMS The meninges are membranes that cover and protect the central nervous system (CNS) along with a fluid called cerebrospinal fluid (CSF) that buoys up the brain. The brain is very soft and mushy; without the meninges and CSF, it

Key Terms

Dorsal Pertaining in direction to the back or upper surface of an organ.

Endothelium A layer of cells called endothelial cells that lines the inside surfaces of body cavities, blood vessels, and lymph vessels.

Glial cell Nerve tissue of the central nervous system other than the signal-transmitting neurons. Glial cells are interspersed between neurons and providing support and insulation. There are three main types of neuroglia: astrocytes, oligodendrocytes, and microglia.

Myelin A white, fatty substance that covers and protects nerves.

Neuron A cell specialized to conduct and generate electrical impulses and to carry information from one part of the brain to another.

Ventral Pertaining in direction to the front or lower surface of an organ.

would be easily distorted and torn under the effects of gravity. The meninges are divided into three membranes: the thick external dura mater provides mechanical strength; the middle web-like, delicate arachnoid mater forms a protective barrier and a space for CSF circulation; and the internal pia mater is continuous with all the contours of the brain and forms CSF. The dura mater contains six major venous sinuses that drain the cerebral veins and several smaller sinuses.

Dural venous sinuses are formed in areas where the two layers of the dura mater separate, forming spaces. The sinuses are triangular in cross-section and lined with endothelium. There are six major dural sinuses that receive cerebral veins. The superior sagittal sinus, straight sinus, and right and left transverse sinuses meet in a structure known as the confluence of the sinuses. Venous blood circulation follows a pathway through the superior sagittal and straight sinuses into the confluence, and then through the transverse sinuses. Each transverse sinus then continues as a sigmoid sinus, carrying the venous blood flow along an S-shaped course until it empties into the internal jugular vein. The major dural sinuses also connect with several smaller sinuses. The inferior sagittal sinus, occipital sinus, and superior and inferior petrosal sinuses all empty into different parts of the major sinus system.

The arachnoid mater follows the general shape of the brain, creating a space between the two membranes. The space between the arachnoid and pia mater is called the subarachnoid space and contains CSF. CSF enters venous circulation through small protrusions into the venous sinus called arachnoid villi. The pia mater forms part of the choroid plexus, a highly convoluted and vascular membranous material that lies within the **ventricular system** of the brain and is responsible for most CSF production.

The brain contains four ventricles. A pair of long, C-shaped lateral ventricles lies within the cerebral hemispheres. The lateral ventricles communicate with the narrow, slit-shaped third ventricle of the diencephalon. The third ventricle then communicates with the tent-shaped fourth ventricle of the pons and medulla, which protrudes into the cerebellum. The CSF of the brain flows in a specific pattern that allows newly formed CSF to replace the old CSF several times a day. The basic pattern of circulation is formation in lateral ventricles, flow into the third and then fourth ventricles, into basal cisterns, up and over the cerebral hemispheres, into the arachnoid villi, where drainage occurs into a venous sinus to return to the venous system. Some CSF diverts from the basal cisterns into the subarachnoid space of the spinal cord. Blockage of the circulation of CSF can cause a condition called **hydrocephalus**, where the CSF pressure rises high enough to expand the ventricles at the sacrifice of the surrounding brain. Blockage of CSF circulation can occur at any point in the pathway. Hydrocephalus conditions are divided into two types, communicating and noncommunicating. The classification depends on whether both lateral ventricles are in communication with the subarachnoid space. Noncommunicating hydrocephalus involves blockage in the ventricular system, which prevents the flow of CSF to the subarachnoid space. Tumors sometimes cause hydrocephalus, through instigating either overproduction or physical obstruction of CSF. CSF circulation may also be obstructed in the subarachnoid space by adhesions that form as a result of meningitis.

CEREBRAL HEMISPHERES The cerebral hemispheres are made up of the cerebral cortex, hippocampus, and basal ganglia containing the amygdala of the limbic system. The cerebral hemispheres are divided by the interhemispheric fissure and are involved in higher motor functions, perception, cognition (pertaining to thought and reasoning), emotion, and memory. The cerebral cortex is divided into four major lobes. The frontal lobe contains the primary motor cortex and premotor area involved in voluntary movement, Broca's area involved in writing and speech, and the prefrontal cortex involved in personality, insight, and foresight. The parietal lobe contains the primary somatosensory cortex involved in tactile and positioning information, while remaining sections are involved in spatial orientation and language comprehension. The temporal lobe contains the primary auditory cortex, Wernicke's area involved in language comprehension, and areas involved in the higher processing of visual input,

along with aspects of learning and memory associated with the limbic system. The occipital lobe contains the primary visual cortex and the visual association cortex.

The limbic lobe is a subdivision consisting of portions of the frontal, parietal, and temporal lobes that form a continuous band called the limbic system.

The limbic system, buried within the cerebrum, is also referred to as the "emotional brain." It includes the thalamus, hypothalamus, amygdala, and hippocampus. Through these structures, the limbic system is involved in drive-related behavior, memory, and emotional responses such as feeding, defense, and sexual behavior. The thalamus and hypothalamus are parts of the diencephalon, while the amygdala and hippocampus are parts of the cerebral hemispheres.

The left and right cerebral hemispheres are not equal in their functionality. In the human brain, the left hemisphere is more important for the production and comprehension of language than the right hemisphere. Damage to the left hemisphere is more likely to cause language deficits than damage to the right hemisphere. Because of this variation in hemisphere contribution, the left hemisphere is most commonly referred to as the dominant hemisphere and the right hemisphere is referred to as the nondominant hemisphere. Nearly all right-handed people and most left-handed people have a left-dominant brain. However, some people have a right-dominant brain or comparable language representation in both hemispheres.

The hippocampus is a curved sheet of cortex folded in the basal medial part of the temporal lobe. It is divided into three multilayered sections, the dentate gyrus, hippocampus proper, and the subiculum acting as a transitional zone between the two. The dentate gyrus receives input from the cortex, and sends output to the hippocampus proper. The hippocampus proper then sends output to the subiculum, which is the principal source of hippocampal output. The hippocampus, referred to as the gateway to memory, is involved in learning and memory functions. The hippocampus converts short-term memory to more permanent memory, is involved in the storage and retrieval of long-term memory, and recalling learned spatial associations.

The basal ganglia are masses of gray matter located deep in the cerebral hemispheres. The basal ganglia contain the corpus striatum, which is involved mostly in motor activity. The striatum is the major point of entry into basal ganglia circuitry, receiving input from almost all cortical areas. It is subdivided into three further divisions called the caudate nucleus, putamen, and globus pallidus. The caudate nucleus is involved more with cognitive function than with motor function. Of all the striatum subdivisions, the putamen is the most highly associated with motor functions of the basal ganglia. The globus pallidus is a wedge-shaped section of the striatum responsible for most basal ganglia output. The basal ganglia also contain the amygdala, a portion of the limbic system involved in memory, emotion, and fear. The amygdala lies beneath the surface of the temporal lobe where it causes a bulge called the uncus. The basal ganglia collectively modulate the output of the frontal cortex involving motor function, but also cognition and motivation.

SPINAL CORD The spinal cord is a cord-like bundle of nerves comprising a major part of the central nervous system, which conducts sensory and motor nerve impulses to and from the brain and the periphery. It is a long tube-like structure extending from the base of the brain, through a string of skeletal vertebrae, to the small of the back. The spinal cord is continuous with the brainstem, and like the brain, it is encased in a triple sheath of membranes. Thirty-one pairs of spinal nerves belonging to the **peripheral nervous system** (PNS) arise from the sides of the spinal cord and branch out to both sides of the body. In addition to carrying impulses to and from the brain, the spinal cord regulates reflexes. Reflexes produce a rapid motor response to a stimulus because the sensory neuron synapses directly with the motor neuron in the spinal cord, so the impulse does not need to travel to and from the brain.

NERVOUS TRACTS Tracts are groups or bundles of nerve fibers that constitute an anatomical and functional unit. Commissural tracts such as the corpus callosum connect the two cerebral hemispheres. Association tracts make connections within the same hemisphere. Projection tracts connect the brain with the spinal cord. Sensory tracts project upward from the spinal cord into regions of the brain, bringing sensory input from the periphery via ascending pathways. Motor tracts project down from the brain into the spinal cord, bringing motor output information to the periphery via descending pathways. The internal capsule is the major structure carrying ascending and descending nerve projection fibers to and from the cerebral cortex. It is a curved, funnel-shaped group of cortical projection fibers divided into five regions, based on each region's relationship to the putamen and globus pallidus of the striatum.

Peripheral nervous system

The peripheral nervous system (PNS) is all of the nervous system outside the brain and spinal cord, including the spinal and cranial nerves. The PNS is divided into the somatic and autonomic subdivisions. The somatic nervous system, regulating activities that are under conscious control such as the voluntary movement of skeletal muscles, includes the spinal and cranial nerves and peripheral sensory receptors. Peripheral neurons that transmit information from the periphery toward the CNS are called afferent neurons, whereas those that transmit information away from the CNS toward the periphery are called efferent neurons.

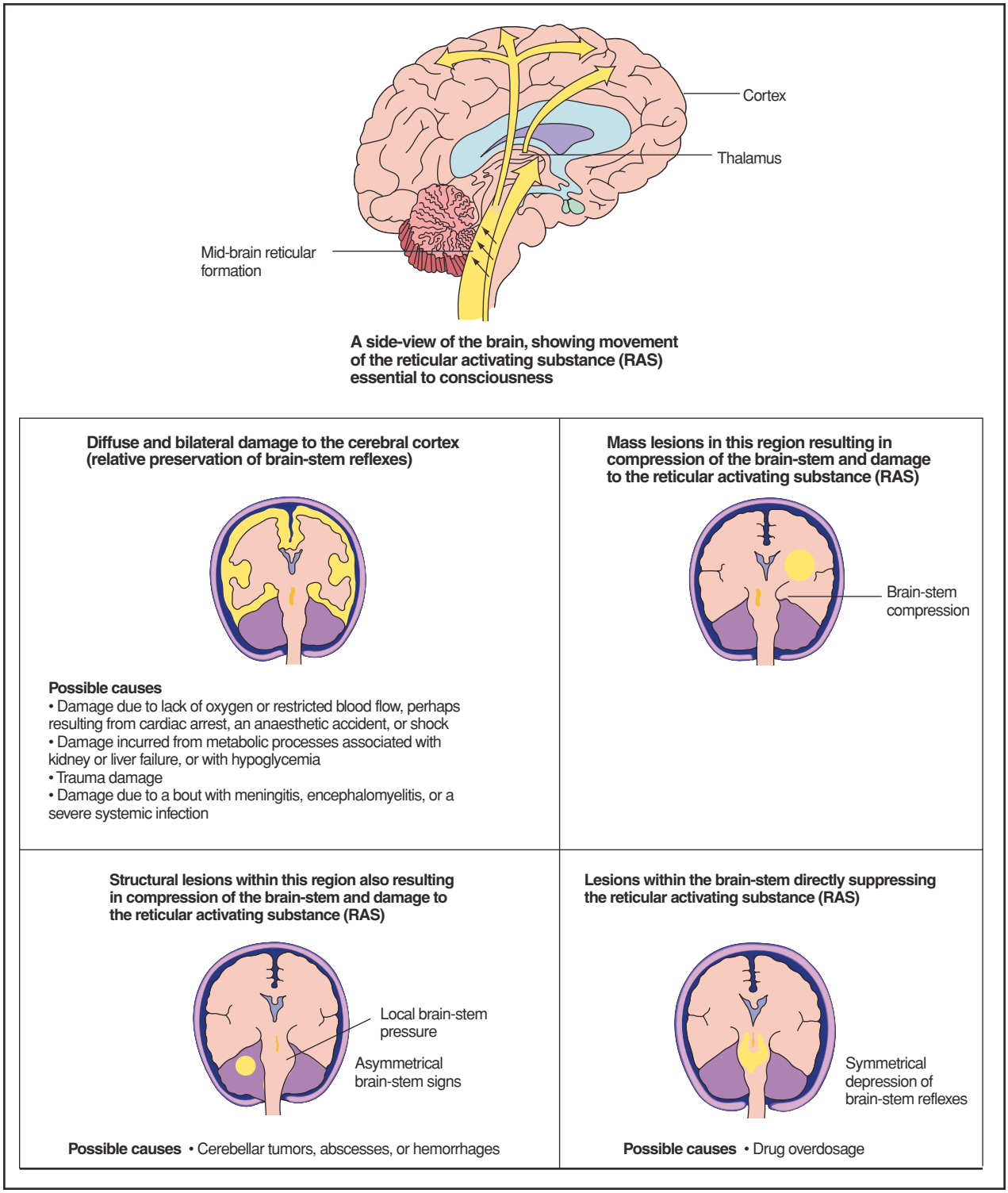


Diagram of the brain indicating sites and causes of possible damage. *(Illustration by Electronic Illustrators Group.)*

The 31 pairs of spinal nerves are each named according to the location of their respective vertebrae. Each spinal nerve consists of a dorsal root and a ventral root. The dorsal roots contain afferent neurons transmitting information to the CNS from various kinds of sensory neurons. The ventral roots contain the axons of efferent motor neurons transmitting information to the periphery. Information travels great distances via interneurons,

which are neurons that connect neurons to each other. Spinal nerves have sensory fibers and motor fibers. The sensory fibers supply nerves to specific areas of skin, while the motor fibers supply nerves to specific muscles. A dermatome, which means "skin-cutting," is an area of skin supplied by nerve fibers originating from a single dorsal nerve root. The dermatomes are named with respect to the spinal nerves that supply them. Dermatomes form bands around the body. In the limbs, dermatome organization is more complex as a result of being "stretched out" during embryological development. There is a high degree of overlap of nerves between adjacent dermatomes. If one spinal nerve loses sensation from the dermatome that it supplies, compensatory overlap from adjacent spinal nerves occurs with reduced sensitivity. In addition to dermatomes supplying the skin, each muscle in the body is supplied by a particular level or segment of the spinal cord and by its corresponding spinal nerve. The muscle, in conjunction with its nerve, makes up a myotome. Although slight variations do exist, dermatome and myotome patterns of distribution are relatively consistent from person to person.

Cranial nerves also carry sensory information from the periphery to the brain, and motor information away from the brain to the periphery. Humans have 12 pairs of cranial nerves numbered by the level at which they enter the brain. Seven of the cranial nerves specialize in information about olfaction, vision, hearing, gustation, and balance. The other cranial nerves control eye and mouth movements, swallowing, and facial expressions. Cranial nerve X is called the vagus nerve; it has effects on visceral gut function and has the ability to slow the heart when stimulated through the parasympathetic nervous system.

The autonomic nervous system includes further sympathetic, parasympathetic, and enteric subdivisions. The autonomic nervous system regulates activities that are not under conscious control but rather are involuntary, such as contractions of the heart and digestion of food. The autonomic nervous system is involved in maintaining homeostasis in the body. The sympathetic and parasympathetic subdivisions of the autonomic nervous system have opposite effects on the organs they control. Most organs controlled by the autonomic nervous system are under the influence of both the sympathetic and parasympathetic nervous systems, which strike a balance with each other to maintain proper body function. The sympathetic nervous system generally stimulates organs, whereas the parasympathetic nervous system generally suppresses organ function or slows it down. An example of this coordination of activity is seen in the fight-or-flight response, which is the body's response to a sudden threatening or stressful situation in which excessive energy is needed to either deal with such an attack or run from it. In the fight-or-flight response, both the sympathetic and parasympathetic nervous systems work in coordination with each other to produce the appropriate results. The sympathetic and parasympathetic nervous systems increase blood pressure and heart rate and slow digestion to enable the physical exertion necessary to respond to the threatening circumstance.

The digestive system contains its own, local nervous system referred to as the enteric, or intrinsic, nervous system. The enteric nervous system is extremely complex and contains as many neurons as does the spinal cord. The enteric nervous system is divided into two networks, or plexuses, of neurons, both of which are embedded in the walls of the digestive tract and extend from the esophagus to the anus. The myenteric plexus is located between the longitudinal and circular layers of muscle in the tunica muscularis and is involved in digestive tract motility. The submucous plexus lies buried in the submucosa. Its principal role is regulating gastrointestinal blood flow and controlling epithelial cell function in response to the environment within the lumen. In regions where these functions are minimal, such as the esophagus, the submucous plexus is sparse. The enteric nervous system functions independently from other nervous systems, but normal digestive function requires communication between the enteric system, other PNS systems, and the CNS. Stimulation of the sympathetic nervous system causes inhibition of gastrointestinal secretions and motor activity, while the parasympathetic nervous system stimulates the same functions. Parasympathetic and sympathetic fibers connect either the central and enteric nervous systems or connect the CNS directly within the digestive tract. In this manner, the digestive system provides sensory information to the CNS, and the CNS is involved in gastrointestinal function. The CNS can also relay input from outside of the digestive system to the digestive system. An example is the sight or smell of food stimulating stomach secretions.

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Maria Basile, PhD

Brain and spinal tumors

Definition

A brain tumor is an abnormal growth of cells (neoplasm) in the skull. A spinal tumor is a growth associated with the spinal cord. Tumors are classified as noncancerous tumors (benign tumors) or cancerous tumors (malignant tumors).

Description

Because the skull is a rigid structure that limits expansion, tumors (both benign and malignant) can exert destructive pressure on neural and support tissues. Although all brain tumors are contained within the rigid skull, tumors can exist within brain tissue (intracranial tumors) or as tumors associated with the outer surface of the brain.

Primary tumors

Tumors that initially arise and grow within the brain are termed primary tumors. Most adult brain cancers are not primary tumors, but are the result of primary cancer that has spread from other areas of the body. Most brain tumors in children, however, are primary tumors. The cells that nourish and support the neurons that compose the brain are most often those cells that exhibit the uninhibited division and growth that results in primary tumor formation. A glioma is a tumor that originates in the cells supporting and nourishing brain neural tissue (glial cells). The most common primary brain tumors include gliomas such as astrocytomas, ependymomas, and oligodendrogliomas.

Primary tumors are sometimes associated with specific genetic diseases such as **tuberous sclerosis** or **neurofibromatosis**. Tumors can also arise following exposure to a sufficient dosage to carcinogens (cancer-causing chemical substances) or nuclear **radiation**.

The most observed form of primary brain tumor found in adults within the general population are diffuse fibrillary astrocytomas that are then divided on the basis of microscopic examination of the tissue (histopathologic diagnosis) into three specific WHO (World Health Organization) grades of malignancy: grade II astrocytomas, grade III anaplastic astrocytomas, and grade IV glioblastoma multiform.

Pilocytic astrocytomas are the most common astrocytic tumors found in children. Desmoplastic cerebral astrocytoma of infancy (DCAI) and desmoplastic infantile ganglioglioma (DIGG) are present as large, superficial, usually benign astrocytomas that most commonly affect children under the age of two years.

Other gliomas and astrocytomas include brainstem gliomas (usually found in children) that are a form of diffuse, fibrillary astrocytoma that often follow a malignant course. The pleomorphic xanthoastrocytomas (PXA) are low-grade astrocytic tumors that are often found in young adults.

Subependymal giant cell astrocytomas (SEGA) are a form of periventricular, astrocytic tumor that are usually benign or low grade.

Other benign tumors include meningioma tumors (a fairly common, usually benign class of intracranial tumor affecting the **meninges**), epidermoid tumors, dermoid tumors, hemangioblastomas (usually benign tumors that occur most frequently in the **cerebellum** and spinal cord of young adults), colloid cysts, pleomorphic xanthoastrocytomas, craniopharyngiomas, and schwannomas. Schwannomas are not strictly a brain or spinal tumor because they arise on peripheral nerves—but they do grow on cranial nerves, particularly the vestibular portion of the acoustic nerve.

Other tumor forms related to diffuse, fibrillary astrocytomas include oligodendrogliomas and oligoastrocytomas. These cerebral tumors are, however, less common than astrocytomas.

Ependymoma tumors are gliomas that are unpredictable. Ependymomas found in the ventricles can be aggressive and highly destructive; other ependymomas are benign spinal cord tumors. Transformation of ependymomas to more malignant forms is rare.

Key Terms

Benign Non-cancerous.

Carcinogen A substance known to cause cancer.

Glioma A tumor that originates in the cells supporting and nourishing brain neural tissue (glial cells).

Neoplasm An abnormal growth of tissue or cells (a tumor) that may be either malignant (cancerous) or benign.

Metastasis The spread of cancer from one part of the body to another. Cells in the metastatic (secondary) tumor are like those in the original (primary) tumor.

Myelogram An x-ray exam of the spinal cord, nerves, and other tissues within the spinal cord that are highlighted by injected contrast dye.

Primary tumor Abnormal growths that originated in the location where they have are diagnosed.

Tumorigenesis Formation of tumors.

Tumors of the choroid plexus tumors are also unpredictable. Occurring in the choroids plexus that line most of the **ventricular system**, they can result in the overproduction of cerebrospinal fluid. As with ependymomas, some are malignant, while others are benign.

Other tumors that are usually malignant include medulloblastomas (a highly malignant tumor usually found in children), atypical meningiomas, and hemangiopericytomas (tumors of the dura that may become aggressive and metastasize.)

Brain and spinal tumors are sometimes associated with diseases or disorders. For example, multiple hemangioblastomas are associated with **von Hippel-Lindau disease** (VHL), an inherited tumor syndrome. Neurological tumor syndromes are those in which patients are genetically predisposed and, therefore, at an increased risk for developing multiple tumors of the nervous system.

Demographics

Brain and spinal tumors occur in people of all races and sexes, but are slightly more common in Caucasian people than other races. About 40,000 people are diagnosed with a brain tumor each year in the United States. Overall, brain tumors tend to occur more frequently in males than females. Meningiomas, however, occur more frequently in females. Most brain tumors occur in people over 70 years of age, and most brain tumors in childhood occur before age eight. Brain and spinal cord tumors in children are the second most common form of childhood cancer, with about 1,500 children developing these tumors each year. Family history may be predictive, especially with regard to chromosomal abnormalities or changes that may result in the loss of tumor suppressor genes. People with family members who have glioma may be at higher risk of developing a brain tumor.

Long-term exposure to certain chemicals may increase the risk of developing a brain tumor. People exposed to acrylonitrile and vinyl chloride while manufacturing some textiles and plastics, pathologists exposed to formaldehyde, and workers in the nuclear industry may all be at higher risk of developing malignant brain tumors.

Almost 10,000 Americans are diagnosed each year with a spinal cord tumor. Primary spinal cord tumors are rare; most are the result of metastasis (spread) from another site of primary cancer in the body. Most primary spinal tumors are not malignant, but as they occupy space surrounding the spinal cord, they may cause **pain** and disability.

Causes and symptoms

With the exception of a few genetic syndromes associated with tumors of the brain and spinal cord, the cause of primary nervous system tumors remains a mystery. As most malignant brain tumors are secondary tumors that result from primary cancer that has spread from elsewhere in the body, factors known to influence the development of other cancers, such as smoking, may be considered related causes.

Although not all of the molecular mechanisms are fully understood, there have been dramatic advances in understanding the causes of the cellular transformations of normal healthy cells into tumor cells (tumorigenesis) within the brain.

Present molecular models identify specific genes that play a role regulating the cell cycle and that data indicate that they play a role suppressing tumor growth (tumor suppressor genes such as the p53 gene). Damage to the gene or loss of the chromosome on which it resides (chromosome 17) correlates to the initiation of astrocytoma tumorigenesis. Oncogenic viruses that interfere with tumor suppressor genes have also been linked to tumor formation. More research is needed into the mechanisms of tumor cell transformation before a definitive link can be established.

Other potential causes of brain or spinal cord tumor development under investigation include head injury, occupational exposure to chemicals, and viruses. Additionally, scientists continue to research the possibility of a relationship between cell phone use and malignant tumors of the **central nervous system**. As of mid-2004, no relationship has yet been established between cell phone use and increased rates of brain cancer.

Symptoms of brain tumors include headaches, nausea, vomiting, **seizures**, and disturbances in vision and hearing that cannot be related to a disorder of the external sensory organs. Changes in personality and developmental problems, motor problems, and balance problems are also characteristic of tumors.

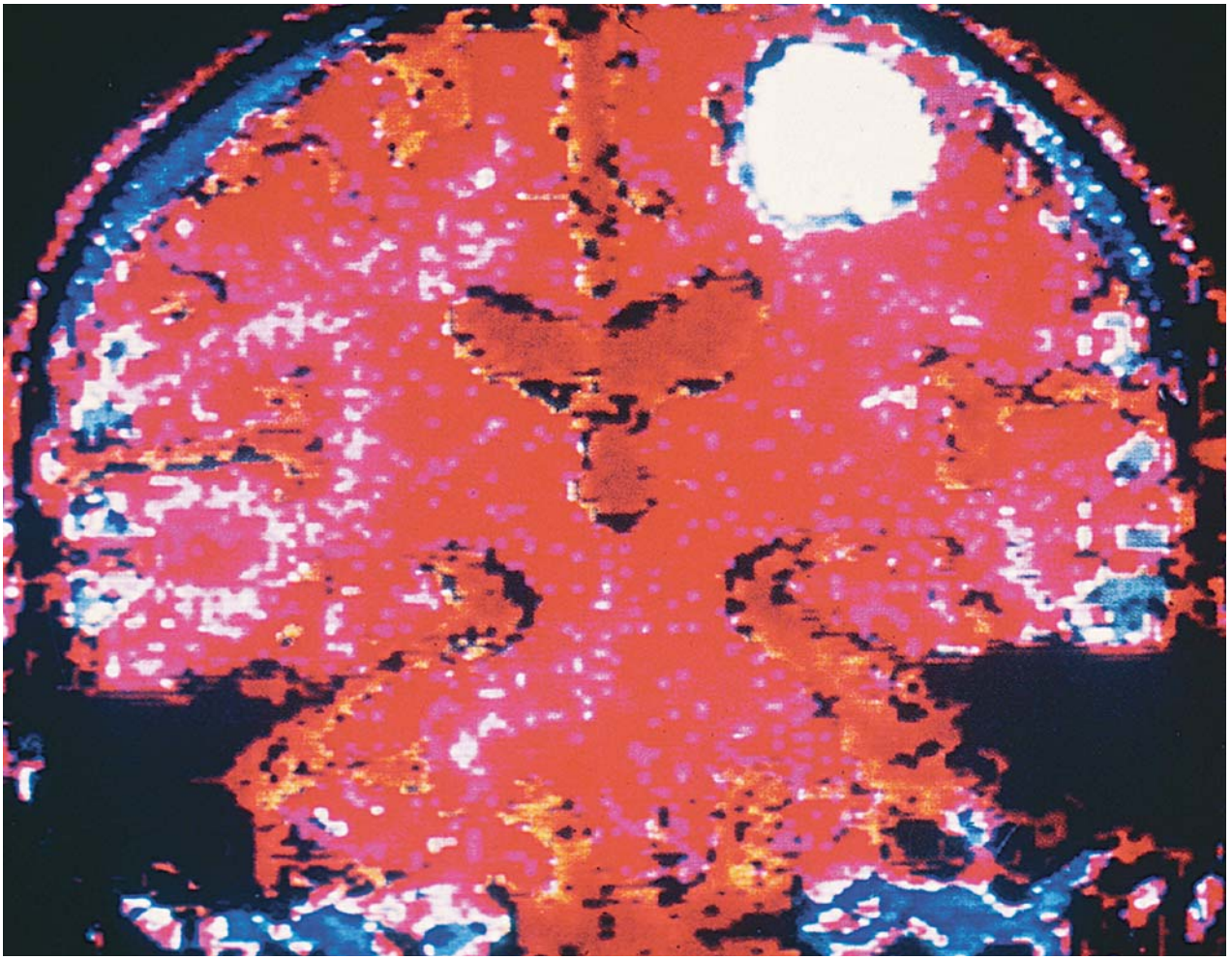
Spinal cord tumor symptoms often include pain, invalid sensory inputs such as numbness in the toes, feet, or legs, and motor coordination problems.

Diagnosis

Brain and spinal tumors may be diagnosed by a combination of neurological examination and imaging such as **magnetic resonance imaging (MRI)** scans, computed tomography (**CT**) **scans**, and **positron emission tomography (PET)**. Other diagnostic tests include laboratory tests (including blood and spinal fluid analysis), myelography, radionucleotide bone scan, **biopsy**, and microscopic examination of tissues.

Brain and spinal tumors are usually confirmed by computerized axial tomography (CAT) scan, or via the more accurate MRI or PET scans.

MRI scans provide the ability to image and anatomically pinpoint tumors of the brain and spinal cord and thus



MRI of a brain tumor (the roundish white area). *(© Visuals Unlimited. Reproduced by permission.)*

provide accurate diagnosis without surgery. Both the MRI and CAT scans produce segmental images of the brain that allow physicians to determine the location and extent of tumors, as well as the extent of damage to neural or surrounding tissue. PET scans use a glucose-and-tracer mixture that is injected into the bloodstream to form a picture of metabolic activity of the brain. As tumor tissue uses more glucose than normal tissue, the tumor presents a brighter image than normal tissue in the picture generated by the scan.

At the tissue level, the presence of cell division at the time of histological examination (tissue exam) is indicative of a higher grade tumor. The greater the rate of mitotic activity (cell division), usually the greater potential for a tumor to advance to a higher and more dangerous type.

GBM tumors are characterized by densely packed cells and the highest high rates of mitotic division. Other tumors such as other gliomas and astrocytomas are diagnosed on the bases of histological examination.

Tumors of the human brain and spinal cord can also be differentiated based on molecular genetic studies that link specific changes in tumors to underlying chromosomal and gene changes (e.g., inactivation of a particular tumor suppressor gene).

Treatment team

In addition to the primary physician, neurologists, and neurosurgeons, treatment often involves oncologists, chemotherapists, and radiation oncologists who can assist the patient and family with treatment decisions. Physical, occupational, and respiratory therapists provide specialized care, as do nurses. Social service consultants coordinate hospital care and community support services.

Treatment

Treatment for brain and spinal tumors is specific to the type of tumor, location of the tumor, and general health of the patient. Surgery, radiation therapy, and

chemotherapy, used alone or in combination, are the three procedures used most to combat brain and spinal cord tumors.

Surgery involves removing as much of the tumor as possible without damage to the surrounding tissues of the brain or spinal cord. Many benign tumors are encapsulated in sac-like membranes or are single structures that can be completely removed. Surgeons use specialized instrumentation and techniques to remove tumors that are irregularly shaped, near vital structures, or are almost inaccessible.

Stereotactic surgery allows surgeons access to tumors in areas of the brain that are difficult to reach. Using computer-assisted instrumentation, surgeons are guided by a three-dimensional map of the brain to remove tissue or implant radiation pellets into the tumor site. Ultrasonic aspirators break up tumor tissue using sound wave pulses, and the tumor fragments are then removed from the brain by suction.

Microsurgery involves a microscope that gives the surgeon a large view of the operative field in the brain or spinal cord. This reduces the possibility of removing surrounding tissue and injuring critical structures. Electrodes inserted into nerves during surgery evoke the potential, or demonstrate the role of specific nerves, thus guiding the surgeon to avoid damage.

Shunting devices are also placed to divert the blocked or excess flow of cerebrospinal fluid that sometimes occurs with a brain tumor. The ventriculoperitoneal shunt is most often used, and is placed in the ventricles of the brain to divert cerebrospinal fluid to the abdomen. Shunting is frequently required with brain tumors in children.

If the tumor is malignant or is in an area of the brain or spinal cord that would cause critical damage to the nervous system, radiation therapy, chemotherapy, or experimental therapies may be recommended. Radiation therapy involves beams of radiation that are aimed at tumor cells to kill them. Traditional radiation therapy is usually given in six-week courses, and involves some damage to surrounding tissues. Radiation therapy using gamma knife technology, also called stereotactic radiosurgery, is much more precise, and focuses approximately 200 beams of gamma radiation guided by MRI at precise points in the tumor simultaneously. Gamma knife technology reduces damage to surrounding tissues.

Chemotherapy drugs are usually given orally or are injected intravenously, and work to kill rapidly dividing cells. As cancer cells divide more rapidly than normal cells, chemotherapy drugs are effective in killing cancer cells. The side effects most associated with chemotherapy, including nausea, hair loss, and skin problems, result from normally dividing cells that are killed along with the cancer cells. Combination chemotherapy drugs are often prescribed for the treatment of brain tumors, such as BCNU and CCNU. Some of the latest chemotherapy modalities use wafers and pumps to deliver chemotherapy drugs directly into tumor tissue.

Steroids are also prescribed in treating brain or spinal cord tumors to reduce swelling the brain tissues. **Anticonvulsants** are given to control seizures. A number of other supportive measures are used to relieve pain and combat unwanted side effects of treatment such as medications used to reduce irritation and relieve nausea during radiation and chemotherapy.

Recovery and rehabilitation

After surgery and other treatments for a brain or spinal cord tumor, patients are monitored for recurrence of the tumor or new tumor growth on a regular basis. Initially, CT or MRI scans are done in periods ranging from one to three months. Later, scans are usually decreased to every six months.

Counseling and cognitive therapy can help with the memory problems and personality changes that some people experience after treatment for a brain tumor. Physical therapy and occupational therapy are useful after treatment for a spinal cord tumor to help with any deficits in mobility, reaching, and positioning. Speech therapists can help with challenges in communication. Physical changes in the structure of the brain after treatment may affect the way a child learns, and a **neuropsychologist** is often helpful in identifying weaknesses and compensation strategies to ease a child's return to school.

Clinical trials

Persons with recurrent tumors or tumors resistant to treatment are often offered participation in an experimental protocol or clinical trial. Experimental treatments include **gene therapy** that introduces substances into the brain tumor, changing the genetic makeup of the tumor cells. Another experimental therapy involves new forms of brachytherapy, where radioactive pellets are implanted directly into the tumor.

The scientific community continually conducts **clinical trials** in the effort to find new drugs and treatments that are effective against cancer, including those types most often occurring in the brain and spinal cord. As of mid-2004, the National Institutes of Health (NIH) and related agencies were sponsoring more than 200 ongoing studies and trials specific for the treatment of brain and spinal cord tumors. Updated information on these and other trials can be found at the NIH website for clinical trials at <http://www.clinicaltrials.gov>.

Prognosis

Symptoms of malignant brain and spinal cord tumors are usually progressive over time. Symptoms become more pronounced and troublesome as tumors invade or otherwise obstruct healthy tissue. Benign tumors can also cause severe dysfunction by placing pressure on surrounding vital structures, but with treatment, they have a more favorable prognosis.

The slowest growing and least serious of these tumor types, grade II astrocytomas (a "low grade" tumor) can still infiltrate surrounding tissue and thus hold a potential for malignancy. Grade III anaplastic astrocytomas are more malignant than type II tumors. This increase in malignancy translates into lower long-term survival rates. Many persons with grade III anaplastic astrocytomas die within two to three years, while may people with the grade II astrocytoma show long-term survival beyond five years.

Patients with the most severe form of astrocytoma (glioblastoma multiforme, or GBH) usually show survival times of less than two years. Patients with oligodendrogliomas and oligoastrocytomas have generally better prognoses than the diffuse astrocytomas. Brainstem gliomas (a form of pediatric diffuse, fibrillary astrocytoma) have a tendency toward malignancy, and survival beyond two years is unusual. Because PXA tumors are usually slow growing and superficial, they are therefore more likely to be successfully treated by surgical removal.

Primary tumors of the spinal cord are often benign, and surgical removal results in a favorable prognosis. With metastatic spinal tumors, prognosis depends on the type of primary cancer.

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National Cancer Institute (NCI), National Institutes of Health. Bldg. 31, Rm. 10A31, Bethesda, MD 20892-2580. (301) 435-3848 or (800) 4CANCER (422-6237); Fax: (847) 827-9918. cancermail@icicc.nci.nih.gov. <http://cancernet.nci.nih.gov>.

Paul Arthur

Brown-Séquard syndrome

Definition

Brown-Séquard syndrome (BSS), also known as hemisection of the spinal cord or partial spinal sensory syndrome, is a rare condition caused by an incomplete lesion of the spinal cord. This damage, most often from physical trauma, results in a contralateral (opposite side of the body) loss of sensation and temperature and ipsilateral (same side of the body) paralysis or extreme weakness.

Description

In 1849, French physiologist Charles Edouard Brown-Séquard published a document discussing the condition that now bears his name. Using information gathered through animal experimentation and human autopsies, he identified and described the hallmark signs of BSS: paralysis affecting only one side of the body (ipsilateral paralysis) and loss of sensation on the opposite side of the body.

Injury or damage to one side of the spinal cord, typically in the cervical (neck) region, results in BSS. The

severity of the condition depends on the amount of damage to the spinal cord and associated neurons. The onset of symptoms may also vary depending on the cause.

Demographics

Information on the prevalence of Brown-Séquard syndrome is collected from 16 **spinal cord injury** centers in the United States. According to The University of Alabama's National Spinal Cord Injury Statistical Center (NSCISC), which compiles the data, approximately 11,000 spinal cord injuries (SCIs) occur each year (as of 2003). Although specific incidence is unknown, BSS is estimated to occur in 200–400 of these injuries.

The average age of a patient sustaining a spinal cord injury is 32 years, with injuries most commonly occurring in individuals between 16 and 30 years. Men account for more than 80% of reported SCIs.

Within the United States, approximately 70% of individuals with BSS are white, nearly 20% are African American, and the remaining 10% comprise other origins, according to NSCISC reports. Little data is known regarding SCIs in countries outside the United States.

Causes and symptoms

In most cases, Brown-Séquard syndrome is caused by severe physical trauma such as a puncture wound or gunshot wound, which partially severs or damages the spinal cord. Nontraumatic conditions that compress the spinal cord may also cause BSS. Examples include tumors, **multiple sclerosis**, **epidural hematoma** (swelling in the area between the brain and skull), meningitis, myelitis (spinal cord inflammation), and tuberculosis.

Physical trauma usually causes a more rapid onset of symptoms than nontraumatic conditions. The two primary symptoms of BSS are loss of sensation and paralysis. The side of the body that sustained injury typically loses touch and vibration senses. The opposite side of the body tends to lose its sense of **pain** and temperature. In both cases, these symptoms occur below the site of the SCI. Paralysis or muscle weakness occurs on the same side of the body as the injury.

Loss of bladder and bowel control may result, but the majority of patients will regain control. Horner syndrome, a condition resulting from damage to the sympathetic facial nerves, has also been known to develop.

Diagnosis

Brown-Séquard syndrome is diagnosed based on the patient's medical history and a physical examination. Imaging studies may be performed to isolate the extent and location of the SCI. These include **magnetic resonance imaging (MRI)**, computed tomography (CT) scans, or x rays. Additional testing may be required for secondary conditions or symptoms.

Several neurological disorders have symptoms similar to BSS, making differential diagnosis very important, especially in those cases related to nontraumatic conditions. The incomplete lesion of the spinal cord in conjunction with the unique presentation of ipsilateral sensory loss and paralysis are key for identifying BSS.

Key Terms

Corticosteroids A group of anti-inflammatory drugs similar to the natural corticosteroid hormones produced by the adrenal glands.

Lesion A change in tissue due to injury or disease.

Paralysis The inability to use a muscle because of injury to or disease of the nerves leading to the muscle.

Treatment team

The team of specialists needed to treat a patient with BSS will vary. Primary members include:

- a **neurologist** to evaluate brain and nerve function
- an orthopedic specialist to monitor the spine and assist with walking therapy
- a physical therapist to help regain muscle strength and walking ability
- an occupational therapist to facilitate adaptation of new physical limitations

Treatment

In cases of physical trauma, treatment begins at the accident site with proper immobilization and emergency medical care to prevent further spinal cord damage. Surgery may be required in these or nontraumatic cases to eliminate the cause, whether a bullet or a fluid-filled cyst.

Treatment of symptoms is the typical focus for this condition. Several studies have shown increased success with early administration of high-dose steroids such as corticosteroids, but this is not yet a standard practice. Other medications are prescribed as needed for secondary symptoms.

Physical therapy should begin immediately in order to maintain muscle strength and agility since most patients

with BSS will regain mobility. Specialized devices, including wheelchairs or braces, may be necessary during this transition.

Recovery and rehabilitation

The recovery time for each patient depends on the extent of nerve damage and underlying cause of the syndrome. The NSCISC reports that individuals with SCIs spend an average of 16 days in the hospital and 44 days in rehabilitation. Rehabilitation may be required outside the hospital for several months or years.

Extensive physical therapy should take place immediately. Initial therapy focuses on respiratory exercises, upright positioning, and range of motion in affected muscles. Progressive therapy gradually helps the patient with the strength and control necessary to be mobile or begin walking again.

Occupational therapy is also important for helping patients return to their daily activities. This therapist provides methods for modifying everyday tasks, evaluates progress, and facilitates the necessary changes to restore independence when possible.

Clinical trials

The National Institute of Child Health and Human Development is currently conducting a clinical trial to evaluate the effectiveness of walking on a treadmill by individuals with incomplete SCIs. As of early 2004, this five-year study was in Phase II and III **clinical trials** and still recruiting patients. The proposed end date for the study is January 2005. For additional information contact: Andrea L. Behrman, PhD (Principal Investigator), University of Florida, "Retraining Walking after Spinal Cord Injury" (Study ID: K01HD01348); Telephone: (352) 273-6117; E-mail: abehrman@hp.ufl.edu.

Prognosis

Patients with Brown-Séquard syndrome usually have a good prognosis. The extent to which a patient recovers depends on the cause of injury and secondary conditions or complications. According to the National Organization for Rare Disorders, more than 90% of affected individuals successfully regain the ability to walk. Additional studies have found that the majority of a patient's motor skills return within the first two months after injury. The recovery period is usually two years, but will vary by patient.

Special concerns

Not all patients with BSS make a full recovery. In these instances, long-term care options need to be considered. By working with the treatment team, individuals can determine their level of activity and recognize areas where adaptation may be required. Some patients and their caregivers could benefit from psychological therapy to discuss the variety of changes that occur after traumatic injury.

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National Organization for Rare Disorders. 55 Kenosia Avenue, P.O. Box 1968, Danbury, CT 06813. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

National Spinal Cord Injury Association. 6701 Democracy Blvd. #300-9, Bethesda, MD 20817. (301) 214-4006 or (800) 962-9629; Fax: (301) 881-9817. info@spinalcord.org. <http://www.spinalcord.org>.

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Bruit *see* **Hearing disorders**

Bulbospinal muscular atrophy *see* **Kennedy's disease**

C

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 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 and people of Saudi Arabian descent.

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. People of Saudi Arabian descent also have a relatively high risk of Canavan disease.

Causes and symptoms

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.

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.

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, most clinical laboratories typically test for only two to three common gene changes. Two of the ASPA gene changes 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 from 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 team

A child with Canavan disease will require treatment from a pediatric **neurologist**, pediatric ophthalmologist, and a pediatric surgeon for the installation of certain kinds of feeding tubes. Physical and occupational therapists can and educational specialists can provide supportive treatment.

Treatment

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

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 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 early embryo. 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.

programs and physical therapy. 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 aspartoacylase 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 life span of a particular individual with Canavan disease.

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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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Carbamazepine

Definition

Carbamazepine is an antiepileptic drug used to reduce or suppress **seizures**. The medication is also commonly prescribed to relieve certain neurogenic **pain** such as **trigeminal neuralgia**. This drug decreases abnormal electrical impulses through nerve cell pathways by inhibiting the activity of sodium channels in neurons. Consequently, it blocks the repetitive impulses that trigger seizures. In the United States, brand names for carbamazepine include Tegretol, Carbatrol, and Epitol. This medication is classified into the following categories: anticonvulsant, antimanic, and antineuralgic.

Purpose

Due to its high efficacy, carbamazepine is in many cases a first-line treatment for **epilepsy**, and is also frequently prescribed to treat acute neuralgias such as trigeminal neuralgia. Sometimes the drug is also used to improve bipolar disorder symptoms, especially during the manic phase of this disease.

Description

Carbamazepine is a lipid-soluble substance metabolized in the liver by enzymes of the P-450 family and therefore, its chronic administration may induce liver toxicity, especially in patients with reduced liver function. In contrast, persons whose P-450 enzymes are very efficient and metabolize the drug rapidly tend to have decreased carbamazepine half-life and therefore, reduced efficacy of the medication. The body slowly absorbs carbamazepine and the drug easily passes through the blood-brain barrier. It is rapidly transported into the **central nervous system** (CNS), where it exerts a depressant effect.

Recommended dosage

For treatment of seizures, the usual initial dose of carbamazepine for adults and children over 12 years of age is 200 milligrams, taken twice daily. The prescribing physician may increase the dosage in weekly intervals until optimum seizure control is achieved. Dosages generally do not exceed a range of 1000–1200 milligrams (mg) per day. For the treatment of trigeminal neuralgia, daily dosages usually range from 800–1200 mg per day during the stage of acute pain and 400–800 mg per day for preventative therapy.

Precautions

The ingestion of alcoholic drinks during carbamazepine therapy is contraindicated because both substances may potentiate (increase) the effects of the other.

Key Terms

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Neurogenic pain Pain originating in the nerves or nervous tissue.

Trigeminal neuralgia A disorder affecting the trigeminal nerve (the 5th cranial nerve), causing episodes of sudden, severe pain on one side of the face.

Other depressants of the central nervous system such as antihistamines, analgesic drugs, muscle relaxants, and tranquilizers, are also potentiated when used with carbamazepine or other antiepileptic medications. Diabetic patients should be monitored during the administration of this drug since it interferes with glucose blood levels. The drug should not be taken during pregnancy due to the absence of safety clinical studies for pregnant women. Tests in animals have shown that carbamazepine causes developmental defects in embryos when administered in high doses. As the drug is found in breast milk, the use of this medication is also contraindicated during breast-feeding. Carbamazepine may interfere with several biomarkers used in medical laboratory tests, and persons taking the medication should report its intake before blood or urine samples are collected for analysis.

Side effects

The intensity of side effects (or adverse effects) of carbamazepine is dose-dependant. Among the mild adverse effects observed during chronic administration of this medication are drowsiness, vertigo, **fatigue**, blurred vision, gastritis, constipation, aching muscles or joints, skin sensitivity to solar **radiation**, loss of appetite, and dry mouth. In most patients, these side effects are mild and tend to decrease in intensity or to completely disappear within a few days of treatment. However, if they are particularly intense or do persist for two or more weeks they should be reported to the physician.

Nevertheless, elderly patients or patients exhibiting one or more severe symptoms in association with carbamazepine intake such as chest pain, blurred vision, mental confusion or hallucinations, numbness, tachycardia, **depression** or marked mood changes, urinary retention or excessive diuresis, peripheral edema, severe diarrhea or vomiting, should report such symptoms to their physicians as soon as possible.

Moreover, immediate medical attention may be required in the presence of one or more of the following adverse effects: presence of blood in the urine or urine with a dark color, black tarry stools or pale stools, unusual bleeding or bruising, skin rashes, ulcers or white spots in the mouth or lips, chills and fever, shallow or uneasy breathing or wheezing chest, jaundice, arrhythmia, sudden blood pressure fall or unusual high blood pressure, cough and/or sore throat. These side effects could indicate the presence of a potentially serious blood disorder.

Interactions

The use of carbamazepine reduces the effectiveness of oral contraceptives and also reduces the effects of corticosteroids. The concomitant use of one of the following drugs inhibits the metabolism of carbamazepine, thereby decreasing its effectiveness: cimetidine, erythromycin, isoniazid, diltiazem, and propoxyphene. Conversely, carbamazepine decreases the plasma levels of phenytoin, another antiepileptic drug. Clarithromycin, an antibiotic, increases the blood levels of carbamazepine and thus, increases the risk of adverse effects.

The use of particular antidepressant medicines known as monoamine oxidase (MAO) inhibitors during carbamazepine therapy, or within the previous two weeks before initiating carbamazepine therapy may increase the risk of fever, severe high blood pressure, **stroke**, and convulsions. Therefore, an interval of at least two weeks is recommended between the administration of these two classes of drugs.

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Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

National Institute of Neurological Disorders and Stroke. P.O. Box 5801, Bethesda, MD, 20892-2540. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov/>.

contact_us.htm> or <http://www.ninds.nih.gov/index.htm>.

Sandra Galeotti

Carotid endarterectomy

Definition

Carotid endarterectomy is a surgical procedure to treat obstruction of the carotid artery caused by atherosclerotic plaque formation.

Purpose

The purpose of surgical therapy for vascular disease is to prevent **stroke**. Stroke can be caused by atherosclerosis of the carotid arteries located in the neck. Atherosclerosis is a degenerative disease of the cardiovascular system, which can occur in the carotid arteries in the neck, resulting in plaques of lipids, cholesterol crystals, and necrotic cells. The plaques in the carotid arteries can result in disease by embolizing, thrombosing, or causing stenosis (narrowing of artery). The plaques in the carotid arteries can cause disease if they obstruct a vessel or get dislodged and obstruct another area.

Precautions

The procedure is contraindicated in patients with an occluded carotid artery and in cases of severe neurologic deficit resulting from cerebral infarction. Additionally, the procedure is not performed in persons with concurrent medical illness severe enough to limit life expectancy. During the operation, precautions should be taken to prevent intraoperation movement of the atherosclerotic plaque. This can occur by excessive manipulation of the carotid bifurcation (the anatomical point where the internal and external carotid is joined together). The internal carotid will extend from the neck and penetrate the brain (to provide the brain with blood), whereas the external carotid will form other smaller arteries to provide blood to structures within the neck region. Atherosclerotic plaques are fragile especially if they are ulcerated. During the operation the surgeon must carefully dissect free other attached vessels such as the common carotid, internal carotid, and external carotid arteries with minimal physical manipulation of the affected carotid vessel.

Description

The first successful carotid endarterectomy was performed by DeBakey in 1953. During the past 40 years the procedure has been optimized and has become the most frequently performed peripheral vascular operation in the United States. There are more than 130,000 cases of carotid endarterectomy performed annually in the United States. Several randomized prospective **clinical trials** have conclusively established both the safety and efficacy of carotid endarterectomy and its superiority for favorable outcomes when compared to the best medical management. Largely due to credible scientific and clinical research, there has been a very large increase in the performance of this procedure over the past ten years. It is understandable that the procedure is common since it is utilized for the treatment of stroke, which is a condition that is associated with high morbidity (death rates) and is frequent. Carotid endarterectomy is the most common surgical procedure in the United States utilized to treat stenosis (narrowing) of the carotid artery. There are approximately more than 700,000 incident strokes annually and 4.4 million stroke survivors. There are 150,000 annual deaths from stroke. Approximately 30% of stroke survivors die within the first 12 months. Within 12 years approximately 66% will eventually die from stroke, making this condition the third leading cause of death in the United States. The cause of atherosclerosis is unknown, but injury to the arteries can occur from infectious agents, hyperlipidemia, cigarette smoking, and hypertension. The aggregate cost associated with approximately 400,000 first strokes in 1990 was $40.6 billion. Among those who have experienced one stroke, the incidence of stroke within five years is 40–50%. Research as of 2002 concludes that carotid endarterectomy remains the standard of care for the treatment of carotid artery atherosclerosis.

Surgical Description

A vertical incision is made in front of the sternocleidomastoid muscle providing optimal exposure of the surgical field. The line of the incision (10 cm in length) begins at the mastoid process and extends to approximately one to two fingerbreadths above the sternal notch. The exact location of carotid bifurcation can be determined before operation by ultrasound studies or arteriography. Muscles and nerves within the area are carefully displaced to allow access to the diseased area (plaque). When the surgical field is cleared of adjacent anatomical structures the endarterectomy portion of the procedure is carried out. This is accomplished by an incision in the common carotid artery at the site below the atherosclerotic plaque. The surgeon then uses an angled scissor (called a Potts scissor) to incise the common carotid artery through the plaque into the normal internal carotid artery. It is vital to extend the arterial incision (arteriotomy) above and below the atherosclerotic plaque. The surgeon utilizes a blunt dissecting instrument called a Penfield instrument to dissect the atherosclerotic plaque from the attachment to the arterial wall.

Arterial Reconstruction

After removing the atherosclerotic plaque, primary closure with sutures, or closure with a vein or prosthetic patch, is performed. Research indicates that utilization of a prosthetic patch is more favorable than suture closing. During this stage of the operation flushing is important to remove debris and air. Vein patch is advantageous because this type of closure reduces the risk of thrombus accumulation and possibly prevents perioperative stroke.

Preparation

As part of the preoperative preparation, routine laboratory tests for blood chemistry (complete blood count, electrolytes), kidney function tests, lipid profiles, and special blood tests to monitor clotting times are ordered by the clinician. Measurement of clotting times is important because blood thinner medications are typically given to patients preoperatively. Neuroimaging studies of the head are important in symptomatic patients to identify old or new cerebral infarcts. Carotid ultrasound studies are the screening test of choice accepted by surgeons to evaluate for **carotid stenosis**. An electrocardiogram (ECG) is important for evaluating past myocardial infarction and ischemic cardiac changes. The importance of ECG monitoring cannot be overemphasized given that the most common cause of postoperative mortality (death) is cardiac arrest. Positioning of the patient is also important. The operating table should be horizontal without head elevation. The head should be partially turned to the opposite side of the surgical field. It may be advantageous to place a rolled towel under the patient's shoulders to exaggerate neck extension. Gentle preparation and cleaning of operative fields should ensure minimal physical manipulation and pressure to avoid dislodging fragments of atherosclerotic plaque. The goals for anesthetic management include control of blood pressure and heart rate, protection of the brain and heart from ischemic insult, and relief of surgical **pain** and operative stress responses. Routine monitors (ECG and pulse oximetry to measure blood oxygen levels) and oxygen face mask are placed prior to anesthetic induction. Typically, any commonly utilized anesthetic and muscle relaxants (nondepolarizing) can be administered for carotid endarterectomy.

Aftercare

Aspirin therapy should be initiated at the time of diagnosis of **transient ischemic attack** (TIA), amaurosis fugax (transient visual loss), or stroke. Recent research from the prospective Aspirin and Carotid Endarterectomy (ACE) trial suggests that low dose (80 to 325 mg per day) of aspirin is optimal in preventing thromboembolic events after carotid endarterectomy. After carotid endarterectomy the patient's blood should be tested (complete blood count and electrolytes). Cardiac function can be monitored with ECG recordings. Frequent neurologic assessment is essential as well as hemodynamic monitoring (with the goal of maintaining blood pressure at its prior range). The patient should be observed for hemotoma formation which could cause airway obstruction. Antiplatelet therapy is necessary. About two weeks postoperatively patients are evaluated for neurologic and wound complications. Carotid ultrasound studies are performed after six months postoperatively and annually scheduled.

Risks

There are several important complications that can occur after carotid endarterectomy. Stroke or transient neurologic deficit can occur within 12 to 24 hours after operation. These conditions are usually caused by thromboembolic complications, which typically originate from the endarterectomy site or damaged vessels that were involved during the operative procedure (internal, common, and external carotid arteries). In approximately 33–50% of patients, hypertension or hypotension can occur. Wound complications such as hemotoma formation can cause pain and tracheal (wind pipe) deviation, which can impair normal breathing. During surgery, damage to vital nerves can occur, such as cervical nerves which supply sensation to the neck region. Patients may complain of numbness in the lower ear, lower neck, and upper face regions. Damage to the hypoglossal nerve (which provides innervations of the tongue), can produce deviation of the tongue to the paralyzed side and speech impairment. Additionally, the problem can reoccur, resulting in stenosis and symptoms.

Normal results

The normal progression of results following carotid endarterectomy is the prevention of stroke which is approximately 1.6% (two-year stroke risk), compared to 12.2% for patients who are medically treated. The results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) reveal that the incidence of stroke for the post-surgical group (those receiving carotid endarterectomy) was 5.1%; for the group treated medically, the incidence was 11%. As with all surgical procedures, it is important for patients to select a surgeon who has expertise in the particular procedure and in the management of the condition. Some studies indicate that surgeons should perform 10 to 12 carotid endarterectomies every year in order to maintain surgical expertise and management skills.

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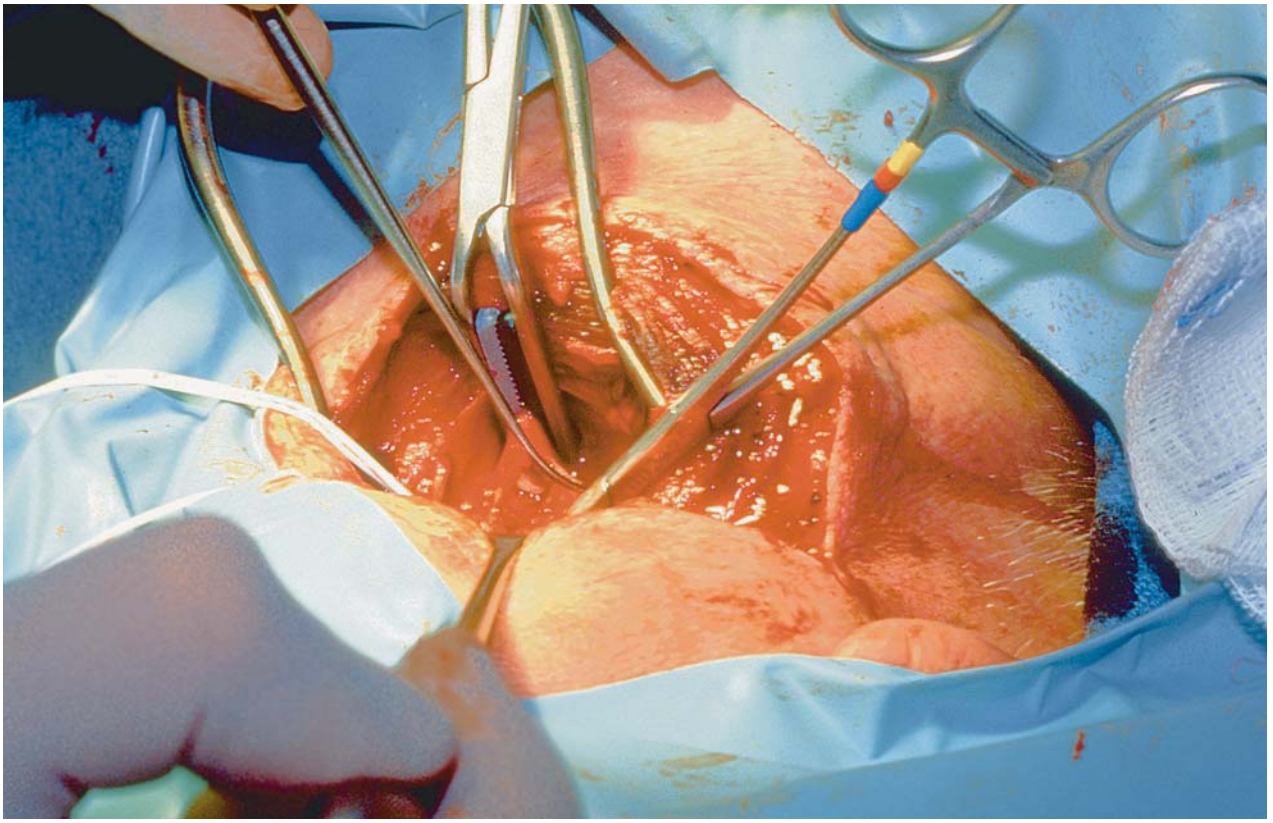

Carotid endarterectomy. *(Custom Medical Stock Photo. Reproduced by permission.)*

Key Terms

Atherosclerotic plaque A deposit of fatty and calcium substances that accumulate in the lining of the artery wall, restricting blood flow.

Cerebral infarction Brain tissue damage caused by interrupted flow of oxygen to the brain.

Electrolytes Salts and minerals that produce electrically charged particles (ions) in body fluids. Common human electrolytes are sodium chloride, potassium, calcium, and sodium bicarbonate. Electrolytes control the fluid balance of the body and are important in muscle contraction, energy generation, and almost all major biochemical reactions in the body.

Hyperlipidemia A condition characterized by abnormally high levels of lipids in blood plasma.

Hypertension Abnormally high arterial blood pressure that if left untreated can lead to heart disease and stroke.

Mastoid process The protrusions of bone behind the ears at the base of the skull.

Myocardial infarction Commonly known as a heart attack, a myocardial infarction is an episode in which some of the heart's blood supply is severely cut off or restricted, causing the heart muscle to suffer and die from lack of oxygen.

Sternocleidomastoid muscle A muscle located in front of the neck that functions to turn the head from side to side.

Stroke Interruption of blood flow to a part of the brain with consequent brain damage. A stroke may be caused by a blood clot or by hemorrhage due to a burst blood vessel. Also known as a cerebrovascular accident.

Transient ischemic attack A brief interruption of the blood supply to part of the brain that causes a temporary impairment of vision, speech, or movement. Usually, the episode lasts for just a few moments, but it may be a warning sign for a full-scale stroke.

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National Stroke Association. 9707 E. Easter Lane, Englewood, Colarado 80112. 303-649-9299 or 1-800-strokes; Fax: 303-649-1328. <http://www.stroke.org>.

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Carotid stenosis

Definition

Carotid stenosis is the medical description of the narrowing or constriction of the carotid artery. The artery is located in the neck, and the narrowing of the artery is caused by the buildup of plaque (fatty deposits). The process of atherosclerosis causes a hardening of the walls of the arteries and, in the case of atherosclerosis in the carotid artery, results in a carotid stenosis that reduces the flow of blood and nutrients to the brain.

Description

The carotid arteries run up the sides of the neck. They are vital arteries, and are a route of blood to the anterior part of the brain and, via branches, to the eyes, forehead, and nose. The deposition of plaque along the inner wall of an artery narrows its diameter. This makes the clogged artery less efficient in transporting blood. Plaque formation can become so severe that an artery is effectively blocked.

Carotid stenosis poses another danger when bits of the plaque dislodge. These pieces, which are referred to as blood clots or emboli, can move upward with the flow of blood towards the brain and can become lodged, blocking blood flow. This blockage interrupts the supply of nutrients and oxygen to the brain, and is one of the causes of cerebral vascular accidents, known as **stroke**. Carotid stenosis is a form of cerebral vascular disease and atherosclerosis.

Demographics

Stroke is the third leading cause of death in the United States after coronary artery disease and cancer, with approximately 750,000 strokes and more than 150,000 deaths occurring each year in the United States. Approximately 50% of these strokes are thought to be the result of carotid stenosis.

Causes and symptoms

The cause of carotid stenosis is the buildup of plaque on the inner wall of the carotid artery. The reduced blood flow to the brain and the blockage of other arteries following the release of emboli can cause a stroke. Increased risk of carotid stenosis is associated with smoking, hypertension, elevated levels of cholesterol, obesity, and a sedentary lifestyle. Some of these factors such as hypertension and cholesterol level may also be related to a person's physiology. Another risk factor is diabetes. Older, less active people are more prone to carotid stenosis. Additionally, the older a person is, the greater the risk posed by carotid stenosis.

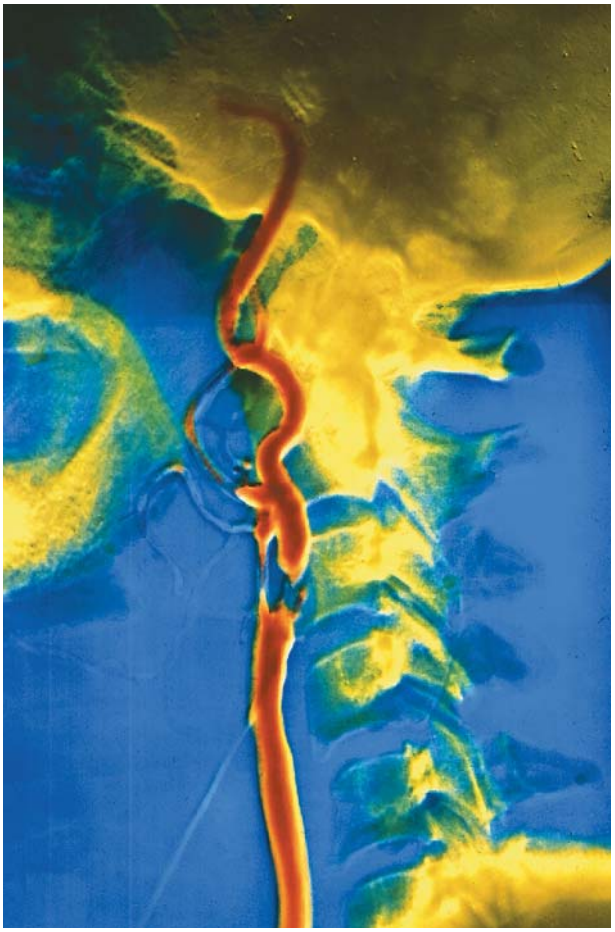
Sometimes, prior to a major stroke, a person can be temporarily affected by the arterial blockage or release of a small embolus. The interrupted flow of blood to the brain, which can be very brief or last a few hours, does not persist longer than 24 hours. Symptoms of this transient event, called a **transient ischemic attack** (TIA), include weakness, as well as visual and speech difficulties. The exact symptoms of carotid stenosis depend on the area of the brain that is affected. Symptoms can also be absent, with the stenosis discovered only incidentally during a clinical examination.

In the event of a stroke, if the blocked blood flow is not restored, brain cells can die, causing permanent brain damage.

Diagnosis

Although not as accurate as other methods, a physician can listen to the pulsing of blood through the carotid artery by means of a stethoscope. The weaker pulse that is a result of stenosis will be evident in the form of altered sounds (bruits) as the blood flows past the area of disturbance.

Sometimes, carotid stenosis is suspected if a person has a transient malfunction of blood flow to the brain, or a TIA. A TIA can last anywhere from a few seconds to several hours. The temporary blockage of the artery can



False-color angiogram showing stenosis in the carotid artery. *(Photograph by Alfred Pasteka. (c) CNRI/ Science Photo Library, National Audubon Society Collection/Photo Researchers, Inc. Reproduced by permission.)*

cause a momentary loss of vision in one eye, a weak or numb sensation on one side of the body, slurred speech, or inability to speak. A TIA can be a warning to a physician of the potential presence of carotid stenosis.

Three main diagnostic tests aid in the diagnosis of carotid stenosis. The first is known as a duplex sonogram, or a carotid duplex. The procedure involves the use of high-frequency sound waves (ultrasound). The ultrasonic waves echo off of the carotid artery to produce a two-dimensional image on a monitor. If narrowing or obstruction of the carotid artery is present, it is often apparent in the image.

Another powerful imaging technique is **magnetic resonance imaging (MRI)** or magnetic resonance **angiography** (MRA). Both rely on the use of magnetism. Pulses of magnetic energy can be used to image the targeted area of the body, based on the interruption of the flow of the electrons in the magnetic field. This information is then converted to a visual image.

Key Terms

Carotid endarterectomy Surgical procedure designed to reduce the accumulation of plaque in the carotid artery and thus prevent stroke.

Cerebral vascular accident Damage to brain cells caused by lack of blood flow in the brain from emboli (clots) plaque, or hemorrhage.

Stenosis Narrowing or constriction of a blood vessel or passage in the body.

The third technique is known as an angiogram or arteriogram. An angiogram is an examination that utilizes x rays after a small tube (catheter) is inserted into the base of the carotid artery. An x-ray dye is then injected. The dye reveals the areas of the regions of the artery that are narrowed or blocked.

Treatment team

Diagnosis and treatment of carotid stenosis involves the primary care physician, nurses, **neurologist**, neurosurgeons, neuroradiologists, and specialists who are skilled in performing angioplasty.

Treatment

Carotid stenosis is treated surgically or medically. One of two surgical treatments is typically used. The first approach is known as microsurgical **carotid endarterectomy**. The second approach is termed endovascular angioplasty and stenting.

Carotid endarterectomy is the surgical exposure of the carotid artery and the removal of the plaque. This re-establishes the uninterrupted flow of blood to the brain. This approach is the method of choice for most patients. However, the technique does itself carry a risk of stroke (stroke can be caused in up to 3% of surgeries).

For patients who are unable to undergo surgery, the angioplasty and stenting approach is used. In this approach a catheter that contains an expandable region at one end is inserted into the carotid artery. The end of the catheter is then expanded. This "balloon" squeezes the plaque against the arterial wall, increasing the effective diameter of the artery. Then, a stent is placed inside the artery. A stent is a tubular arrangement of fibers somewhat similar visually to wire fencing rolled up into a tube. The stent reinforces the carotid artery to prevent its collapse and to keep the plaque tightly against the arterial wall.

Surgery and the associated risks may not be warranted in patients whose arterial blockage is less than 50%.

Anticoagulant medications such as aspirin can be used instead to reduce the tendency of blood clots to form. Treatment can also consist of lifestyle modifications such as stopping smoking, limiting cholesterol intake, or use of cholesterol-lowering medications.

Clinical trials

As of February 2004, a clinical trial designed to investigate the relative effectiveness of carotid angioplasty with stenting versus carotid endarterectomy in preventing stroke, myocardial infarction, and death was recruiting patients in the United States and Canada. Participants should have symptoms of carotid stenosis. The trial, called "Carotid Revascularization Endarterectomy versus Stent Trial (CREST)," was being coordinated by the National Institute for Neurological Diseases and Stroke.

Another clinical trial was designed to examine the role of diet (specifically high doses of vitamin E) on the metabolism of low-density lipoprotein, which is critical in plaque formation. This trial was being coordinated by the National Institute of Health's National Center for Complimentary and Alternative Medicine. Information on both **clinical trials** may be found at the National Institute of Health Clinical Trials website: www.clinicaltrials.gov.

Prognosis

With prompt medical treatment, including surgery, recovery from carotid stenosis can be complete with no residual effects. However, if treatment is delayed or if a stroke occurs, damage can be permanent.

If carotid stenosis is dealt with promptly by surgery, medicine, or lifestyle modifications, prognosis is good. For example, at the Johns Hopkins Medical School, carotid stenosis corrective surgery has a mortality rate of 0.8% (80 in 1,000 people) and a morbidity rate (the person survives, but with some complication) of 1.8% (18 in 1,000 people).

However, undiagnosed stenosis can result in stroke. Depending on the severity of the stroke, prognosis is variable. An estimated 325,000 strokes and 75,000 deaths occur each year in the United States due to carotid stenosis.

Special concerns

Even if there are no symptoms associated with the presence of carotid stenosis, the malady is often a warning sign of possible blockage of the arteries of the heart, or coronary artery disease. Thus, people diagnosed with carotid stenosis should be carefully monitored for coronary artery disease.

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American Stroke Association, a division of the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231. (888) 4-STROKE. <http://www.strokeassociation.org>.

Centers for Disease Control and Prevention (CDC). 1600 Clifton Road, Atlanta, GA 30333. (404) 639-3311 or (800) 311-3435. <http://www.cdc.gov>.

National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

Brian Douglas Hoyle, PhD

Carpal tunnel syndrome

Definition

Carpal tunnel syndrome is an entrapment neuropathy of the wrist. It occurs when the median nerve, which runs through the wrist and enervates the thumb, pointer finger, middle finger and the thumb side of the ring finger, is aggravated because of compression. Symptoms include numbness, tingling and **pain** in the fingers the median nerve sensitizes. Some people have difficulty grasping items and may have pain radiating up the arm. Carpal tunnel syndrome is common in people who work on assembly lines, doing heavy lifting and packing involving repetitive motions. Other repetitive movements such as

typing; are often implicated in cause carpal tunnel syndrome, however some clinical evidence contradicts this association. Additional causes of the syndrome include pregnancy, diabetes, obesity or simply wrist anatomy in which the carpal tunnel is narrow. Treatment includes immobilization with a splint or in severe cases surgery to release the compression of the median nerve.

Key Terms

Median nerve A nerve that runs through the wrist and into the hand. It provides sensation and some movement to the hand, the thumb, the index finger, the middle finger, and half of the ring finger.

Neuropathy A disease or abnormality of the peripheral nerves (the nerves outside the brain and spinal cord). Major symptoms include weakness, numbness, paralysis, or pain in the affected area.

Description

Carpal tunnel syndrome (CTS) is caused by a compression of the median nerve in the wrist, a condition known as nerve entrapment. Nerve entrapments occur when a nerve that travels through a passage between bones and cartilage becomes irritated because a hard edge presses against it. In almost every case of nerve entrapment, one side of the passage is moveable and the repetitive rubbing exacerbates the injury.

Three sides of the carpal tunnel are made up of three bones that form a semicircle around the back of the wrist. The fourth side of the carpal tunnel is made up of the transverse carpal tunnel ligament also called the palmar carpal ligament, which runs across the wrist on the same side as the palm. This ligament is made of tissue that cannot stretch or contract, making the cross sectional area of the carpal tunnel a fixed size. Running through the carpal tunnel are nine tendons that assist the muscles that move the hand and the median nerve. The median nerve enervates the thumb, forefinger, middle finger, and the thumb side of the ring finger. The ulnar nerve that serves the little finger side of the ring finger and the little finger runs outside of the transverse carpal tunnel ligament and is therefore less likely to become entrapped in the wrist.

The tendons that run through the carpal tunnel are encased in a lubricating substance called tensynovium. This substance can become swollen when the tendons rub quickly against one another, as occurs when the finger muscles are used repeatedly. When this happens, there is less space within the carpal tunnel for the median nerve and it becomes compressed or pinched.

When a nerve is compressed, the blood supply to the nerve is interrupted. In an attempt to alleviate the problem, the body's immune system sends new cells called fibroblasts to the area to try to build new tissue. This eventually results in scar tissue around the nerve. In an area that cannot expand this only worsens the situation and puts more pressure on the nerve. A compressed nerve can be likened to an electrical wire that has been crimped. It cannot transmit electrical signals to the brain properly and the result is a feeling of numbness, tingling or pain in the areas that the nerve enervates.

Compression of the median nerve causes tingling and numbness in the thumb, forefinger, middle finger and on the thumb-side of the fourth finger. It may also cause pain in the forearm and occasionally into the shoulder. Some persons have a difficult time gripping and making a fist.

People who suffer from CTS range from those who are mildly inconvenienced and must wear a splint at night to relieve pressure on the median nerve to those who are severely debilitated and lose use of their hands. Problems associated with CTS can invade a person's life making even simple tasks such as answering the phone, reading a book or opening a door extremely difficult. In severe cases, surgery to release the median nerve is often suggested by an orthopedist. The carpal tunnel ligament is cut, relieving the pressure within the carpal tunnel. Rates of success are quite high with the surgical procedure.

Demographics

Carpal tunnel syndrome is more common in women than in men, perhaps because the carpal tunnel generally has a smaller cross section in women than in men. The ratio of women to men who suffer from CTS is about three to one. CTS is most often diagnosed in people who are between 30 and 50 years old. It is more likely to occur in people whose professions require heavy lifting and repetitive movements of the hands such as manufacturing, packing, cleaning and finishing work on textiles.

Causes and symptoms

Carpal tunnel syndrome may occur when anything causes the size of the carpal tunnel to decreases or when anything puts pressure on the median nerve. Often the cause is simply the result of an individual's anatomy; some people have smaller carpal tunnels than others. Trauma or injury to the wrist, such as bone breakage or dislocation can cause CTS if the carpal tunnel is narrowed either by the new position of the bones or by associated swelling. Development of a cyst or tumor in the carpal tunnel will also result in increased pressure on the median nerve and likely CTS. Systemic problems that result in swelling may

also cause CTS such as hypothyroidism, problems with the pituitary gland, and the hormonal imbalances that occur during pregnancy and menopause. Arthritis, especially rheumatoid arthritis, may also cause CTS. Some patients with diabetes may be more susceptible to CTS because they already suffer from nerve damage. Obesity and cigarette smoking are thought to aggravate symptoms of CTS.

Much evidence suggests that one of the more common causes of CTS involves performing repetitive motions such as opening and closing of the hands or bending of the wrists or holding vibrating tools. Motions that involve weights or force are thought to be particularly damaging. For example, the types of motions that assembly line workers perform such as packing meat, poultry or fish, sewing and finishing textiles and garments, cleaning, and manufacturing are clearly associated with CTS. Other repetitive injury disorders such as data entry while working on computers are also implicated in CTS. However, some clinical data contradicts this finding. These studies show that computer use can result in bursitis and tendonitis, but not CTS. In fact, a 2001 study by the Mayo Clinic found that people who used the computer up to seven hours a day were no more likely to develop CTS than someone who did not perform the type of repetitive motions required to operate a keyboard.

The two major symptoms of carpal tunnel syndrome include numbness and tingling in the thumb, forefinger, middle finger and the thumb side of the fourth finger and a dull aching pain extending from the wrist through the shoulder. The pain often worsens at night because most people sleep with flexed wrists, which puts additional pressure on the median nerve. Eventually the muscles in the hands will weaken, in particular, the thumb will tend to lose strength. In severe cases, persons suffering from CTS are unable to differentiate between hot and cold temperatures with their hands.

Diagnosis

Diagnosis of carpal tunnel syndrome begins with a physical exam of the hands, wrists and arms. The physician will note any swelling or discoloration of the skin and the muscles of the hand will be tested for strength. If the patient reports symptoms in the first four fingers, but not the little finger, then CTS is indicated. Two special tests are used to reproduce symptoms of CTS: the Tinel test and the Phalen test. The Tinel test involves a physician taping on the median nerve. If the patient feels a shock or a tingling in the fingers, then he or she likely has carpal tunnel syndrome. In the Phalen test, the patient is asked to flex his or her wrists and push the backs of the hands together. If the patient feels tingling or numbness in the hands within one minute, then carpal tunnel syndrome is the likely cause.

A variety of electronic tests are used to confirm CTS. Nerve conduction velocity studies (NCV) are used to measure the speed with which an electrical signal is transferred along the nerve. If the speed is slowed relative to normal, it is likely that the nerve is compressed. **Electromyography** involves inserting a needle into the muscles of the hand and converting the muscle activity to electrical signals. These signals are interpreted to indicate the type and severity of damage to the median nerve. Ultrasound imaging can also be used to visualize the movement of the median nerve within the carpal tunnel. X rays can be used to detect fractures in the wrist that may be the cause of carpal tunnel syndrome. **Magnetic resonance imaging (MRI)** is also a useful tool for visualizing injury to the median nerve.

Treatment team

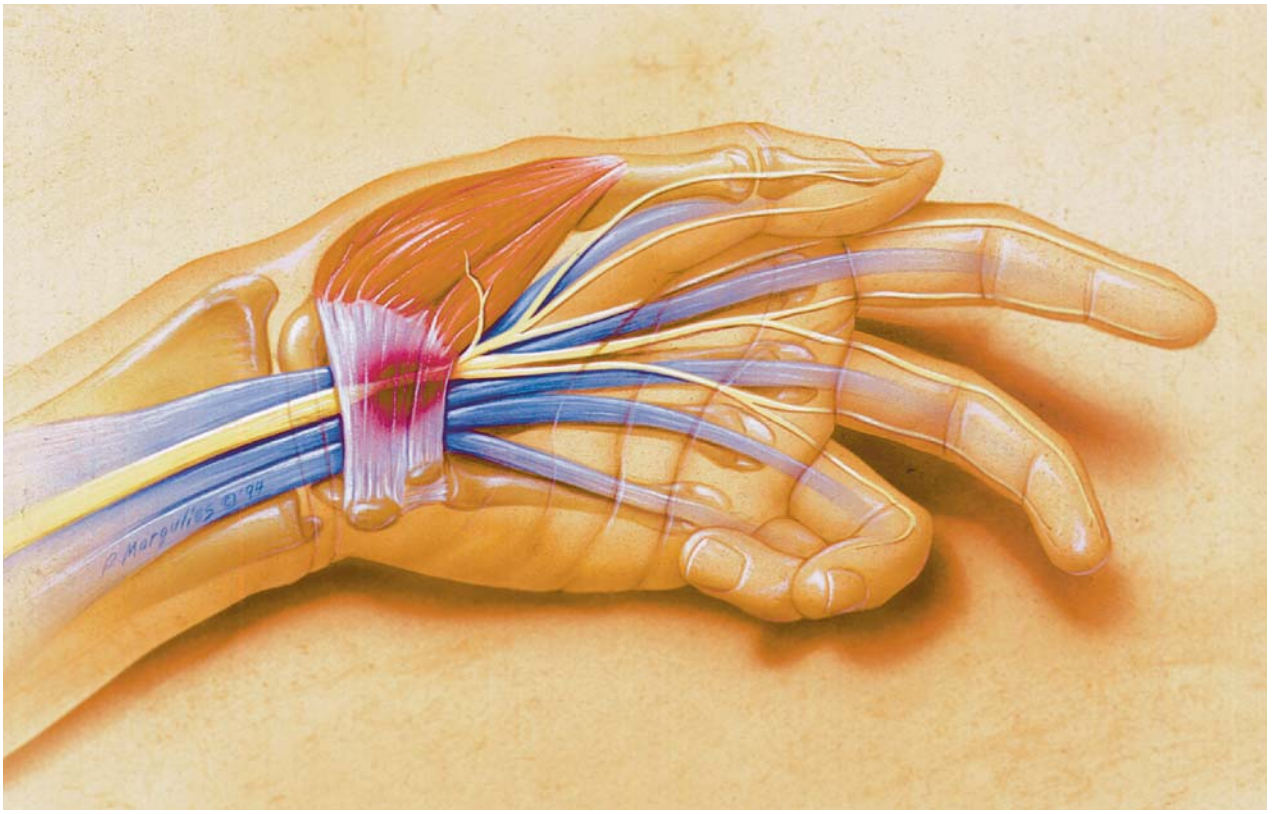
Treatment for carpal tunnel syndrome usually involves a physician specializing in the bones and joints (orthopedist) or a **neurologist**, along with physical and occupational therapists, and if necessary, a surgeon.

Treatment

Lifestyle changes are often the first type of treatment prescribed for carpal tunnel syndrome. Avoiding activities that aggravate symptoms is one of the primary ways to manage CTS. These activities include weight-bearing repetitive hand movements and holding vibrating tools. Physical or occupational therapy is also used to relieve symptoms of CTS. The therapist will usually train the patient to use exercises to reduce irritation in the carpal tunnel and instruct the patient on proper posture and wrist positions. Often a doctor or therapist will suggest that a patient wear a brace that holds the arm in a resting position, especially at night. Many people tend to sleep with their wrists flexed, which decreases the space for the median nerve within the carpal tunnel. The brace keeps the wrist in a position that maximizes the space for the nerve.

Doctors may prescribe non-steroidal anti-inflammatory medications to reduce the swelling in the wrist and relieve pressure on the median nerve. Oral steroids are also useful for decreasing swelling. Some studies have shown that large quantities of vitamin B-6 can reduce symptoms of CTS, but this has not been confirmed. Injections of corticosteroids into the carpal tunnel may also be used to reduce swelling and temporarily provide some extra room for the median nerve.

Surgery can be used as a final step to relieve pressure on the median nerve and relieve the symptoms of CTS. There are two major procedures in use, both of which involve cutting the transverse carpal tunnel ligament. Dividing this ligament relieves pressure on the median nerve and allows blood flow to the nerve to increase. With time,



Medical illustration of left wrist and hand showing carpel tunnel syndrome. The yellow lines represent the median nerve, the blue bands the tendons. Repetitive motion of the wrist and hand causes swelling, and the resulting compression of the nerve results in pain and sometimes nerve damage. *(© R. Margulies. Custom Medical Stock Photo. Reproduced by permission.)*

the nerve heals and as it does so, the numbness and pain in the arm are reduced.

Open release surgery is the standard for severe CTS. In this procedure, a surgeon will open the skin down the front of the palm and wrist. The incision will be about two inches long stretching towards the fingers from the lowest fold line on the wrist. Then next incision is through the palmar fascia, which is a thin connective tissue layer just below the skin, but above the transverse carpal ligament. Finally, being careful to avoid the median nerve and the tendons that pass through the carpal tunnel, the surgeon carefully cuts the transverse carpal ligament. This releases pressure on the median nerve.

Once the transverse carpal tunnel ligament is divided, the surgeon stitches up the palma fascia and the skin, leaving the ends of the ligament loose. Over time, the space between the ends of the ligament will be joined with scar tissue. The resulting space, which studies indicate is approximately 26% greater than prior to the surgery, is enlarged enough so that the median nerve is no longer compressed.

A second surgical method for treatment of CTS is endoscopic carpal tunnel release. In this newer technique, a surgeon makes a very small incision below the crease of the wrist just below the carpal ligament. Some physicians will make another small incision in the palm of the hand, but the single incision technique is more commonly used. The incision just below the carpal ligament allows the surgeon to access the carpal tunnel. He or she will then insert a plastic tube with a slot along one side, called a cannula, into the carpal tunnel along the median nerve just underneath the carpal ligament. Next an endoscope, which is a small fiber-optic cable that relays images of the internal structures of the wrist to a television screen, is fed through the cannula. Using the endoscope, the surgeon checks that the nerves, blood vessels and tendons that run through the carpal tunnel are not in the way of the cannula. A specialized scalpel is fed through the cannula. This knife is equipped with a hook on the end that allows the surgeon to cut as he or she pulls the knife backward. The surgeon positions this knife so that it will divide the carpal ligament as he pulls it out of the cannula. Once the knife is pulled through the cannula, the carpal ligament is severed,

but the palma fascia and the skin are not cut. Just as in the open release surgery, cutting the carpal ligament releases the pressure on the median nerve. Over time, scar tissue will form between the ends of the carpal ligament. After the cannula is removed from the carpal tunnel, the surgeon will stitch the small incision in patient's wrist and the small incision in the palm if one was made.

The two different surgical techniques for treating CTS have both positive and negative attributes and the technique used depends on the individual case. In open release, the surgeon has a clear view of the anatomy of the wrist and can make sure that the division of the transverse ligament is complete. He or she can also see exactly which structures to avoid while making the incision. On the other hand, because the incision to the exterior is much larger than in endoscopic release, recovery time is usually longer. While the symptoms of CTS usually improve rapidly, the pain associated with the incision may last for several months. Many physicians feel that the recovery time associated with endoscopic release is faster than that for open release because the incision in the skin and palma fascia are so much smaller. On the other hand, endoscopic surgery is more expensive and requires training in the use of more technologic equipment. Some believe that are also risks that the carpal ligament may not be completely released and the median nerve may be damaged by the cannula, or the specialized hooked knife. Research is ongoing in an attempt to determine whether open or endoscopic release provides the safest and most successful results.

Success rates of release surgery for carpal tunnel syndrome are extremely high, with a 70–90% rate of improvement in median nerve function. There are complications associated with the surgery, although they are generally rare. These include incomplete division of the carpal ligament, pain along the incisions and weakness in the hand. Both the pain and the weakness are usually temporary. Infections following surgery for CTS are reported in less than 5% of all patients.

Recovery and rehabilitation

One day following surgery for carpal tunnel syndrome, a patient should begin to move his or her fingers, however gripping and pinching heavy items should be avoided for a month and a half to prevent the tendons that run through the carpal tunnel from disrupting the formation of scar tissue between the ends of the carpal ligament.

After about a month and a half, a patient can begin to see an occupational or physical therapist. Exercises, massage and stretching will all be used to increase wrist strength and range of motion. Eventually, the therapist will prescribe exercises to improve the ability of the tendons within the carpal tunnel to slide easily and to increase dexterity of the fingers. The therapist will also teach the patient techniques to avoid a recurrence of carpal tunnel syndrome in the future.

Clinical trials

There are a variety of **clinical trials** underway that are searching for ways to prevent and treat carpal tunnel syndrome. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports this research on CTS. Their website is <http://clinicaltrials.gov/search/term=Carpal+Tunnel+Syndrome>.

One trial seeks to determine which patients will benefit from surgical treatments compared to non-surgical treatments using a new magnetic resonance technique. The study is seeking patients with early, mild to moderate carpal tunnel syndrome. Contact Brook I. Martin at the University of Washington for more information. The phone number is (206) 616–0982 and the email is bim@u.washington.edu.

A second trial compares the effects of the medication amitriptyline, **acupuncture**, and placebos for treating repetitive stress disorders such as carpal tunnel syndrome. The study is located at Harvard University. For information contact Ted Kaptchuk at (617) 665–2174 or tkaptchu@caregroup.harvard.edu.

A third study is evaluating the effects of a protective brace for preventing carpal tunnel syndrome in people who use tools that vibrate in the workplace. The brace is designed to absorb the energy of the vibrations while remaining unobtrusive. For information on this study contact Prosper Benhaim at the UCLA Hand Center. The phone number is (310) 206–4468 and the email address is pbenhaim@mednet.ucla.edu.

Prognosis

Persons with carpal tunnel syndrome can usually expect to gain significant relief from prescribed surgery, treatments, exercises, and positioning devices.

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American Chronic Pain Association (ACPA). P.O. Box 850, Rocklin, CA 95677. (916) 632-0922 or (800) 533-3231. ACPA@pacbell.net. <http://www.theacpa.org>.

National Chronic Pain Outreach Association (NCPOA). P.O. Box 274, Millboro, VA 24460. (540) 862-9437; Fax: (540) 862-9485. ncpoa@cfw.com. <http://www.chronicpain.org>.

National Institute of Arthritis and Musculoskeletal and Skin Dieseases (NIAMS). National Institutes of Health, Bldg. 31, Rm. 4C05, Bethesda, MD 20892. (301) 496-8188; Fax: (540) 862-9485. ncpoa@cfw.com. <http://www.niams.nih.gov/index.htm>.

Juli M. Berwald, Ph.D.

Catechol-O-methyltransferase inhibitors

Key Terms

Ataxia Loss of muscle coordination due to nerve damage.

Carbidopa A drug combined with levodopa to slow the breakdown of the levodopa, used to treat the symptoms of Parkinson's disease.

Levodopa A precursor of dopamine which is converted to dopamine in the brain, and the drug most commonly used to treat the symptoms of Parkinson's disease.

Definition

Catechol-O-methyltransferase (COMT) inhibitors are a class of medication used in combination with levodopa and carbidopa in the treatment of symptoms of **Parkinson's disease** (PD). COMT inhibitors such as tolcapone and entacapone optimize the active transport of levodopa to the **central nervous system** (CNS) and allow the administration of lower doses of both levodopa and carbidopa, which decreases or even prevents the side effects related to these two drugs.

Purpose

Levodopa is a drug that helps to supplement dopamine, a neurotransmitter, to the brain of persons with PD. A neurotransmitter is a chemical that is released during a nerve impulse that transmits information from one nerve cell to another. In PD, levels of the neurotransmitter dopamine progressively decrease as the disease evolves. Drug therapy with levodopa also leads to dopamine formation in tissues outside the brain and in the gastrointestinal tract, causing undesirable side effects and reduced availability of levodopa to the nerve cells. The addition of carbidopa to the treatment regimen inhibits this action and thus, increases levodopa uptake into the brain. However, the inhibition of dopamine results in activation of certain enzymes (including catechol-O-methyltransferase) that compete with levodopa for transport to the brain. By giving drugs that reduce these enzymes, competition is reduced, and more levodopa is utilized by the brain. The administration of a COMT inhibitor drug prolongs the duration of each levodopa dose, and allows the reduction of doses of both levodopa and carbidopa by approximately 30%.

Description

Tolcapone was the first COMT inhibitor approved by the United States Food and Drug Administration to be taken orally in association with the levodopa/carbidopa regimen. Tolcapone is readily absorbed through the gastrointestinal tract and has a fairly rapid action. The drug is metabolized in the liver and eliminated from the body through the feces and urine. However, its COMT inhibitory activity lasts much longer, due to the high affinity of tolcapone with the enzyme.

Entacapone, another COMT inhibitor, was first approved in the European Union and its effects are similar to those obtained with tolcapone when added to levodopa/carbidopa regimen.

Recommended dosage

The physician will adjust the dose of either tolcapone or entacapone to each patient in accordance with other individual clinical characteristics.

Precautions

The use of tolcapone requires a reduction of levodopa/carbidopa to prevent the occurrence of levodopa-related side effects, such as low blood pressure and **dizziness** when rising, loss of appetite, nausea, drowsiness, and hallucinations. Patients with liver disorders or reduced liver function should not receive tolcapone due to its high toxicity to the liver cells. All patients using tolcapone should be regularly monitored by their physician and laboratory blood tests to determine the concentrations of liver

enzymes should be periodically performed. As the chronic use of tolcapone may cause irreversible liver injury, any signs of dark urine, pale stools, unusual **fatigue**, fever, jaundice, persistent nausea or vomiting, and tenderness in the upper right side of the abdomen should be reported to the physician. Tolcapone is contraindicated in pregnant women and during breast-feeding, or to patients already suffering from low blood pressure. Kidney deficiency reduces the elimination rate of tolcapone metabolites and increases the severity of adverse effects.

Entacapone is metabolized in the liver and a pre-existing reduced liver function or chronic deficiency should be reported to the physician to allow for adjustments in dosage. Dosage adjustments or special precautions may be also necessary when entacapone is administered to patients under treatment with one or more of the following medications: isoproterenol, epinephrine, apomorphine, isoetherine, or bitolterol. Except for selegiline, all monoamine oxidase (MAO) inhibitors are contraindicated when using entacapone.

Side effects

The more common tolcapone-related side effects are abdominal **pain**, nausea, vomiting, diarrhea, drowsiness, sleep disorders, **headache**, and dizziness, especially in the first few days of treatment. Elderly patients may have hallucinatory episodes (sensations of seeing, hearing or feeling something that does not exist). Some patients report irritability, aching joints and neck, muscle cramps, agitation, **ataxia**, difficulty in concentrating, and increased urination. Severe episodes of diarrhea may occur after the second month of treatment.

Common side effects with entacapone are abdominal discomfort (constipation, nausea, diarrhea, abdominal pain) and fatigue, which tend to disappear as the body adapts to the medication. Some patients may experience gastritis, heartburns, belching, sleep disorders, increased perspiration, drowsiness, agitation, irritation and mood changes, and fatigue.

Interactions

Patients should inform the physician of any other medication in use when tolcapone prescription is being considered. The concomitant use of entacapone and methyldopa may cause heart rhythm disturbances and abrupt changes in blood pressure.

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National Parkinson Foundation. 1501 N.W. 9th Avenue, Bob Hope Research Center, Miami, FL 33136-1494. (305) 243-6666 or (800) 327-4545; Fax: (305) 243-5595. mailbox@parkinson.org. <http://www.parkinson.org/>.

Sandra Galeotti

Causalgia *see* **Reflex sympathetic dystrophy**

Cavernous angioma *see* **Cerebral cavernous malformation**

Cavernous malformation *see* **Cerebral cavernous malformation**

Central cervical cord syndrome *see* **Central cord syndrome**

Central cord syndrome

Definition

Central cord syndrome is an "incomplete lesion," a condition in which only part of the spinal cord is affected. In central cord syndrome, there is greater weakness or outright paralysis of the upper extremities, as compared with the lower extremities. Unlike a complete lesion, that causes loss of all sensation and movement below the level of the injury, an incomplete lesion causes only a partial loss of sensation and movement.

Description

Central cord syndrome specifically affects the central part of the spinal cord, also known as the "grey matter." The segment of spinal cord affected by central cord syndrome is the cervical segment, the part of the spinal cord that is encased within the first seven vertebrae, running from the base of the brain and into the neck. The central

Key Terms

Cervical Pertaining to a neck.

Lesion An abnormal or injured area.

Paralysis Loss of the ability to move.

Spondylosis A degenerative condition of the cervical spine, causing narrowing of the bony canal through which the spinal cord passes.

Stenosis Abnormal narrowing.

Syringomyelia A chronic disease involving abnormal accumulations of fluid within the spinal column.

part of the cervical spinal cord is responsible for carrying information to and from the upper extremities and the brain, resulting in movement. Because the outer (peripheral) areas of the cervical spinal cord are spared, information going to and from the brain and the lower extremities is not as severely affected.

The specific degree of impairment depends on the severity of the injury. More mild impairment may result in problems with fine motor control of the hands, while more severe impairment may cause actual paralysis of the upper limbs. While the lower limbs are less severely affected in central cord syndrome, in more serious injuries the lower extremities may demonstrate some degree of weakness, loss of sensation, or discoordination. Loss of bladder control may be evident as well.

Central cord syndrome often strikes people who are already suffering from a degenerative spinal disease called spondylosis or spinal stenosis. In spondylosis, a progressive narrowing of the spinal canal puts increasing pressure on the spinal cord, resulting in damage and debilitation. Often, a fall or other injury that causes a person with spondylosis to extend his or her neck will cause the already-narrowed spinal canal to injure the spinal cord, resulting in central cord syndrome.

Demographics

As with other types of spinal cord injuries, men are more frequently affected by central cord syndrome than women. Because central cord syndrome can result from either injury or as a sequelae to the spinal disease spondylosis, there are two age peaks for the condition: in younger individuals (secondary to trauma) or in older individuals (secondary to spondylosis).

Causes and symptoms

Any injury or condition that preferentially damages the central, gray matter of the cervical spinal cord can lead to central cord syndrome. The most common causes include complications of the progressive, degenerative spinal disease called spondylosis, as well as traumatic injury to the cervical spine, such as fractures or dislocations. Injuries to a cervical spine that is already abnormally narrow due to disease is a particularly common cause of central cord syndrome. Tumors or **syringomyelia** (a chronic disease involving abnormal accumulations of fluid within the spinal column) may also lead to central cord syndrome.

Individuals with central cord syndrome may first notice neck **pain** and shooting or burning pains in the arms and hands. Tingling, numbness, and weakness may also be evident. Fine motor control of the upper extremities may be significantly impaired. Sensation in the upper limbs may be dulled or completely lost. Sensation from the legs may be lost, as well, and the lower extremities may demonstrate some degree of weakness and impaired movement. Bladder control may be weakened or lost.

Diagnosis

Diagnosis is usually accomplished through imaging of the cervical spine, with plain x rays, **CT scans**, and/or **MRI** imaging.

Treatment team

The treatment team for central cord syndrome will consist of a **neurologist** and a neurosurgeon, as well as multiple rehabilitation specialists, including physiatrists, physical therapists, and occupational therapists.

Treatment

Usually, intravenous steroids are immediately administered to patients suspected of suffering from central cord syndrome, to decrease swelling and improve outcome. Surgery may be performed in certain cases, in order to stabilize the spine or in order to decompress the spinal cord.

Prognosis

Many patients will be able to rehabilitate their less-severely affected lower extremities and will continue walking, although sometimes with a permanently abnormal, stiff, spastic gait. Many individuals also regain some strength and function of their upper extremities. Upper extremity fine motor coordination, however, usually remains impaired.

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National Spinal Cord Injury Association. 6701 Democracy Blvd. #300-9, Bethesda, MD 20817. 301-214-4006 or 800-962-9629; Fax: 301-881-9817. info@spinalcord.org. <http://www.spinalcord.org>.

Rosalyn Carson-DeWitt, MD

Central nervous system

Definition

The central nervous system (CNS) is composed of the brain and spinal cord. The brain receives sensory information from the nerves that pass through the spinal cord, as well as other nerves such as those from sensory organs involved in sight and smell. Once received, the brain processes the sensory signals and initiates responses. The spinal cord is the principle route for the passage of sensory information to and from the brain.

Information flows to the central nervous system from the **peripheral nervous system**, which senses signals from the environment outside the body (sensory-somatic nervous system) and from the internal environment (autonomic nervous system). The brain's responses to incoming information flow through the spinal cord nerve network to the various effector organs and tissue regions where the target responsive action will take place.

Description

Brain

The brain is divided into three major anatomical regions, the prosencephalon (forebrain), mesencephalon (midbrain), and the rhombencephalon (hindbrain). The brain also contains a **ventricular system**, which consists of four ventricles (internal cavities): two lateral ventricles, a third ventricle, and a fourth ventricle. The ventricles are filled with cerebrospinal fluid and are continuous with the spinal canal. The ventricles are connected via two interventricular foramen (connecting the two lateral ventricles to the third venticle), and a cerebral aqueduct (connecting the third ventricle to the fourth ventricle).

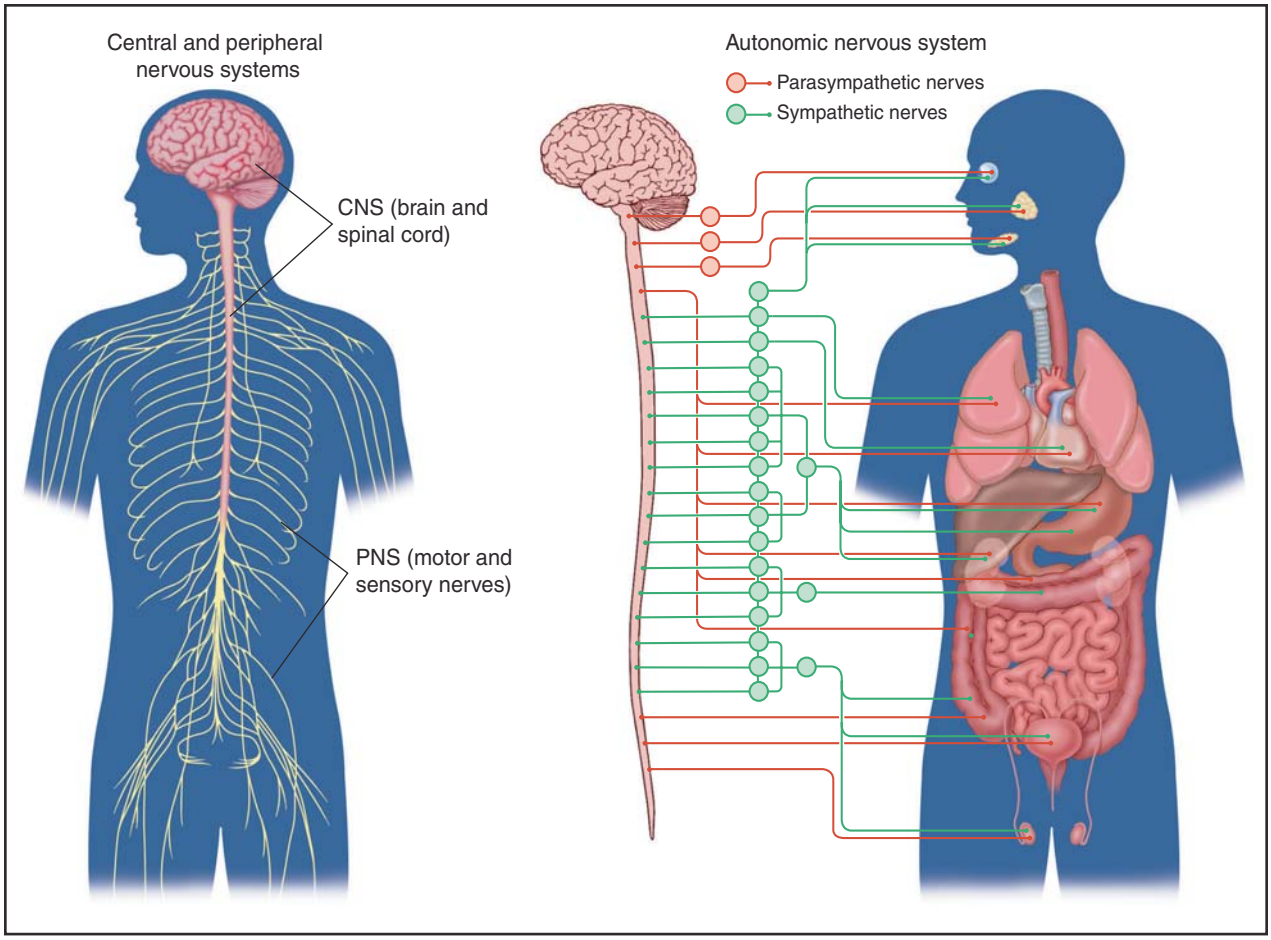
The brain and spinal cord are covered by three layers of **meninges** (dura matter, arachnoid matter, and pia mater) that dip into the many folds and fissures. The meninges are three sheets or layers of connective tissue that cover all of the spinal cord and the brain. Infections of the meninges are called meningitis. Bacterial, viral, and protozoan meningitis are serious and require prompt medical attention. Between the arachnoid and the pia matter is a fluid called the cerebrospinal fluid. Bacterial infections of the cerebrospinal fluid can occur and are life-threatening.

GROSS ANATOMY OF THE BRAIN The prosencephalon is divided into the **diencephalon** and the telencephalon (also known as the cerebrum). The cerebrum contains the two large bilateral hemispherical cerebral cortex that are responsible for the intellectual functions and house the neural connections that integrate, personality, speech, and the interpretation of sensory data related to vision and hearing.

The midbrain, or mesencephalon region, serves as a connection between higher and lower brain functions, and contains a number of centers associated with regions that create strong drives to certain behaviors. The midbrain is involved in body movement. The so-called pleasure center is located here, which has been implicated in the development of addictive behaviors.

The rhombencephalon, consisting of the medulla oblongata, pons, and **cerebellum**, is an area largely devoted to lower brain functions, including autonomic functions involved in the regulation of breathing and general body coordination. The medulla oblongata is a cone-like knot of tissue that lies between the spinal cord and the pons. A median fissure (deep, convoluted fold) separates swellings (pyramids) on the surface of the medulla. The pons (also known as the metencephalon) is located on the anterior surface of the cerebellum and is continuous with the superior portion of the medulla oblongata. The pons contains large tracts of transverse fibers that serve to connect the left and right cerebral hemispheres.

The cerebellum lies superior and posterior to the pons at the back base of the head. The cerebellum consists of left and right hemispheres connected by the vermis. Specialized tracts (peduncles) of neural tissue also connect the



(Illustration by Frank Forney.)

Key Terms

Central nervous system (CNS) Composed of the brain and spinal cord.

cerebellum with the midbrain, pons, and medulla. The surface of the cerebral hemispheres (the cortex) is highly convoluted into many folds and fissures.

The midbrain serves to connect the forebrain region to the hindbrain region. Within the midbrain a narrow aqueduct connects ventricles in the forebrain to the hindbrain. There are four distinguishable surface swellings (colliculi) on the midbrain. The midbrain also contains a highly vascularized mass of neural tissue called the red nucleus that is reddish in color (a result of the vascularization) compared to other brain structures and landmarks.

Although not visible from an exterior inspection of the brain, the diencephalon contains a dorsal thalamus (with a large posterior swelling termed the pulvinar) and a ventral hypothalamus that forms a border of the third ventricle of the brain. In this third ventral region lies a number of important structures, including the optic chiasma (the region where the ophthalmic nerves cross) and infundibulum.

Obscuring the diencephalon are the two large, well-developed, and highly convoluted cerebral hemispheres that comprise the cerebrum. The cerebrum is the largest of the regions of the brain. The corpus callosum is connected to the two large cerebral hemispheres. Within each cerebral hemisphere lies a lateral ventricle. The cerebral hemispheres run under the frontal, parietal, and occipital bones of the skull. The gray matter cortex is highly convoluted into folds (gyri) and the covering meninges dip deeply into the narrow gaps between the folds (sulci). The divisions of the superficial anatomy of the brain use the gyri and sulci

as anatomical landmarks to define particular lobes of the cerebral hemispheres. As a rule, the lobes are named according to the particular bone of the skull that covers them. Accordingly, there are left and right frontal lobes, parietal lobes, an occipital lobe, and temporal lobes.

In a reversal of the pattern found within the spinal cord, the cerebral hemispheres have white matter tracts on the inside of the hemispheres and gray matter on the outside or cortex regions. Masses of gray matter that are present within the interior white matter are called basal ganglia or basal nuclei.

Spinal cord

The spinal cord is a long column of neural tissue that extends from the base of the brain, downward (inferiorly) through a canal created by the spinal vertebral foramina. The spinal cord is between 16.9 and 17.7 inches (43 and 45 centimeters) long in the average woman and man, respectively. The spinal cord usually terminates at the level of the first lumbar vertebra.

The spinal cord is enclosed and protected by the vertebra of the spinal column. There are four regions of vertebrae. Beginning at the skull and moving downward, there are the eight cervical vertebrae, 12 thoracic vertebrae, five lumbar vertebrae, five sacral vertebrae, and one set of fused coccygeal vertebra.

Along the length of the spinal cord are positioned 31 pairs of nerves. These are known as mixed spinal nerves, as they convey sensory information to the brain and response information back from the brain. Spinal nerve roots emerge from the spinal cord that lies within the spinal canal. Both dorsal and ventral roots fuse in the intervertebral foramen to create a spinal nerve.

Although there are only seven cervical vertebra, there are eight cervical nerves. Cervical nerves one through seven (C1–C7) emerge above (superior to) the corresponding cervical vertebrae. The last cervical nerve (C8) emerges below (inferior to) the last cervical vertebrae from that point downward the spinal nerves exit below the corresponding vertebrae for which they are named.

In the spinal cord of humans, the myelin-coated axons are on the surface and the axon-dendrite network is on the inside. In cross-section, the pattern of contrasting color of these regions produces an axon-dendrite shape that is reminiscent of a butterfly.

The nerves of the spinal cord correspond to the arrangement of the vertebrae. There are 31 pairs of nerves, grouped as eight cervical pairs, 12 thoracic pairs, five lumbar pairs, five sacral pairs, and one coccygeal pair. The nerves toward the top of the cord are oriented almost horizontally. Those further down are oriented on a progressively upward slanted angle toward the bottom of the cord.

Toward the bottom of the spinal cord, the spinal nerves connect with cells of the sympathetic nervous system. These cells are called pre-ganglionic and ganglionic cells. One branch of these cells is called the gray ramus communicans and the other branch is the white ramus communicans. Together they are referred to as the rami. Other rami connections lead to the pelvic area.

The bi-directional (two-way) communication network of the spinal cord allows the reflex response to occur. This type of rapid response occurs when a message from one type of nerve fiber, the sensory fiber, stimulates a muscle response directly, rather than the impulse traveling to the brain for interpretation. For example, if a hot stove burner is touched with a finger, the information travels from the finger to the spinal cord and then a response to move muscles away from the burner is sent rapidly and directly back. This response is initiated when speed is important.

Development and histology of the CNS

Both the spinal cord and the brain are made up of structures of nerve cells called neurons. The long main body extension of a neuron is called an axon. Depending on the type of nerve, the axons may be coated with a material called myelin. Both the brain and spinal cord components of the central nervous system contain bundles of cell bodies (out of which axons grow) and branched regions of nerve cells that are called dendrites. Between the axon of one cell body and the dendrite of another nerve cell is an intervening region called the synapse. In the spinal cord of humans, the myelin-coated axons are on the surface and the axon-dendrite network is on the inside. In the brain, this arrangement is reversed.

The brain begins as a swelling at the cephalic end of the neural tube that ultimately will become the spinal cord. The neural tube is continuous and contains primitive cerebrospinal fluids. Enlargements of the central cavity (neural tube lumen) in the region of the brain become the two lateral, third, and forth ventricles of the fully developed brain.

The embryonic brain is differentiated in several anatomical regions. The most cephalic region is the telencephalon. Ultimately, the telencephlon will develop the bilateral cerebral hemispheres, each containing a lateral ventricle, cortex (surface) layer of gray cells, a white matter layer, and basal nuclei. Caudal (inferior) to the telecephalon is the diencephalon that will develop the epithalamus, thalamus, and hypothalamus

Caudal to the diencephalon is the mesencephalon, the midbrain region that includes the cerebellum and pons. Within the myelencephalon region is the medulla oblongata.

Neural development inverts the gray matter and white matter relationship within the brain. The outer cortex is

composed of gray matter, while the white matter (myelinated axons) lies on the interior of the developing brain.

The meninges that protect and help nourish neural tissue are formed from embryonic mesoderm that surrounds the axis established by the primitive neural tube and notochord. The cells develop many fine capillaries that supply the highly oxygen-demanding neural tissue.

Diseases and disorders of the CNS

Diseases that affect the nerves of the central nervous system include rabies, polio, and sub-acute sclerosing panencephalitis. Such diseases affect movement and can lead to mental incapacitation. The brain is also susceptible to disease, including toxoplasmosis and the development of empty region due to prions. Such diseases cause a wasting away of body function and mental ability. Brain damage can be so compromised as to be lethal.

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Brian Douglas Hoyle, PhD
Paul Arthur

Central nervous system stimulants

Definition

Central nervous system (CNS) stimulants are drugs that increase activity in certain areas of the brain. These drugs are used to improve wakefulness in patients that have **narcolepsy**. CNS stimulants are also used to treat patients that have **attention deficit hyperactivity disorder** (ADHD). There are four different types of central nervous system stimulants available in the United States: mixed amphetamine salts (brand name Adderall); dextroamphetamine (Dexedrine and Dextrostat); methylphenidate (Ritalin, Metadate, Methylin, and Concerta); and pemoline (Cylert).

Purpose

Central nervous system stimulants are used to keep patients who suffer from narcolepsy from falling asleep. Narcolepsy is a disorder that causes people to fall asleep during daytime hours.

These drugs are also used to treat behavioral symptoms associated with attention deficit hyperactivity disorder. Although it seems contradictory to give patients with ADHD drugs that are stimulants, these medications are often effective at treating symptoms of impulsivity, inattention, and hyperactivity, which are hallmark features of the disorder.

Description

The exact way that CNS stimulants work in treating narcolepsy and ADHD is not understood. The drugs' mechanism of action appears to involve enhanced activity of two **neurotransmitters** in the brain, norepinephrine and dopamine. Neurotransmitters are naturally occurring chemicals that regulate transmission of nerve impulses from one cell to another. A proper balance between the various neurotransmitters in the brain is necessary for healthy mental well-being.

Central nervous system stimulants increase the activities of norepinephrine and dopamine in two different ways. First, the CNS stimulants increase the release of norepinephrine and dopamine from brain cells. Second, the CNS stimulants may also inhibit the mechanisms that normally terminate the actions of these neurotransmitters. As a result of the dual activities of central nervous system stimulants, norepinephrine and dopamine have enhanced effects in various regions of the brain. Some of these brain areas are involved with controlling wakefulness and others are involved with controlling motor activities. It is believed that CNS stimulants restore a proper balance of neurotransmitters, which alleviates symptoms and features associated with narcolepsy and ADHD.

Although the intended actions of central nervous system stimulants are in the brain, their actions may also affect norepinephrine in other parts of the body. This can cause unwanted side effects such as increased blood pressure and heart arrhythmias due to reactions of norepinephrine on the cardiovascular system.

Recommended dosage

The usual dosage of amphetamine salts is 5–60 mg per day taken two or three times a day, with at least 4–6 hours between doses. The extended release form of amphetamine salts is taken as 10–30 mg once a day. Like amphetamine salts, the dose of immediate-release methylphenidate tablets is also 5–60 mg per day taken two or three times a day. Additionally, methylphenidate is

Key Terms

Attention deficit hyperactivity disorder (ADHD) A mental disorder characterized by impulsiveness, lack of attention, and hyperactivity.

Milligram One thousandth of a gram; the metric measure equals 0.035 ounces.

Narcolepsy An extreme tendency to fall asleep when surroundings are quiet or monotonous.

Neurotransmitter Naturally occurring chemicals that regulate transmission of nerve impulses from one cell to another.

available in sustained-release dosage forms and extended-release dosage forms, which are typically taken only once a day.

The usual dosage of dextroamphetamine is 5–60 mg per day given two or three times a day, with at least 4–6 hours between doses. A sustained-release form of dextroamphetamine is also available, which may be given once a day. The recommended dose of pemoline is 37.5–112.5 mg per day taken only once a day. However, due to pemoline's association with life-threatening liver dysfunction, pemoline is rarely used at the present time.

The therapeutic effects of central nervous system stimulants are usually apparent within the first 24 hours of taking the drugs. If effects are not evident, the dosages of CNS stimulants may be slowly increased at weekly intervals. CNS stimulants should always be used at the lowest effective dosages to minimize unwanted side effects. When the drugs are used for treating ADHD in children, therapy should be interrupted occasionally to determine whether symptoms reoccur and whether the drug is still necessary.

Precautions

Central nervous system stimulants are widely abused street drugs. Abuse of these drugs may cause extreme psychological dependence. As a result, new hand-written prescriptions must be obtained from physicians each month and any time a dosage adjustment is made. These drugs are best avoided in patients with a prior history of drug abuse.

CNS stimulants may cause anorexia and weight loss. Additionally, these drugs slow growth rates in children. Height and weight should be checked every three months in children who need to use these medications on a long-term basis.

The use of CNS stimulants should be avoided in patients with even mild cases of high blood pressure since the drugs may elevate blood pressure further.

Side effects

Central nervous system stimulants may increase heart rates and cause irregular heart rhythms, especially at high doses.

Symptoms of excessive stimulation of the central nervous system include restlessness, difficulty sleeping, tremor, **headaches**, and even psychotic episodes.

Loss of appetite and weight loss may also occur with central nervous system stimulants. It is necessary to monitor liver function regularly in patients who take pemoline since this drug has been associated with life-threatening liver disease.

Interactions

CNS stimulants should not be administered with certain types of antidepressant medications, including monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs). Patients taking CNS stimulants should avoid MAOIs since the combination may elevate blood pressure to dangerously high levels, while SSRIs are best avoided since they may increase the central nervous system effects of CNS stimulants if the drugs are taken together.

Antacids may prevent CNS stimulants from being eliminated by the body and can increase the side effects associated with use of the stimulants.

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Central pain syndrome

Definition

Central **pain** syndrome is a type of pain that occurs because of injuries to the brain or spinal cord.

Description

Central pain syndrome can occur in conjunction with a number of conditions involving the brain or spinal cord, including **stroke**; traumatic injury to, or tumors involving, the brain or spinal cord; **Parkinson's disease**; **multiple sclerosis**; or **epilepsy**.

The pain of central pain syndrome is an extremely persistent, intractable type of pain that can be quite debilitating and depressing to the sufferer. The pain may be localized to a particular part of the body (such as the hands or feet), or may be more widely distributed. The quality of the pain may remain the same or may change. Some of the types of pain experienced in central pain syndrome include sensations of crampy muscle spasms; burning; an increased sensitivity to painful stimuli; pain brought on by normally unpainful stimuli (such as light touch or temperature changes); shooting, lightening, or electric shock–like pains; tingling, pins-and-needles, stinging, numbness, or burning pain; sense of painful abdominal or bladder bloating and burning sensations in the bladder.

Central pain syndrome can be divided into two categories: pain related to prior **spinal cord injury** and pain related to prior brain injury. Spinal cord–related pain occurs primarily after traumatic injury, usually due to motor vehicle accidents. Other reasons for spinal cord–related pain include complications of surgery, tumors, congenital disorders (conditions present at birth), blood vessel–related injury (such as after a **spinal cord infarction** or stroke), and inflammatory conditions involving the spinal cord. Brain-related central pain usually follows a stroke, although tumors and infection may also lead to brain-related central pain.

Demographics

Eight percent of all stroke patients will experience central pain syndrome; 5% will experience moderate to severe pain. The risk of developing central pain syndrome is higher in older stroke patients, striking about 11% of patients over the age of 80. Spinal cord–related pain occurs in a very high percentage; research suggests a range of 25-85% of all individuals with spinal cord injuries will experience central pain syndrome.

Causes and symptoms

In general, central pain syndrome is thought to occur either because the transmission of pain signals in the nerve tracts of the spinal cord is faulty, or because the brain isn't processing pain signals properly. Although details regarding the origin of central pain syndrome remain cloudy, some of the mechanisms that may contribute to its development include muscle spasm; **spasticity** of muscles (chronically increased muscle tone); instability of the vertebral column (due to vertebral fracture or damage to ligaments); compression of nerve roots; the development of a fluid-filled area of the spinal cord (called a **syringomyelia**), which puts pressure on exiting nerves; and overuse syndrome (muscles that are used to compensate for those that no longer function normally are overworked, resulting in muscle strain).

The pain of central pain syndrome can begin within days of the causative insult, or it can be delayed for years (particularly in stroke patients). While the specific symptoms of central pain syndrome may vary over time, the presence of some set of symptoms is essentially continuous once they begin. The pain is usually moderate to severe in nature and can be very debilitating. Symptoms may be made worse by a number of conditions, such as temperature change (especially exposure to cold), touching the painful area, movement, and emotions or stress. The pain is often difficult to describe.

Diagnosis

Diagnosis is usually based on the knowledge of a prior spinal cord or brain injury, coupled with the development of a chronic pain syndrome. Efforts to delineate the cause of the pain may lead to neuroimaging (**CT** and **MRI** scanning) of the brain, spinal cord, or the painful anatomical area (abdomen, limbs); electromyographic and nerve conduction studies may also be performed. In many cases of central pain syndrome, no clear-cut area of pathology will be uncovered, despite diagnostic testing. In fact, this is one of the frustrating and confounding characteristics of central pain syndrome; the inability to actually delineate an anatomical location responsible for generating the pain, which creates difficulty in addressing the pain.

Treatment team

Neurologists will usually be the mainstay for treating central pain syndrome. Physical and occupational therapists may help an individual facing central pain syndrome obtain maximal relief and regain optimal functioning. Psychiatrists or psychologists may be helpful for supportive psychotherapy, particularly in patients who develop **depression** related to their chronic pain.

Treatment

A variety of medications may be used to treat central pain syndrome. Injection of IV lidocaine can significantly improve some aspects of central pain syndrome, but the need for intravenous access makes its chronic use relatively impractical. Tricyclic antidepressants (such as nortriptyline or amitriptyline) and antiepileptic drugs (such as **lamotrigine**, **carbamazepine**, **gabapentin**, **topiramate**) have often been used for neurogenic pain syndromes (pain due to abnormalities in the nervous system), and may be helpful to sufferers of central pain syndrome. When muscle spasms or spasticity are part of the central pain syndrome, a variety of medications may be helpful, including baclofen, tizanidine, **benzodiazepines**, and dantrolene sodium. In some cases, instilling medications (such as baclofen) directly into the cerebrospinal fluid around the

spinal cord may improve spasms and spasticity. Newer therapy with injections of **botulinum toxin** may help relax painfully spastic muscles. Chronically spastic, painful muscles may also be treated surgically, by cutting through tendons (tendonotomy).

Severe, intractable pain may be treated by severing causative nerves or even severing certain nervous connections within the spinal cord. However, while this seems to provide pain relief in the short run, over time, about 60-80% of patients develop the pain again.

Counterstimulation uses electrodes implanted via needles in the spinal cord or specific nerves. These electrodes stimulate the area with electric pulses in an effort to cause a phenomenon referred to as "counter-irritation," which seems to interrupt the transmission of painful impulses. **Deep brain stimulation** requires the surgical implanatation of an electrode deep in the brain. A pulse generator that sends electricity to the electrode is implanted in the patient's chest, and a magnet passed over the pulse generator by the patient activates the brain electrode, stimulating the thalamic area.

Prognosis

Although central pain syndrome is never fatal, it can have serious consequences for an individual's level of functioning. Severe, chronic pain can be very disabling and have serious psychological consequences. Furthermore, central pain syndrome remains difficult to completely resolve; treatments may provide relief, but rarely provide complete cessation of pain.

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American Pain Foundation. 201 North Charles Street Suite 710, Baltimore , MD 21201-4111. 410-783-7292 or 888-615-PAIN (7246); Fax: 410-385-1832. info@painfoundation.org. <http://www.painfoundation.org>.

National Foundation for the Treatment of Pain. P.O. Box 70045, Houston , TX 77270. 713-862-9332 or 800-533-3231; Fax: 713-862-9346. markgordon@paincare.org. <http://www.paincare.org>.

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Cerebellar dysfunction *see* **Ataxia**

Cerebellar-pontine angle tumors *see* **Vestibular Schwanomma**

Cerebellum

Definition

The cerebellum is a cauliflower-shaped brain structure located just above the brainstem, beneath the occipital lobes at the base of the skull.

Description

The word cerebellum comes from the Latin word for "little brain." The cerebellum has traditionally been recognized as the unit of motor control that regulates muscle tone and coordination of movement. There is an increasing number of reports that support the idea that the cerebellum also contributes to non-motor functions such as cognition (thought processes) and affective state (emotion).

The cerebellum comprises approximately 10% of the brain's volume and contains at least half of the brain's neurons. The cerebellum is made up of two hemispheres (halves) covered by a thin layer of gray matter known as the cortex. Beneath the cortex is a central core of white matter. Embedded in the white matter are several areas of gray matter known as the deep cerebellar nuclei (the fastigial nucleus, the globise-emboliform nucleus, and the dentate nucleus). The cerebellum is connected to the brainstem via three bundles of fibers called peduncles (the superior, middle, and inferior).

Anatomy

The cerebellum is a complex structure. At the basic level, it is divided into three distinct regions: the vermis, the paravermis (also called the intermediate zone), and the cerebellar hemispheres. Fissures, deep folds in the cortex that extend across the cerebellum, further subdivide these regions into 10 lobules, designated lobules I–X. Two of

Key Terms

Autoantibodies Antibodies that attack the body's own cells or tissues.

Axon A long, threadlike projection that is part of a neuron (nerve cell).

Gray matter Areas of the brain and spinal cord that are comprised mostly of unmyelinated nerves.

Multiple sclerosis A progressive, autoimmune disease of the central nervous system characterized by damage to the myelin sheath that covers nerves. The disease, which causes progressive paralysis, is marked by periods of exacerbation and remission.

White matter A substance, composed primarily of myelin fibers, found in the brain and nervous system that protects nerves and allows messages to be sent to and from the brain and various parts of the body. Also called white substance.

these fissures in particular, the posterolateral fissure and the primary fissure, separate the cerebellum into three lobes that have different functions: the flocculonodular lobe, or the vestibulocerebellum (lobule X); the anterior lobe (lobules I–V); and the posterior lobe (lobules VI–IX).

The cerebellum plays an important role in sending and receiving messages (nerve signals) necessary for the production of muscle movements and coordination. There are both afferent (input) and efferent (output) pathways. The major input pathways (also called tracts) include:

- dorsal spinocerebellar pathway
- ventral spinocerebellar pathway
- corticopontocerebellar pathway
- cerebo-olivocerebellar pathway
- cerebroreticulocerebellar pathway
- cuneocerebellar pathway
- vestibulocerebellar pathway

The major output pathways include the following:

- globose-emboliform-rubral pathway
- fastigial reticular pathway
- dentatothalamic pathway
- fastigial vestibular pathway

There is a network of fibers (cells) within the cerebellum that monitors information to and from the brain and the spinal cord. This network of neural circuits links the input pathways to the output pathways. The Purkinje fibers and the deep nuclei play key roles in this communication process. The Purkinje fibers regulate the deep nuclei, which have axons that send messages out to other parts of the **central nervous system**.

Function

The flocculonodular lobe helps to maintain equilibrium (balance) and to control eye movements. The anterior lobe parts of the posterior lobe (the vermis and paravermis) form the spinocerebellum, a region that plays a role in control of proximal muscles, posture, and locomotion such as walking. The cerebellar hemispheres (part of the posterior lobe) are collectively known as the cerebrocerebellum (or the pontocerebellum); they receive signals from the cerebral cortex and aid in initiation, coordination, and timing of movements. The cerebrocerebellum is also thought to play a role in cognition and affective state.

The cerebellum has been reported to play a role in psychiatric conditions such as **schizophrenia**, **autism**, mood disorders, **dementia**, and **attention deficit hyperactivity disorder** (ADHD). Currently, the relationship between the cerebellum and psychiatric illness remains unclear. It is hoped that further research will reveal insights into the cerebellar contribution to these conditions.

Disorders

There are a variety of disorders that involve or affect the cerebellum. The cerebellum can be damaged by factors including:

- toxic insults such as alcohol abuse
- paraneoplastic disorders; conditions in which autoantibodies produced by tumors in other parts of the body attack neurons in the cerebellum
- structural lesions such as strokes, **multiple sclerosis**, or tumors
- inherited cerebellar degeneration such as in **Friedreich ataxia** or one of the spinocerebellar ataxias
- congenital anomalies such as cerebellar hypoplasia (underdevelopment or incomplete development of the cerebellum) found in **Dandy-Walker syndrome**, or displacement of parts of the cerebellum such as in **Arnold-Chiari malformation**

Typical symptoms of cerebellar disorders include **hypotonia** (poor muscle tone), movement decomposition (muscular movement that is fragmented rather than smooth), dysmetria (impaired ability to control the distance, power, and speed of an act), gait disturbances (abnormal pattern of walking), abnormal eye movement, and **dysarthria** (problems with speaking).

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National Institute of Mental Health. 6001 Executive Boulevard, Room 8184, MSC 9663, Bethesda, MD 20892-9663. (301) 443-4513 or (866) 615-6464; TTY: (301) 443-8431; Fax: (301) 443-4279. nimhinfo@nih.gov. <http://www.nimh.nih.gov/>.

National Institute of Neurological Disorders and Stroke (NINDS), NIH Neurological Institute. P.O. Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424; TTY: (301) 468-5981. <http://www.ninds.nih.gov/>.

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Cerebral aneurysm *see* **Aneurysm**

Cerebral arteriosclerosis *see* **Stroke**

Cerebral gigantism *see* **Hypoxia, Sotos syndrome**

Cerebral angiitis

Definition

Cerebral angiitis is an inflammation of the small arteries in the brain.

Description

Cerebral angiitis is a type of **vasculitis** in which an aberrant immune response results in inflammation and destruction of the small arteries that feed brain tissue. As a result of the inflammation, blood clots form within the arteries, compromising blood flow and resulting in decreased oxygen delivery to vulnerable brain tissue. Two types of cerebral angiitis have been recognized. The first type is considered to be an encephalopathic type, which results in wide-spread, slowly progressive damage to the brain. The second type causes abrupt, acute damage to a focal area of the brain, similar to a **stroke**.

Demographics

While cerebral angiitis can affect people of all ages, it is most common in the middle aged. Cerebral angiitis affects slightly more males than females. It may also be responsible for the unusual presentation of vasculitis in children, often following a simple chicken pox infection. Cerebral angiitis can also occur as a rare complication of allogeneic bone marrow transplant (bone marrow transplant received from a donor).

Causes and symptoms

Cerebral angiitis may occur spontaneously, with no known cause, or in conjunction with, or as a sequela to (an aftereffect of) a variety of viral infections, including herpes zoster (shingle), varicella zoster (chicken pox), and HIV/AIDS.

Symptoms can include slowly progressive **headache**, nausea, vomiting, stiff neck, confusion, irritability, loss of memory, **seizures**, and **dementia**. Cerebral angiitis may also cause the sudden onset of more acute and focal loss

Key Terms

Encephalopathic Widespread brain disease or dysfunction.

Vasculitis A condition characterized by inflammation of blood vessels.

of function, such as sudden loss of the use of one side of the body or the inability to speak.

Diagnosis

Cerebral angiitis may be diagnosed by examining a sample of cerebrospinal fluid, which will likely reveal increased levels of protein and abnormal white cell activity. **MRI** scanning of the brain will usually show a diffuse pattern of lesions throughout the white matter of the brain, although the stroke-like type of cerebral angiitis may reveal a more focal area of damage. **Biopsy** of a sample of brain tissue is the most definitive diagnostic test; it will reveal inflammation and immune system activity affecting the damaged small arteries of the brain.

Treatment team

Individuals with cerebral angiitis may be treated by a **neurologist** or a rheumatologist.

Treatment

Treatment for cerebral angiitis addresses the inflammation and the immune response, both of which are responsible for the complications of the condition. Corticosteroids (to quell inflammation) and cyclophosphamide (to dampen the immune system) may be given in tandem, often at high doses for about six weeks, and then at lower doses for up to a year. Occasionally, symptoms rebound after the dose is dropped, requiring that the higher dose be reutilized; even after supposed cure, relapse may supervene, necessitating another course of corticosteroids and cyclophosphamide.

Some patients with cerebral angiitis will also benefit from the administration of anticoagulant agents to thin the blood and prevent arterial obstruction by blood clots.

Recovery and rehabilitation

The type of rehabilitation program required will depend on the types of deficits caused by cerebral angiitis, but may include physical therapy, occupational therapy, and speech and language therapy.

Prognosis

Untreated cerebral angiitis will inevitably progress to death, often within a year of the onset of the disease. More research is needed to define the prognosis of treated cerebral angiitis; current research suggests that slightly more than half of all treated patients have a good outcome.

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Cerebral cavernous malformation

Definition

Cerebral cavernous malformations (CCM) are tangles of malformed blood vessels located in the brain and/or spinal cord.

Description

The blood vessels composing a cerebral cavernous malformation are weak and lack supporting tissue, thus they are prone to bleed. If seen under a microscope, a cavernous malformation appears to be composed of fairly large blood-filled caverns. A characteristic feature of a CCM is slow bleeding, or oozing, as opposed to the dangerous sudden rupture of an aneurysm (a weak, bulging area of a blood vessel). However, depending on the size and location of the CCM, and the frequency of bleeding, a CCM can also create a dangerous health emergency. Cerebral cavernous malformations are also known as cavernomas or cavernous angiomas.

Key Terms

Aneurysm A weak, bulging area of a blood vessel.

Autosomal dominant inheritance A pattern of inheritance where only one parent must have the illness for it to be passed on to offspring. The risk of an affected parent passing the condition to an offspring is 50% with each pregnancy.

CCM is usually distinct from the surrounding brain tissue and resembles a mass or a blood clot. It can occur either sporadically or in a familial (inherited) pattern. Usually, only one or two lesions are present when the CCM occurs sporadically. Those with a familial pattern of CCM usually have multiple lesions of malformed blood vessels, along with a strong family history of **stroke** or related neurological difficulties. Familial CCM has a pattern of autosomal dominant inheritance, meaning that only one parent must have the illness for it to be passed on to offspring, and the risk of an affected parent passing the condition to an offspring is 50%. The first gene (CCM1) involved in this disease was recently identified and mapped to the long arm of chromosome 7. Additionally, two other genes responsible for CCM formation were also identified, one mapped to the short arm of chromosome 7 (the CCM2 gene) and the other mapped to the long arm of chromosome 3 (the CCM3 gene).

The size of the malformation varies greatly and can change depending on the amount and severity of each bleeding episode. Typically, they range from something microscopic to something the size of an orange. It is possible for a CCM not to bleed, and the ones that do so, may not necessarily bleed with the severity or intensity that requires surgery. Depending on the size and location of the lesion, the blood can reabsorb causing symptoms to disappear.

Demographics

Cavernous malformations occur in people of all races and both sexes. The male-female ratio is about equal. Family history may be predictive, especially in patients of Hispanic descent. CCM can be found in any region of the brain, can be of varying size, and present with varying symptoms. In a general population of one million people, 0.5% or 5,000 people may be found to have a cavernous malformation, although many are not symptomatic.

In the United States alone, 1.5 million people, or 1 in 200, are estimated to have some form of CCM. This translates to approximately 0.5% of the population. Approximately 20–30% of the diagnoses are made in children and 60% of affected adults are diagnosed in their 20s and 30s. It is estimated that approximately 20 million people worldwide have some kind of vascular malformation.

Causes and symptoms

Most familial cerebral cavernous malformations are present at birth (congenital). They are thought to arise between three and eight weeks of gestation, although the exact mechanism of CCM formation is not understood.

Vascular malformations can potentially occur many years after **radiation** therapy to the brain. Additionally, it is also assumed that severe or repeated head trauma can cause cerebral capillaries to bleed. Over time, the brain attempts to repair itself and control the bleeding by developing a lesion. Researchers assume that these theories may answer the question why some people develop the sporadic form of CCM.

Although these common neurovascular lesions affect almost 0.5% of the population, only 20–30% of these individuals experience symptoms. Symptoms include **seizures**, **dizziness**, stroke, vomiting, uncontrollable hiccups, periodic weakness, irritability and/or changes in personality, **headaches**, difficulty speaking, vision problems or, rarely, brain hemorrhage.

Symptoms are caused by the pressure of accumulated blood in and around the CCM on adjacent brain tissue. If the area of bleeding is small, it may take several subsequent bleeding episodes until enough pressure is built up in order for symptoms to be noticeable. The CCM could also bleed substantially, causing immediate problems and symptoms. Finally, the CCM could remain dormant without any evidence of bleeding.

Diagnosis

Cerebral cavernous malformations are usually diagnosed by computerized axial tomography (CAT) scan or, more accurately, a **magnetic resonance imaging (MRI)** scan with gradient echo sequencing.

MRI has provided the ability to image and localize otherwise hidden lesions of the brain and provide accuracy of diagnosis before surgery. Both the MRI and CAT scans produce images of slices through the brain. These tests help physicians to see exactly where the cavernoma is located. Cavernomas cannot be seen on a cerebral angiogram.

Often, CCMs are diagnosed when the person becomes symptomatic. However, it is common for CCMs to be diagnosed by accident when a CAT scan or MRI is conducted to investigate other health problems. Despite the presence of a CCM, it often remains inactive, meaning there is no evidence that the lesion produces bleeding.

Treatment team

Treatment for CCMs must be specific for each case. A team of cerebrovascular experts (neurologists, neurosurgeons, neuroradiologists, and radiation oncologists), together with the patient and families, decide on whether treatment is necessary and the best treatment option.

Treatment

There are three main treatment options for CCM, including observation, stereotactic radiosurgery, and surgery. If the person with CCM has no symptoms, the first treatment option is to simply observe the CCM with periodic MRI scans to assess for change. This option may be indicated if the lesion is discovered incidentally.

Stereotactic radiosurgery involves delivering highly-focused radiation in a single treatment to the CCM. This has been used almost exclusively for lesions causing repeated hemorrhages located in areas of the brain that are not surgically accessible. It is often difficult to determine if radiosurgery is effective unless the lesion never bleeds again. In certain cases, radiosurgery has likely decreased the repeat hemorrhage rate; however, radiosurgery has never been shown to completely eliminate the malformation.

Surgery is the most common option when treatment is necessary. Because these malformations are so distinct from the surrounding brain tissue, cavernous malformations often can be completely removed without producing any new problems. It is very important to remove the entire malformation as it can regenerate if a small piece is left behind. The risk of the operation depends on the size and location of the cavernous malformation and the general health of the patient.

Clinical trials

Although there are no **clinical trials** for treatment of CCM ongoing as of early 2004, much of the current research focuses on the genetics of the disorder. Duke University's Center for Inherited Neurovascular Diseases was recruiting individuals with familial CCM for participation in research designed to develop a blood test for detecting CCM. For information about participating in the study, contact Ms. Sharmila Basu at (410) 614–0729, or via email at sbasu4@jhmi.edu.

Prognosis

Persons experiencing CCM-related symptoms are likely to remain symptomatic or experience a worsening of symptoms without treatment. Frequent or uncontrolled seizures, increase in lesion size on MRI, or hemorrhage are indications for removal of surgically accessible CCM lesions. Persons treated surgically experience remission or a reduction of symptoms in most cases. Approximately half of patients experience elimination of seizures, and the remainder usually have fewer, less frequent seizures. Successfully excised CCM lesions are considered cured, and it is unusual for them to return.

Special concerns

There are differing opinions about activity restriction for a person diagnosed with CCM lesions. Some physicians encourage their patients to continue their usual activities; others advocate avoiding activities where the risk for head trauma is high, such as sports including football, soccer, hockey, skiing, or skating. It is important to discuss this issue with the physician, wear approriate protective equipment when particiapting in sports, and make decisions pertaining to activity level based on the current status of the CCM and general health. It is also helpful to keep an activity record, to document any relationship between activities and symptoms.

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National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD (6673); Fax: (203)

798-2291. orphan@rarediseases.org.
<http://www.rarediseases.org>.

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Cerebral circulation

Definition

Cerebral circulation, the supply of blood to the brain

Understanding how the brain is supplied with blood is important because a significant number of neurological disorders that result in hospital admissions are due to problems with cerebral vascular disease. In some hospitals, nearly half the admissions due to neurologic disorders relate in some form to problems with cerebral circulation.

Insufficient supply of blood to the brain can cause **fainting** (syncope) or a more severe loss of consciousness. A continuous supply of highly oxygenated blood is critical to brain tissue function and a decrease in pressure or oxygenation (percentage of oxygen content) can cause tissue damage within minutes. Depending on a number of other physiological factors (e.g., temperature, etc.), brain damage or death may occur within two to 10 minutes of severe oxygen deprivation. Although there can be exceptions—especially when the body is exposed to cold temperatures—in general, after two minutes of oxygen deprivation, the rate of brain damage increases quickly with time.

Anatomy of cerebral circulation

Arterial supply of oxygenated blood

Four major arteries and their branches supply the brain with blood. The four arteries are composed of two internal carotid arteries (left and right) and two vertebral arteries that ultimately join on the underside (inferior surface) of the brain to form the arterial circle of Willis, or the circulus arteriosus.

The vertebral arteries actually join to form a basilar artery. It is this basilar artery that joins with the two internal carotid arteries and their branches to form the circle of Willis. Each vertebral artery arises from the first part of the subclavian artery and initially passes into the skull via holes (foramina) in the upper cervical vertebrae and the foramen magnum. Branches of the vertebral artery include the anterior and posterior spinal arteries, the meningeal branches, the posterior inferior cerebellar artery, and the medullary arteries that supply the medulla oblongata.

Key Terms

Cerebral collateral blood flow Anatomical and physiological mechanisms that allow blood destined for one hemisphere of the brain to crossover and nourish tissue on the other side of the brain when the supply to the other side of the brain is impaired.

Circle of Willis Also known as the circulus arteriosus; formed by branches of the internal carotid arteries and the vertebral arteries.

The basilar artery branches into the anterior inferior cerebellar artery, the superior cerebellar artery, the posterior cerebral artery, the potine arteries (that enter the pons), and the labyrinthine artery that supplies the internal ear.

The internal carotids arise from the common carotid arteries and pass into the skull via the carotid canal in the temporal bone. The internal carotid artery divides into the middle and anterior cerebral arteries. Ultimate branches of the internal carotid arteries include the ophthalmic artery that supplies the optic nerve and other structures associated with the eye and ethmoid and frontal sinuses. The internal carotid artery gives rise to a posterior communicating artery just before its final splitting or bifurcation. The posterior communicating artery joins the posterior cerebral artery to form part of the circle of Willis. Just before it divides (bifurcates), the internal carotid artery also gives rise to the choroidal artery (also supplies the eye, optic nerve, and surrounding structures). The internal carotid artery bifurcates into a smaller anterior cerebral artery and a larger middle cerebral artery.

The anterior cerebral artery joins the other anterior cerebral artery from the opposite side to form the anterior communicating artery. The cortical branches supply blood to the cerebral cortex.

Cortical branches of the middle cerebral artery and the posterior cervical artery supply blood to their respective hemispheres of the brain.

The circle of Willis is composed of the right and left internal carotid arteries joined by the anterior communicating artery. The basilar artery (formed by the fusion of the vertebral arteries) divides into left and right posterior cerebral arteries that are connected (anastomsed) to the corresponding left or right internal carotid artery via the respective left or right posterior communicating artery. A number of arteries that supply the brain originates at the circle of Willis, including the anterior cerebral arteries that originate from the anterior communicating artery.

In the embryo, the components of the circle of Willis develop from the embryonic dorsal aortae and the embryonic intersegmental arteries.

The circle of Willis provides multiple paths for oxygenated blood to supply the brain if any of the principal suppliers of oxygenated blood (i.e., the vertebral and internal carotid arteries) are constricted by physical pressure, occluded by disease, or interrupted by injury. This redundancy of blood supply is generally termed collateral circulation.

Arteries supply blood to specific areas of the brain. However, more than one arterial branch may support a region. For example, the **cerebellum** is supplied by the anterior inferior cerebellar artery, the superior cerebellar artery, and the posterior inferior cerebellar arteries.

Venous return of deoxygenated blood from the brain

Veins of the cerebral circulatory system are valve-less and have very thin walls. The veins pass through the subarachnoid space, through the arachnoid matter, the dura, and ultimately pool to form the cranial venous sinus.

There are external cerebral veins and internal cerebral veins. As with arteries, specific areas of the brain are drained by specific veins. For example, the cerebellum is drained of deoxygenated blood by veins that ultimately form the great cerebral vein.

External cerebral veins include veins from the lateral surface of the cerebral hemispheres that join to form the superficial middle cerebral vein.

Nourishing brain tissue

The cerebral arteries provide blood to the brain, but a sufficient arterial blood pressure is required to provide an adequate supply of blood to all brain tissue. Unlike the general body blood pressure, the cerebral blood pressure and cerebral blood flow remain relatively constant, a feat of regulation made possible by rapid changes in the resistance to blood flow within cerebral vessels. Resistance is lowered, principally through changes in the diameter of the blood vessels, as the cerebral arterial pressure lowers, and resistance increases as the incoming arterial pressure increases.

A complex series of nerves, including a branch of the glossopharyngeal nerve (the sinus nerve), relate small changes in the size of the carotid sinus (a dilation or enlargement of the internal carotid artery) such that if arterial pressure increases and causes the sinus to swell, the nervous impulses transmit signals to areas of the brain that inhibit the heart rate.

An oxygenated blood supply is critical to brain function

An adequate blood supply is critical to brain function and healthy neural tissue. Physiological studies utilizing radioisotopes and other traceable markers establish that the majority of the blood originally passing through the left vertebral and left internal carotid arteries normally supply the left side of the brain, with a similar situation found on the right with the right vertebral and right internal carotid arteries. Accordingly, the left half of the brain receives its blood supply from the left internal carotid and left vertebral artery. The right half of the brain receives its blood supply from the right internal carotid and right vertebral artery.

The two independent blood supplies do not normally mix or crossover except for a small amount in the posterior communicating artery (and in some cases, the arterial circle of Willis).

Compensating mechanisms

However, if there is some obstruction of blood flow (cerebral ischemia), there is a compensating mechanism. The two left and right supplies of blood normally do not mix in the posterior communicating artery because they are at roughly equal pressures. Even after the two vertebral arteries join to form the basilar artery prior to joining the arterial circle of Willis, the bloodstreams from the two vertebral arteries remain largely separated as though there were a partition in the channel.

If there is an obstruction on one side that reduces the flow of blood, the pressures of the two sides do not remain equal and so blood from the unaffected side (at a relatively higher pressure) is able to crossover and help nourish tissue on the occluded side of the brain.

The arterial circle of Willis can also permit crossover flow when the pressures are altered by an obstruction or constriction in an internal carotid or vertebral artery.

In addition to crossover flow, the size of the communicating arteries and the arteries branching from the circle of Willis is able to change in response to increased blood flow that accompanies occlusion or interruption of blood supply to another component of the circle.

Accordingly, oxygenated blood from either vertebral artery or either internal carotid may be able to supply vital oxygen to either cerebral hemisphere.

Vascular disorders

The disorders that result from an inadequate supply of blood to the brain depend largely on which artery is occluded (blocked) and the extent of the occlusion.

There are three general types of disorders that can result in inadequate blood flow to the brain. Although there are pressure-compensating mechanisms in the cerebral circulation, heart disease and diseases that affect blood pressure in the body can also influence cerebral blood pressure. Sometimes people get lightheaded or dizzy when they stand up suddenly after sitting for long periods. The **dizziness** is often due to postural hypotension, an inadequate supply of blood to the brain due to a lowered cerebral arterial blood pressure initially caused by an obstruction to the return of venous blood to the heart. Shock can also cause a lowering of cerebral blood pressure.

Disorders or diseases that result in the blockage of arteries can certainly have a drastic impact on the quality of cerebral circulation. A clot (thrombus) that often originates in plaque lining the carotid or vertebral arteries can directly obstruct blood flow in the cerebral circulation. Cerebral **aneurysms**, small but weakening dilations of the cerebral blood vessels, can rupture, trauma can cause hemorrhage, and a number of other disorders can directly impair blood flow.

Lastly, diseases that affect the blood vessels themselves, especially the arterial walls, can result in vascular insufficiency that can result in loss of consciousness, paralysis, or death.

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Cerebral dominance

Definition

Cerebral dominance refers to the dominance of one cerebral hemisphere over the other in the control of cerebral functions.

Description

Cerebral dominance is the ability of one cerebral hemisphere (commonly referred to as the left or right side of the brain) to predominately control specific tasks. Accordingly, damage to a specific hemisphere can result in an impairment of certain identifiable functions. For example, trauma to the left hemisphere can impair functions associated with speech, reading, and writing. Trauma to the right hemisphere can result in a decreased ability to perform such tasks as judging distance, determining direction, and recognizing tones and similar artistic functions.

Key Terms

Cerebral dominance The preeminence of one cerebral hemisphere over the other in the control of cerebral functions.

Handedness The preference of either the right or left hand as the dominant hand for the performance of tasks such as writing.

Cerebral dominance and handedness

Cerebral dominance is also related to handedness—whether a person has a strong preference for the use of their right or left hand. More than 90% of people are right-handed and in the vast majority of these individuals, the left hemisphere controls language-related functions.

In left-handed individuals, however, only about 75% have language functions predominantly controlled by the left hemisphere. The remainder of left-handed individuals have language functions controlled by the right hemisphere, or do not have a dominant hemisphere with regard to language and speech.

A very small percentage of people are ambidextrous, having no preference for performing tasks with either hand.

One aspect of cerebral dominance theory that has received considerable research attention is the relationship between a lack of cerebral dominance and **dyslexia**. Some research data suggest that indeterminate dominance with regard to language—a failure of one hemisphere to clearly dominate language functions—results in dyslexia. Evidence to support this hypothesis is, however, not uniform or undisputed.

In general terms, for right-handed people the left side of the brain is usually associated with analytical processes while the right side of the brain is associated with intuitive or artistic abilities. The data to support such generalizations is, however, not uniform.

The cortex is divided into several cortical areas, each responsible for separate functions such as planning of complex movements, memory, personality, elaboration of thoughts, word formation, language understanding, motor coordination, visual processing of words, spatial orientation, and body spatial coordination. The association areas

of the cortex receive and simultaneously analyze multiple sensations received from several regions of the brain. The brain is divided into two large lobes interconnected by a bundle of nerves, the corpus callosum. It is now known that in approximately 95% of all people, the area of the cortex in the left hemisphere can be up to 50% larger than in the right hemisphere, even at birth. Both Wernicke's and the Broca's areas (specific anatomical regions) are usually much more developed in the left hemisphere, which gave origin to the theory of left hemisphere dominance. The motor area for hand coordination is also dominant in nine of out 10 persons, accounting for the predominance of right-handedness among the population.

Studies also show that the non-dominant hemisphere plays an important role in musical understanding, composition and learning, perception of spatial relations, perception of visual and other esthetical patterns, understanding of connotations in verbal speeches, perception of voice intonation, identification of other's emotions and mood, and body language.

One hindrance to the acceptance of data relating to cerebral dominance is the fact that social pressure to conform to the norm can drive some left-handed people to adopt the predominant use of their right hand.

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Cerebral hematoma

Definition

Cerebral hematoma involves bleeding into the cerebrum, the largest section of the brain, resulting in an expanding mass of blood that damages surrounding neural tissue.

Description

A hematoma is a swelling of blood confined to an organ or tissue, caused by hemorrhaging from a break in one or more blood vessels. As a cerebral hematoma grows, it damages or kills the surrounding brain tissue by compressing it and restricting its blood supply, producing the symptoms of **stroke**. The hematoma eventually stops growing as the blood clots, the pressure cuts off its blood supply, or both.

Cerebral hematomas are categorized by their diameter and estimated volume as small, moderate, or massive. The neurologic effects produced by a cerebral hematoma are quite variable, and depend on its location, size, and duration (length of time until the body breaks down and absorbs the clot). Additional bleeding into the ventricles, which contain the cerebrospinal fluid (CSF), may occur. Blood in the CSF presents a risk for further neurologic damage.

Intracerebral hematoma (ICH) is another frequently used term for the condition. The initials "ICH" may also be seen in different places denoting several related conditions—an *intracerebral hematoma* is due to an *intracerebral hemorrhage*, which is one type of *intracranial hemorrhage*. However, the causes and symptoms of all three are roughly the same.

Demographics

The two basic types of stroke are hemorrhagic (including ICH) and ischemic (blockage in a blood vessel). Each year 700,000 people in the United States, or about 1 in 50 individuals, experience a new or recurrent stroke. Of these, about 12% are due to intracranial hemorrhage. Stroke kills an estimated 170,000 people each year in the United States, and is the leading cause of serious, long-term disability. Thirty-five percent of individuals suffering a hemorrhagic stroke die within 30 days, while the one-month mortality rate for ischemic stroke is 10%.

Stroke occurs somewhat more frequently in men than in women. Compared to whites, the incidence of first-occurrence strokes in most other ethnic groups in the United States is slightly higher, except African-Americans, whose rate is nearly twice as high. In adults, the risk of stroke increases with age. The highest risk for stroke in children is in the newborn period (especially in premature infants), with an incidence of 1 in 4000. The risk then decreases throughout childhood to a low of 1 in 40,000 in teen-agers. Twenty-five percent of strokes in children are due to intracranial hemorrhage.

Causes and symptoms

The most frequent causes of intracranial hemorrhage, including ICH, are:

- Hypertension-induced vascular damage
- Ruptured aneurysm or arteriovenous malformation (AVM)

Key Terms

Aneurysm A weakened area in the wall of a blood vessel which causes an outpouching or bulge. Aneurysms may be fatal if these weak areas burst, resulting in uncontrollable bleeding.

Cerebrum The largest section of the brain, which is responsible for such higher functions as speech, thought, vision, and memory.

Hematoma A localized collection of blood, often clotted, in body tissue or an organ, usually due to a break or tear in the wall of blood vessel.

Hemorrhage Severe, massive bleeding that is difficult to control. The bleeding may be internal or external.

Hypertension Abnormally high arterial blood pressure that if left untreated can lead to heart disease and stroke.

Ischemia A decrease in the blood supply to an area of the body caused by obstruction or constriction of blood vessels.

Stroke Interruption of blood flow to a part of the brain with consequent brain damage. A stroke may be caused by a blood clot or by hemorrhage due to a burst blood vessel. Also known as a cerebrovascular accident.

- Head trauma
- Diseases that result in a direct or indirect risk for uncontrolled bleeding
- Unintended result from the use of anticoagulant (anticlotting) or thrombolytic (clot dissolving) drugs for other conditions
- Complications from arterial amyloidosis (cholesterol plaques)
- Hemorrhage into brain tumors

Preventable factors that increase the risk for stroke include chronic hypertension, obesity, high cholesterol (atherosclerosis), sedentary lifestyle, and chronic use of tobacco and/or alcohol. These factors primarily increase the risk for ischemic stroke, but play a role in ICH as well.

As previously noted, a massive ICH can result in sudden loss of consciousness, progressing to coma and death within several hours. For small and moderate hemorrhages, the usual symptoms are sudden **headache** accompanied by nausea and vomiting, and these may remit, recur, and worsen over time. Other, more serious symptoms of stroke include weakness or paralysis on one side of the body (hemiparesis/hemiplegia), difficulty speaking (**aphasia**), and pronounced confusion with memory loss. **Seizures** are not a common symptom of ICH. Hydrocephalus—increased fluid pressure in the brain—may result if pressure from the hematoma or a clot obstructs normal circulation of the CSF. Again, the severity and type of symptoms depend greatly on the location and size of the hematoma.

Diagnosis

Symptoms may indicate the possibility of an ICH, but the diagnosis can only be made by visualizing the hematoma using either a computed tomography (**CT**) or **magnetic resonance imaging (MRI)** scan. In some cases, more sophisticated imaging methods such as functional-MRI, SPECT, or **PET** scans can be used to visualize damaged areas of the brain.

Treatment team

An ICH producing mild symptoms might prompt a direct or referred visit to a **neurologist**, while individuals with more serious symptoms are first seen by hospital emergency room staff. Once the diagnosis of ICH is made, other specialists consulted or involved could include a neurosurgeon, radiologist, neurologist, and intensive care unit (ICU) staff. Long-term care might involve a psychiatrist/psychologist, dietitian, occupational/physical/speech therapists, rehabilitation specialists, and health professionals from assisted-living facilities or home-care agencies.

Treatment

Initial treatments in patients who have lost consciousness involve stabilizing any affected systems such as respiration, fluid levels, blood pressure, and body temperature. In many cases, monitoring intracranial pressure (ICP) is critical, since elevated ICP poses a serious risk for coma and death. Management of elevated ICP can be attempted with medication or manipulation of blood oxygen levels, but surgery is sometimes required. The possibility of further hemorrhaging in the brain poses a serious risk, and requires follow-up imaging scans.

If an ICH is detected very early, a neurosurgeon may attempt to drill through the skull and insert a small tube to remove (aspirate) the blood. Once the blood has clotted, however, aspiration becomes more difficult or impossible. Surgery to remove a hematoma is usually not advised unless it threatens to become massive, is felt to be life-threatening, or is causing rapid neurologic deterioration.

Recovery and rehabilitation

Recovery and rehabilitation centers around regaining as much neurologic function as possible, along with developing adaptive and coping skills for those neurologic problems that might be permanent. Recovery from neurologic injury caused by hemorrhagic stroke is frequently long and difficult, but there are many sources of information and support available.

Rehabilitation is most often done on an outpatient basis, but more serious cases may require nursing assistance at home or institutional care. Those who lapse into a coma or persistent vegetative state will need 24-hour professional care, and may take days, months, or years to recover, or they may never recover.

Clinical trials

Research is under way to develop effective, safer medications and methods to both stop a hemorrhage while it is occurring, and dissolve clots within the brain once they have formed. Direct injection of a local-acting clotting agent into an expanding hematoma, or of a thrombolytic drug, such as recombinant tissue plasminogen activator (rt-PA), into the clot are two avenues of research.

Prognosis

The prognosis after an ICH varies anywhere from excellent to fatal, depending on the size and location of the hematoma. However, ICH is the most serious form of stroke, with the highest rates of mortality and long-term disability, and the fewest available treatments. Only a small proportion of patients with an ICH can be given a good or excellent prognosis.

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Brain Injury Association. 8201 Greensboro Drive, Suite 611, McLean, VA 22102. 800-444-6443; Fax: 703-761-0755. <http://www.biausa.org>.

Brain Trauma Foundation. 523 East 72nd Street, 8th Floor, New York , NY 10021. 212-772-0608; Fax: 212-772-0357. <http://www.braintrauma.org>.

National Institute on Disability and Rehabilitation Research (NIDRR). 600 Independence Ave., S.W., Washington, DC 20013-1492. 202-205-8134. <http://www.ed.gov/offices/OSERS/NIDRR>.

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National Stroke Association. 9707 East Easter Lane, Englewood, CO 80112-3747. 800-787-6537; Fax: 303-649-1328. <http://www.stroke.org>.

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Cerebral palsy

Definition

Cerebral palsy is a term used to describe a group of chronic conditions affecting body movements and muscle coordination. It is caused by damage to one or more specific areas of the brain, usually occurring during fetal development or during infancy.

Description

Cerebral palsy (CP) is an umbrella-like term used to describe a group of chronic disorders impairing movement control that appear in the first few years of life and generally do not worsen over time. The disorders are caused by faulty development or damage to motor areas in the brain that disrupt the brain's ability to control movement and posture. The causes of such cerebral insults include vascular, metabolic, infectious, toxic, traumatic, hypoxic (lack of oxygen) and genetic causes. The mechanism that originates cerebral palsy involves multi-factorial causes, but much is still unknown.

Cerebral palsy distorts messages from the brain to cause either increased muscle tension (hypertonus) or reduced muscle tension (hypotonus). Sometimes this tension will fluctuate, becoming more or less obvious.

Symptoms of CP include difficulty with fine motor tasks (such as writing or using scissors) and difficulty maintaining balance or walking. Symptoms differ from

Key Terms

Ataxic Muscles that are unable to perform coordinated movements due to damage to one or more parts of the brain.

Contracture Chronic shortening of muscle fibers resulting in stiffness and decrease in joint mobility.

Hypertonus Increased tension of a muscle or muscle spasm.

Hypotonus Decreased tension of a muscle, or abnormally low muscle tone.

Hypoxic Oxygen deficient.

Ischemic Having inadequate blood flow.

Orthotic device Devices made of plastic, leather, or metal which provide stability at the joints or passively stretch the muscles.

Spasticity Increased muscle tone, resulting in involuntary muscle movements, muscle tightness, and rigidity.

Teratogenic Able to cause birth defects.

person to person and may change over time. Some people with CP are also affected by other medical disorders, including **seizures** or mental impairment. Early signs of CP usually appear before three years of age. Infants with this disease are frequently slow to reach developmental milestones such as learning to roll over, sit, crawl, smile, or walk.

Causes of CP may be congenital (present at birth) or acquired after birth. Several of the causes that have been identified through research are preventable or treatable: head injury, jaundice, Rh incompatibility, and rubella (German measles). Cerebral palsy is diagnosed by testing motor skills and reflexes, examining the medical history, and employing a variety of specialized tests. Although its symptoms may change over time, this disorder by definition is not progressive. If a patient shows increased impairment, the physician considers an alternative diagnosis.

Demographics

Cerebral palsy is one of the most common causes of chronic childhood disability. About 3,000 babies are born with the disorder each year in the United States, and about 1,500 preschoolers are diagnosed with cerebral palsy during the first three years of life. In almost 70% of cases, CP is found with some other disorder, the most common being **mental retardation**. In all, around 500,000–700,000 Americans have some degree of cerebral palsy.

Dan Keplinger, author of the 1999 Oscar-winning documentary "King Gimp," sits in a wheelchair among his paintings on display at the Phillis Kind Gallery in New York. *(AP/Wide World Photos. Reproduced by permission.)*

The prevalence of CP has remained very stable for many years. The incidence increases with premature or very low-weight babies regardless of the quality of care. Twins are also four times more likely to develop CP than single births.

Despite medical advances, in some cases the incidence of CP has actually increased over time. This may be attributed to medical advances in areas related to premature babies or the increased usage of artificial fertilization techniques.

Causes and symptoms

CP is caused by damage to an infant's brain before, during or shortly after delivery. The part of the brain that is damaged determines what parts of the body are affected.

There are a number of factors which appear to predispose a child to CP including:

- Exposure of the expectant mother to certain infections like rubella, toxoplasmosis and cytomegalovirus,
- Exposure of the expectant mother to certain chemicals like alcohol, cigarettes, cocaine and teratogenic (capable of causing birth defects) agents,
- Severe physical trauma to the mother during pregnancy, multiple births or maternal illness,
- Children who are born prematurely (less than 32 weeks) or who are very low birth weight (less than 1,500 grams or about $3\frac{1}{3}$ pounds),
- Failure of the brain to develop properly or neurological damage to the infant's developing brain, including **hypoxia** (lack of oxygen) during birth,
- Bacterial meningitis and other infections, bleeding in the brain, lack of oxygen, severe jaundice, and head injury during the first few years of a child's life.

Cerebral palsy is categorized into four different groups that are characterized by different symptoms. Generally, babies that are severely affected may have obvious signs immediately following birth. Many infants do not display immediate CP symptoms. Parents are usually able to notice developmental delays, especially if they have another unaffected child. At the age of about three months, parents may notice a lack of facial expressions or that their baby does not respond to some sounds, or does not follow movement with their eyes. Certain other indicative symptoms may appear at around six months of age, including inability to lift the head or roll over and difficulty feeding. An affected child may be unable to crawl, sit, or stand without support and drooling is a common problem because of poor facial and throat muscle control. CP symptoms depend on the individual and the type of CP and, in particular, whether or not there is a mixed form of the condition.

The four main categories of cerebral palsy are:

- Spastic CP: Children with spastic CP have increased muscle tone. Their muscles are stiff and their movements can be awkward. Seventy to eighty percent of people with this disease have **spasticity**. Spastic CP is usually described further by what parts of the body are affected. In spastic diplegia, the main effect is found in both legs. In spastic hemiplegia, one side of the person's body is affected. Spastic quadriplegia affects a person's whole body (face, trunk, legs, and arms).
- Athetoid or dyskinetic CP: Children with athetoid CP have slow, writhing movements that they cannot control. The movements usually affect a person's hands, arms, feet, and legs. Sometimes the face and tongue are affected and the person has a hard time talking. Muscle tone can change from day to day and can vary even during a single day. Ten to twenty percent of people with CP have the athetoid form of the condition.
- Ataxic CP: Children with ataxic CP have problems with balance and depth perception. They might be unsteady when they walk. They might have a hard time with quick movements or movements that need a lot of control, like writing. Controlling their hands or arms when they reach for something is often difficult. People with ataxic CP can have increased or decreased muscle tone.
- Mixed CP: Some people have more than one type of CP, but this is most often a mixture of spasticity and athetoid movements, with tight muscle tone and involuntary reflexes.

Diagnosis

Diagnosing CP in an infant is often a difficult and slow process that takes time to establish with certainty, as there other health problems that can mimic the condition. The physician may suspect that the infant has CP because of a history of difficulties at birth, seizures, feeding problems or low muscle tone. Detailed medical and developmental history, including the history of the pregnancy and delivery, medications taken by the mother during fetal development, infections and fetal movement are all considered. A detailed family history, including the mother's history of miscarriage, relatives with similar conditions, ethnic background, and consanguinity (marriage between close blood relatives) can also prove helpful. The child's physician will perform a thorough physical examination and may order vision and hearing testing.

Infants suffering from brain injury are often slow to reach developmental milestones including rolling over, sitting up, crawling, walking and talking. Healthcare professionals are often hesitant to reach an early diagnosis because the child may recover and they may use other, less emotive terms in labeling the condition such as: neuromotor dysfunction, developmental delay, motor disability, static **encephalopathy** and **central nervous system** dysfunction.

Physicians must test the child's motor skills, using many of the techniques outlined above and looking for evidence of slow development, abnormal muscle tone, and unusual posture. Healthcare professionals will move slowly and carefully towards a positive diagnosis only after eliminating all other possible causes of the child's condition.

Neuroimaging studies can help to evaluate brain damage and to determine those at risk of developing CP. No study exists to support definitive diagnosis of CP. Computed tomography (**CT**) **scans** provide information to help diagnose congenital malformations and intracranial hemorrhages in the infant. **Magnetic resonance imaging**

(**MRI**) is most useful after two to three weeks of life, and is also used to detect brain disease in an older child.

Ultrasound in the neonate (newborn) provides information about the structures of the brain as well as diagnostic information on possible hemorrhage or hypoxic-ischemic (lack of oxygen) injury.

Evoked potentials are used to evaluate the anatomic pathways of the nerves responsible for hearing and vision. Electroencephalogram (EEG) is useful in evaluating severe hypoxic-ischemic injury.

Treatment team

A **neurologist** may help to differentiate cerebral palsy from other neurological disorders. Consultation with a neurologist also may be helpful in treatment of patients with seizures. Pulmonologists (lung specialists) may help treat the patient with bronchopulmonary dysplasia or frequent aspiration pneumonia. Orthopedic surgery consultation may be needed to help correct any structural deformities. An ophthalmologist may be indicated to follow up with any patient experiencing visual deficits. Audiologists help screen for hearing deficits. A gastroenterologist (specialist on digestive disorders) may help with reflux and constipation and may be helpful in coordinating feedings to regulate weight gain or weight loss if needed. A periodic nutrition consultation is important to make sure the child does not suffer from growth failure or nutritional deficiencies.

Treatment

Drug therapy is used for those who have seizures associated with CP. Anticonvulsant medications are usually very effective in preventing seizures associated with CP. Drugs are also used to control spasticity in some cases. Medications used most often are **diazepam**, a general relaxant of the brain and body, baclofen, which blocks signals sent from the spinal cord to contract the muscles, and datrolene, which interferes with the process of muscle contraction. These drugs are used for short periods, but long-term control of spasticity is more difficult to achieve.

Persons with athetoid CP are sometimes given drugs to help reduce abnormal movements, usually **anticholinergics**. Anticholinergics reduce the activity of acetylcholine, a chemical messenger that helps some brain cells communicate and trigger muscle contraction. Physicians may inject drugs directly into a muscle to reduce spasticity for a short period.

Surgery is used when muscle contractures are severe enough to create problems in movement. The surgeons lengthen the muscle that is too short. Lengthening a muscle usually makes it weaker, so surgery for contractures is usually followed by an extended recovery and therapy period. To reduce spasticity in the legs, surgery called selective dorsal root rhizotomy sometimes proves effective. It reduces the amount of stimulation that reaches leg muscles by the nerves.

Recovery and rehabilitation

Cerebral palsy cannot be cured. Treatment can, however, help a person take part in family, school, and work activities as much as possible. There are many treatments, including physical therapy, occupational therapy, medicine, operations, and orthotic devices that help maintain the highest possible state of wellness and activity.

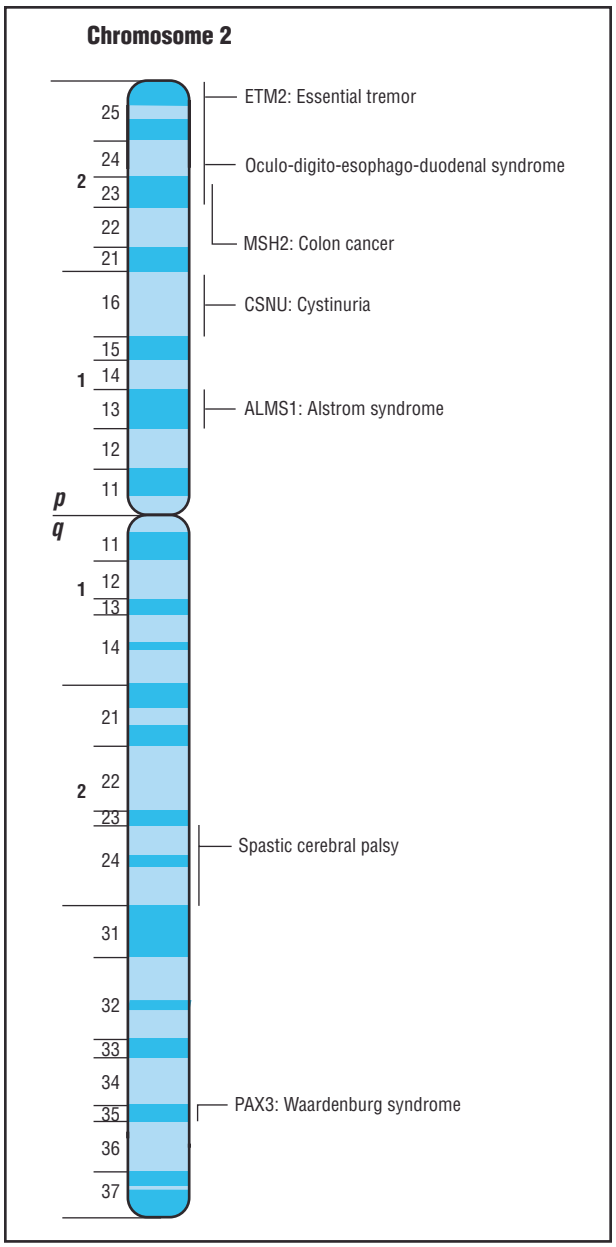
Specialized Therapies

Physical therapy improves infant-caregiver interaction, gives family support, and supplies resources for parental education, as well as promoting motor and developmental skills. Physical therapists teach the parent or caregiver exercises or activities necessary to help the child reach his or her full potential.

Daily range of motion (ROM) exercises are important to prevent or delay contractures (fixed, rigid muscles) secondary to spasticity, and to maintain mobility of joints and soft tissues. Stretching exercises are performed to increase motion. Progressive resistance exercises also increase strength. Age-appropriate play and adaptive toys and games using the desired exercises are important to elicit the child's full cooperation. Strengthening knee extensor muscles helps to improve crouching and stride length. Postural and motor control training is important following the normal developmental sequence of children (i.e., achieve head and neck control if possible before advancing to trunk control).

Occupational therapists keep the child's developmental age in mind and use adaptive equipment as needed to help attain these milestones. For example, if a child is developmentally ready to stand and explore the environment, but is limited by lack of motor control, a stander or modified walker is used. Performance based upon previous success is encouraged to maintain the child's interest and cooperation. Assistive devices and durable medical equipment help attain function that may not be possible otherwise. Orthotic devives frequently are required to maintain functional joint position especially in persons who are non-ambulatory. Frequent reevaluation of orthotic devices is important as children quickly outgrow them and can develop skin irritation from improper use of orthotic devices.

Recreational therapy, especially hippotherapy (horseback riding therapy) is frequently a well-liked activity of parents and patients alike to help with muscle tone, range



Cerebral palsy, on chromosome 2. *(Gale Group.)*

of motion, strength, coordination, and balance. Hippotherapy also offers many potential cognitive, physical, and emotional benefits. Incorporation of play into all of a child's therapies is important. The child should view physical and occupational therapy as fun, not work. Caregivers should seek fun and creative ways to stimulate children, especially those who have decreased ability to explore their own environments.

Many children with dyskinetic CP have involvement of the face and oropharynx causing difficulty swallowing properly, drooling, and speech difficulties. Speech therapy can be implemented to help improve swallowing and communication. Those patients with athetoid CP may benefit the most from speech therapy, as most have normal intelligence and communication is an obstacle secondary to abnormal muscle movements that affect their speech. Adequate communication is probably the most important goal for enhancing function in the athetoid CP patient.

Clinical trials

As of mid-2004, there were numerous open **clinical trials** for the study and treatment of cerebral palsy, including:

- "Botulinum Toxin (BOTOX) for CP," "Relaxation Training to Decrease **Pain** and Improve Function in Adolescents with CP," and "Constraint-based Therapy to Improve Motor Function in Children with CP," sponsored by the National Institute of Child Health and Human Development (NICHD),
- "Classification of CP Subtypes," "Eye-Hand Coordination in Children with Spastic Diplegia," "Beneficial Effects of Antenatal Magnesium Sulfate (BEAM Trial)," and "Brain Control of Movements in CP," sponsored by National Institute of Neurological Disorders and Stroke (NINDS),
- Study of Tongue Pressures, sponsored by Warren G. Magnuson Clinical Center.

Updated information about these clinical trials can be found at the National Institutes of Health website for clinical trials at www.clinicaltrials.gov.

Prognosis

The prognosis of persons with CP varies according to the severity of the disorder. Some children have only mild problems in muscle tone and no problems with daily activities, while others are unable to purposefully move any part of the body. Regression, or worsening of long-term symptoms, is not characteristic of CP. If regression occurs, it is necessary to look for a different cause of the child's problems. In order for a child to be able to walk, a major cascade of events in motor control have to occur. A child must be able to hold up his head before he can sit up on his own, and he must be able to sit independently before he can walk on his own. It is generally assumed that if a child is not sitting up by himself by age four or walking by age eight, he will never be an independent walker. But a child who starts to walk at age three will certainly continue to walk unless he has a disorder other than CP.

In people with severe CP, motor problems often lead to medical complications, including more frequent and serious infections, severe breathing problems, feeding intolerance, and skin breakdown. These medical complications

can lead to frequent hospitalizations and a shortened life expectancy.

Epilepsy also occurs in about a third of children with CP and is more frequent in patients with spastic quadriplegia or mental retardation. Cognitive impairment occurs more frequently in CP than in the general population, and mental delays or some form of learning disability has been estimated to occur in over two thirds of CP cases.

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ORGANIZATIONS

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605. (914) 428-7100 or (888) 663-4637; Fax: (914) 428-8203. askus@marchofdimes.com. <http://www.marchofdimes.com>.

United Cerebral Palsy (UCP). 1600 L Street, NW, Suite 700, Washington, DC 20036. (202) 776-0406 or (800) USA-5UCP (872-5827); Fax: (202) 776-0414. national@ucp.org. <http://www.ucp.org>.

Francisco de Paula Careta
Iuri Drumond Louro

Cerebrovascular accident (CVA) *see* **Stroke**

Cervical disc herniation *see* **Disc herniation**

Cervical radiculopathy *see* **Radiculopathy**

Channelopathies

Definition

Channelopathies are inherited diseases caused by defects in cell proteins called ion channels.

Channelopathies include a wide range of neurologic diseases, including **periodic paralysis**, congenital myasthenic syndromes, malignant hypothermia, a form of Charcot-Marie-Tooth disease, and several other disorders. Cystic fibrosis and long Q-T syndrome, which are not neurological diseases, are also types of channelopathy.

Description

Cells of the body, including nerve and muscle cells, are surrounded by thin coverings called membranes. Embedded in these membranes are a large and varied set of proteins that control the movement of materials across the membrane, in and out of the cell. One major type of material that crosses through such proteins are called ions, and the proteins that transport them are called ion channels.

Ions perform many different functions in cells. In neurons (nerve cells), they help transmit the electrical messages that allow neurons to communicate with each other, and with muscle cells. In muscle cells, they allow the muscle to contract. When the ion channels are defective, these activities may be disrupted.

Inheritance

The proteins responsible for channelopathies are made by genes, and defects in genes are the cause for the diseases. Genes are inherited from both parents. If two defective copies of a gene are needed in order for a person to develop the disease, this is known as a recessive inheritance pattern. Two parents, each of whom carry one defective copy, have a 25% chance with each pregnancy of having a child with the disease.

If only one defective copy of the gene is needed in order to develop the disease, this is known as a dominant inheritance pattern. A single parent who carries the disease gene (and likely has the disease as well) has a 50% chance with each pregnancy of having a child with the disease.

Types of Channelopathies

Periodic paralysis

A person with periodic paralysis experiences sudden onset of weakness, which gradually subsides, only to return again later. Two forms of periodic paralysis exist, termed "hyperkalemic," referring to the excessively high levels of potassium in the blood which can trigger attacks,

and "hypokalemic," in which excessively low levels of potassium are the culprit. Each is caused by different genetic mutations of a potassium ion channel, and both exhibit the dominant inheritance pattern. Onset is usually in childhood for the hyperkalemic form, and childhood to adulthood for the hypokalemic form. Dietary restrictions can reduce the frequency of attacks of both forms, with a high-carbohydrate, low-potassium diet for the hyperkalemic form, and a low-carbohydrate, high-potassium diet for the hypokalemic form.

Congenital myasthenic syndromes

Congenital myasthenic syndromes are a group of related disorders caused by inherited defects in the acetylcholine receptor. This protein sits on the surface of muscle cells; when a nearby neuron releases the chemical acetylcholine, it binds to the receptor, causing the muscle to contract. Defects cause myasthenia ("muscle weakness") and **fatigue**, and may be life-threatening in some individuals. Most forms display the recessive inheritance pattern. Onset is in infancy. Treatment usually includes the drug mestinon, which blocks the breakdown of the acetylcholine after it is released, prolonging its action, and another drug, called 3,4-DAP, which increases the amount of acetylcholine released.

Malignant hyperthermia

Malignant hyperthermia is caused by mutations in the gene for a membrane protein inside the muscle cell, called the ryanodine receptor, which controls calcium ion movement within the muscle. Another form is due to mutation in a different muscle protein controlling calcium. Malignant hyperthermia is usually triggered by exposure to certain kinds of anesthetics or muscle relaxants. It causes a dangerous increase in the rate of activity within the muscle, and a sharp rise in temperature, leading to a cascade of crises which may include severe damage to muscle cells, heart malfunction, swelling of tissues including the brain, and death. It is treated with dantrolene, an antispasticity medication that blocks calcium ion movement in the muscle. Awareness of the condition has led to better screening for it among anesthesia patients and a significant reduction in mortality.

X-linked Charcot-Marie-Tooth disease

X-linked Charcot-Marie-Tooth disease (CMTX) is caused by a defect in connexin 32. This protein forms connections between adjacent cells, allowing ions to flow between them. The cells affected are those that surround neurons and provide their electrical insulation. Outside the brain and spinal cord (together called the **central nervous system**, or CNS), this job is performed by Schwann cells. Inside the CNS, the insulating cells are called oligodendrocytes. Like other forms of CMT, CMTX causes slowly progressing muscle weakness in the distal muscles (those furthest away from the body center), including the hands and feet. There may also be decreased sensation in the extremities. CMTX is inherited on the X chromosome, of which males have one and females have two. For this reason, CMTX usually affects males more severely than females because they have only one X chromosome, and therefore lack a second normal copy of the gene.

Resources

WEBSITES

Muscular Dystrophy Association. <www.mdausa.org>.

Charcot-Marie-Tooth Association. <www.cmta.org>.

Richard Robinson

Charcot-Marie-Tooth disorder

Definition

The name Charcot-Marie-Tooth disorder (CMT) refers to a group of hereditary diseases, all involving chronic motor and sensory neuropathies. Drs. Charcot and Marie of France, and Dr. Tooth of England first described the disorder in 1886 when they found patients with progressive muscle weakness and muscle loss in their feet and lower legs. Over time, this weakness progressed to their hands and forearms. More is now known about the numerous disease subtypes, including their complex genetics and inheritance patterns.

Description

Charcot-Marie-Tooth disorder is also known by the names hereditary motor and sensory neuropathy, and peroneal muscular atrophy. A person with CMT often has distal muscle weakness and atrophy that involves the feet, legs, and hands. Many people with CMT are diagnosed later in life as adults. However, diagnosis can happen as early as the first to third decade of life when there is a family history of CMT. The muscle weakness may begin painlessly, symmetrically, and slowly. Many CMT subtypes seem similar and may only be identified through further neurological or genetic testing.

Learning problems are not commonly associated with CMT, but psychological issues from living with progressive muscle weakness can occur. Only some rare X-linked forms of CMT involve **mental retardation** or deafness as

Key Terms

Atrophy Wasting or loss of tissue.

Biopsy Process of removal of tissue for study.

Chronic Ongoing and long-term.

Distal Situated away from the center of the body, like the legs and hands.

Duplication Extra genetic material due to a duplicate copy.

Electromyography Testing that shows the electrical activity associated with muscle movements and actions.

Gait The way in which one walks.

Motor Having to do with movement.

Mutation A change in the order of deoxyribonucleic acid (DNA) bases that make up genes.

Nerve conduction study Testing that shows electrical impulse activity along nerves.

Neuropathy Term for any disorder affecting the nervous system or cranial nerves.

Peroneal Related to the legs.

Pes cavus A highly arched foot.

Scoliosis Curving of the spine bones.

Sensory Related to the senses, or the ability to feel.

occasional symptoms, but these are not typical of classical CMT.

Demographics

CMT is the most common genetic cause of neuropathy. It is estimated to affect between one in 2,500 to one in 5,000 people, with most of them having CMT type 1 (CMT1). About 20% of people who come to neuromuscular clinics with a chronic **peripheral neuropathy** have some form of CMT. The condition affects people of all ethnic groups worldwide. Most forms affect males and females equally, with the exception of the X-linked form, which usually affects males more severely than females.

As of 2004, numerous genes have been found responsible for various subtypes of CMT. Genetic testing is available for some types. For other types, genetic testing is not yet available.

Causes and symptoms

Mutations in several genes cause the various types of CMT to occur. The most common form of the disorder, CMT1A, is caused by duplication in the peripheral myelin protein 22 (PMP22) gene. In these cases, the PMP22 gene is too active from the extra genetic material, so it makes too much myelin protein. The correct amount of myelin protein is important for normal muscle strength and movement, so the extra amount can cause these problems.

CMT is inherited in many ways, as seen by varying family histories of the condition. CMT1 and CMT2 are typically inherited in an autosomal dominant manner. This means that an affected individual has a 50/50 chance of passing a disease-causing mutation to his or her children, regardless of gender. In these cases, a strong family history of the condition may be seen.

CMT4 and some forms of CMT2 are inherited in an autosomal recessive manner. This means that an affected individual has parents who each carry the CMT gene. These parents run the risk of having a child with CMT with every pregnancy.

CMT is also inherited in an X-linked manner, and the most common type is called CMTX. Women may be carriers of this type. They are usually more at risk to have affected sons. Daughters may be carriers and they may or may not show milder symptoms.

The neurological symptoms in CMT can progress slowly, but may become problematic over time. Muscle weakness is usually found first in the foot and lower leg muscles. It can eventually include the upper leg and hips in severely affected people. Since the middle of the legs are usually stronger, most people with CMT can still usually walk with the aid of ankle splints.

Some early signs of CMT may be gait abnormalities, or clumsiness in running. Many people with CMT develop *pes cavus* with very high arches in their feet, and this can be associated with curled-up toes. Loss of nerve functioning can lead to the inability to notice very hot and cold sensations, or the sensation of touch.

Upper limb muscles may become weaker, and this includes the hands and forearms. Due to this, people may have difficulty with fine motor tasks like writing. People with more advanced CMT may develop bone changes, like scoliosis. This may cause **back pain** if it is very severe.

A specific sign of CMT1A is the "onion bulb" formation in muscular nerves. Nerves with repeated myelination and demyelination (due to abnormalities in the

PMP22 gene) may eventually take on the shape of an onion bulb, which is how the finding was named.

Diagnosis

Until the discovery of the CMT genes, the diagnosis of the condition was made on a clinical basis. The difficulties lie in the similarities with other neuropathies like hereditary neuropathy with liability to pressure palsies (HNPP) and those associated with disorders like alcoholism, drug dependence, and diabetes.

An important first step to diagnosing CMT is taking a careful family history. A positive family history is an indicator that the neuropathy may be hereditary. Additionally, the pattern of affected individuals can give clues about the inheritance type in the family.

Carefully documenting the timing of symptoms is also important. Only a minority of people with CMT seek a medical opinion in childhood, since most are diagnosed later in life. An exception might be the highly informed family in which there is a strong history of the condition.

Skeletal signs like *pes cavus* and scoliosis occur in hereditary neuropathies, but tend to show up when the symptoms begin early. They may be absent when the onset is later in life, even in CMT. This may be an important clue when attempting to diagnose CMT. CMT may also include symptoms like mental retardation and hearing loss, as seen in some rarer X-linked forms.

A slow progression of symptoms is typical of CMT. Some hereditary neuropathies, like HNPP, may have periods of severe symptoms that get better and then worsen later. Again, careful documentation of symptoms is important to diagnose CMT.

Some signs of CMT are found through electrophysiological studies, like **electromyography** (EMG) and nerve conduction velocity (NCV) testing. EMG results are usually abnormal, and NCV studies may show slowed nerve conduction, a sign of muscle weakness. Those with CMT type 1 usually show severe slowing in NCV studies, and type 2 is associated with mild or no slowing.

EMG and NCV studies are very important tools for physicians to use when thinking of a hereditary neuropathy. These are often abnormal, with reduced NCV values. A nerve **biopsy** is rarely necessary to pinpoint a specific type of CMT, because onion-bulb abnormalities are a sign of CMT1A.

It may still be difficult to diagnose CMT with electrophysiological test results and clinical information. The results from testing may help to determine which genetic testing to pursue. Genetic testing is useful for confirming a clinical diagnosis or for family testing when there is an identified CMT gene mutation in the family. As of 2004, genetic testing for CMT type 1 is more available than testing for CMT type 2.

Genetic testing is not perfect and results can be tricky to interpret. An informative test result is one that identifies a known mutation in a CMT gene, and this confirms that the person has CMT. A negative test result means a mutation was not found in the gene. This either means that the tested individual does not have CMT, or has a mutation that cannot be found through testing. It may also mean the individual has a different type of CMT or another disorder altogether. Medical geneticists and genetic counselors can be very helpful in interpreting complex genetic test results.

Treatment team

Treatment for people with CMT is often dependent upon symptoms. A multi-disciplinary team and approach can be helpful. A treatment team may include a **neurologist**, medical geneticist, genetic counselor, orthopedic surgeon, otolaryngologist, physical therapist, occupational therapist, social worker, physiatrist, **neuropsychologist**, and a primary care provider. Oftentimes there are pediatric specialists in these fields who aid in the care for children. The key is good communication between the various specialists to coordinate medical care.

Treatment

There is no cure for Charcot-Marie-Tooth disorder. No specific treatment is known to reverse, slow, or stop the progressive nature of the disease.

In order to keep flexibility and muscle length in the ankles and feet, daily stretching of the heel cords can be helpful. Special shoes with ankle and orthopedic inserts may help to improve walking and movement. Corrective surgery by an orthopedic surgeon is required in some cases. Others need forearm crutches or canes to keep stable while walking, but fewer than 5% of people with CMT need wheelchair assistance. Splints, specific exercises, orthopedic devices, and sometimes surgery are needed to keep hands functioning well.

Certain medications can be helpful for people with CMT, while others should be avoided because they can cause nerve damage. Examples of drugs to be avoided include alcohol, high doses of vitamins A and D, penicillin, taxol, and certain chemotherapy medications (vincristine, cisplatin).

For overall health, a good diet and regular **exercise** are recommended. Exercise is particularly important because it keeps muscles functioning and maintains endurance levels.

Recovery and rehabilitation

Rehabilitation can be ongoing in CMT, particularly if the muscle weakness has progressed considerably. Since the disorder does not typically get better with time, physical therapy and strength maintenance is very important. The disease's early stages may not cause problems for walking or daily activities, but over time it can greatly impact a person's life. Physical therapy may be relatively infrequent early on, but may increase as time goes on.

Children may have difficulty with tasks in school, such as writing and other fine motor skills. Occupational therapists, often available at school, are helpful in these situations. Overall, a person's time spent in recovery and rehabilitation is variable. Specialists in physical medicine and rehabilitation can be helpful in coordinating a plan to help someone retain his or her strength for as long as possible.

Prognosis

Prognosis for someone with Charcot-Marie-Tooth disorder is unique to the person. The severity of the symptoms can vary greatly, even within the same family. Those who develop the disease as children may have more severe muscle weakness by the time others first see signs of the disease. However, only about 5% of people with CMT need wheelchairs at any point in their lives. CMT is not considered a fatal disease. Symptoms are chronic and progressive, and can negatively impact a person's life.

Genetic testing now helps identify people before they even develop symptoms, so personalized medical care can begin as early as possible. This has helped to reduce the risk of complications and increase the quality of life for many. Medical screening may be further tailored to the individual as scientific studies identify medical complications associated with specific CMT mutations in families.

Special concerns

Due to specific muscular weakness and difficulty with fine motor tasks, careful career and job consideration is helpful for people with CMT.

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Online Mendelian Inheritance in Man. (March 30, 2004). <http://www.ncbi.nlm.nih.gov/omim/>.

ORGANIZATIONS

Charcot-Marie-Tooth Association. 2700 Chestnut Street, Chester, PA 19013-4867. (800) 606-CMTA; Fax: (610) 499-9267. CMTAssoc@aol.com. <www.charcot-marie-tooth.org>.

CMT World. P.O. Box 601, Hillsburgh, Ontario N0B 1Z0, Canada. (519) 855-6376; Fax: (519) 855-6746. info@cmtworld.org. <www.cmtworld.org/index.php>.

Muscular Dystrophy Campaign U.K. 7-11 Prescott Place, London SW4 6BS, U.K. +44 (0)171-720-8055; Fax: +44 (0)171-498-0670. info@muscular-dystrophy.org. <www.muscular-dystrophy.org>.

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Chiari malformation *see* **Arnold-Chiari malformation**

Cholinergic stimulants

Definition

Cholinergic stimulants are a class of drugs that produce the same effects as those of the body's parasympathetic nervous system. Cholinergic drugs are used for a variety of purposes, including the treatment of **myasthenia gravis** and during anesthesia.

Purpose

The parasymapthetic nervous system is responsible for conserving and restoring energy in the body by regulating day-to-day functions such as digestion, sphincter muscle relaxation, salivation, and reducing heart rate and blood pressure. Nerve impulses in the parasympathetic nervous system are transmitted from one nerve junction to another with the help of acetylcholine, the most common neurotransmitter in the parasympathetic nervous system. Cholinergic drugs are drugs that affect the levels of acetylcholine at the nerve junction.

Cholinergic stimulants result in increased acetylcholine accumulation at the neuromuscular junction and prolong its effect. Cholinergic stimulant drugs are used in the diagnosis and treatment of myasthenia gravis, a disorder of nerve impulse transmission at the neuromuscular junction, resulting in severe muscle weakness. Cholinergic stimulants are also used in surgery to reduce urinary retention and to counteract the effects of some muscle relaxant medications given during anesthesia.

Description

Cholinergic stimulant drugs include edrophonium chloride, (brand name, Tensilon), neostigmine (Prostigmine), piridogstimina (Mestinon), and ambenonium chloride (Mytelase). Cholinergic stimulants are available in tablet, syrup, time-release tablet, and injectable forms.

Recommended dosage

Cholinergic stimulants are given in varying dosages according to the reason for use. In the treatment of myasthenia gravis, cholinergic stimulant dosages are tailored to the individual person. Patients are encouraged to keep a diary and record their response to each dose during the initial treatment period, as well as during periods of increased muscle weakness, stress, and other illness, as these conditions frequently require adjustments in dosage.

Precautions

Cholinergic stimulant drugs may not be suitable for persons with asthma, heart block or slow heart rate, **epilepsy**, hyperactive thyroid gland, bladder obstruction, gastrointestinal tract obstruction, or stomach ulcer. Patients should notify their physicians if they have any of these conditions before taking these drugs.

Side effects

The adverse effects of cholinergic stimulants include mostly rash and digestive system complaints, including queasiness, loose stools, nausea, vomiting, abdominal cramps, muscle **pain**, increased salivation, increase in stomach acid production, and diarrhea. Rare and potentially more serious side effects include reduced heart rate, possibly leading to cardiac arrest, and weak, shallow breathing.

Key Terms

Acetylcholine The neurotransmitter, or chemical, that works in the brain to transmit nerve signals involved in regulating muscles, memory, mood, and sleep.

Myasthenia gravis A chronic autoimmune disease characterized by fatigue and muscular weakness, especially in the face and neck, that results from a breakdown in the normal communication between nerves and muscles caused by the deficiency of acetylcholine at the neuromuscular junction.

Neuromuscular junction The junction between a nerve fiber and the muscle it supplies.

Neurotransmitter Chemical that allows the movement of information from one neuron across the gap between the adjacent neuron.

Parasympathetic nervous system A branch of the autonomic nervous system that tends to induce secretion, increase the tone and contraction of smooth muscle, and cause dilation of blood vessels.

Interactions

Certain antibiotics, especially neomycin, streptomycin, and kanamycin, can exacerbate the effects of some cholinergic stimulants. These antibiotics should be used with caution by people with myasthenia gravis.

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ORGANIZATIONS

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Adrienne Wilmoth Lerner

Cholinesterase inhibitors

Definition

Cholinesterase inhibitors are a group of drugs prescribed to treat symptoms resulting from the early and middle stages of **Alzheimer disease**.

Key Terms

Acetylcholine The neurotransmitter, or chemical that works in the brain to transmit nerve signals, involved in regulating muscles, memory, mood, and sleep.

Alzheimer disease A neurological disorder characterized by slow, progressive memory loss due to a gradual loss of brain cells.

Neurotransmitter Chemicals that allow the movement of information from one neuron across the gap between the adjacent neuron.

Purpose

Cholinesterase inhibitors are drugs that block the activity of an enzyme in the brain called cholinesterase. Cholinesterase breaks apart the neurotransmitter acetylcholine, which is vital for the transmission of nerve impulses. Cholinesterase inhibitors are used to reduce the action of cholinesterase, thereby making more acetylcholine available to nerve cells in the brain.

For normal nerve-to-nerve communication to occur, the excess acetylcholine must be dissolved following the transmission of a nerve impulse. This is the normal function of cholinesterase. This enzyme dissolves acetylcholine into its component molecules; acetate and choline. These building blocks can then be recycled to form more acetylcholine for the next round of nerve signal transmission.

In disorders such as Alzheimer disease, Lewy body disease, and vascular **dementia**, the production of acetylcholine is decreased. As a result, nerve communication is less efficient, with consequent problems of memory and other brain and body functions. The use of cholinesterase inhibitors impedes the normal enzymatic breakdown of the little acetylcholine that is present. Although improved nerve function results with the use of cholinesterase inhibitors, the damage to brain cells caused in Alzheimer disease cannot be halted or reversed.

Description

As of mid-2004, there are four types of cholinesterase inhibitors that are available. These include donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Reminy®), and tacrine (Cognex®). Tacrine is not available for use in Canada.

Donepezil was approved for use in the United States by the U.S. Food and Drug Administration (USFDA) in 1996. It is marketed by Pfizer as Aricept®. Rivastigmine received USFDA approval in 2000 and is sold by Novartis Pharmaceuticals as Exelon®. Galatamine received its USFDA approval in 2001 and is marketed in the U.S. as Reminyl® by Jassen Pharmaceuticals and Ortho-McNeil. Pointing out the importance of the natural world in providing therapeutic compounds, galatamine is extracted from the bulbs of daffodils. Finally, the drug tacrine is the oldest of the cholinesterase inhibitors, having received USFDA approval in 1993. Its use has declined due to incidents of serious side effects that include reversible liver damage.

Cholinesterase inhibitors are typically used to treat the early and middle stage symptoms of diseases such as Alzheimer's. This is because the deterioration in the production of acetylcholine accelerates over time, as more and more brain cells become damaged. Thus, the best chance to achieve a benefit for a person lies at the beginning of the disease path.

The benefits of cholinesterase inhibitors are judged by three patterns of the symptoms. In the early stages of Alzheimer disease, cholinesterase inhibitors may improve a person's condition, resulting in improvement of symptoms. As the disease progresses, cholinesterase inhibitors may act to stabilize the symptoms. Finally, the symptoms continue to worsen, but at a rate that is slower than would occur if the drug(s) were not taken.

One symptom that benefits from the use of cholinesterase inhibitors is called cognition. Cognition encompasses memory, language, and orientation (knowing the date, time, and a proper sense of direction). By improving, or at least retarding the rate of loss of cognition, the drugs can improve a person's quality of life. The benefits bestowed by cholinesterase inhibitors last only as long as effective levels of the drugs are present. Discontinuing the drug leads the return of symptoms within weeks.

Studies that have charted the time course of cognitive changes after taking the various cholinesterase inhibitors have demonstrated that improvements tend to peak about

three months after the particular drug is first taken. After that time, a person's mental condition slowly begins to decline back to their starting point over the next six to nine months. If the drug continues to be taken, the cognitive decline becomes slower than in people who do not take the medication.

Recommended dosage

The recommended dosage of cholinesterase inhibitors varies with the approving agency in a particular country. But, dosages tend not to vary appreciably. The maximum daily dose of donepezil is normally 5–10 milligram (mg). This dose is taken just once a day, either in the morning or in the evening. The maximum daily dose of rivastimine is 6–12 mg. The drug is taken twice a day with meals (typically breakfast and dinner). The maximum daily dose of galantamine is 16–24 mg, and it is also taken twice a day with meals.

Precautions

As with any prescription drug, the recommended daily dosage and schedule for the drugs should not be changed independent of a physician's notification. Neither should someone stop taking cholinesterase inhibitors without seeking advice from a physician.

Side effects

Cholinesterase inhibitors can cause side effects. These are usually relatively minor, and constitute problems in digesting food, loss of appetite, nausea, vomiting, abdominal **pain**, and diarrhea. Not everyone will experience each discomfort, and the severity of the side effects can vary from person to person, depending on their tolerance to the discomfort. The drugs can vary in the severity of side effects caused. For example, rivastigmine produces greater weight loss and degree of nausea that the other drugs.

Less commonly, cholinesterase inhibitors can slow the heartbeat, cause **dizziness**, **fainting**, insomnia, **fatigue**, and produce muscle cramps in the legs. In general, the side effects tend to be mild and lessen after a drug has been taken for a few weeks. A notable exception is tacrine, which can cause liver damage. Periodic blood testing in order to monitor enzymes that relate to liver function is usually part of therapy with tacrine.

Interactions

Some cholinesterase inhibitors should be used with caution in persons with asthma or lung disease, as cholinesterase inhibitors may interact with theophylline, a drug commonly used to treat both conditions.

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Alzheimer's Association. 225 N. Michigan Avenue, Chicago, IL 60601. (312) 335-8700 or (800) 272-3900; Fax: (312) 335-1110. info@alz.org. <http://www.alz.org>.

Brian Douglas Hoyle, PhD

Chorea

Definition

Chorea refers to brief, repetitive, jerky, or dancelike uncontrolled movements caused by muscle contractions that occur as symptoms of several different disorders. The English word "chorea" itself comes from the Greek word *choreia*, which means "dance." The symptom takes its name from the rapid involuntary jerking or twitching movements of the patient's face, limbs, and upper body.

Description

A patient with chorea may appear restless, fidgety, or unable to sit still. The body movements are continually changing and may appear to move from one part of the

Key Terms

Athetosis A symptom of movement disorders that consists of slow, writhing, wavelike movements, usually in the hands or feet. It is also known as mobile spasm. It may occur together with chorea; the combined symptom is called choreoathetosis.

Ballismus Involuntary violent flinging movements that may take the form of uncontrollable flailing. It is also called ballism. Ballismus that occurs with chorea is known as choreoballismus or choreoballism.

Basal ganglia (singular, ganglion) Groups of nerve cell bodies located deep within the brain that govern movement as well as emotion and certain aspects of cognition (thinking).

Chorea gravidarum Chorea occurring in the early months of pregnancy.

Dopamine A neurotransmitter that acts within certain parts of the brain to help regulate movement and emotion.

Encephalitis Inflammation of the brain.

Hemichorea Chorea that affects only one side of the body.

Hyperthyroidism Abnormally high levels of thyroid hormone. About 2% of patients with this condition develop chorea.

Hypocalcemia Abnormally low levels of calcium in the blood.

Neurosyphilis Late-stage syphilis that affects the central nervous system.

Neurotransmitter Any of a group of chemicals that transmit nerve impulses across the gap (synapse) between two nerve cells.

body to another. Jerking or twitching of the hands and feet may resemble piano playing or dancing. The patient may assume strange postures or make clumsy or wide-swinging leg movements when trying to walk. If the chest muscles are affected, the patient may have difficulty speaking normally, or make grunting or groaning noises. Facial expressions may be distorted by twitching of the lips, cheeks, eyebrows, or jaw. In severe cases, involuntary movements of the arms and legs may result in falling on the ground or throwing objects placed in the hand.

Other symptoms that may occur together with chorea include athetosis, which refers to slow, sinuous, writhing movements of the hands and feet, and ballismus, which refers to violent flinging or flailing of the limbs. A patient with one of these symptoms in addition to chorea may be said to have choreoathetosis or choreoballismus.

In some cases, only one side of the patient's body is affected by the involuntary movements. This condition is known as hemichorea.

Causes and associated disorders

The basic cause of choreic movements is overactivity of a neurotransmitter called dopamine in a set of structures deep within the brain known as the basal ganglia. The basal ganglia belong to a larger part of the nervous system that controls the muscles responsible for normal movement.

Several different unrelated disorders and conditions may lead to imbalances of dopamine in the basal ganglia, including:

- **Huntington**'s chorea (HC), an incurable hereditary disorder caused by a mutation in a gene on the short arm of human chromosome 4. It is characterized by **dementia** and psychiatric disturbances as well as chorea.
- **Sydenham's chorea**, a treatable complication of rheumatic fever following a streptococcal throat infection. It occurs most often in children and adolescents.
- Chorea gravidarum or chorea occurring in the first three months of pregnancy. It is most likely to affect women who had rheumatic fever or Sydenham's chorea in childhood.
- Senile chorea, which is gradual in onset, is not associated with other causes of chorea, does not cause personality changes, and develops in people over the age of 60. At one time, senile chorea was thought to be a late-onset form of HC, but is presently considered to be the result of a different genetic mutation.
- Blockage or rupture of one of the arteries supplying the basal ganglia.
- Metabolic disorders. About 2% of patients with abnormally high levels of thyroid hormone (hyperthyroidism) develop chorea. Abnormally low levels of calcium (hypocalcemia) may also produce chorea.
- Infectious diseases that affect the **central nervous system**. Chorea may be a symptom of viral encephalitis or late-stage neurosyphilis.
- Medications. Some drugs, most commonly those used to treat psychotic disorders or **Parkinson's disease**, cause

chorea as a side effect. Other drugs that sometimes cause chorea include **anticonvulsants** (**antiepileptic drugs**), lithium, amphetamines, and some antinausea medications.

Diagnosis

A doctor diagnosing the cause of chorea is guided by such factors as the patient's age and sex as well as medication history and family history. A patient with symptoms of Huntington's chorea is typically an adult over 35, whereas Sydenham's chorea most often occurs in children aged six to 14. Huntington's chorea affects both sexes equally, whereas Sydenham's chorea affects girls twice as often as boys. A patient with a family history of Huntington's can be given a blood test to detect the presence of the gene that causes HC. A history of a recent throat infection or rheumatic fever suggests Sydenham's chorea. Metabolic disorders can be detected by blood tests.

Hemichorea or chorea accompanied by ballismus may indicate a vascular disorder affecting the basal ganglia, particularly when the chorea is sudden in onset. The doctor will order imaging studies, usually computed tomography (**CT**) **scans** or **magnetic resonance imaging (MRI)** if an arterial blockage or rupture is suspected. Neurosyphilis and encephalitis are diagnosed by testing a sample of the patient's cerebrospinal fluid.

Treatment

In general, chorea is not treated by itself unless the movements are so severe as to cause embarrassment or risk injury to the patient. Drugs that are given to treat chorea suppress the activity of dopamine in the basal ganglia but may also produce such undesirable side effects as muscular rigidity or drowsiness. These drugs cannot be given to women with chorea gravidarum because they may harm the fetus; pregnant patients may be given a mild benzodiazepine tranquilizer instead. Drugs given to treat patients with HD may help to control chorea, but cannot stop the progression of the disease.

Prognosis

The prognosis of chorea depends on its cause. Huntington's chorea is incurable, leading to the patient's death 10–25 years after the first symptoms appear. Almost all children with Sydenham's chorea, however, recover completely within one to six months. Chorea gravidarum usually resolves by itself when the baby is born or shortly afterward. Chorea caused by a vascular disorder may last for six to eight weeks after the blockage or rupture is treated. Chorea associated with metabolic disorders usually goes away when the chemical or hormonal imbalance is corrected.

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American Geriatrics Society (AGS). Empire State Building, 350 Fifth Avenue, Suite 801, New York, NY 10118. (212) 308-1414; Fax: (212) 832-8646. info@americangeriatrics.org. <http://www.americangeriatrics.org>.

Huntington's Disease Society of America (HDSA). 158 West 29th Street, 7th Floor, New York, NY 10001-5300. (212)

242-1968 or (800) 345-HDSA; Fax: (212) 239-3430. hdsainfo@hdsa.org. <http://www.hdsa.org>.

National Institute of Neurological Disorders and Stroke (NINDS). 9000 Rockville Pike, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

Worldwide Education and Awareness for Movement Disorders (WE MOVE). 204 West 84th Street, New York, NY 10024. (212) 875-8389 or (800) 437-MOV2. wemove@wemove.org. <http://www.wemove.org>.

Rebecca Frey, PhD

Chronic inflammatory demyelinating polyneuropathy

Key Terms

Demyelination Loss of the myelin sheath that surrounds and insulates the axons of nerve cells and is necessary for the proper conduction of neural impulses.

Electromyography A test that detects electric activity in muscle that is used to determine nerve or muscle damage.

Myelin The fatty covering that is wrapped around the outside of a nerve cell.

Neuropathy A disorder of the nervous system or a nerve.

Definition

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a disorder that affects the nerves outside of the brain and spinal cord (peripheral nerves). Specifically, the fatty covering, or sheath, that is wrapped around the outside of a nerve cell is damaged. The covering is called myelin, and the damage is called demyelination. The nerve damage becomes apparent as weakness in the legs and arms increases in severity with time.

Description

The demyelination of peripheral nerves causes a weakness in the legs and arms that grows progressively more severe over time. The ability of the limbs to feel sensory impulses such as touch, **pain**, and temperature can also be impaired. Typically, the malady is first apparent as a tingling or numbness in the toes and the fingers. The symptoms can both spread and become more severe with time.

The symptoms, treatment, and prognosis of CIDP is very similar to another nerve disease known as **Guillain-Barré syndrome**. In fact, CIDP has been historically known as "chronic Guillain-Barré syndrome" (Guillain-Barré syndrome is an acute malady whose symptoms appear and clear up more rapidly). Despite their similarities, however, CIDP and Guillain-Barré are two distinct conditions. CIDP is also known as chronic relapsing polyneuropathy.

Demographics

CIDP can occur at any age. However, the malady is more common in young adults, and in men more than in women. The disorder is rare in the general population.

Causes and symptoms

CIDP is an immune system disorder. Specifically, the immune system mistakenly recognizes the myelin sheath of the peripheral nerve cells as foreign. Damage to the sheath occurs when the immune system attempts to rid the body of the invader. There is no evidence to support a genetic basis for the disease, such as a family history of CIDP or other, similar disorders. CIDP cannot be inherited.

As with Guillain-Barré syndrome, it is strongly suspected that CIDP is at least triggered by a recent viral infection. For example, critical immune cells can be damaged in viral infection such as occurs in acquired immunodeficiency syndrome (**AIDS**), leading to malfunction of the immune system. Whether viral or other microbial infections are the direct cause of CIDP is not clear.

CIDP is different from Guillain-Barré syndrome in that the viral infection often does not occur within several months of the first appearance of the symptoms. In Guillain-Barré syndrome, a viral or bacterial infection typically immediately precedes the appearance of the symptoms.

CIDP typically begins with a tingling or prickling sensation, or numbness in the fingers and toes. This can spread to the arms and legs (an ascending pattern of spread). Both sides of the body can be affected; this is described as a symmetrical pattern. Other symptoms that can develop over time include the loss of reflexes in some tendons (a condition referred to as areflexia), extreme tiredness, and muscle ache. In some people, these symptoms develop slowly, reach a peak over several weeks or months, and then resolve themselves over time. However, for the majority of people with CIDP, the symptoms do not improve without treatment, and the symptoms can persist for many months to years.

Diagnosis

An important part of the diagnosis of CIDP is the detection of muscle weakness by a neurological examination. One relevant neurological test is nerve conduction velocity. In this test, a patch that is attached to the skin's surface over the target muscle is stimulated. A very mild electrical current stimulates the nerves in the muscle. A measurement called the nerve conduction velocity is then calculated as the time it takes for the impulses to travel the known distance between electrodes.

In demyelinating diseases such as CIDP, the nerves are not capable of transmitting electrical impulses as speedily as normal, myelinated nerves. Thus, the damaged nerves will display a greater conduction velocity than that displayed by an unaffected person.

Another test called **electromyography** (EMG) is used to measure muscle response to electrical stimulation. In EMG, an electrode contained within a needle is pushed through the skin into the muscle; several electrodes may need to be inserted throughout a muscle to accurately measure the muscle's behavior. Stimulation of a muscle causes a visual or audio pattern. The pattern of wavelengths carries information about the muscle's response. The characteristic pattern of wavelengths produced by a healthy muscle, which is called the action potential, can be compared to a muscle in someone suspected of having CIDP. For a nerve-damaged muscle, the action potential's wavelengths are smaller in height and less numerous than displayed by a normal muscle.

An electrocardiogram can be used to record the electrical activity of the heart when paralysis of the heart muscle is suspected. Nerve damage will alter the normal pattern of the heartbeat.

Finally, an examination of the cerebrospinal fluid by a lumbar puncture (also known as a spinal tap) may detect a higher than normal level of protein in the absence of an increase in the number of white blood cells (WBCs). An increase in WBCs occurs when there is a microbial infection.

Treatment team

CIDP treatment typically involves neurologists, immunologists, and physical therapists. Support groups are a useful adjunct to treatment.

Treatment

The treatments for CIDP and Guillain-Barré syndrome are similar. The use of corticosteroids such as prednisone, which lessen the response of the immune system, can reduce the amount of demyelination that occurs. Corticosteroids can be prescribed alone or in combination with other immunosupressant drugs.

The medical procedure known as plasmapheresis, or plasma exchange, can be another useful treatment. In plasmapheresis, the liquid portion of the blood that is known as plasma is removed from the body. The red blood cells are retrieved from the plasma and added back to the body with antibody-free plasma or intravenous fluid. Although plasmapheresis can lessen the symptoms of CIDP, it is not known exactly why plasmapheresis works. Because the blood plasma withdrawn from the body of a CIDP patient can contain antibodies to the nerve myelin sheath, the subsequent removal of these antibodies may lessen the effects of the body's immune attack on the nerve cells.

Another procedure that produces similar results involves the administration of intravenous immunoglobulin (IVIG). IVIG is a general all-purpose treatment for immune system-related neuropathies. As with plasmapheresis, immunoglobulin may help reduce the amount of anti-myelin antibodies, and so suppress the immune response. As well, IVIG contains healthy antibodies from the donated blood. These antibodies can help neutralize the defective antibodies that are causing the demyelination. When more standard approaches fail, alternative forms of immunosuppressive therapies are sometimes considered, including the drugs azathioprine, cyclophosphamide, and cyclosporine.

Physical therapy is helpful. Caregivers can move a patient's arms and legs to help improve the strength and flexibility of the muscles, and minimize the shrinkage of muscles and tendons that are not being actively used.

Recovery and rehabilitation

Recovery from CIDP varies from person to person. Some people recover completely without a great deal of medical intervention, while others may relapse again and again. Because some people can display permanent muscle weakness or numbness, physical therapy can be a useful part of a rehabilitation regimen.

Clinical trials

The National Institutes of Health (NIH) sponsored four **clinical trials** for the study and treatment of CIDP, all completed by 2001. The National Institute of Neurological Disorders and Stroke supports continued broad research for demyelinating diseases, although no further clinical trials are ongoing as of March 2004.

Prognosis

A patient's prognosis can range from complete recovery to a pattern of a periodic reappearance of the symptoms and residual muscle weakness or numbness.

Special concerns

The potential exists that IVIG will increase the risk of kidney damage in older or diabetic patients. Enoxaparin, a drug that can be prescribed to reduce the risk of blood clotting in patients with high blood pressure, can make a patient more prone to bleeding. This risk can be greater when enoxaparin is given at the same time as aspirin or anti-inflammatory drugs. The use of corticosteroids can restrict the efficiency of the immune system, which can increase the risk that other microorganisms will establish a secondary, or opportunistic, infection. Medical staff regularly monitor people receiving these treatments for signs of complication.

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American Autoimmune Related Diseases Association. 22100 Gratiot Avenue, Eastpointe, MI 48201-2227. (586) 776-3900 or (800) 598-4668; Fax: (586) 776-3903. aarda@aol.com. <http://www.aarda.com>.

Guillain-Barre Syndrome Foundation International. P.O. Box 262, Wynnewood, PA 19096. (610) 667-0131; Fax: (610) 667-7036. info@gbsfi.com. <http://www.aarda.org>.

National Organization for Rare Disorders. P.O. Box 1968, Danbury, CT 06813-1968. (203) 744-0100. orphan@rarediseases.org. <http://www.rarediseases.org>.

Neuropathy Association. 60 East 42nd Street, New York, NY 10165-0999. (212) 692-0662 or (800) 247-6968; Fax: (212) 696-0668. info@neuropathy.org. <http://www.neuropathy.org>.

Brian Douglas Hoyle, PhD

Circle of Willis *see* **Cerebral circulation**

Clinical trials

Definition

A clinical trial is a carefully designed research study that is carried out with human volunteers. The trial is designed to answer specific questions concerning the effectiveness of a drug, treatment, or diagnostic method, or to improve patients' quality of life.

Description

Qualification for a clinical trial involves the selection of various desirable criteria (inclusion criteria), as well as criteria by which volunteers are rejected (exclusion criteria). Typical criteria include age, gender, the type and severity of the disease, prior treatment, and other medical conditions.

Depending on the clinical trial, the volunteers that are recruited could be healthy or ill with the disease under study. There are a number of different types of clinical trials that utilize differing types of study plans (protocols). A treatment trial evaluates a new treatment, new drug combinations, new surgical strategies, or innovative **radiation** therapy. A prevention trial seeks to find better ways to prevent disease from occurring or prevent disease from returning. Medicines, vaccines, vitamins, and lifestyle changes can all be candidates for a prevention trial. A diagnostic trial is designed to find better means of diagnosis for a particular disease or medical condition. A screening trial is designed to determine the best way to detect a particular disease or medical condition. Finally, a quality of life trial (supportive care trial) seeks to improve the comfort and daily life of people with a chronic illness.

Clinical trials, particularly treatment and prevention trials, often have several components, or phases. The following phases (I-IV) relate to the scope of the trial:

- Phase I trial evaluates the new drug or treatment in a small group of people (less than 100). Humans do not necessarily need to participate in such a trial. Experiments in the lab using microbiological cultures or tissue cells may suffice. The trial's purpose is to provide early indications of a drug or treatment's safety, safe dosage range, and reveal any side effects.
- Phase II trial follows a phase I trial. A promising drug or treatment is tested on a larger group of people (100–300) to better determine the effectiveness and to monitor safety more critically. Use of a larger population can help reveal side effects that could be hidden by the use of only a few volunteers.
- Phase III trial evaluates a drug or treatment that has proven effective in the phase I and II trials and is tested

Key Terms

Double blind study A study or clinical trial designed to minimize any bias, in that neither participant or study director knows who is assigned to the control group and who is assigned to the test group until the end of the study.

Exclusion criteria A predetermined set of factors that make a potential participant not eligible for inclusion in a clinical trial or study.

Inclusion criteria A predetermined set of factors that make a potential participant eligible for inclusion in a clinical trial or study.

Placebo A drug containing no active ingredients, such as a sugar pill, that may be used in clinical trials to compare the effects of a given treatment against no treatment.

on a large population (1,000–3,000) to confirm its effectiveness, reveal any rarer side effects, and gather information that will allow the drug or treatment to be safely marketed.

- Phase IV trial occurs after a product has been released in the marketplace. Monitoring of a drug or treatment in very large numbers of people provides further information on benefits and risks.

A typical clinical trial involves medical doctors and nurses, although **social workers** and other health care workers may also contribute. The members of the clinical team monitor the health of each volunteer at the outset and during the trial, give instructions, and often provide follow-up after the trial is completed. For a clinical trial volunteer, this means more visits to the health care facility than would normally occur, although compensation such as transportation expense is sometimes provided.

A critical part of a clinical trial is obtaining the consent of volunteers for their participation. It is mandatory that a trial's risks (i.e., side effects, little or no effect of treatment) and benefits (i.e., more proactive role in health care, access to new therapies, advance medical care) be clearly explained to participants. Once this is done, volunteers provide their informed consent by signing a document. This document is not legally binding, so volunteers are not obligated to complete the trial. An ethical clinical trial will never reveal the identities of the volunteers.

In addition to the drug being studied, clinical trials of new drugs will typically use a pill, liquid, or powder that looks the same as the active compound, but that has no medicinal value. This inactive compound, known as a placebo, is usually given to the control group of volunteers, who are compared to the test group that receives the active drug. Usually the volunteers do not know whether they receive a placebo or the active drug. A clinical trial can be designed so that the researchers are also unaware of which people receive the active drug. When volunteers and researchers are both unaware, the trial is described as being double blind. Volunteers are often assigned to the control or test groups at random. This action is designed to minimize any bias due to age, gender, race, or other factors.

Resources

OTHER

"An Introduction to Clinical Trials." *ClinicalTrials.gov.* January 21, 2004 (March 30, 2004). <http://www.clinicaltrials.gov/ct/info/whatis>.

ORGANIZATIONS

National Institutes of Health, Clinical Center. 6100 Executive Blvd., Suite 3C01MSC 7511, Bethesda, MD 20892-7511. (301) 496-2563 or (800) 411-1222; Fax: (301) 402-2984. occc@cc.nih.gov. <http://www.cc.nih.gov/home.cgi>.

Brian Douglas Hoyle, PhD

Cluster headache *see* **Headache**

Complex regional pain syndrome *see* **Reflex sympathetic dystrophy**

Congenital facial diplegia *see* **Moebius syndrome**

Congenital vascular cavernous malformation *see* **Cerebral cavernous malformation**

Congenital myasthenia

Definition

Congenital myasthenia is an inherited condition present at birth that interferes with nerve messages to the muscles. Although some symptoms are similar (muscle weakness worsened by use), congenital myasthenia differs from **myasthenia gravis**, which usually presents in adulthood and is almost always due to an autoimmune disorder rather than an inherited genetic defect.

Description

Most cases of congenital myasthenia are noticeable at or shortly after birth. In rare cases, symptoms don't present themselves until some time later in childhood or in early adult life.

Normal muscle function requires a chemical messenger called acetylcholine (ACh) to travel from the nerve cell to a receptor on the muscle endplate, in order to stimulate muscle contraction and movement. After the ACh has initiated muscle contraction, it is degraded by an enzyme.

In congenital myasthenia, one of three problems occurs with this system:

- Too little ACh is produced, or its release from the nerve cell is impaired
- The enzyme that should degrade ACh is faulty, resulting in prolonged stimulation of the muscle by excess ACh and ultimately in muscle damage
- The area of the muscle that should be stimulated by the presence of ACh (called the endplate receptor) is defective, and therefore the muscle can not be sufficiently stimulated

Demographics

Figures regarding the frequency of congenital myasthenia are not available, but it is considered to be a very rare condition.

Causes and symptoms

Most cases of congenital myasthenia are inherited in a recessive fashion, meaning that a baby has to receive a defective gene from each parent to actually manifest the condition.

Babies with congenital myasthenia are often described as "floppy," with weak muscle tone, droopy eyelids, excessive **fatigue**, compromised eye movements, facial weakness, feeding problems and delayed developmental milestones (such as holding up head, sitting, crawling). In more severe conditions, the muscles that aid breathing are affected, resulting in respiratory difficulties.

The baseline degree of weakness is exacerbated by any activity, including feeding, crying, or moving. Episodes of more severe symptoms may be precipitated by illness, emotional upset, or fever. Some cases of congenital myasthenia progress over time, so that initially mild symptoms can become more severe as the individual ages.

Diagnosis

The diagnosis of congenital myasthenia will usually be suspected when a careful physical examination reveals muscle weakness that is worsened by use of a particular muscle. Certainly, a family history of congenital myasthenia heightens such a suspicion.

A test called **electromyography** measures muscle activity after stimulation. When muscle activity decreases with repeated stimulation, congenital myasthenia is suspected. Testing the blood for the presence of specific antibodies can help distinguish between myasthenia gravis and congenital myasthenia. Very specific microelectrode testing of the muscle endplate receptors can help define whether faulty receptors are responsible for the impairment. Genetic testing and muscle **biopsy** examination are being researched, but are not currently used for routine diagnosis.

Treatment team

Children with congenital myasthenia will usually be treated by a team consisting of a pediatric **neurologist**, as well as a physical therapist, occupational therapist, and speech and language therapist. If respiratory problems ensue, a pulmonologist and respiratory therapist may need to be consulted.

Treatment

There are no treatments available to cure congenital myasthenia. A number of medications may improve symptoms in children with congenital myasthenia. The specific medication that will be most helpful depends on whether the impairment is due to decreased ACh production and release, impaired enzyme degradation of ACh, or faulty ACh receptors in the muscle endplates. Some of the types of medications available include:

- Anticholinesterase medications: Inhibit the degradation of ACh, allowing more to be available to stimulate muscles.
- 3,4, diaminopyridine: Increases the release of ACh from the nerve cells.
- Qunidine or fluoxetine: Prevents overstimulation of ACh receptors on muscle endplates, thus preventing muscles from damage secondary to prolonged stimulation.

Prognosis

The severity of symptoms, responsiveness to medication, and ultimate prognosis varies widely among congenital myasthenia patients.

Resources

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ORGANIZATIONS

Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718. (800) 572-1717. mda@mdausa.org. <http://www.mdausa.org>.

Rosalyn Carson-DeWitt, MD

Congenital myopathies

Definition

Myopathies are diseases that cause weakness and **hypotonia** (poor tone) in the muscles that control voluntary movements. Congenital myopathies are a group of myopathies, usually present from birth, that display structural changes in the skeletal muscles. The list of diseases defined as congenital myopathies varies. Three inherited conditions in particular are definitively known as congenital myopathies: central core disease, nemaline **myopathy**, and centronuclear (myotubular) myopathy. These myopathies lead to generalized muscle weakness, decreased muscle tone, weak muscle reflexes, poor muscle bulk, and often a characteristic facial and bodily appearance.

Key Terms

Congenital Present at birth.

Fetal Refers to the fetus. In humans, the fetal period extends from the end of the eighth week of pregnancy to birth.

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.

Nerve conduction The speed and strength of a signal being transmitted by nerve cells. Testing these factors can reveal the nature of nerve injury, such as damage to nerve cells or to the protective myelin sheath.

Serum The fluid part of the blood that remains after blood cells, platelets, and fibrogen have been removed. Also called blood serum.

Description

Central core disease

First described in 1956, central core disease (CCD) is named for the abnormalities found in the muscle biopsies of affected people. The central parts, or cores, of certain muscle cells lack structures called mitochondria, the energy-producing parts of the cells. CCD is a variable disorder with onset in early infancy to childhood. Hip displacement is not uncommon. Some children with CCD show mildly delayed motor milestones and appear only slightly uncoordinated. Others have more significant delays, though they eventually walk and move about with some limitation. Some children use braces for walking, and a few use wheelchairs.

Nemaline myopathy

Also known as rod myopathy or rod body disease, nemaline myopathy (NM) was first described in two separate reports in 1963. NM is named for the thread-like structures known as nemaline bodies that are visible on muscle **biopsy**. The term "nemaline" comes from the Greek word *nema* meaning "thread." The main features of NM are muscle weakness, loss of muscle tone, and absent or weak deep tendon reflexes (for example, knee and ankle jerks). Based on the age of onset and severity of symptoms, NM has been classified into six forms: neonatal (severe congenital), Amish nemaline myopathy (a congenital form), intermediate congenital form, typical congenital form, childhood-onset form, and adult-onset form. Most cases (over 80%) are one of the congenital forms. All six forms of NM are unified by the presence of nemaline rods, abnormal structures that are found in the sarcoplasm of the muscles.

Centronuclear (myotubular) myopathy

Centronucler myopathy, also known as myotubular myopathy (MTM), is an extremely variable condition characterized by a poor muscle tone and weakness. The centronuclear myopathies are called "myotubular myopathies" due to the presence of myotubes, immature muscle cells found in affected individuals. Myotubes have nuclei (structures that contain the chromosomes) that are central rather than peripheral (at the edge). Mature muscle cells have peripheral nuclei. Although MTM can lead to death in infancy, it can be a mildly progressive condition that begins as late as early adulthood. There are X-linked, autosomal dominant and autosomal recessive forms of the disorder. The X-linked form, also known as X-linked myotubular myopathy or XLMTM, is thought to be the most common form of the condition and typically is the most severe form of MTM.

Demographics

Although central core disease is thought to be rare, the incidence of this congenital myopathy remains unknown. Both males and females are affected. Due to the range of severity observed in CCD, it is possible that there

are undiagnosed cases within CCD families and within the general population. The X-linked form of centronuclear myopathy affects approximately 1/50,000 newborn males. The autosomal recessive and autosomal dominant forms are apparently less common; however, the frequency of these forms remains unknown. Nemaline myopathy occurs in about 1/50,000 live births.

Causes and symptoms

Causes

CENTRAL CORE DISEASE Central core disease is inherited in an dominant manner, due to a mutation in one copy of the RYR1 (ryanodine receptor) gene on the long arm of chromosome 19. Researchers think that mutations in this receptor affect the way calcium flows out of the sarcoplasmic reticulum, a functional unit in the muscle. Mutations in the RYR1 gene are also known to cause malignant hyperthermia (MH), a genetic predisposition that makes an individual prone to serious reactions to certain general anesthetics. In fact, MH is a feature of CCD. 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.

NEMALINE ROD MYOPATHY Nemaline myopathy is caused by alterations in genes that affect filament proteins. When the filament proteins aren't working, muscles can't contract and there is a subsequent loss of tone and strength. Nemaline myopathy can be inherited as an autosomal dominant or an autosomal recessive condition. Autosomal dominant inheritance implies that the affected person has one altered or non-functioning copy and one normal copy of a particular NM gene. The changed gene may occur for the first time in that individual (*de novo*) or may be inherited from a parent (familial). When NM occurs as an autosomal recessive condition, the affected individual has two altered or non-functioning NM genes, one from each parent. As of March 2004, there were five genes known to cause NM abbreviated as ACT1, NEB, TNNT1, TMP2, and TMP3; each gene codes for protein components of thin filament, a type of muscle fiber.

MYOTUBULAR MYOPATHY The MTM1 gene on the long arm of the X chromosome encodes myotubularin, a protein thought to promote normal muscle development. As of 2004, the precise mechanisms by which MTM1 mutations cause XLMTM were unresolved. X-linked MTM primarily affects males because they have only one X chromosome and therefore lack a second, normal copy of the gene responsible for the condition. Female carriers of the X-linked MTM have one X chromosome with a normal MTM1 gene and one X chromosome with a non-working MTM1 gene. As of March 2004, researchers were working to identify the gene or genes responsible for the autosomal recessive form of centronuclear myopathy. One gene, the myogenic factor-6 gene (MYF6) has been shown to cause some cases of the autosomal dominant form. It is possible that other genes will be discovered in the future.

Symptoms

CENTRAL CORE DISEASE Central core disease is characterized by a mild, non-progressive muscle weakness. Signs of central core disease usually appear in infancy or early childhood and may present even earlier. There may be decreased fetal movements and breech (feet first) presentation *in utero*. The main features of CCD are poor muscle tone (hypotonia), muscle weakness, and skeletal problems including congenital hip dislocation, scoliosis (curvature of the spine), *pes cavus* (high-arched feet), and clubbed feet. Children with CCD experience delays in reaching motor milestones and tend to sit and walk much later than those without the disorder. A child with the disease usually cannot run easily, and may find that jumping and other physical activities are often impossible. Although central core disease may be disabling, it usually does not affect intelligence or life expectancy.

People who have central core disease are sometimes vulnerable to **malignant hyperthermia** (MH), a condition triggered by anesthesia during surgery. MH causes a rapid, and sometimes fatal, rise in body temperature, producing muscle stiffness.

NEMALINE MYOPATHY There is variability in age of onset, presence of symptoms, and severity of symptoms in nemaline myopathy. Most commonly, NM presents in infancy or early childhood with weakness and poor muscle tone. In some cases there may have been pregnancy complications such as polyhydramnios (excess amniotic fluid) and decreased fetal movements. Affected children with NM tend to have delays in motor milestones such as rolling over, sitting and walking. Muscle weakness commonly occurs in the face, neck and upper limbs. Over time, a characteristic myopathic face (a long face that lacks expression) develops. Skeletal problems including chest deformities, scoliosis, and foot deformities may develop. In the most severe cases of NM, feeding difficulties and potentially fatal respiratory problems may also occur. In those who survive the first two years of life, muscle weakness tends to progress slowly or not at all.

CENTRONUCLEAR MYOPATHY Typically the X-linked form of MTM (XLMTM) is the most severe of the three forms (X-linked, autosomal recessive, and autosomal dominant). XLMTM usually presents as a newborn male with poor muscle tone and respiratory distress. The pregnancy may have been complicated by polyhydramnios and decreased fetal movements. Of those who survive the newborn period, many will at least partially depend on a ventilator for breathing. Because of the risk of aspiration,

many will also have a gastrostomy tube (G-tube). Boys with XLMTM can experience significant delays in achieving motor milestones and may not ever walk independently. They tend to be tall with a characteristic facial appearance (long, narrow face with a highly arched roof of the mouth and crowded teeth). Intelligence is generally not affected. Medical complications that may develop include: scoliosis, eye problems (eye muscle paralysis and droopy eyelids), and dental malocclusion (severe crowding). In X-linked MTM, other problems including undescended testicles, spherocytosis, peliosis, elevated liver enzymes, and gallstones may occur.

The autosomal recessive and autosomal dominant forms of MTM tend to have a milder course than the X-linked form. The autosomal recessive form can present in infancy, childhood, or early adulthood. Common features include generalized muscle weakness with or without facial weakness and ophthalmoplegia (paralysis of the eye muscles). Although feeding and breathing problems can occur, affected individuals usually survive infancy. Onset of the autosomal dominant form ranges from late childhood through early adulthood. It tends to be the mildest of the three forms of MTM. Unlike the X-linked form of the condition, problems with other organs (such as the liver, kidneys, and gall bladder) haven't been reported with the autosomal recessive and autosomal dominant forms of MTM.

Diagnosis

Diagnosis of a congenital myopathy generally includes evaluation of the patient's personal and family history, physical and neurological examinations that test reflexes and strength, and specialized tests. Since there is overlap between the symptoms of a congenital myopathy and other neuromuscular disorders, a number of tests may be performed to help narrow down the diagnosis. Serum CK (creatinine kinase) analysis, EMG (electromyelogram), nerve conduction studies, and muscle ultrasound tend to be of limited value in making this diagnosis. The definitive diagnosis of a congenital myopathy usually relies upon genetic testing and/or muscle biopsy. Also, muscle biopsy can be used to determine a patient's susceptibility to malignant hyperthermia.

Central core disease

The muscle biopsy from a person with CCD typically displays a metabolically inactive "core" or central region that appears blank when stained (tested) for certain metabolic enzymes (proteins) that should be there. These central regions also lack mitochondria, the energy producing "factories" of the cells. Genetic testing for RYR1 mutations is available on a research basis. The same genetic test may be used to determine the presence of the gene change in family members who may have or be at-risk for the disease. For families in which a RYR1 mutation has been found, prenatal diagnosis may be possible using the DNA of fetal cells obtained from chorionic villus sampling (CVS) or amniocentesis.

Nemaline myopathy

The clinical diagnosis of NM is suspected in an infant under age one with muscle weakness and hypotonia (decreased muscle tone). Definitive diagnosis of nemaline myopathy is made by demonstration of nemaline bodies, rod-shaped structures characteristic of this disease, using a specific stain known as "Gomori trichrome" on a muscle biopsy sample. Muscle biopsy may also show predominance of structures known as type I fibers. As of 2004, genetic testing was available on a clinical basis for one gene, the ACTA1 gene located on the long arm of chromosome 1. About 15% of NM cases are due to mutations in this gene. Prenatal diagnosis is possible for families with known ACTA1 mutations. The DNA of a fetus can be tested using cells obtained from chorionic villus sampling (CVS) or amniocentesis.

Centronuclear (myotubular) myopathy

Diagnosis of X-linked MTM is usually made on muscle biopsy. Findings include: centrally located nuclei in muscle fibers that look like myotubules, absence of structures known as myofibrils, and possibly, persistence of certain proteins usually seen in fetal muscle cells. If timing is not an issue, genetic testing may be undertaken. Gene testing detects a mutation (disease-causing gene change) in up to 97-98% of people with the X-linked form. Though genetic testing is available, it tends to be time intensive and used to confirm a diagnosis, to screen potential carriers, or for prenatal testing.

Treatment team

Management of a congenital myopathy requires a multidisciplinary approach. In addition to the patient's primary health care professionals, medical professionals involved in the care of patients with may include specialists in neurology, neonatology, pulmonology, gastroenterology, orthopedics, ophthalmology, and orthodontistry. Additional specialists in physical therapy, speech therapy and occupational therapy may be needed. Patients with one of the congenital myopathies may receive comprehensive services through a **muscular dystrophy** association (MDA) clinic and/or a Shriner's Hospital for Children. Genetic evaluation and counseling may be helpful to the patient and family, especially at the time of diagnosis. Psychological counseling and support groups may also assist families in coping with this condition.

Treatment

As of 2004, there is no cure for the congenital myopathies. The purpose of treatment, which is largely supportive, is to help patients optimize function and to manage any medical complications associated with the disorder. Treatment measures for the congenital myopathies greatly depend on the severity of the individual's symptoms, and especially upon the degree of muscle weakness and presence of skeletal deformities. Treatment mainly consists of respiratory and feeding support, and orthopedic intervention. Ophthalmologic and dental care is also important to help manage problems that may arise such as dry eyes and dental crowding. In the case of X-linked MTM, management of associated complications including undescended testicles, spherocytosis, peliosis, elevated liver enzymes, and gallstones is also recommended.

Affected infants, especially those with X-linked myotubular myopathy or nemaline myopathy, usually require a feeding tube (a gastrostomy or G-tube) for nutrition and mechanical ventilation through a tracheostomy to help with breathing. Other means of ventilation such as BiPAP (bilevel positive airway pressure) may be used. Even children and adults who don't require help with daytime breathing may require respiratory support at night, since respiratory failure during sleep can occur.

Braces or surgery may be necessary to treat scoliosis, dislocated hips, and foot deformities. Since individuals with central core disease can develop malignant hyperthermia during surgery, they should consult a **neurologist** or anesthesiologist prior to these or other surgeries.

Recovery and rehabilitation

Given the rarity of the congenital myopathies, the potential for rehabilitation in these disorders is largely unknown. Speech, physical, and occupational therapies may be recommended. Though intellect is typically normal, educational support through early intervention services and/or through an individualized education plan (IEP) may also be appropriate for some children. In severe cases, consideration may be given to placement in a residential care facility that can provide 24-hour care and support services.

The goal of rehabilitation for the congenital myopathies is to maintain or improve the patient's existing functions. Physical therapy may be recommended to improve mobility and muscle strength. For example, people with central core disease can benefit from **exercise**, under the direction of a physician. Speech therapy can help a person with a congenital myopathy to learn speech and/or ways to communicate. For example, a boy with X-linked myotubular myopathy who has a tracheostomy may need help learning how to communicate with sign language and, later, with writing boards. Occupational therapy can teach patients to use adaptive techniques and devices that may help compensate for muscle weakness. For example, someone with a severe form of nemaline myopathy may benefit from a walker, wheelchair or other device in order to get around.

Clinical trials

As of March 2004, one clinical trial was recruiting patients with congenital myopathy. A study designed to learn more about the natural history of inherited neurological disorders and the role of heredity in their development will be conducted in the United States. Updated information on this trial can be found at <http://www.clinicaltrials.gov> or by contacting the patient recruitment and public liaison office of the National Institute of Neurological Disorders and Stroke (NINDS) at 1-800-411-1222 or <prpl@mail.cc.nih.gov>.

Prognosis

The outlook for children with central core disease is generally positive. Although they begin life with some developmental delays, many improve as they get older and stay active throughout their lives. The outcome for patients with nemaline rod myopathy is quite variable. Depending upon disease severity, affected individuals can have normal life span, despite progressive muscle weakness, or they can die in infancy due to respiratory problems. Severe neonatal respiratory disease and the presence of arthrogryposis (limited joint movement due to contracted muscles and tendons) generally predict a poor outcome with death by age one. The prognosis for myotubular myopathy varies according to the presence and severity of respiratory disease and scoliosis. X-linked myotubular myopathy was once described as fatal in the first few months of life. Yet, it is now known that support of feeding (G-tube) and ventilation (tracheostomy) can significantly improve life expectancy and quality of life.

Special concerns

Malignant hyperthermia, a problem seen in some individuals with central core disease is a severe and potentially life-threatening complication of anesthesia. People with central core disease or a family history of the disease should consult their doctors about anesthesia risks. Also, wearing a medical alert bracelet may be advised.

Individuals with even mild cases of myotubular myopathy can experience potentially serious breathing problems such as **hypoxia** (lack of oxygen) during sleep. It is crucial that even patients with minimal disease severity be monitored for respiratory problems as they may require help with breathing at night.

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Muscular Dystrophy Association (MDA). *Nemaline Myopathy Page.* <http://www.mdausa.org/disease/nm.html>.

Muscular Dystrophy Association (MDA). *Myotubular Myopathy Page.* <http://www.mdausa.org/disease/mm.html>.

National Institute of Neurological Disorders and Stroke (NINDS). *Congenital Myopathies Information Page.* <http://www.ninds.nih.gov/health_and_medical/disorders/myopathy_congenital.htm>.

ORGANIZATIONS

Muscular Dystrophy Association, 3300 East Sunrise Drive, Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717; Fax: (520) 529-5300. mda@mdausa.org. <http://www.mdausa.org>.

Myotubular Myopathy Resource Group. 2602 Quaker Drive, Texas City, TX 77590. (409) 945-8569. info@mtmrg.org. <http://www.mtmrg.org>.

Nemaline Myopathy Foundation. P. O. Box 5937, Round Rock, TX 78683-5937. <http://www.davidmcd.btinternet.co.uk>.

Dawn J. Cardeiro, MS, CGC

Conjugate eye movements *see* **Visual disturbances; Traumatic brain injury**

Corpus callosotomy

Definition

Corpus callosotomy is a treatment for **epilepsy**, in which a group of fibers connecting the two sides of the brain, called the corpus callosum, is cut.

Purpose

Corpus callosotomy is used to treat epilepsy that is unresponsive to drug treatments. A person with epilepsy may be considered good candidate for one type of epilepsy surgery or another if he or she has **seizures** that are not adequately controlled by drug therapy, and has tried at least two (perhaps more, depending on the treatment center's guidelines) different anti-epileptic drugs.

The seizures of epilepsy are due to unregulated spreading of electrical activity from one part of the brain to other parts. In many people with epilepsy, this activity begins from a well-defined focal point, which can be identified by electrical testing. Surgical treatment of focal-origin seizures involves removal of the brain region containing the focal point, usually in a procedure called temporal lobectomy. In other people, no focal point is found, or there may be too many to remove individually. These patients are most likely to receive corpus callosotomy.

The purpose of a corpus callosotomy is to prevent spreading of seizure activity from one half of the brain to the other. The brain is divided into two halves, or hemispheres, that are connected by a thick bundle of nerve fibers, the corpus callosum. When these fibers are cut, a seizure that begins in one hemisphere is less likely to spread to the other. This can reduce the frequency of seizures significantly.

The initial surgery may cut the forward two-thirds of the corpus callosum, leaving the rest intact. If this does not provide sufficient seizure control, the remaining portion may be cut.

Corpus callosotomy is most often performed for children with "drop attacks," or atonic seizures, in which a sudden loss of muscle tone causes the child to fall to the floor. It is also performed in people with uncontrolled generalized tonic-clonic, or grand mal, seizures, or with massive jerking movements. Of the 20,000 to 70,000 people in the United States considered candidates for any type of epilepsy surgery, approximately 5,000 receive surgery per year. Between 1985 and 1990, more than 800 corpus

callosotomies were performed, and the number has increased since then. Corpus callosotomy is performed by a special neurosurgical team, at a regional epilepsy treatment center.

Description

During corpus callosotomy, the patient is under general anesthesia, lying on the back. The head is fixed in place with blunt pins attached to a rigid structure. The head is shaved either before or during the procedure.

Incisions are made in the top of the skull to remove a flap of bone, exposing the brain. The outer covering is cut, and the two hemispheres are pulled slightly apart to expose the corpus callosum. The fibers of the corpus callosum are cut, taking care to avoid nearby arteries and ventricles (fluid-filled cavities in the brain).

Once the cut is made and any bleeding is controlled, the brain covering, bone, and scalp are closed and stitched.

Preparation

The candidate for any type of epilepsy surgery will have had a wide range of tests prior to surgery. These include **electroencephalography** (EEG), in which electrodes are placed on the scalp, on the brain surface, or within the brain to record electrical activity. EEG is used to attempt to locate the focal point(s) of the seizure activity.

Several neuroimaging procedures are used to obtain images of the brain. These may reveal structural abnormalities that the neurosurgeon must be aware of. These procedures may include **magnetic resonance imaging (MRI)**, x rays, computed tomography (**CT**) **scans**, or **positron emission tomography (PET)** imaging.

Neuropsychological tests may be done to provide a baseline against which the results of the surgery are measured. A Wada test may also be performed. In this test, a drug is injected into the artery leading to one half of the brain, putting it to sleep, allowing the **neurologist** to determine where language and other functions in the brain are localized, which may be useful for predicting the result of the surgery.

Aftercare

The patient remains in the hospital for about a week, possibly more depending on any complications that have occurred during surgery and on the health of the patient. There may be some discomfort afterwards. Tylenol with codeine may be prescribed for **pain**. Bending over should be avoided if possible, as it may lead to **headache** in the week or so after the procedure. Ice packs may be useful for pain and itchiness of the sutures on the head. Another several weeks of convalescence at home are required before the patient can resume normal activities. Heavy lifting or straining may continue to cause headaches or nausea, and should be avoided until the doctor approves. A diet rich in fiber can help avoid constipation, which may occur following surgery. Patients remain on anti-seizure medication at least for the short term, and may continue to require medication.

Risks

There is a slight risk of infection or hemorrhage from the surgery, usually less than 1%. Disconnection of the two hemispheres of the brain can cause some neuropsychological impairments such as decreased spontaneity of speech (it may be difficult to bring the right words into one's mind) and decreased use of the non-dominant hand. These problems usually improve over time. Complete cutting of the corpus callosotomy produces more long-lasting, but very subtle deficits in connecting words with images. These are usually not significant, or even noticed, by the patient.

Serious morbidity or mortality occurs in 1% or less of patients. Combined major and minor complication rates are approximately 20%.

Normal results

Patients typically experience a marked reduction in number and severity of seizures, with a small percentage of people becoming seizure free. Drop attacks may be eliminated completely in approximately 70% of patients. Other types of seizure are also reduced by 50% or more from corpus callosotomy surgery.

Resources

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Devinsky, O. *A Guide to Understanding and Living with Epilepsy.* Philadelphia: EA Davis, 1994.

ORGANIZATIONS

Epilepsy Foundation. <www.epilepsyfoundation.org>.

Richard Robinson
Rosalyn Carson-DeWitt, MD

Corticobasal degeneration

Definition

Corticobasal degeneration (CBD) is a rare, progressive, neurodegenerative disease that causes **movement disorders** and **dementia**.

Description

CBD occurs when brain cells in two areas of the brain—the cortex and the basal ganglia—die off. The cause of this neurodegeneration is unknown. CBD is also

called cortical basal degeneration and corticobasal ganglionic degeneration.

Demographics

It is not known exactly how many people have CBD. In the United States, the number is probably fewer than 10,000. Men and women are equally affected. Symptoms usually appear when a person is 50 or 60 years old.

Causes and symptoms

The ultimate cause of CBD is unknown. No genes have been found to be responsible, and no environmental or other risk factors have been identified. The brain areas affected are the cerebral cortex and the basal ganglia. The cerebral cortex is the center of mental activities such as planning, memory, language, and reasoning. The basal ganglia help control movements.

The symptoms of CBD may begin with either movement disorders or cognitive disorders. The movement disorders seen in CBD are similar to those in **Parkinson's disease** (PD), and CBD is often initially misdiagnosed as PD. In CBD, movements become slow and stiff, and may be accompanied by sustained abnormal postures (**dystonia**) or sudden violent jerks (**myoclonus**). Cognitive symptoms include memory impairment, loss of judgment, and difficulty planning or executing movements. Additional features may include impaired speech, and the "alien hand" phenomenon, in which the patient feels disconnected from, and not in control of, a hand or limb. Loss of sensation may also occur.

Diagnosis

Corticobasal degeneration is diagnosed with a neurological exam (testing of reflexes, coordination, sensation, etc.) and neuroimaging studies, including computed tomography (CT) scan and **magnetic resonance imaging (MRI)** to detect characteristic loss of brain tissue. **Neuropsychological testing** is also usually done to determine the kind and degree of cognitive impairment.

Treatment team

The treatment team includes a **neurologist**, **neuropsychologist**, speech/language pathologist, geriatric medicine specialist, and possibly a physical or occupational therapist.

Treatment

There are no treatments that can slow or reverse the course of CBD. Some symptoms can be lessened with drugs, although these are inconsistently effective and become less effective as time passes.

Key Terms

Basal ganglia Brain structure at the base of the cerebral hemispheres involved in controlling movement.

Neurodegenerative Relating to degeneration of nerve tissues.

Drugs used against PD are often prescribed, although they are rarely as effective in CBD. These drugs include levodopa and dopamine agonists, as well as **anticholinergics** such as trihexyphenidyl. Drugs used for Alzheimer's disease may also be tried for the cognitive symptoms.

A speech/language pathologist can help the patient with swallowing difficulties, although over time this problem will become worse and the patient may require the use of a feeding tube. The same specialist can advise about the use of assistive communication devices to improve communication as the ability to speak is lost.

Prognosis

Ability to move without a wheelchair is usually lost within five years of diagnosis. Within 10 years, swallowing difficulties often put the patient at risk for developing aspiration pneumonia, or lung infection from food in the airways. Death from pneumonia is common in CBD.

Resources

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National Institute of Neurological Disorders and Stroke (NINDS). *Corticobasal Degeneration Information Page.* (April 19, 2004). <http://www.ninds.nih.gov/health_and_medical/disorders/cortico_doc.htm>.

Richard Robinson

Cranial arteritis *see* **Temporal arteritis**

Craniosynostosis

Definition

Craniosynostosis is a defect in which one or more of the flexible and fibrous joints (cranial sutures) between the skull bones closes too soon; it occurs before birth or within a few months after birth. The skull cannot expand normally with growth of the brain, and so assumes an abnormal shape. Craniosynostosis can occur alone or as part of a syndrome of craniofacial defects.

Key Terms

Cranial sutures The fibrous joints (sutures) that hold together the five bones comprising the skull of a newborn.

Description

The skull of a newborn is composed of five bones that are held together by the fibrous sutures positioned at the front, top, sides, and back of the skull. By remaining open, the sutures allow the skull to normally expand in all directions as the brain is growing.

The premature closing of one or more of these cranial sutures stops the normal capacity of the skull to expand in early childhood. As not all of the cranial sutures will close, the skull expands in the areas that are still flexible. This results in an abnormally shaped skull or face. The forehead may be very pronounced and inclined forward. Viewed from above, the skull may be more rectangular in shape rather than oval.

Other forms of craniosynostosis include coronal craniosynostosis (affecting the coronal suture that crosses the top of the skull from temple to temple), metopic craniosynostosis (affecting the metopic suture of the forehead), sagittal craniosynostosis (affecting the sagittal suture that unites the two parietal bones), and lambdoidal craniosynostosis (affecting the lambdoid suture between the occipital and parietal bones of the skull).

Demographics

Craniosynostosis is a rare occurrence. The sagittal form of the disorder, in which the sagittal suture closes prematurely, is the most common form of craniosynostosis, occurring in three to five of every 1,000 babies, typically males. The frequencies of the various types of craniosynostosis are 50–60% sagittal, 20–30% coronal, 4–10% metopic, and 2–4% lambdoid.

Causes and symptoms

Craniosynostosis is usually caused by a genetic mutation. Mutations in several genes (designated TWIST, FGFR-1, FGFR-2, and FGFR-3) have been linked with craniosynostosis. In particular, the protein encoded for by TWIST is critical in the initiation and maintenance of the cranial suture process. As of 2004, the favored hypothesis is that the protein that normally functions to ensure that the formation of the cranial sutures occurs at the right time in development somehow goes awry and causes premature fusion of the bones of the brain.

Research published in 2003 in the *Annals of the Royal College of Surgeons of England* identified Saethre-Chotzen syndrome (a rare disorder characterized by an exaggerated forehead and drooping eyelids) as a genetic disorder that produces craniosynostosis.

Craniosynostosis can also be caused by maladies that affect the metabolism (rickets, vitamin D deficiency, overactive thyroid) and by bone marrow disorders. Furthermore, some cases have been associated with an abnormally small head (**microcephaly**) and the accumulation of cerebrospinal fluid in the brain (**hydrocephalus**).

Involvement of the different sutures produces different effects. Closure of the sagittal suture (located at the top of the skull and to the rear) produces an elongated head, prominent and protruding forehead, and narrow temples. Closure of the coronal suture (located on the side of the skull) produces a flattened forehead, higher-than-normal eye socket, abnormal nose, and a skull that slants from side to side. Closure of the metopic suture (which runs down the front-middle portion of the skull) results in a pointed-shaped forehead, triangular-shaped skull, closer-than-normal eyes, and a protruding rear portion of the skull. Finally, closure of the lambdoidal suture (located at the back of the skull) produces a mild flattening of the back of the head, forward-shifted ears, and the coronal symptoms.

Diagnosis

Diagnosis is made on the basis of a physical examination.

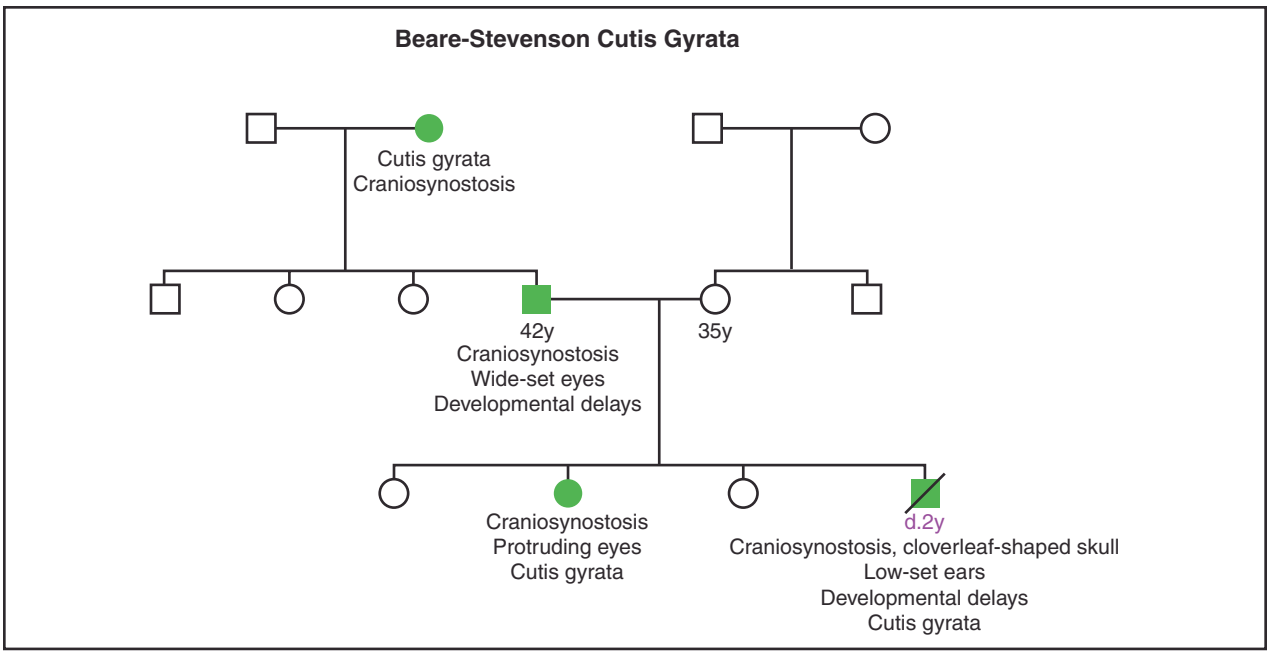
Treatment team

Treatment involves medical specialists (pediatric neurosurgeons, pediatric plastic surgeons, craniofacial surgeons) and specialized nurses.

Treatment

Surgery is the common treatment for craniosynostosis. The traditional surgeries involve the exposure of the skull, physical breakage of the fused suture region, and the restoration of the scalp. These surgeries all carry the risks associated with surgery in the brain region. Also, the surgeries produce much bleeding (sometimes a blood transfusion is necessary) and leave a large scar, and transient swelling and bruising can occur.

A new surgical technique called endoscopic strip craniectomy has been pioneered by two pediatric surgeons from the University of Missouri Health Care Center. This surgery is much less invasive, produces only a relatively small scar, and leaves little physical after effects



See Symbol Guide for Pedigree Charts. *(Gale Group.)*

such as swelling and bruising. In the procedure, an endoscope is used to remove the closed suture through incisions that are only several inches in length. In the more than 100 surgeries performed as of January 2001, most of the infants were in a condition satisfactory enough to leave the hospital the following day. Endoscopic strip craniectomy can only be done on infants under six months of age. After the surgery, the baby wears a protective helmet for several months, which molds the growing head into the correct shape.

Recovery and rehabilitation

Regardless of the type of surgery performed to correct the defects associated with craniosynostosis, the child will be restricted from vigorous activity or rough play while healing. The protective helmet is required for children after endoscopic strip craniectomy, while permanent plates inserted during other corrective surgeries eliminate the need for the helmet. Children who have had surgery to repair craniosynostosis will continue to need periodic examination by the surgeon until approximately age 18, when the skull has grown to its adult size and shape.

Clinical trials

The National Institute for Neurological Diseases and Stroke directly undertakes and funds a range of studies examining the mechanisms of early neurological development. However, there are no **clinical trials** scheduled to study craniosynostosis as of January 2004.

Prognosis

The outlook for a complete recovery for a child with craniosynostosis depends on whether just one suture is involved or whether multiple sutures have closed. Also, the presence of other abnormalities can lessen the confidence of a satisfactory outcome. Without surgical intervention, craniosynostosis can lead to increased brain pressure, delayed mental development, **mental retardation**, **seizures**, or blindness. After surgery is accomplished, the prognosis is excellent.

Resources

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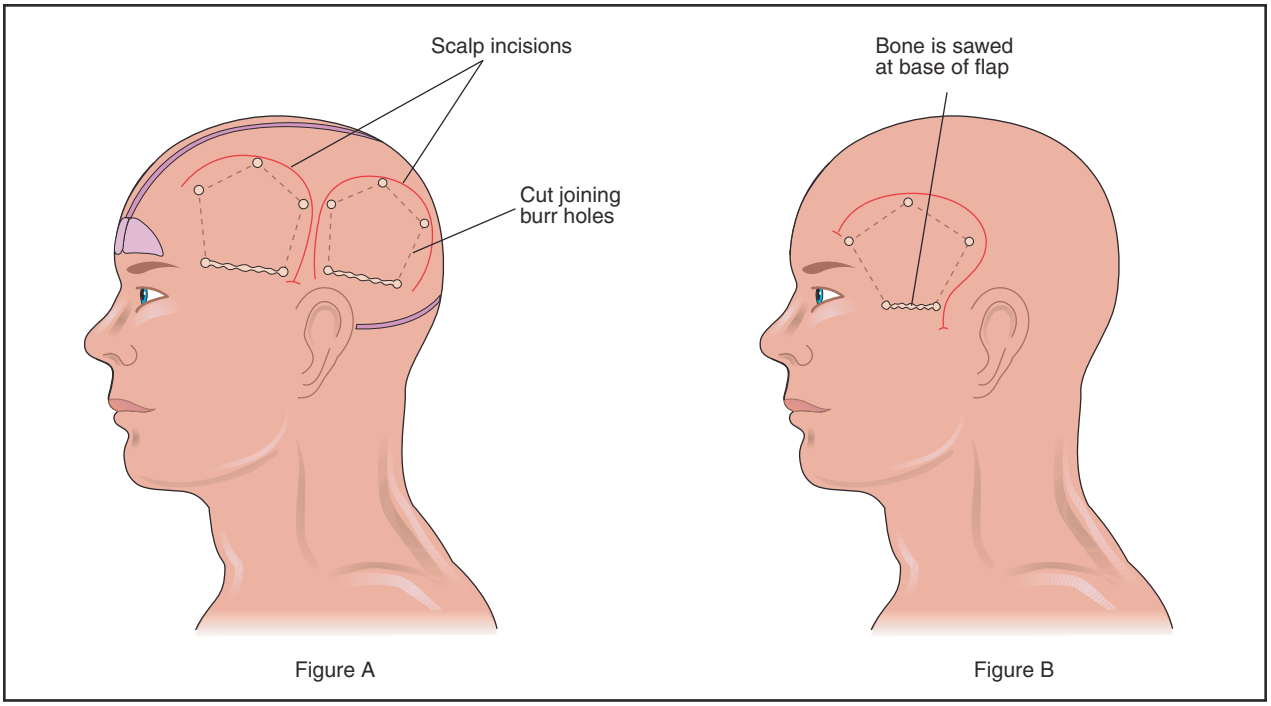
ORGANIZATIONS

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605. (914) 428-7100 or



In a craniotomy, the skin over a part of the skull is cut and pulled back. Small holes are drilled into the skull, and a special saw is used to cut the bone between the holes. The bone is removed, and a tumor or other defect is visualized and repaired. The bone is then replaced and the skin closed. *(Illustration by Electronic Illustrators Group.)*

(888) 663-4637; Fax: (914) 428-8203. askus@marchofdimes.com. <http://www.marchofdimes.com>.

National Organization for Rare Disorders. 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

World Craniofacial Foundation. 7777 Forest Lane, Suite C-621, Dallas, TX 75251-5838. (972) 566-6669 or (800) 533-3315; Fax: (972) 566-3850. worldcf@worldnet.att.net. <http://www.worldcf.org/cran_3c5.html>.

Brian Douglas Hoyle, PhD

Craniotomy

Definition

A craniotomy is a procedure to remove a lesion in the brain through an opening in the skull (cranium).

Purpose

A craniotomy is a type of brain surgery. It is the most commonly performed surgery for brain tumor removal. It also may be done to remove a blood clot (hematoma), to control hemorrhage from a weak, leaking blood vessel (cerebral aneurysm), to repair **arteriovenous malformations** (abnormal connections of blood vessels), to drain a brain abscess, to relieve pressure inside the skull, to perform a **biopsy**, or to inspect the brain.

Demographics

Because craniotomy is a procedure that is utilized for several conditions and diseases, statistical information for the procedure itself is not available. However, because craniotomy is most commonly performed to remove a brain tumor, statistics concerning this condition are given. Approximately 90% of primary brain cancers occur in adults, more commonly in males between 55 and 65 years of age. Tumors in children peak between the ages of 3 and 12. Brain tumors are presently the most common cancer in children (4 out of 100,000).

Description

There are two methods commonly utilized by surgeons to open the skull. Either an incision is made at the nape of the neck around the bone at the back (occipital bone) or a curving incision is made in front of the ear that arches above the eye. The incision penetrates as far as the thin membrane covering the skull bone. During the skin incision, the surgeon must seal off many small blood vessels because the scalp has a rich blood supply.

Key Terms

Abscess A localized collection of pus or infection that is walled off from the rest of the body.

Arteriogram An x-ray study of an artery that has been injected with a contrast dye.

Arteriovenous malformation Abnormal, direct connection between the arteries and veins. Arteriovenous malformations can range from very small to large.

Cerebral aneurysm An abnormal, localized bulge in a blood vessel that is usually caused by a congenital weakness in the wall of the vessel.

Cranium Skull; the bony framework that holds the brain.

Computed tomography (CT) An imaging technique that produces three-dimensional pictures of organs and structures inside the body using a 360° x-ray beam.

Edema An accumulation of watery fluid that causes swelling of the affected tissue.

Hematoma An accumulation of blood, often clotted, in a body tissue or organ, usually caused by a break or tear in a blood vessel.

Hemorrhage Very severe, massive bleeding that is difficult to control.

Magnetic resonance imaging (MRI) An imaging technique that uses magnetic fields and radio waves to create detailed images of internal body organs and structures, including the brain.

The scalp tissue is then folded back to expose the bone. Using a high-speed drill, the surgeon drills a pattern of holes through the cranium (skull) and uses a fine wire saw to connect the holes until a segment of bone (bone flap) can be removed. This gives the surgeon access to the inside of the skill and allows him to proceed with surgery inside the brain. After removal of the internal brain lesion or other procedure is completed, the bone is replaced and secured into position with soft wire. Membranes, muscle, and skin are sutured into position. If the lesion is an aneurysm, the affected artery is sealed at the leak. If there is a tumor, as much of it as possible is resected (removed). For arteriovenous malformations, the abnormality is clipped and the repair redirects the blood flow to normal vessels.

Diagnosis/Preparation

Since the lesion is in the brain, the surgeon uses imaging studies to definitively identify it. Neuroimaging is usually accomplished by the following:

- **Computed tomography** (**CT**) uses x rays and injection of an intravenous dye to visualize the lesion.
- **Magnetic resonance imaging** (**MRI**) uses magnetic fields and radio waves to visualize a lesion.
- An arteriogram is an x ray of blood vessels injected with a dye to visualize a tumor or cerebral aneurysm.

Before surgery the patient may be given medication to ease anxiety and to decrease the risk of **seizures**, swelling, and infection after surgery. Blood thinners (Coumadin, heparin, aspirin) and nonsteroidal anti-inflammatory drugs (ibuprofen, Motrin, Advil, Naprosyn, Daypro) have been correlated with an increase in blood clot formation after surgery. These medications must be discontinued at least seven days before the surgery to reverse any blood thinning effects. Additionally, the surgeon will order routine or special laboratory tests as needed. The night before surgery the patient should not eat or drink after midnight. The patient's scalp is shaved in the operating room just before the surgery begins.

Aftercare

Craniotomy is a major surgical procedure performed under general anesthesia. Immediately after surgery, the patient's pupil reactions are tested, mental status is assessed after anesthesia, and movement of the limbs (arms/legs) is evaluated. Shortly after surgery, breathing exercises are started to clear the lungs. Typically after surgery patients are given medications to control **pain**, swelling, and seizures. Codeine may be prescribed to relieve **headache**. Special leg stockings are used to prevent blood clot formation after surgery. Patients can usually get out of bed in about a day after surgery and usually are hospitalized for five to fourteen days after surgery. The bandages on the skull are be removed and replaced regularly. The sutures closing the scalp are removed by the surgeon, but the soft wires used to reattach the portion of the skull that was removed are permanent and require no further attention. Patients should keep the scalp dry until the sutures are removed. If required (depending on area of brain involved) occupational therapists and physical therapist assess patients status postoperatively and help the patient improve strength, daily living skills and capabilities, and speech. Full recovery may take up to two months, since it

is common for patients to feel fatigued for up to eight weeks after surgery.

Risks

The surgeon will discuss potential risks associated with the procedure. Neurosurgical procedures may result in bleeding, blood clots, retention of fluid causing swelling (edema), or unintended injury to normal nerve tissues. Some patients may develop infections. Damage to normal brain tissue may cause damage to an area and subsequent loss of brain function. Loss of function in specific areas can cause memory impairment. Some other examples of potential damage that may result from this procedure include deafness, double vision, numbness, paralysis, blindness, or loss of the sense of smell.

Normal results

Normal results depend on the cause for surgery and the patient's overall health status and age. If the operation was successful and uncomplicated recovery is quick, since there is a rich blood supply to the area. Recovery could take up to eight weeks, but patients are usually fully functioning in less time.

Morbidity and mortality rates

There is no information about the rates of diseases and death specifically related to craniotomy. The operation is performed as a neurosurgical intervention for several different diseases and conditions.

WHO PERFORMS THE PROCEDURE AND WHERE IS IT PERFORMED?

The procedure is performed in a hospital with a **neurosurgery** department and an **intensive care unit**. The procedure is performed by a board certified neurosurgeon, who has completed two years of **general surgery** training and five years of neurosurgical training.

QUESTIONS TO ASK THE DOCTOR

- How is this procedure done?
- What kinds of tests and preparation are necessary before surgery?
- What risks are associated with the procedure?
- How often is normal brain tissue damaged during this type of surgery?
- What is the expected outcome of the surgery?
- What complications may result from this type of surgery?
- What is the recovery time?
- How many of these procedures have you done in the past year?

Resources

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Connolly, E. Sanders, ed. *Fundamentals of Operative Techniques in Neurosurgery.* New York: Thieme Medical Publishers, 2002.

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ORGANIZATIONS

American Association of Neurological Surgeons. 5550 Meadowbrook Drive, Rolling Meadows, IL 60008. (888) 566-AANS (2267). Fax: (847) 378-0600. info@aans.org. <http://www.neurosurgery.org/aans/index.asp>.

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Creutzfeldt-Jakob disease

Definition

Creutzfeldt-Jakob disease (CJD) is a rapidly progressive disease causing damage to the brain. It is one of a group of rare diseases that affects humans and animals, known as transmissible spongiform encephalopathies (TSE) and is believed to be caused by a prion, a newly

identified type of disease-causing agent. Creutzfeldt-Jakob disease is characterized by **dementia** and walking difficulties. Death can occur up to two years after the first symptoms; however, most people die within seven months. There is no treatment or cure.

Description

Creutzfeldt-Jakob disease is a serious progressive degenerative disorder of the brain that was first described in the 1920s by two German researchers, and is characterized by sudden development of rapidly progressive neurological and neuromuscular symptoms. When symptoms begin, affected individuals may develop confusion, **depression**, behavioral changes, impaired vision, and/or impaired coordination. As the disease progresses, there may be rapidly progressive deterioration of thought processes and memory (dementia), resulting in confusion and disorientation, impairment of memory control, personality disintegration, agitation, and restlessness. Affected individuals also develop neuromuscular abnormalities such as muscle weakness and loss of muscle mass (wasting); irregular, rapid, shock-like muscle spasms (**myoclonus**); and/or relatively slow, involuntary, continual writhing movements, particularly in the arms and legs. Later stages of the disease may include further loss of physical and intellectual functions, a state of unconsciousness (coma), and increased susceptibility to repeated infections of the respiratory tract. In many affected individuals, life-threatening complications may develop less than a year after the disorder becomes apparent.

There are three main forms of CJD, each one with its distinctive basic features. The sporadic CJD, which accounts for approximately 85% of all cases worldwide and occurs by chance, is associated with the presence of a misshapen protein in the brain, known as a prion ("proteinaceous infectious particle"). Sporadic CJD cannot be caught from another person or animal, is not related to diet, nor can it be inherited. On the contrary, inherited (or familial) CJD accounts for 5–10% of all cases of CJD and is caused by a faulty gene called prion-related protein (PRPN) that is passed down from parents to their children in a dominant inheritance, which means patients will develop the disease if they inherit a defective gene from just one parent. Symptoms are similar to sporadic CJD, but they appear earlier and have a longer time course.

Unlike the previous two CJD forms, acquired CJD affects those people who have not inherited the condition by two other ways. The iatrogenic CJD occurs due to accidental infection after medical procedures such as human pituitary hormone injection or dura mater transplantation. The variant CJD (vCJD), a type of CJD that was first identified in 1996, is passed from cows with bovine spongiform **encephalopathy** (BSE, or "mad cow disease") to humans. The variant form affects mostly younger adults and has different clinical and pathological characteristics.

Key Terms

Encephalopathy A disease or dysfunction of the brain.

Myoclonus Twitching muscular contractions.

Prion A protein particle lacking nucleic acid and thought to be the cause of certain infectious diseases of the central nervous system, such as Creutzfeldt-Jakob disease.

All forms of CJD can be present in a person for long periods (often more than 20 years) during which there are no symptoms. The duration of the illness before death varies from a matter of weeks (typical of sporadic CJD) to three to twelve months (typical of variant CJD). However, there have been exceptions in both types.

Demographics

CJD appears to affect males and females in equal numbers. It occurs worldwide with an incidence rate that has remained stable at approximately one case per million people, annually. It usually first appears in mid-life, beginning between ages 20 and 68, with the average age at onset of symptoms being around age 50. The onset of the iatrogenic form depends on the age of exposure.

Causes and symptoms

All forms of CJD are caused by the presence of a faulty protein in the brain, called prion. Prions occur in both a normal form, which is a harmless protein found in the body's cells, and in an infectious form, which causes disease. The harmless and infectious forms of the prion protein are nearly identical, but the infectious form takes a different folded shape. Sporadic CJD may develop because some of a person's normal prions spontaneously change into the infectious form of the protein and then alter the prions in other cells in a chain reaction by a mechanism that is not yet understood. Misfolded protein molecules then spread through the brain and stick together to form fibers and/or clumps called plaques that can be seen with powerful microscopes. These bundles of twisted protein disrupt brain cells and eventually leave large holes in the brain tissue, giving the brain a spongy appearance. Fibers and plaques may start to accumulate years before symptoms of CJD begin to appear. It is still unclear what role these abnormalities play in the disease or how they might affect symptoms.

About 5–10% of all CJD cases are inherited. These cases arise from a mutation, or change, in the gene PRPN that controls formation of the normal prion protein. While prions themselves do not contain genetic information and do not require genes to reproduce themselves, infectious prions can arise if a mutation occurs in the gene for the body's normal prions. If the prion gene is altered in a person's sperm or egg cells, the mutation can be transmitted to the person's offspring. Several different mutations in the prion gene have been identified. The particular mutation found in each family affects how frequently the disease appears and what symptoms are most noticeable. However, not all people with mutations in the prion gene develop CJD. This suggests that the mutations merely increase susceptibility to CJD and that other, still-unknown factors also play a role in the disease.

CJD does not cause any symptoms at first. The first symptoms to appear include slow thinking, difficulty concentrating, impaired judgment, memory loss, personality and behavioral changes, and difficulties with coordination and vision. These symptoms rapidly give way to increasing mental deficits leading to severe, progressive dementia (mental decline) associated with self-neglect, apathy or irritability, and prominent muscle spasms (myoclonus). **Seizures** commonly occur as the disease progresses. Symptoms continue to worsen until both mental and physical functions are lost; patients are completely bedridden, and eventually lapse into coma. Comatose patients may die as a result of infection associated with being immobile, such as pneumonia.

Diagnosis

There is currently no single diagnostic test for CJD. Indeed, the only definitive diagnosis can be assessed by a postmortem examination (autopsy) of the brain or examining a sample of brain tissue (brain **biopsy**). However, CJD should be considered in adults who experience a sudden onset of rapidly progressive dementia and neuromuscular symptoms such as myoclonus.

An electroencephalogram (EEG) and a **magnetic resonance imaging (MRI)** scan may be useful in determining abnormalities in the brain. People may be diagnosed as having "probable CJD." Although not definitive, all those who have been diagnosed as probable CJD in life, and who subsequently had an autopsy, were found to have been a CJD patient. Genetic testing can be carried out in people suspected of having the inherited form of CJD, in order to increase certainty of diagnosis. Such people usually report a family history of the disease.

Iatrogenic CJD is usually diagnosed on the basis of the affected person's medical history. Those at risk include people having received hormones derived from humans before 1992, or dura mater transplant grafts before 1985.

Treatment team

A **neurologist** or a psychiatrist is normally the primary consultant for CJD, and continual nursing care may be necessary as disease progresses. Physical therapist may also be required.

Treatment

As of 2004, no treatment has been shown to be effective against CJD. Treatments are available to alleviate some symptoms, such as morphine for muscle **pain**, and clonazepam (Rivotril) or sodium valproate (Epilim) for jerky movements. A wide range of drugs has been tested for their ability to slow the progress of the disease, but none has been shown to be useful.

At present, care consists of managing the specific problems faced by patients with CJD. Speech therapy and occupational therapy may help, and the support of district nurses and social services is often invaluable for people with CJD and their caregivers.

Recovery and rehabilitation

Because CJD is an incurable, fatal disease with a fast progression, recovery and rehabilitation are not possible. The emphasis in treatment is placed upon comfort and support of the affected individual and the caregivers.

Clinical trials

As of mid 2004, there are no ongoing **clinical trials** for CJD.

Prognosis

The outcome for a person with CJD is usually very poor. Complete dementia commonly occurs within six months or less after the appearance of the first symptoms, with the person becoming totally incapable of self-care. The disorder is fatal in a short time, usually within seven months, but a few people survive as long as one or two years after diagnosis. The cause of death is usually infection, heart failure, or respiratory failure.

Special concerns

Hospitals and health care providers take special precautions to minimize the risk of transferring prions from surgical equipment or donated tissues. Medical histories of potential cornea donors that indicate a familial history of possible Creutzfeldt-Jacob disease rule out the use of those corneas for transplantation. Additionally, regulations and records regarding livestock feed and transfer of livestock are maintained by the United States Department of Agriculture.

A patient about to undergo a CAT scan to check for brain cancer. *(© Roger Ressmeyer/CORBIS. Reproduced by permission.)*

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Creutzfeldt-Jakob (CJD) Foundation Inc. P.O. Box 5312, Akron, OH 44334. (330) 668-2474 or (800) 659-1991. crjakob@aol.com. <http://www.cjdfoundation.org>.

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CT scan

Definition

Computed tomography (also known as CT, CT scan, CAT, or computerized axial tomography) scans use x rays to produce precise cross-sectional images of anatomical structures.

Description

With the development of modern computers, the scans enhanced digital capabilities allowed the development of computed tomography imaging (derived from the Greek *tomos*, meaning "to slice"). The diagnostic potential of CT scans was first realized by English physician Godfrey Hounsfield.

CT scans differ from conventional x ray by collecting x rays that have passed through the body (those not absorbed by tissue) with an electronic detector mounted on a rotating frame rather than on film. The x-ray source and collector rotate around the patient as they emit and absorb x rays. CT technology then utilizes advanced computer-based mathematical algorithms to combine different readings or views of a patient into a coherent picture usable for diagnosis.

Key Terms

Computerized axial tomographic (CAT) scan A scanning method, also called CT scanning, that uses diagnostic x rays and a computer to give cross-sectional images at different angles of the brain and other parts of the body.

Radiologist A physician who specializes in imaging techniques such as x rays, CAT scans, MRI scans, and certain scans using radioactive isotopes.

X ray Electromagnetic radiation of very short wavelength, and very high energy.

CT scans increase the scope and safety of imaging procedures that allow physicians to view the arrangement and functioning of the body's internal structures. With particular regard to neurology, CT scans are used to determine the presence or absence of brain tumors. CT scans usually take about an hour and a half, including preparation time, with the actual examination of neural tissue in a brain scan taking 15–45 minutes.

CT scanners are now often combined with **positron emission tomography (PET)** scanners into one unit. PET-CT scanners have the ability to link the functional image created by a **PET** scan with the anatomical image produced by a CT scan. The combined scanning technique enhances a physician's ability to detect metabolic abnormalities (some no larger than 0.15 in [4 mm] in size) and to precisely map the location of the anomaly.

Increased accuracy reduces the number of unusable results and also results in less retesting.

The combined PET-CT scanners offer physicians the opportunity to differentiate, for example, between Alzheimer's disease and **multi-infarct dementia**. In addition, the enhanced images allow the differentiation of brain tumors from cerebral necrosis.

The physics

The physical basis of the CT scans lies in the fact that different tissues absorb x rays at different rates. The density and atomic number of the elements present are critical factors in determining whether a particular x ray is absorbed or passes through the body. The opacity of an image is related directly to the type of tissue or element. Dense bone appears white, while gaseous air in the lungs appears black.

CT scans are also used by some security agencies to examine packages and baggage.

CT scan procedures

CT scan allow the construction of detailed images and offer another, and in many cases, more affordable means of diagnosis without invasive surgical procedures. CT scans can also be used to guide the course of surgical procedures.

CT scans often utilize a medium or contrast enhancer, provided in the form of a drinkable liquid or via injection into the patient's bloodstream. Approximately 45 minutes before a patient is examined, the individual is given an intravenous injection of a radiopharmaceutical tracer. A brain scan and scan of the spinal cord can take less than 30 minutes.

Radiation exposure from a CT exam is roughly equal to a normal year's worth of exposure to natural background radiation—more than from a conventional x-ray examination, but less than that of other x-ray exams such as a skull x ray.

Because x rays are high energy rays that can damage critical cells in the developing embryo, women who suspect that they are pregnant should inform their doctor and the CT scan technologist prior to the exam. Nursing mothers are often advised to wait 24 hours after the injection of the contrast medium before resuming breast-feeding.

Because CT scans provide only axial cross-sections, an **MRI** test is often used to more carefully examine unusual or suspect findings.

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Paul Arthur

Cumulative trauma disorders *see* **Repetitive motion disorders**

Cushing syndrome

Definition

Cushing syndrome was first described by an American neurosurgeon in the early twentieth century named Harvey Cushing. Cushing recognized a specific set of symptoms that collectively he identified as part of a syndrome. In this disease, prolonged exposure to abnormal

levels of the hormone cortisol results in the collection of symptoms that Harvey Cushing described. Cushing Syndrome can also be associated with abnormal levels of another hormone, adrenocorticotropin (ACTH), and both ACTH and cortisol overproduction can often occur as part of other disorders.

Description

Cushing syndrome affects the body in many ways and can lead to severe medical complications if untreated. Effects of the disorder are manifested clinically, physically, and emotionally. Physically, patients develop an abnormal fat distribution that sometimes leads to feelings of insecurity or unattractiveness. Clinically, people with Cushing syndrome are often at risk for a variety of significant medical problems including diabetes, high blood pressure, hair loss (especially in women), and heart disease. Cushing syndrome is relatively rare. Severe **fatigue** can also develop and this has many ramifications in terms of complications related to daily living. Cushing syndrome is sometimes referred to as hypercortisolism.

Demographics

According to the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK), an estimated 10 to 15 individuals out of every million people will be affected each year with Cushing syndrome. These individuals are usually adults between the ages of twenty to fifty years old. Pituitary adenomas cause the majority of Cushing syndrome cases, and women that have these types of tumors are at a five-fold higher risk for developing the disease than men.

Causes and symptoms

The function of cortisol is to regulate blood pressure, act as an anti-inflammatory mediator, and to regulate insulin metabolism. Cortisol plays a role during the metabolic activities associated with fat, protein, and carbohydrate metabolism. High levels of cortisol can cause sodium and water retention. Therefore, overproduction of cortisol can have medically important health-related implications that affect muscle contractions, heartbeat, and blood cell function.

The adrenal glands are located on top of each kidney, and are responsible for releasing cortisol. The site of cortisol production is in the outer layer of the adrenal gland called the adrenal cortex. Release of cortisol is stimulated by ACTH, which is produced by another gland. This gland, called the pituitary gland, is juxtaposed to the base of the brain and serves as a type of control center for many other glands in the body. ACTH production occurs only when there is a low concentration of cortisol in the blood. Therefore, cortisol production can be abnormal due to abnormalities in the function of the adrenal gland or the pituitary gland. It can also be overproduced by abnormal regulation of ACTH.

The role of cortisol in tumor formation

Cortisol overproduction can also be caused by many different types of tumors resulting in abnormalities in the function or regulation of the adrenal or pituitary glands. These tumors are usually not malignant and are found in the pituitary and adrenal glands. In the pituitary gland, a specific type of tumor called an adenoma can develop. Pituitary adenomas often can excessively overproduce ACTH in the absence of the normal stimulatory signals. People that develop Cushing syndrome are most likely to develop this disease due to these types of tumors. ACTH overproduction can also occur when the tumor is located outside of the pituitary gland; this condition is known as ectopic ACTH syndrome. These tumors, unlike pituitary adenomas, tend to be cancerous. Tumors can also develop in the adrenal gland and result in excessive cortisol production. Adrenal tumors can often result in malignancy, and patients with these tumors often quickly become symptomatic due to the high levels of cortisol produced.

Familial Cushing syndrome

Cushing syndrome can also develop in multiple individuals from the same family. This familial form is due to a genetically inherited susceptibility to developing specific endocrine tumors. The specific nature of the genetic components have not been clearly elucidated, except in cases of a rare genetic disease called Multiple Endocrine Neoplasia (MEN). MEN is caused by a genetic mutations in a specific gene involved in cell cycle regulation resulting in pituitary tumors that can lead to Cushing syndrome.

The symptoms associated with Cushing syndrome can be easily recognizable by an experienced physician. These clinical manifestations include physical characteristics that involve the face, neck, shoulders, and abdomen. Generally, most affected individuals develop obesity of the upper portion of their bodies. They often have thin arms and legs. The facial feature that characterizes Cushing syndrome is the typically developed round, moon-shaped face. An accumulation of fat pads are often observed on or below the base of the neck, on the patients back, between the patient's shoulders, as well as on the abdomen. Abdominal fat accumulation can be significant and can also be associated with vertical purplish striations (stretch marks). Stretch marks also can be observed on their thighs, arms, breasts, and buttocks. Affected children often suffer from obesity along with growth retardation.

Other clinical manifestations resulting from excessive cortisol production can be quite serious. **Myopathy**, or

Key Terms

Adrenocorticotropic hormone (ACTH) Also called adrenocorticotropin or corticotropin, this hormone is produced by the pituitary gland to stimulate the adrenal cortex to release various corticosteroid hormones.

Cortisol A steroid hormone secreted by the adrenal cortex that is important for maintenance of body fluids, electrolytes, and blood sugar levels. Also called hydrocortisone.

Pituitary gland The most important of the endocrine glands (glands that release hormones directly into the bloodstream), the pituitary is located at the base of the brain. Sometimes referred to as the "master gland," it regulates and controls the activities of other endocrine glands and many body processes including growth and reproductive function. Also called the hypophysis.

wasting away of the muscles often occurs. Due to the abnormal blood cell development that results from cortisol overproduction, the skin bruises more frequently and wounds do not heal as quickly. Skin tends to be fragile and thin. People with Cushing syndrome are susceptible to developing fractures, especially in the pelvic and spinal regions. Women are at a higher risk for developing osteoporosis or brittle bones. Men also frequently develop weak bones. For all affected individuals, difficulty with activities such as lifting objects or getting up from a sitting position can lead to **back pain** and fractures. Because cortisol is also important for regulating insulin, patients with Cushing syndrome are at risk for developing diabetes.

Diagnosis

The diagnosis of Cushing syndrome is based on the patient's family history and the results from several laboratory tests. The most definitive diagnostic laboratory test is to monitor cortisol production in the person's urine during a 24-hour collection period. A 50–100 microgram result represents the normal cutoff, with any higher value suggestive of Cushing syndrome.

When cortisol is found to be high, x rays are usually requested to identify pituitary or adrenal tumors. A dexamethasone suppression test is often requested with a positive finding on x ray and is used to distinguish between ACTH overproduction due to pituitary adenomas or other tumors. Dexamethasone is a synthetic hormone that, when used to help diagnose Cushing syndrome, is usually orally administered for four days at increasing dosages, during which time the urine is collected. The effect on blood and urine cortisol concentrations can be determined and the different effects can distinguish these two types of ACTH-producing tumors. Radiological imaging such as **MRI** scans sometimes allow endocrinologists (physicians who specialize in hormone-related health concerns) to directly visualize the glands and determine their size and shape.

Treatment team

Several types of medical doctors are usually required for the diagnosis and treatment of Cushing syndrome. This includes an oncologist, a pathologist, or an endocrinologist. Although it is unlikely that a child would develop this disease, treatment would depend on whether the child has progressed through puberty. As Cushing syndrome in children can result in growth retardation, a pediatric endocrinologist would be the most likely specialist to monitor the child's development.

Treatment

Determining the appropriate treatment for individuals with Cushing syndrome relies on the accurate determination of the cause of excessive cortisol production. As there are a variety of causes, selecting the appropriate treatment depends on characterizing the disease based on the precipitating spectrum of clinical manifestations. For example, abnormal function of the pituitary gland or the adrenal cortex can be important indicators of causation. For this reason, it is important that affected individuals have a comprehensive clinical evaluation by an experienced physician. Tumors of the pituitary gland or the adrenal cortex can stimulate overproduction of ACTH or cortisol. Medical treatments with cortisone for unrelated conditions may also alter the amount of cortisol exposure and concentration circulating within the body.

In cases that involve pituitary tumors as the cause of Cushing syndrome, surgical removal represents a formidable treatment in cases where chemotherapy or **radiation** is ineffective. Transsphenoidal adenomectomy, a surgical procedure, is the most widely used treatment for pituitary adenomas that cause Cushing syndrome. This usually requires a specialized surgeon or treatment center, as it is a relatively rare and difficult procedure. The success rate is high and synthetic hormone replacement therapy, typically with prednisone, is only necessary for approximately one year. As an alternative, radiation therapy is also a possibility. There are also therapeutic agents that inhibit cortisol production that can be used.

Adrenal gland tumors are usually always surgically removed, whether they are benign or malignant. Adrenal gland removal typically does not affect endocrine function

due to compensation from other glands in producing hormones. Hormone therapy is required with removal of both adrenal glands.

If the cause of Cushing syndrome is drug-induced, due to prolonged exposure to steroids called **glucocorticoids** that are used to treat other ailments, the physician will lower this dose as long as symptoms continue to be manifested.

Recovery and rehabilitation

Transsphenoidal adenomectomy performed by an experienced surgeon has a high success rate, with more than 80% of patients cured. In the event that the surgery is not successful or it provides only a temporary cure, it is often repeated with fairly favorable results. For radiation therapy, adding one of many drugs that suppresses cortisol production such as mitotane can enhance recovery time. These drugs have been considered to be effective when used alone in up to 40% of patients.

As scientists and clinicians better understand how cortisol and ACTH are produced and how disturbances in hormonal regulation affect the body, more treatment modalities will likely become available.

Clinical trials

The National Institutes of Health sponsors several scientists in clinical translational research in Cushing syndrome treatment, as well as the development of drugs leading to **clinical trials**. As of early 2004, there were at least eight ongoing clinical trials recruiting patients. These include long term post-operative follow ups, the evaluation of novel imaging techniques, understanding the role of stress and **depression** in Cushing syndrome, and other studies investigating adrenal and pituitary gland tumors. Further information on clinical trials can be found at the National Institutes of Health website on clinical trials, *ClinicalTrials.gov,* available at: <http://www.clinicaltrials.gov/ct/search?term=cushing+syndrome>.

Prognosis

The prognosis for individuals who receive treatment for Cushing syndrome is good with a high likelihood of being cured. However, in affected individuals that are not treated, the prognosis can be poor, with death eventually resulting from complications from hypertension, diabetes, or heart disease.

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Cushing's Support and Research Foundation, Inc. 65 East India Row 22B, Boston, MA 02110. (617) 723-3824 or (617) 723-3674. cushinfo@csrf.net. <http://csrf.net/>.

Pituitary Network Association. P.O. Box 1958, Thousand Oaks, CA 91358. (805) 499-9973; Fax: (805) 480-0633. pna@pituitary.org. <http://www.pituitary.org>.

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Cytomegalic inclusion body disease

Definition

Cytomegalic inclusion body disease (CIBD) is a condition caused by infection with cytomegalovirus (CMV), a type of herpes virus. A hallmark of CIBD is the periodic reappearance of symptoms throughout life, as the virus cycles through periods of latency and active infection.

Description

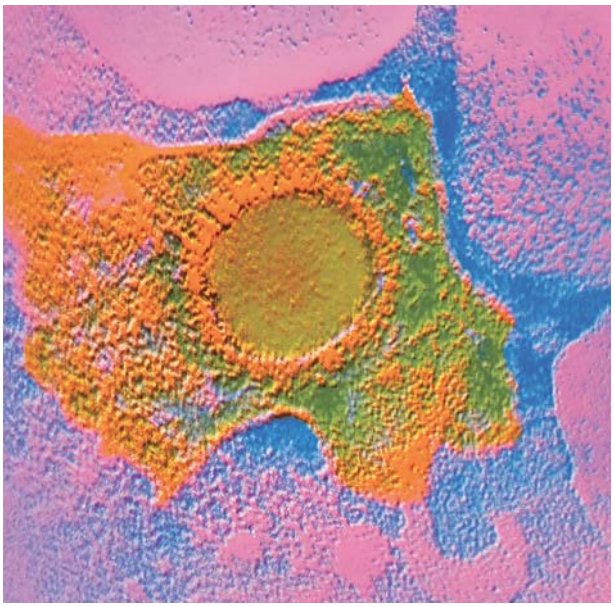
CMV is one of the members of the herpes virus group, which includes herpes simplex types 1 and 2, and the viruses that cause chicken pox and infectious mononucleosis. The virus causes enlargement of cells of some organs and the development of inclusion bodies—bits of cellular material—in the cytoplasm or nucleus of these cells. A hallmark of the virus group is the ability to infect a host and then become dormant. CMV can remain dormant for years. Even in periods without symptoms, the

Key Terms

Cytomegalovirus A member of the herpes virus group found throughout all geographic locations and socioeconomic groups; virus usually remains dormant throughout life, reactivating when the body's immune system is severely debilitated.

Immunocompromised An abnormal condition in which the body's ability to fight infection is decreased, due to a disease process, certain medications, or a condition present at birth.

Inclusion body A small intracellular body found within the cytoplasm or nucleus of another cell, characteristic of disease.



Part of the cytomegalovirus. *(CNRI / Photo Researchers, Inc.)*

virus can still be periodically shed from the body in fluids like tears, saliva, blood, semen, and breast milk. The virus can infect another person through close contact.

Many people with CMV can harbor the virus and display no symptoms. However, if the immune system is damaged or otherwise not functioning efficiently, the virus can reactivate from its dormancy. Cytomegalic inclusion body disease is also known as giant cell inclusion disease, cytomegalovirus infection, and salivary gland disease.

Demographics

The latent infection caused by CMV occurs virtually all over the world and is very common in any population. In the United States, up to 50–85% of people will be infected by the age of 40. CMV infection without symptoms is common in infants and young children. CMV infection is most widespread in economically debilitated regions, although people in developed countries are also susceptible.

Additionally, the virus can be readily transferred from a pregnant mother to the fetus. An infected pregnant woman may not display any symptoms. However, the fetus of a mother with CIBD is at risk for problems, including lung disease, bleeding, anemia, liver damage, or brain damage. CIBD is also a problem among those whose immune systems are not functioning properly or have not yet matured. This includes the unborn, people infected with the human immunodeficiency virus (HIV), and those whose immune systems have been deliberately disabled (i.e., organ transplant recipients).

Causes and symptoms

The cytomegalovirus is the cause of CIBD. When the infection occurs in healthy people after birth, symptoms can be minimal or even nonexistent. Some people experience mild symptoms similar to those of mononucleosis, including a prolonged fever, **fatigue**, mild hepatitis, and tender lymph nodes.

In a fetus, newborn, or a person with a compromised immune system, CIBD can be much more severe. With CIDB, people suffering from acquired immunodeficiency syndrome (**AIDS**) or people recovering from kidney and or other transplant surgeries can also develop inflammation of the retina of the eyes (retinitis) or encephalitis. Retinitis is more common, and in severe cases, blindness can result.

CIBD can cause death of a fetus or a premature birth. In infected newborns, CIBD can be apparent as a lung infection, excessive bleeding, anemia, liver damage, enlargement of the spleen, **seizures**, and inhibited brain development. The latter can result in hearing loss, developmental delays, and difficulty in coordination.

CMV-related polyradiculopathy also causes leg weakness, bowel dysfunction, and bladder dysfunction in end-stage AIDS patients suffering CMV infection.

Diagnosis

Diagnosis is based on the detection of the symptoms of CIBD. Because symptoms can be absent, diagnosis is often overlooked or difficult. If the virus is actively dividing, antibodies to the virus may be detectable by immunological tests of the blood such as the enzyme-linked

immunosorbant assay (ELISA). As the antibodies persist for life, their detection is not a guarantee of an ongoing infection. The virus can also be isolated from urine and other body fluids.

One diagnostic feature associated with retinitis is the description of moving black spots in the eye. Although these "floaters" are common even in healthy individuals, they can also be the result of inflammation of the retina, and can alert a physician to the possibility of CIBD.

Treatment team

Treatment is usually maintained by the primary care physician for otherwise healthy patients. For those who are deliberately immunocompromised, newborns, and AIDS patients, a battery of specialists, including immunologists and specialists in infectious disease, can be involved in treatment and care.

Treatment

There is no cure for CIBD. Typically, good hygiene, including proper hand washing, is recommended to avoid transmission of the virus from person to person. **Antiviral drugs** such as ganciclovir and acyclovir can be administered, particularly to AIDS patients to reduce the amount of virus in the body. These drugs are taken throughout life. There are no vaccines for CIBD.

Recovery and rehabilitation

The CMV infection persists throughout life, therefore, rehabilitation efforts focus on supportive measures to combat CMV-caused complications, minimize the effect of symptoms, and minimize the possibility for transmission of the virus.

Clinical trials

As of February 2004, there are no specific CIBD **clinical trials** underway.

Prognosis

Most people who are infected with CMV display no symptoms and have no residual effects of the infection. However, in immunocompromised people, newborns, and unborn babies, the infection can cause serious illness or death.

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National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

Brian Douglas Hoyle, PhD

Cytomegalovirus infection *see* **Cytomegalic inclusion body disease**

D

Dancing eyes-Dancing feet syndrome *see* **Opsoclonus myoclonus**

Dandy-Walker syndrome

Definition

Dandy-Walker syndrome refers to a group of specific, congenital (present at birth) brain malformations, and is a common cause of **hydrocephalus** (increased fluid in the brain).

Description

Dandy-Walker syndrome is more often referred to as Dandy-Walker malformation (DWM) or Dandy-Walker complex. The condition is named for doctors Walter E. Dandy and Arthur E. Walker, who described the signs and symptoms of the condition in the early 1900s.

The brain contains four ventricles, which are inner, hollow portions filled with cerebrospinal fluid (CSF). The first and second (lateral) ventricles are inside the cerebral hemispheres, and the third and fourth ventricles are below them, closer to the brainstem. DWM consists of a specific group of brain malformations, including enlargement of the fourth ventricle, complete or partial agenesis (lack of development) of the cerebellar vermis (the middle portion of the **cerebellum**, which lies directly behind the cerebral hemispheres), and cyst formation and dilation of the posterior fossa (a small, hollow section between the lower cerebellum and skull).

A further defining characteristic of DMW is blockage or closure of the foramina (openings) of Magendie and Luschka, two channels at the base of the brain through which CSF normally flows. When these openings are obstructed, CSF produced in the ventricles has no outlet for normal circulation. This causes fluid pressure to build, and the ventricles to enlarge (always the fourth, and often the third and lateral ventricles).

Demographics

About one in 1,000 children is born with hydrocephalus. Of those, 10% have DWM as the underlying cause of their condition. DWM has not been shown to be more frequent in any particular ethnic group or race. About 85% of babies born with DWM have one or more other congenital malformations, or some type of recognizable syndrome. The 15% that have no other malformations may be said to have "isolated" DWM.

Causes and symptoms

The true cause of DWM is unknown. However, the components of the malformation seem to be related to a disruption in development of the middle portion of the lower part of the brain in the embryonic stage. This affects growth and development of the cerebellum, especially the vermis, and the brainstem such that the foramina of Magendie and Luschka are partially or completely closed.

Most cases of isolated DWM occur by chance (sporadic) and have very little risk of recurrence in siblings or children of the affected individual. In a few cases, DWM may be inherited as an autosomal recessive trait, which would imply a 25% risk for recurrence in siblings.

Some syndromes that may occur with DWM are chromosomal (abnormal number of chromosomes in every cell of the body—usually sporadic), while others are hereditary. The empiric recurrence risk for non-syndromic DWM with other anomalies is about 5% for siblings or children of the affected individual.

Outward physical signs of DWM may be a bulging occiput (lower rear portion of the skull) and an increased total head circumference. Symptoms of DWM are those caused by hydrocephalus (if present) and dysgenesis/agenesis of the cerebellar vermis. In infants, symptoms can include irritability, **seizures**, vomiting, abnormal breathing, nystagmus (jerky eye movements), and slow motor development. Older children and adults may have **headaches**, **ataxia** (difficulties with coordination), **visual disturbances**, and/or developmental delay/mental retardation.

Key Terms

Cerebellum The part of the brain involved in the coordination of movement, walking, and balance.

Cerebrospinal fluid The clear, normally colorless fluid that fills the brain cavities (ventricles), the subarachnoid space around the brain, and the spinal cord and acts as a shock absorber.

Hydrocephalus An abnormal accumulation of cerebrospinal fluid within the brain. This accumulation can be harmful by pressing on brain structures, and damaging them.

Ventricles The four fluid-filled chambers, or cavities, found in the two cerebral hemispheres of the brain, at the center of the brain, and between the brain stem and cerebellum, and linked by channels, or ducts, allowing cerebral fluid to circulate through them.

Ventriculoperitoneal shunt A tube equipped with a low-pressure valve, one end of which is inserted into a cerebral ventricle, the other end of which is routed into the peritoneum, or abdominal cavity.

Diagnosis

DWM may be diagnosed in pregnancy by ultrasound as early as 12–14 weeks after conception, although ultrasounds later in pregnancy are more sensitive. A level II ultrasound, a more detailed examination that can only be performed 18 weeks or later after conception, may be suggested to confirm the diagnosis of DWM and will look for the presence of other malformations. An amniocentesis, a procedure to analyze fetal chromosomes, is also usually offered.

After birth, DWM may be suspected because of physical or neurological signs, but it is only possible to establish the diagnosis of DWM by performing imaging studies of the brain through a computed tomography (CT) scan or **magnetic resonance imaging (MRI)**.

Treatment team

A neurosurgeon would perform any surgical procedures (such as shunts) needed to help relieve hydrocephalus or intracranial cysts. Depending on the severity of any neurological symptoms and the presence or absence of other congenital malformations, various specialists involved in the care of a child with DWM can include a neonatologist (specialist in the care of newborns), developmental pediatrician, geneticist, **neurologist**, specialized nursing care, and occupational/physical therapists (OT/PT).

Treatment

The primary treatment for DWM and associated hydrocephalus is the placement of a ventriculoperitoneal (VP) shunt. This is a procedure in which a neurosurgeon places one end of a small tube in a ventricle in the brain, and threads the other end under the skin down to the peritoneal (abdominal) cavity. The tube helps to direct excess CSF to the peritoneal cavity where it is reabsorbed by the body.

In some cases, the neurosurgeon may attempt a procedure called endoscopic fenestration. In this procedure a small, flexible viewing device, called an endoscope, is inserted into the brain and an opening is made between the third and fourth ventricles or in the foramina at the base of the brain. It is hoped that opening these passages will equalize CSF pressure throughout the **central nervous system**.

Other treatments include those for the symptoms of hydrocephalus and cerebellar agenesis, such as anti-seizure medications, and OT/PT for neuromuscular problems.

Recovery and rehabilitation

Some children recover completely after a shunt is placed, while others receive partial benefit. Shunting procedures are not always successful, and they carry a risk for serious infection. A child who retains neurologic deficits will likely require long-term care by a neurologist and OT/PT. Special accommodations for home care may also be needed.

Clinical trials

There are no **clinical trials** for Dandy-Walker syndrome.

Prognosis

Prognosis for DWM varies anywhere from excellent to fatal. The overall prognosis for DWM that occurs and is diagnosed as part of a known syndrome will depend on the possible prognoses for that particular syndrome, although the presence of DWM may have a negative impact. In other cases, DWM without other anomalies has a much better prognosis. As noted, prognosis is also critically dependent on the degree of hydrocephalus already present at birth or at the time of diagnosis.

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Dandy-Walker Syndrome Network. 5030 142nd Path W, Apple Valley, MN 55124. (952) 423-4008.

Hydrocephalus Association. 870 Market Street, Suite 705, San Francisco, CA 94102. (888) 598-3789; Fax: (415) 732-7044. <http://www.hydroassoc.org>.

Hydrocephalus Research Foundation. 1670 Green Oak Circle, Lawrenceville, GA 30243. (770) 995-9570; Fax: (770) 995-8982.

Hydrocephalus Support Group, Inc. PO Box 4236, Chesterfield, MO 63006-4236. (636) 532-8228; Fax: (314) 995-4108.

National Hydrocephalus Foundation. 12413 Centralia Road, Lakewood, CA 90715-1623. (888) 857-3434; Fax: (562) 924-6666. <http://nhfonline.org>.

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Dawson disease *see* **Subacute sclerosing parencephalitis**

de Morsier syndrome *see* **Septo-optic dysplasia**

Deafness *see* **Hearing disorders**

Decerebrate posturing *see* **Abnormal body posture**

Decorticate posturing *see* **Abnormal body posturing**

Deep brain stimulation

Definition

In deep brain stimulation (DBS), electrodes are implanted within the brain to deliver a continuous low electric current to the target area. The current is passed to the electrodes through a wire running under the scalp and skin to a battery-powered pulse generator implanted in the chest wall.

Purpose

DBS is used to treat **Parkinson's disease** (PD) and essential tremor (ET). It has also been used to treat **dystonia**, chronic **pain**, and several other conditions

The **movement disorders** of PD and ET are due to loss of regulation in complex circuits within the brain that control movement. While the cause of the two diseases differ, in both cases, certain parts of the brain become overactive. Surgical treatment can include destruction of part of the overactive portion, thus rebalancing the regulation within the circuit. It was discovered that the same effect could be obtained by electrically stimulating the same areas, which is presumed to shut down the cells without killing them.

DBS may be appropriate for patients with PD or ET whose symptoms are not adequately controlled by medications. In PD, this may occur after five to ten years of successful treatment. Continued disease progression leads to decreased effectiveness of the main treatment for PD, levodopa. Increasing doses are needed to control symptoms, and over time, this leads to development of unwanted movements, or dyskinesias. Successful DBS allows a reduction in levodopa, diminishing dyskinesias.

For PD, deep brain stimulation is performed on either the globus pallidus internus (GPi) or the subthalamic nucleus (STN). Treatment of essential tremor usually targets the thalamus. Each of these brain regions has two halves, which control movement on the opposite side of the body: right controls left, and left controls right. Unilateral (one-sided) DBS may be used if the symptoms are much more severe on one side. Bilateral DBS is used to treat symptoms on both sides.

Precautions

DBS is major brain surgery. Bleeding is a risk, and patients with bleeding disorders or who are taking blood thinning agents may require special management. DBS leaves metal electrodes implanted in the head, and patients are advised not to undergo diathermy (tissue heating) due to the risk of severe complications or death. Diathermy is used to treat chronic pain and other conditions. Special cautions are required for patients undergoing **MRI** after implantation.

Description

In DBS, a long thin electrode is planted deep within the brain, through a hole in the top of the skull. To make sure the electrode is planted in the proper location, a rigid "stereotactic frame" is attached to the patient's head before surgery. This device provides a three-dimensional coordinate system, used to locate the target tissue and to track the placing of the electrodes.

A single "burr hole" is made in the top of the skull for a unilateral procedure. Two holes are made for a bilateral procedure. This requires a topical anesthetic. General anesthesia is not used, for two reasons. First, the brain does not feel any pain. Second, the patient must be awake and responsive in order to respond to the neurosurgical team as they monitor the placement of the electrode. The target structures are close to several nerve tracts that carry information throughout the brain. Abnormalities in vision, speech, or other cognitive areas may indicate that the electrode is too close to one of these regions, and thus needs repositioning.

Other procedures may be used to ensure precise placement of the electrode, including electrical recording and injection of a contrast dye into the spinal fluid. The electrical recording can cause some minor odd sensations, but is harmless.

The electrode is connected by a wire to an implanted pulse generator. This wire is placed under the scalp and skin. A small incision is made in the area of the collarbone, and the pulse generator is placed there. This portion of the procedure is performed under general anesthesia.

Preparation

A variety of medical tests are needed before the day of surgery to properly locate the target (GPi, thalamus, or STN), and fit the frame. These may include CT scans, MRI, and injection of dyes into the spinal fluid or ventricles of the brain. The frame is attached to the head on the day of surgery, which may be somewhat painful, although the pain is lessened by local anesthetic. A mild sedative is given to ease anxiety.

Aftercare

Implantation of the electrodes, wire, and pulse generator is a lengthy procedure, and the patient will require a short hospital stay afterward to recovery from the surgery. Following this, the patient will meet several times with the **neurologist** to adjust the stimulator settings, in order to get maximum symptomatic improvement. The batteries in the pulse generator must be replaced every three to five years. This is done with a small incision as an outpatient procedure.

The patient's medications are adjusted after surgery. Most PD patients will need less levodopa after surgery, especially those who receive DBS of the STN.

Risks

Risks from DBS include the surgical risks or hemorrhage and infection, as well as the risks of general anesthesia. Patients who are cognitively impaired may become more so after surgery. Electrodes can be placed too close to other brain regions, which can lead to visual defects, speech problems, and other complications. If these occur, they may be partially reduced by adjusting the stimulation settings. DBS leaves significant hardware in place under the skin, which can malfunction or break, requiring removal or replacement.

Normal results

Deep brain stimulation improves the movement symptoms of PD by 25–75%, depending on how carefully the electrodes are placed in the optimal target area, and how effectively the settings can be adjusted. These improvements are seen most while off levodopa; DBS does little to improve the best response to levodopa treatment. DBS does allow a reduction in levodopa dose, which usually reduces dyskinesias by 50% or more. This is especially true for DBS of the STN; DBS of the GPi may lead to a smaller reduction. Levodopa dose will likely be reduced, leading to a significant reduction in dyskinesias.

DBS in essential tremor may reduce tremor in the side opposite the electrode by up to 80%.

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International Essential Tremor Foundation. P.O. Box 14005, Lenexa, Kansas 66285-4005. 913-341-3880 or 888-387-3667; Fax: 913-341-1296. staff@essentialtremor.org. <http://www.essentialtremor.org/>.

Richard Robinson

Delirium

Definition

Delirium is a transient, abrupt, usually reversible syndrome characterized by a disturbance that impairs consciousness, cognition (ability to think), and perception.

Description

The word delirium is derived from the Latin *delirare* which literally translates "to go out of the furrow." Delirium is typically an acute change in thinking with a disturbance in consciousness. Delirium is not a disease, but a syndrome that can occur as a result of many different

underlying conditions. Typically, there is a broad range of accompanying symptoms. Delirium is also called acute confusional state. Delirium is a medical emergency and affects 10–30% of hospitalized patients with medical illness. It is a widespread condition that affects more than 50% of persons in certain high-risk population. Often the condition can be reversed, but delirium is associated with increased morbidity and mortality rates.

Demographics

Patients who develop delirium during hospitalization have a mortality rate of 22–76% and a high death rate months after discharge. Approximately 80% of patients develop delirium near death, and 40% of patients in the intensive care units have symptoms of delirium. The prevalence of postoperative delirium following general surgery is 5–10%, and 42% following orthopedic surgery. Delirium is very common in nursing homes. The exact incidence of delirium in emergency departments is unknown. Delirium is present in approximately 20% of medical patients at the time of hospital admission. The prevalence in hospitalized patients is approximately 10% on a general medical service, 8–12% on a psychiatric service, 35–80% on a geriatric unit, and 40% on a neurologic service. In the elderly and postoperative patients, delirium may result in long-term disability, increased complications, and prolonged hospital stay. Geriatric patients have the highest risk for developing delirium. The incidence is higher among young children, females, and Caucasians. Medications are the most common cause of delirium in the elderly, which accounts for 22–39% of cases. Medications are the most common reversible causes of delirium. Approximately 25% of hospitalized patients with cancer and 30–40% of patients with HIV (**AIDS**) infection develop delirium during hospitalizations.

Abnormal mechanisms causing delirium

There are three types of delirium based on the state of arousal. They include hyperactive delirium, hypoactive delirium, and mixed delirium. The hyperactive delirium is associated with drug intake such as alcohol withdrawal (or intoxication), amphetamine, phencyclidine (PCP), and lysergic acid diethylamide (LSD), a psychedelic compound. Hypoactive delirium is observed in patients with hypercapnia and hepatic **encephalopathy**. Patients who exhibit mixed delirium often exhibit nocturnal agitation, behavioral problems, and daytime sedation. The exact pathophysiological mechanisms that elicit delirium are not fully understood. Research that primarily studied subjects with alcohol withdrawal and hepatic encephalopathy indicated that delirium is caused by a reversible impairment of cerebral oxidative metabolism and multiple neurotransmitter abnormalities.

Key Terms

Central nervous system (CNS) Contains the brain and spinal cord.

Cerebral oxidative metabolism Using oxygen to generate energy by complex chemical reactions that occur in brain cells.

Dementia A disorder characterized by loss of intellectual abilities; impairments in judgment, abstract thinking, and memory; and personality changes.

Hepatic encephalopathy A change in mental state due to toxic substance buildup in the blood that is caused by liver failure.

Hypercapnia Excess carbon dioxide in the blood.

Hypoglycemia Low levels of glucose in the blood.

Interleukins Chemicals released in the body as a result of stress to the body.

Neurotransmitter abnormality

Acetylcholine is an excitatory chemical in the **central nervous system** (CNS). Anticholinergic medications, which disrupt release of acetylcholine, typically cause acute confusional states (delirium). Additionally, patients with diseases such as Alzheimer's disease with impaired cholinergic transmission and decreased acetylcholine are susceptible to delirium. Patients who develop postoperative delirium have an increase in serum anticholinergic activity.

Another neurotransmitter in the brain called dopamine causes delirium if there is an excess of dopaminergic activity. Dopaminergic and cholinergic activity in the brain exhibit a reciprocal relationship (i.e., a decrease in cholinergic activity leads to delirium, while an increase in dopaminergic activity leads to delirium). Studies have demonstrated that serotonin levels are increased in patients with septic delirium and encephalopathy. Serotoninergic agents, which are medications that may have unwanted side effects, leading to impaired serotonin release, can also cause delirium. Gama-aminobutyric acid (GABA) is an inhibitory neurochemical in the central nervous system. GABA is increased in patients with hepatic encephalopathy; this is probably caused by increases in ammonia levels.

Inflammatory mechanisms

Recent research indicates that there is a role for specific chemical mediators such as interleukin-1 (IL-1) and interleukin-6 (IL-6). These chemical mediators are

released from cells after a broad range of infectious and toxic insults. Head trauma and ischemia, which are frequently associated with delirium, cause brain responses that are mediated by IL-1 and IL-6. Abnormal release can cause damage to nerve cells.

Structural mechanisms

Specific objective nerve pathways in the brain that induce delirium are unknown. Neuroimaging studies in patients with **traumatic brain injury** (TBI), **stroke**, and hepatic encephalopathy indicate that certain anatomical nerve pathways may contribute to a delirious state more than others. A specific pathway called the dorsal tegmental is also involved in delirium.

Summary of causes

In general, the causes of delirium fall within 11 categories: infectious, withdrawal, acute metabolic, trauma, CNS disease, hypoxic, deficiencies, environmental, acute vascular, toxins/drugs, and heavy metals. Examples of diseases or disorders in each category include:

- infectious: sepsis (infections that spread in blood and cause infections in the brain), encephalitis, meningitis, syphilis, CNS abscess
- withdrawal: as a result of drug withdrawal from alcohol or sedatives
- acute metabolic: acidosis, electrolyte disturbance, liver and kidney failure, other metabolic disturbances (glucose, Mg++, Ca++, conditions that affect the body's regulation of acid and electrolyte balance)
- trauma: head trauma, burns (delirium can occur secondary to traumatic events or severe burns)
- CNS disease such as stroke, bleeding in the brain, or seizures
- **hypoxia**: as a result of hypoxia (lack of oxygen), chronic obstructive lung disease (e.g., emphysema, bronchitis), or low blood pressure
- deficiencies of vitamins, especially B-complex vitamins
- environmental: severe changes in body temperature, either a decrease (hypothermia) or an increase (hyperthermia); hormonal imbalance (diabetes and thyroid problems)
- acute vascular: conditions affecting blood vessels in the brain, such as hemorrhage or blockage of a blood vessel from a clot
- toxins/drugs: chemical toxins such as street drugs, alcohol, pesticides, industrial poisons, carbon monoxide, cyanide, and solvents
- heavy metals: exposure to certain metals such as lead or mercury

Other common causes of delirium include hypoglycemia and hyperthermia.

Diagnostic criteria for delirium

The diagnosis of delirium is clinical, requiring physical examination and the analysis of symptoms because there is no single test that can successfully measure this condition. A careful history is essential to establish the diagnosis. Delirium is clinically characterized by an acutely transient alteration in mental status. Patients can have problems in orientation and short-term memory, difficulty sustaining attention, poor insight, and impaired judgment. In the hyperactive subtype of delirium, patients have an increased state of arousal, hypervigilance, and psychomotor abnormalities. Conversely, patients with the hypoactive subtype are typically withdrawn, less active, and sleepy. The mixed subtype category often presents with delirium as the primary symptom of an underlying illness. Mental status can be checked quickly and should include assessment of memory, attention, concentration, orientation, constructional tasks, spatial discrimination, writing, and arithmetic ability. Two of the most sensitive indicators for delirium are dysgraphia (impaired writing ability) and dysnomia (inability to name objects correctly).

Psychological deficit

The psychological diagnostic criteria for delirium include:

- change in cognition (i.e., disorientation, language disturbance, perceptual disturbance): this alteration cannot be accounted for by a preexisting, established, or evolving dementia
- disturbance of consciousness (i.e., reduced clarity of awareness of the environment) occurs with a reduction in ability to focus, maintain, or shift (change) attention
- the alterations develop over a short period (hours to days) and exhibit fluctuation during the day
- evidence exists from history, medical and/or laboratory findings, which indicates that the delirium is caused by a general medical condition, substance intoxication, substance withdrawal, medication use, or more than one cause (multiple etiologies)

Diagnostic instruments

There are several instruments that help establish the diagnosis of delirium. They include the Confusion Assessment Method (CAM), the Delirium Symptom Interview (DSI), and the Folstein Mini-Mental State Examination (MMSE). Delirium symptom severity can be assessed utilizing the Memorial Delirium Assessment Scale (MDAS) and the Delirium Rating Scale (DRS).

Lab studies

Glucose levels can help diagnose delirium causes by hypoglycemia or uncontrolled diabetes. A complete blood count with differential cell analysis can help to diagnose infection and anemia. Electrolyte analysis can diagnose high or low levels. Renal (kidney) and liver function test (LFTs) can diagnose liver and/or kidney failure. Other tests that can assist with identifying the underlying cause of delirium include urine analysis (urinary tract infections), urine/blood drug screen (to diagnose the presence of toxic substance), thyroid function tests (to diagnose an underfunctioning thyroid gland, a condition called hypothyroidism), and special tests to diagnose bacterial and viral causes of infection.

Neuroimaging studies such as computerized axial tomography (CAT) and **magnetic resonance imaging (MRI)** can be helpful to establish a diagnosis due to structural lesions or hemorrhage. Electroencephalogram (EEG), a special test that records brain activity in waves can be helpful to establish a diagnosis, especially in patients with hepatic encephalopathy (diffuse slow waves) and alcohol/sedative withdrawal (faster wave pattern).

Treatment

Clinicians must be vigilant to aggressively identify the underlying etiology of delirium, since the condition is a medical emergency. Symptomatic treatment for delirium may include the use of antipsychotic drugs. These medications help to control hallucinations, agitation, and help to improve the level of orientation and attention abilities (sensorium). Haloperidol (Haldol) is a highly researched medication and is often administered in the symptomatic management of delirium. The typical dose for patients with delirium of moderate severity is 1–2 mg twice daily and repeated every four hours as needed. Haldol can be administered orally, intravenously, or by intramuscular injection. Elderly patients should start with lower doses of Haldol, typically 0.25–1.0 mg twice daily and repeated every four hours as needed.

Environmental interventions

Treatment of delirium can be worsened by over stimulation or under stimulation in the environment. It is important to provide support and orientation to the patient. Additionally, providing the patients an environment with few distractions such as removing unnecessary objects in the room, use of clear language when talking to them, and avoidance of sensory extremes can be conducive to treatment planning.

Clinical trials

Information concerning **clinical trials** and research on delirium can be obtained from the National Institutes of Health (NIH). Research related to delirium is active at the Mayo Clinic Foundation, including research on Alzhiemer's disease, postoperative delirium in orthopedic surgical patients, and pharmacological treatment of **Parkinson's disease**.

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ORGANIZATIONS

National Institute of Neurological Disorders and Stroke (NINDS) Neurological Institute. P.O. Box 5801, Bethesda, MD 20824.

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Dementia with Lewy bodies *see* **Lewy body dementia**

Dementia, subcortical *see* **Binswanger disease, Dementia**

Dementia

Definition

The term dementia refers to symptoms, including changes in memory, personality, and behavior, that result from a change in the functioning of the brain. These declining changes are severe enough to impair the ability of a person to perform a function or to interact socially. This operating definition encompasses 70–80 different types of

dementia. They include changes due to diseases (Alzheimer's and Creutzfeld-Jakob diseases), changes due to a heart attack or repeated blows to the head (as suffered by boxers), and damage due to long-term alcohol abuse.

Dementia is not the same thing as **delirium** or **mental retardation**. Delirium is typically a brief state of mental confusion often associated with hallucinations. Mental retardation is a condition that usually dates from childhood and is characterized by impaired intellectual ability; mentally retarded individuals typically have IQ (intelligence quotient) scores below 70 or 75.

Description

The absent-mindedness and confusion about familiar settings and tasks that are hallmarks of dementia used to be considered as part of a typical aging pattern in the elderly. Indeed, dementia historically has been called senility. Dementia is now recognized not to be a normal part of aging. The symptoms of dementia can result from different causes. Some of the changes to the brain that cause dementia are treatable and can be reversed, while other changes are irreversible.

Demographics

An estimated two million people in the United States alone have severe dementia. Up to five million more people in the United States have milder forms of cognitive impairment of the dementia type. The elderly are most prone to dementia, particularly those at risk for a **stroke**. The historical tendency of women to live longer than men has produced a higher prevalence of dementia in older women. However, women and men are equally prone to dementia. Over age 80, more than 20% of people have at least a mild form of dementia.

Causes and symptoms

Dementia is especially prominent in older people. The three main irreversible causes are Alzheimer's disease, dementia with Lewy bodies, and **multi-infarct dementia** (also called vascular dementia).

Degenerative forms of dementia are long lasting (chronic) and typically involve a progressive loss of brain cell function. In disorders like Alzheimer's and Creutzfeld-Jakob diseases, this can involve the presence of infectious agents that disturb the structure of proteins that are vital for cell function. Other forms of dementia are chemically based. For example, **Parkinson's disease** involves the progressive loss of the ability to produce the neurotransmitter dopamine. Interrupted transmission of nerve impulses causes the progressive physical and mental deterioration. Huntington's disease is an inherited form of dementia that occurs when neurons (brain cells) degenerate.

Key Terms

Amyloid plaques A waxy protein substance that forms clumps in brain tissues, leading to brain cell death as in Alzheimer disease.

Lewy bodies Spheres, found in the bodies of dying cells, that are considered to be a marker for Parkinson's disease.

Multi-infarct dementia Deterioration in mental function caused by numerous areas in the brain where narrowing of blood vessels has resulted in atherosclerotic plaque formation and damage to brain cells.

Alzheimer's disease is the most common cause of dementia. The progressive death of nerve cells in the brain is associated with the formation of clumps (amyloid plaques) and tangles of protein (neurofibrillary tangles) in the brain. The loss of brain cells with time is reflected in the symptoms; minor problems with memory become worse, and impairment in normal function can develop. Alzheimer's patients also have a lower level of a chemical that relays nerve impulses between nerve cells. As the brain damage progresses, other complications can ensue from the damage and these can prove fatal. Put another way, people die with Alzheimer's, not from it.

Dementia resulting from the abnormal formation of protein in the brain (Lewy bodies) is the second most common form of dementia in the elderly. It is unclear whether these structures are related to the brain abnormalities noted in Alzheimer's patients. Lewy body formation differs from Alzheimer's in that the speed of brain functions is affected more so than memory.

In multi-infarct dementia, blood clots can dislodge and impede the flow of blood in blood vessels in the brain. The restricted flow of blood can lead to death of brain cells and a stroke.

Dementias that are caused by the blockage of blood vessels are generally known as vascular dementia. This type of dementia can sometimes be reversed if the blood-vessel blockage can be alleviated. In contrast, the dementia associated with Alzheimer's disease is non-reversible.

Less common causes of dementia include Binwanger's disease (another vascular type of dementia), Parkinson's disease, Pick's disease, Huntington's disease, **Creutzfeldt-Jakob disease**, and acquired immunodeficiency syndrome (**AIDS**).

A study published in 2002 documented a link between elevated levels of an amino acid called homocysteine in the blood and the risk of developing dementia,

likely vascular dementia. As homocysteine concentration can be modified by diet, the finding holds the potential that one risk factor for dementia may be controllable.

Symptoms of dementia include repeatedly asking the same question; loss of familiarity with surroundings; increasing difficulty in following directions; difficulty in keeping track of time, people, and locations; loss of memory; changes in personality or emotion; and neglect of personal care. Not everyone displays all symptoms. Indeed, symptoms vary based on the cause of the dementia. Also, symptoms can progress at different rates in different people.

Diagnosis

Diagnosis of dementia typically involves a medical examination, testing of mental responses (such as memory, problem solving, and counting), and knowledge of the patient's medical history (e.g., prescription and non-prescription drug use, nutrition, results of a physical examination, and medical history). Testing of the composition of the blood and urine can be helpful in ruling out specific causes such as thyroid disease or a deficiency in vitamin B_{12}. Some blood tests can help alert clinicians to the possibility of dementia. For example, persons infected with the human immunodeficiency virus (HIV) have distinct proteins in their blood that are often associated with the presence of dementia.

Visual examination of the brain can reveal structural abnormalities associated with dementia. Tests that are typically performed are computerized tomography (CT), **magnetic resonance imaging (MRI)**, and **positron emission tomography (PET)**. While accurate, such tests are not commonplace, and are rarely encountered outside of the research setting. Neuroimaging (**CT** or **MRI** scans) can be useful in excluding the possibility that dementia has resulted from an occlusion of a blood vessel, as in a stroke or due to the presence of a tumor.

Treatment team

Family physicians, medical specialists such as neurologists and psychiatrists, physical therapists, counselors, personal caregivers, and family members can all be part of the treatment team for someone afflicted with dementia.

Treatment

Drugs can help delay the progression of symptoms, particularly for Alzheimer's disease. The high blood pressure that is associated with multi-infarct dementia can also be controlled by drug therapy. Other stroke risk factors that can be treated include cholesterol level, diabetes, and smoking. Medicines such as antidepressants, antipsychotics, and **anxiolytics** can also be used to treat behaviors associated with dementia, including insomnia, anxiety, **depression**, and nervousness.

Other treatments that do not involve drugs are the maintenance of a healthy diet, regular **exercise**, stimulating activities and social contacts, and making the home as safe as possible. Hobbies can help keep the mind occupied and stimulated. "Things-to-do" lists can be a helpful memory prompt for persons with early dementia. With more advanced disease, a facility specializing in Alzheimer's treatment often provides a stimulating modified environment along with meeting increasing medical and personal care needs.

Recovery and rehabilitation

Irreversible causes of dementia reduce or eliminate the chances of recovery and rehabilitation. Stimuli such as favorite family photographs and calendars provide clues to cognitive orientation, while devices such as walkers help maintain mobility for as long as possible.

Clinical trials

As of early 2004, there are 64 **clinical trials** for dementia study and treatment in the United States that are recruiting subjects. The trials range from improved strategies of care and telephone support to active interventions in the outcome of various forms of dementia. The bulk of the trials are concerned with Alzheimer's disease. Information about the trials can be found at the National Institutes of Health (NIH) sponsored clinical trials website.

Prognosis

For those with irreversible progressive dementia, the outlook often includes slow deterioration in mental and physical capacities. Eventually, help is often required when swallowing, walking, and even sitting become difficult. Aid can consist of preparing special diets that can be more easily consumed and making surroundings safe in case of falls. Lift assists in areas such as the bathroom can also be useful.

For those with dementia, the expected lifespan is often reduced from that of a healthy person. For example, in Alzheimer's disease, deterioration of areas of the brain that are vital for body functions can threaten survival.

Special concerns

Caring for an individual with dementia almost always challenges family resources. Licensed social service providers at hospitals and facilities for the elderly can provide information and referrals regarding support groups,

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Resources

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Alzheimer's Association. 919 Michigan Avenue, Suite 1100, Chicago, IL 60611-1676. (312) 335-8700 or (800) 272-3900; Fax: (312) 335-1110. info@alz.org. <http://www.alz.org>.

Alzheimer's Disease Education and Referral Center. P. O. Box 8250, Silver Spring, MD 20907-8250. (301) 495-3334 or (800) 438-4380. adear@alzheimers.org. <http://www.alzheimers.org>.

National Institute on Aging. 31 Center Drive, MSC 2292, Building 31, Room 5C27, Bethesda, MD 20892. (301) 496-1752 or (800) 222-2225. karpf@nia.nih.gov. <http://www.nia.nih.gov>.

National Institute for Neurological Disorders and Stroke. P. O. Box 5801, Bethesda, MD 20824. (301) 496-5761 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Institute of Mental Health. 6001 Executive Boulevard, Room 8184, MSC 9663, Bethesda, MD 20892-9663. (301) 443-4513 or (866) 615-6464; Fax: (301) 443-4279. nimhinfo@nih.gov. <http://www.nimh.nih.gov>.

Brian Douglas Hoyle, PhD

Depression

Definition

When discussing depression as a symptom, a feeling of hopelessness is the most often described sensation. Depression is a common psychiatric disorder in the modern world and a growing cause of concern for health agencies worldwide due to the high social and economic costs involved. Symptoms of depression, like the disorder itself, vary in degree of severity, and contribute to mild to severe mood disturbances. Mood disturbances may range from a sudden transitory decrease in motivation and concentration to gloomy moods and irritation, or to severe, chronic prostration.

With treatment, more than 80% of people with depression respond favorably to medications, and the feeling of hopelessness subsides. With treatment, most people are able to resume their normal work and social activities.

Depression may occur at almost any stage of life, from childhood to middle or old age, as a result of a number of different factors that lead to chemical changes in the brain. Traumatic experiences, chronic stress, emotional loss, dysfunctional interpersonal relationships, social isolation, biological changes, aging, and inherited predisposition are common triggers for the symptoms of depression. Depression is classified according to the symptoms displayed and patterns of occurrence. Types of depression include major depressive disorder, bipolar depressive disorder, psychotic depressive disorder, postpartum depression, premenstrual dysphoric disorder, and seasonal disorder. Additional types of depression are included under the label of atypical depressive disorder. Many symptoms overlap among the types of depression, and not all people with depression experience all the symptoms associated with their particular type of the disorder.

Description

Symptoms of a depressive disorder include at least five of the following changes in the individual's previous characteristics: loss of motivation and inability to feel pleasure; deep chronic sadness or distress; changes in sleep patterns; lack of physical energy (apathy); feelings of hopelessness and worthlessness; difficulty with concentration; overeating or loss of appetite; withdrawal from interpersonal interactions or avoidance of others; death wishes, or belief in his/her own premature death. In children, the first signs of depression may be irritation and loss of concentration, apathy and distractibility during classes, and social withdrawal. Some adults initially complain of constant **fatigue**, even after long hours of sleep, digestive disorders, headaches, anxiety, recurrent memory lapses, and insomnia or excessive sleeping. An episode of major

Key Terms

Anorexia Loss of appetite.

Bipolar disorder A mood disorder characterized by periods of excitability (mania) alternating with periods of depression.

Dysthymia A chronic mood disorder characterized by mild depression.

Major depressive disorder A mood disorder characterized by overwhelming and persistent feelings of hopelessness, often accompanied by sleep disturbances, withdrawal from normal social and personal care activities, and an inability to concentrate.

Manic A period of excess mental activity, often accompanied by elevated mood and disorganized behavior.

Serotonin A type of neurotransmitter, a brain chemical that carries messages between brain cells. Low levels of serotonin in the brain are associated with feelings of depression.

depression may be preceded by a period of dysthymia, a mild but persistent low mood state, usually accompanied by diminished sexual drive, decreased affective response, and loss of interest in normal social activities and hobbies.

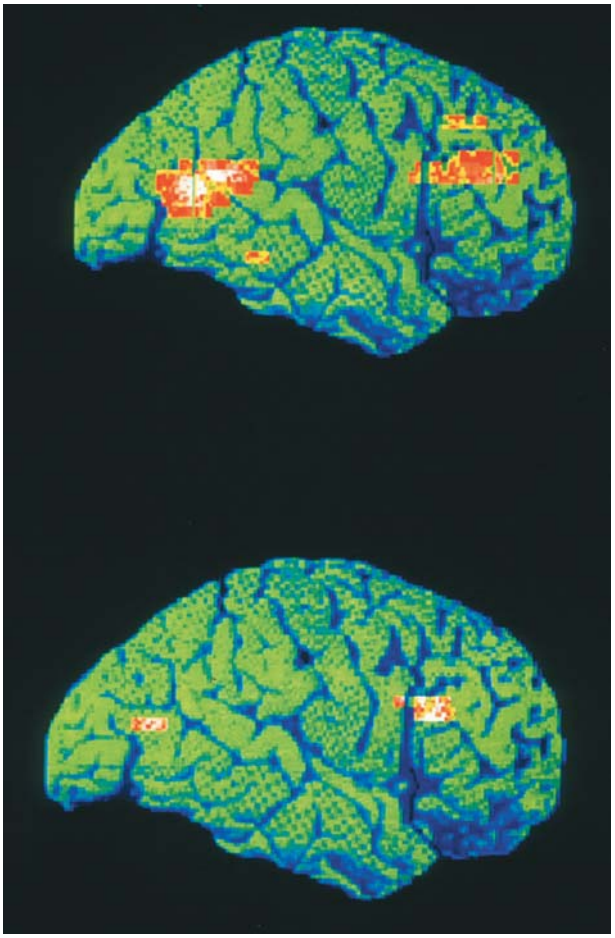
Most individuals with depression have difficulty in dealing with the challenges of daily life, and even minor obstacles or difficulties may trigger exaggerated emotional responses. Frustrating situations are frequently met with feelings of despair, dejection, resentment, and worthlessness, with people easily desisting from their goals. People with depression may try to avoid social situations and interpersonal interactions. Some people with depression overeat, while others show a sharp loss of appetite (anorexia). In some individuals, medical treatments for some other existing illness may also cause depression as an adverse reaction. For instance, antihypertensive drugs, steroids, muscle relaxants, anticancer drugs, and opioids, as well as extensive surgery such as a coronary bypass, may lead to depression. Cancer and other degenerative diseases, chronic painful conditions, metabolic diseases or hormonal changes during adolescence, or after childbirth, menopause, or old age may be potential triggers for depression. When the first onset of depression occurs after the age of 60, there is a greater possibility that the causative factor is a cerebrovascular (blood vessels in the brain) degeneration.

Molecular genetics research has recently shown that mutations in a gene coding for a protein that transports serotonin (a neurotransmitter) to neurons may determine how an individual will cope with stressful situations. A two-decade study involving 847 people of both sexes has shown that those who inherited two copies of the long version of the gene 5-HTT have a 17% risk of suffering a major depressive episode due to exposure to four or more identified stressful situations in their lives, whereas those with one long and one short version of the gene had the risk increased to 33%. The study has also shown that individuals with two short copies of the gene have a 43% probability of a major depressive episode when exposed to four or more stressful life events. The shorter version of the gene 5-HTT does not directly causes depression, but offers less protection against the harmful effects of traumatic or stressful situations to the brain. Studies of population genetics have also shown that about 50% of the world's Caucasian population carry one short and one long version of 5-HTT genes.

Depressive episodes may be associated with additional psychiatric disorders. Neurotic depression is often triggered by one or more adverse life events or traumatic experiences that have historically caused anxiety in the life of the person experiencing depression. For example, loss of social or economical status, chronic failure in living up to the expectations of parents, teachers, or bosses, death of a close relation, work-related competitive pressures, and other stressful situations such as accidents, urban violence, wars, and catastrophic events may lead to a depressive episode. Conversely, anxiety disorders such as panic syndrome, phobias, generalized anxiety, and post-traumatic stress disorder may trigger a major depressive crisis. Psychotic depressive disorders are likely to be associated with other psychiatric diseases or caused by them. Eating disorders such as bulimia, anorexia nervosa, and binge-eating disorder are generally accompanied by depression or may be caused by an existing depressive state. Neurodegenerative diseases such as Alzheimer's, Huntington's, and Parkinson's diseases frequently have depression among their symptoms.

Dysthymia is a mild but chronic depressed state, characterized by melancholic moods, low motivation, poor affective responsiveness, and a tendency for self isolation. A dysthymic state lasting two years or longer is a risk factor for the onset of a major depressive episode. However, many dysthymic individuals experience a chronic low mood state throughout their daily lives. Dysthymia is a frequent occurrence in individuals involved in chronic dysfunctional marriages or unsatisfying work conditions. Such chronic stressful situations alter the brain's neurochemistry, thus the opportunity arises for symptoms of depression to develop.

Psychotic depression is a particularly serious illness and possesses biological and cognitive (thought) components. Psychotic depression involves disturbances in



Colored positron emission tomography (PET) scans showing the brain of a depressed person (top) and the brain of a healthy person. *(© Photo Researchers. Reproduced by permission.)*

brain neurochemistry as a consequence of either a congenital (from birth) condition or due to prolonged exposure to stress or abuse during early childhood. Prolonged exposure to severe stress or abuse in the first decade of life induces both neurochemical and structural permanent changes in the developing brain with a direct impact on emotional aspects of personality. Normal patterns of perception and reaction give way to flawed mechanisms in order for a person to cope with chronic fear, abuse, and danger. Perception becomes fear-oriented and conditioned to constantly scan the environment for danger, with the flight-or-fight impulse underlying the individual's reactions. Delusions, misinterpretation of interpersonal signals, and a pervading feeling of worthlessness may impair the individual's ability to deal with even minor frustrations or obstacles, precipitating deep and prolonged episodes of depression, often with a high risk of suicide. Hallucinations may also occur, such as hearing voices or experiencing visions, as part of depression with psychosis.

A major depressive disorder (MDD) or clinical depression may consist of a single episode of severe depression requiring treatment or constitute the initial sign of a more complex disorder such as bipolar disorder. MDD may last for several months or even years if untreated and is associated with a high risk of suicide. In bipolar disorder, manic (hyper-excited and busy) periods alternate with deep depressive episodes, and are characterized by abnormal euphoria (an exaggerated feeling of happiness and well-being) and reckless behavior, followed by deep distress and prostration, often requiring hospitalization.

Major episodes of depression may last for one or more years if not treated, leading to a deep physical and emotional prostration. The person with major depression often moves very slowly and reports a sensation of heaviness in the arms and legs, with simple walking requiring an overwhelming effort. Personal hygiene is neglected and the person often desires to stay secluded or in bed for days or weeks. Suicidal thoughts may frequently occupy the mind or become recurrent patterns of thinking. Painful or unsettling memories are often recalled, and contribute to feelings of helplessness.

Atypical depression causes a cyclic behavior, alternating periods of severe and mild depressive states, punctuated by mood swings, hypersensitivity, oversleeping, overeating, with or without intermittent panic attacks. This depressive disorder is more common in women, with the onset usually occurring during adolescence.

Premenstrual dysphoric disorder (PDD) is not premenstrual stress. It is a more severe mood disorder that can cause deep depression or episodes of heightened irritation and aggressiveness, starting one or two weeks before menstruation and usually persisting during the entire period. Premenstrual dysphoric disorder is associated with abnormal changes in levels of hormones that affect brain neurochemistry.

Seasonal affective disorder (SAD) is caused by disturbances in the circadian cycle, a mechanism that controls conversion of serotonin into melatonin in the evening and mid-afternoon, and the conversion of melatonin into serotonin during daytime. Serotonin is the neurotransmitter responsible for sensations of satiety and emotional stability, which is converted at nighttime into melatonin, the hormone that regulates sleep and other functions. Some people are especially susceptible to the decreased exposure to daylight during long winter months and become depressed and irritable. Overeating and oversleeping during the winter season are common signs of seasonal affective disorder, along with irritation and depressed moods. However, as the amount of light increases during the spring and summer seasons, the symptoms disappear.

Postpartum depression is a severe and long-lasting depressive state also associated with abnormal changes in

hormone levels affecting brain neurochemistry. If untreated, postpartum depression may last for months or even years, and is highly disruptive to family and maternal-child relations.

Without treatment, the risk of suicide as a consequence of depression should not be underestimated. Suicide accounts for approximately 15% of deaths among people with significant depression, and half of all suicide attempts in the United States are associated with depression. Persistent and recurrent depressive episodes are important contributors to other diseases alike such as myocardial infarction, hypertension, and other cardiovascular disorders.

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Sandra Galeotti

Dermatomyositis

Definition

Dermatomyositis is one member of a group of diseases that are collectively called inflammatory myopathies. A **myopathy** is a disorder of a muscle. Hallmarks of dermatomyositis disease are a widespread rash and muscle weakness.

Description

Dermatomyositis is characterized by the onset of symptoms that can be severe, with rash and muscle weakness occurring over a large portion of the body. The term dermatomyositis stems from the root word "derm," referring to the skin, and the word "myositis," which means inflammation of muscles. Dermatomyositis, therefore, means an inflammation of the muscles and the skin. The disease was first described in 1887 in Germany.

Demographics

Both children and adults can be affected with dermatomyositis, but females are twice as likely to have the disorder as males. One-third of the cases occur in people over the age of 50. People of European ancestry have typically been more affected than people of African ancestry. As of 2004, however, the incidence of dermatomyositis is rising faster in African Americans than in whites. In the United States, the estimated prevalence of the disease is 5.5 cases per million people.

Causes and symptoms

The cause of dermatomyositis is a disruption in the functioning of the immune system, although the precise details of the malfunction are not yet known. While the basis of the disease may be due to a genetic mutation, conclusive evidence is lacking. Infection with certain viruses, or a bacterium called *Borrelia* (the cause of **Lyme disease**), has been suggested as possible triggers of the disease.

Dermatomyositis is often first apparent as a rash. The rash, which can be bluish-purple in color, reminiscent of bruising, typically occurs in patches on the face, neck, shoulders, upper portion of the chest, elbows, knuckles, knees, and back. Sometimes there can be accumulation of calcium as hard bumps underneath the skin in the region of the rash. The skin may break open and become very itchy, to the point of disturbing sleep.

The other principle symptom, which usually appears after the rash, but which can also be coincident with the rash, is muscle weakness. The muscles most often affected are those that are near the central part of the body, such as muscles of the chest and the upper arms and legs. As the disease progresses, muscles toward the outer parts of the arms and legs can weaken. As well, the affected muscles can become sore and painful to the touch.

The muscle weakness can make it hard for the affected person to get up from a sitting position, climb up stairs, lift even moderately heavy objects, and to reach up over their head. Swallowing can become difficult. People may also feel tired, lose weight, and develop a slight fever.

Except for the presence of rash, the symptoms of dermatomyositis are virtually the same as a related disease

Key Terms

Glucocorticoid medications A group of medications that produces effects of the body's own cortisone and cortisol. Glucocorticoids are commonly called steroids and, among other functions, work to reduce inflammation.

Myositis Inflammation of a muscle.

known as **polymyositis** (inflammation of many muscles). In about 40% of those with dermatomyositis, only the skin is affected. In these people, the disease can also be called amyopathic dermatomyositis (ADM), or DM sine myositis.

Diagnosis

Diagnosis is based on the presence of skin rash, muscle weakness, and higher than normal levels of some muscle enzymes (due to breakdown of muscle cells). A muscle **biopsy**, in which a sample of muscle is obtained, can reveal inflammation and the death of muscles cells associated with the weakening muscle.

Because of the presence of cancer in a significant proportion of elderly people who develop the disease, diagnosis is often accompanied by procedures like a chest x ray, mammogram in women, prostate examination in men, and sometimes a scan of the abdomen using the technique of computed tomography.

Treatment team

The treatment team for a case of dermatomyositis is typically made up of the family physician, **neurologist**, physical therapists, and family members or caregivers. Sometimes the team also includes a dermatologist (specialist in the structure, functions, and diseases of the skin) and a rheumatologist (specialist in conditions that cause swelling or **pain** in the muscles and joints).

Treatment

Treatment principally consists of therapy with glucocorticoid medications, which help quell an immune response that can exacerbate the rash. The steroid that is typically given is prednisone. In some people, this drug is not effective or tolerated well. Alternate drugs that can be given are azathioprine and methotrexate. An immune compound called immunoglobulin can also be given intravenously.

Recovery and rehabilitation

Physical therapy is often used to try to maintain or minimize the loss of muscle strength and function. As dermatomyositis is a chronic condition, emphasis is placed not on recovery, but on maintaining optimum muscle function.

Clinical trials

As of April 2004, there are seven **clinical trials** related to dermatomyositis or other related conditions recruiting participants in the United States. Some of the trials are evaluating new treatments such as novel drugs and irradiation. Other trials are trying to uncover how the disorder develops in children. Updated information about ongoing trials can be found at the National Institutes of Health website for clinical trials at <http://www.clinicaltrials.org>.

As well as the clinical trials, research is being undertaken to unravel the mechanisms of development of the disease, with a goal to prevent, treat, and ultimately, cure dermatomyositis.

Prognosis

The disease is seldom fatal, although muscle weakness can persist for life. Most cases of dermatomyositis do respond to therapy, which improves a person's outlook. However, the prognosis may not be as good if the disease is accompanied by heart or lung problems. In the latter cases, a person may become confined to a wheelchair. On rare occasions, heart or lung muscles weakened by dermatomyositis can cause death.

Special concerns

Approximately one-third of older people who develop dermatomyositis also have cancer. In some cases, the cancer may not yet be diagnosed. Therefore, a thorough physical examination of all body systems is important after receiving a diagnosis of dermatomyositis.

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Myositis Association. 1233 20th Street, NW, Washington, DC 20036. (202) 887-0084 or (800) 821-7356; Fax: (202) 466-8940. tma@myositis.org. <http://www.myositis.org>.

National Institute for Neurological Diseases and Stroke (NINDS), 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). 31 Center Dr., Rm. 4C02 MSC 2350, Bethesda, MD 20892-2350. (301) 496-8190 or (877) 226-4267. NIAMSinfo@mail.nih.gov. <http://www.niams.nih.gov>.

National Organization for Rare Disorders. 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Brian Douglas Hoyle, PhD

Developmental dyspraxia *see* **Dyspraxia**

Devic syndrome

Key Terms

Ataxia Loss of coordinated muscle movement caused by a disturbance of the nervous system.

Myelin sheath Insulating layer around some nerves that speeds the conduction of nerve signals.

Optic neuritis Inflammation of the optic nerve, often accompanied by vision loss.

Transverse myelitis A neurologic syndrome caused by inflammation of the spinal cord.

Definition

Devic Syndrome is a rare neurological disorder that affects both the protective sheet that lines the spinal cord and the optic nerve of the eye. People that have Devic syndrome lose the fatty covering of the spinal cord (myelin) and experience eye **pain** due to an exaggerated inflammatory response that occurs in the eye. The resulting spinal cord damage is known as **transverse myelitis** and the resulting eye inflammation is known as optic neuritis. Devic syndrome is a severe neurodegenerative disorder that can lead to blindness, paralysis, and incontinence (loss of bowel or bladder control).

Description

Devic syndrome is an autoimmune disorder that is considered by many scientists to be a form of **multiple sclerosis**, another neurodegenerative disease that affects the protective coating of the spinal cord called the myelin sheath. In Devic syndrome, the course of the disease is more rapid and severe. Symptoms typically observed in patients that have multiple sclerosis usually appear after symptoms associated with Devic syndrome, distinguishing the two neurodegenerative diseases. Devic syndrome is also known as Devic disease and neuromyelitis optica.

It is still controversial whether Devic syndrome is a variant of multiple sclerosis. It is considered by some scientists to be a variant of a disease caused by exposure to the varicella zoster virus that results in **acute disseminated encephalomyelitis** (ADEM).

Demographics

Devic syndrome can occur spontaneously, or in conjunction with multiple sclerosis or systemic **lupus** erythematosus. It affects males and females equally. Devic syndrome is a rare disorder, affecting less than an estimated five persons per million population per year.

Causes and symptoms

Devic syndrome is a chronic and degenerative disorder that usually affects both eyes. The eyes develop diminished sensitivity to bright lights, color vision impairment, and diminished light reflexes. Approximately two-thirds of persons with Devic syndrome experience complete visual loss. The symptoms begin with significant loss of vision that precedes muscle weakness, **ataxia** (coordination difficulties and unsteady gait, or manner of walking), and numbness. Inflammatory sites of attack are usually the optic nerve chiasma, optic tract, and spinal cord. Usually, the optic neuropathy (damage to the optic nerve) is accompanied by severe transverse myelitis, which involves an acute inflammation of the spinal cord. The optic neuropathy usually happens before the transverse myelitis occurs, but in approximately 20% of patients it occurs in the reverse order.

Persons with Devic syndrome can also experience urinary, gastrointestinal, and sexual dysfunction. This occurs due to degeneration of the nerves that exit the spinal

cord and serve the body's trunk and limbs. Patients with Devic syndrome rarely experience clinical signs that involve defects beyond symptoms arising from the spinal cord and optic nerve. There are also characteristic brain **MRI** scan findings including swelling and signal changes that are typically observed, as well as increased protein content in the cerebral spinal fluid.

Diagnosis

Diagnosis is usually made by a **neurologist** and an ophthalmologist, by examining the eye and initiating several neurological exams including an MRI of the brain.

Treatment team

The neurologist and an ophthalmologist are the physicians that will be involved in making the diagnosis and providing follow-up treatment for persons with Devic syndrome. Patients that lose their eyesight will also require an occupational therapist that specializes in assisting individuals that become blind.

Treatment

There is no cure available for Devic syndrome. Treatment, therefore, is based solely on lessening the symptoms and providing comfort care for individuals that are in the more advanced stages of the disease. Steroidal anti-inflammatory medications such as corticosteroids might be helpful and are commonly prescribed for patients with this disorder. There is no defined standard of treatment for the disorder.

Recovery and rehabilitation

Recovery from attacks manifested by acute inflammation is often variable. Devic syndrome is a chronic disease, often progressive, and complete rehabilitation is usually not observed, as with many neurodegenerative diseases.

Clinical trials

Currently, the National Institute of Neurological Disorder and Stroke (NINDS) at the National Institutes of Health (NIH) are investigating how to repair damage to the **central nervous system** while restoring full strength to injured areas. As of mid-2004, there is currently a Phase III clinical trial to determine the effectiveness of plasma exchange in the treatment of acute severe attacks of inflammatory demyelinating disease in patients with degenerative neurological disorders who do not respond to intravenous steroid therapy. Although the study is no longer recruiting participants, anticipated results are not yet published.

Prognosis

The prognosis for individuals that have Devic syndrome is poor, as the disorder is eventually fatal for many patients. Isolated acute demyelinated encephalomyelitis (ADE) affects the optic nerve and the spinal cord in a similarly to Devic syndrome, but occurs after an infection or a common cold, and is distinct from Devic syndrome. ADE patients can fully recover, although many have associated permanent deficits, and in rare cases ADE can also be fatal.

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National Eye Institute (NEI), National Institutes of Health, DHHS. 31 Center Drive, Rm. 6A32 MSC 2510, Bethesda, MD 20892-2510. (301) 496-5248 or (800) 869-2020. 2020@nei.nih.gov. <http://www.nei.nih.gov>.

Transverse Myelitis Association. 3548 Tahoma Place West, Tacoma, WA 98466. (253) 565-8156. ssiegel@myelitis.org. <http://www.myelitis.org>.

Bryan Richard Cobb, PhD

Dexamethasone *see* **Glucocorticoids**

Diabetic neuropathy disease

Definition

Diabetic neuropathy (DN) is a neurological disorder caused by consequences of a primary disease—diabetes mellitus. The diabetic neuropathy may be diffuse, affecting

Key Terms

Autoimmune Pertaining to an immune response by the body against its own tissues or types of cells.

Biopsy The surgical removal and microscopic examination of living tissue for diagnostic purposes or to follow the course of a disease. Most commonly the term refers to the collection and analysis of tissue from a suspected tumor to establish malignancy.

Carpal tunnel syndrome A condition caused by compression of the median nerve in the carpal tunnel of the hand, characterized by pain.

Diabetes mellitus The clinical name for common diabetes. It is a chronic disease characterized by the inability of the body to produce or respond properly to insulin, a hormone required by the body to convert glucose to energy.

Electromyography (EMG) A diagnostic test that records the electrical activity of muscles. In the test, small electrodes are placed on or in the skin; the patterns of electrical activity are projected on a screen or over a loudspeaker. This procedure is used to test for muscle disorders, including muscular dystrophy.

Gastroparesis Nerve damage of the stomach that delays or stops stomach emptying, resulting in nausea, vomiting, bloating, discomfort, and weight loss.

Insulin A hormone or chemical produced by the pancreas that is needed by cells of the body in order to use glucose (sugar), a major source of energy for the human body.

Ketoacidosis Usually caused by uncontrolled type I diabetes, when the body isn't able to use glucose for energy. As an alternate source of energy, fat cells are broken down, producing ketones, toxic compounds that make the blood acidic. Symptoms of ketoacidosis include excessive thirst and urination, abdominal pain, vomiting, rapid breathing, extreme tiredness, and drowsiness.

multiple parts of the body, or focal, targeting a specific nerve or body part.

Description

Neurological damage is the result of chronically elevated blood sugar. Among all complications of diabetes, DN can be one of the most frustrating and debilitating conditions, because of the **pain**, discomfort, and disability it may cause, and because available treatments are limited and not always successful.

There are three main types of DN:

- Sensory neuropathy (or **peripheral neuropathy**, usually just referred to as neuropathy)—affects the nerves that carry sensation information to the brain, from various parts of the body, i.e.: how hot or cold something is, what the texture of something feels like, or the pain caused by a sharp object. This is the most common form of diabetic neuropathy.
- Autonomic neuropathy—affects the nerves that control involuntary activities of the body, such as the action of the stomach, intestine, bladder, and even the heart.
- Motor neuropathy—affects the nerves that carry signals from the brain to muscles, allowing all motions to occur, i.e. walking, moving the fingers, chewing. This form of neuropathy is very rare in diabetes.

The longer a person has diabetes, the more likely the development of one or more forms of neuropathy. Approximately 60–70% of patients with diabetes show signs of neuropathy, but only about five percent experience painful symptoms.

According to the categories described above, DN can lead to muscular weakness, loss of feeling or sensation, and loss of autonomic functions such as digestion, erection, bladder control, sweating, and so forth.

Demographics

In the United States, DN occurs in 10–20% of patients newly diagnosed with diabetes mellitus (DM), and its prevalence is up to 50% in elderly patients with DM. Most studies agree that the overall prevalence of symptomatic DN is approximately 30% of all patients with DM. The incidence of DN in the general population is approximately two percent.

Internationally, DN is found in 20–30% of individuals with type-2 diabetes. This number depends on the fiber type being tested and the sensitivity of the exam. Individuals with type-1 diabetes usually develop neuropathy after more than ten years of living with the disease.

It affects men and women equally, but neuropathic pain appears more frequently in females. Minority group members have more secondary complications, such as

lower extremity amputations. These individuals tend to also have more hospitalizations due to neuropathic complications.

Causes and symptoms

Causes of diabetic neuropathy are likely to be different for different types of the disorder. Nerve damage is probably due to a combination of factors, such as:

- Metabolic factors: high blood glucose, long disease duration, low levels of insulin and abnormal blood fat levels
- Neurovascular factors, leading to blood vessel damage and consequent insufficient delivery of oxygen and nutrients to the nerves
- Autoimmune factors, causing nerve inflammation
- Mechanical nerve injury, such as carpal tunnel syndrome
- Inherited traits that increase susceptibility to nerve disease
- Lifestyle factors, such as smoking or alcohol use

Symptoms depend on the neuropathy type and affected nerves. Some people show no symptoms at all. Often, symptoms are minor at first, and because most nerve damage occurs over several years, mild cases may go unnoticed for a long time. Symptoms may include:

- Numbness, tingling, or pain in the toes, feet, legs, hands, arms, and fingers
- Wasting of feet or hands muscles
- Indigestion, nausea, or vomiting
- Diarrhea or constipation
- **Dizziness** or faintness due to a drop in postural blood pressure
- Problems with urination
- Erectile dysfunction (impotence) or vaginal dryness
- Weakness

In addition, weight loss and **depression** are not a direct consequence of the neuropathy but, nevertheless, often accompany it.

Diagnosis

Diabetic neuropathy is diagnosed on the basis of a clinical evaluation, analyzing the patient's history, symptoms and the physical exam. During the exam, the doctor may check blood pressure and heart rate, muscle strength, reflexes, and sensitivity to position, vibration, temperature, or a light touch.

The physician may also do other tests to help determine the type and extent of nerve damage:

- A comprehensive foot exam assesses skin, circulation, and sensation. Other tests include checking reflexes and assessing vibration perception.
- Nerve conduction studies check the transmission of an electrical current through a nerve. This test allows the doctor to assess the condition of all the nerves in the arms and legs.
- Electromyography (EMG) shows how well muscles respond to electrical signals transmitted by nearby nerves. This test is often done at the same time as nerve conduction studies.
- Quantitative sensory testing (QST) uses the response to stimuli, such as pressure, vibration, and temperature, to check for overt neuropathy. QST is increasingly used to recognize sensation loss and excessive irritability of nerves
- Heart rate variability shows how the heart responds to deep breathing and to changes in blood pressure and posture.
- Nerve or skin biopsies are used in research settings

Treatment team

Proper management of diabetic patients requires a skilled team including collaborating specialists. Depending on the qualifications of the patient's primary physician, other professionals are recruited as needed, such as an ophthalmologist, podiatrist, cardiologist, nutritionist, nurse educator, **neurologist**, vascular surgeon, endocrinologist, gastroenterologist and urologist. A nurse educator can ease the interface between otherwise independent specialists. Without such a team mentality, the diabetic patient is often set adrift, forced to cope with conflicting instructions and unneeded repetition of tests.

Treatment

The first step is to bring blood glucose levels down to the normal range to prevent further nerve damage. Blood glucose monitoring, meal planning, **exercise**, and oral drugs or insulin injections are needed to control blood glucose levels. Although, symptoms may get temporarily worse when blood sugar is first brought under control, over time, maintaining normal glucose levels helps lessen neuropathic symptoms. Importantly, good blood glucose control may also help prevent or delay the onset of further complications.

Additional treatments depend on the type of nerve problem in consideration, and are include:

- Foot care—Clean the feet daily, using warm water and a mild soap. Inspect the feet and toes every day for cuts, blisters, redness, swelling, calluses, or other problems.

Always wear shoes or slippers to protect feet from injuries, and prevent skin irritation by wearing thick, soft, seamless socks. Schedule regular visits with a podiatrist.

- Pain relief—To relieve pain, burning, tingling, or numbness, the physician may suggest aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. People with renal disease should use NSAIDs only under a doctor's supervision. A topical cream called capsaicin is another option. Tricyclic antidepressant medications such as amitriptyline, imipramine, and nortriptyline, or anticonvulsant medications such as **carbamazepine** or **gabapentin** may relieve pain in some people. Codeine may be prescribed for a short time to relieve severe pain. Also, mexiletine, used to regulate heartbeat, has been effective in reducing pain in several **clinical trials**.
- Gastrointestinal problems—To relieve mild symptoms of stomach discomfort, doctors suggest eating small, frequent meals, avoiding fats, and eating less fiber. When symptoms are severe, the physician may prescribe erythromycin to speed digestion, metoclopramide for the same reason and to help relieve nausea, or other drugs to help regulate digestion or reduce stomach acid secretion.
- Urinary and sexual problems—To treat urinary tract infections, physicians can prescribe antibiotics and suggest drinking plenty of fluids. Several methods are available to treat erectile dysfunction caused by neuropathy, including taking oral drugs, using a mechanical vacuum device, or injecting a vasodilating drug into the penis before intercourse. In women, vaginal lubricants may be useful when neuropathy causes vaginal dryness.

Recovery and rehabilitation

Physical therapy may be a useful adjunct to other therapies, especially when muscular pain and weakness are a manifestation of the patient's neuropathy. The physical therapist can instruct the patient in a general exercise program to maintain his/her mobility and strength.

Occupational therapy may be necessary in cases where a person loses a limb due to secondary complications and needs functional training to regain his/her independence.

Clinical trials

There are numerous open clinical trials for diabetic neuropathy disease:

- Gene Therapy to Improve Wound Healing in Patients With Diabetes, at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
- Long-Term Treatment and Re-Treatment of Lower Extremity Diabetic Ulcers with Regranex or Placebo, sponsored by Johnson & Johnson Pharmaceutical Research and Development
- RhVEGF (Telbermin) for Induction of Healing of Chronic, Diabetic Foot Ulcers, sponsored by Genentech
- Study of Three Fixed Doses of EAA-090 in Adult Outpatients with Neuropathic Pain Associated with Diabetic Neuropathy, sponsored by Wyeth-Ayerst Research
- Treatment for Symptomatic Peripheral Neuropathy in Patients with Diabetes, LY333531 Treatment for Symptomatic Peripheral Neuropathy in Patients with Diabetes and Treatment of Peripheral Neuropathy in Patients with Diabetes, sponsored by Eli Lilly and Company
- VEGF for Diabetic Neuropathy, at the Caritas St. Elizabeth's Medical Center of Boston.

For updated information on clinical trials, visit the website www.clinicaltrials.org, sponsored by the United States government.

Prognosis

The mechanisms of diabetic neuropathy are poorly understood. At present, treatment alleviates pain and can control some associated symptoms, but the process is generally progressive.

Complications of diabetic neuropathy may include:

- Progression to cardiovascular autonomic neuropathy, a relatively rare occurrence which can eventually cause death
- Peripheral neuropathy that leads to foot ulcers and leg amputations
- Injuries associated with automonic neuropathy, including those from dizziness and falling
- gastric distress leading to nausea and vomiting, diarrhea and dehydration, which could impair the ability to regulate blood sugar.

Special concerns

Prevention of diabetic neuropathy can be achieved by establishing good control over blood sugar levels at the onset of diabetes. Even when symptoms of neuropathy are already present, maintaining normal blood sugar levels reduces pain significantly. Drugs such as some over-the-counter anti-inflamatories may aid in prevention, as well as deterrence, of neuropathy by keeping inflammation to a minimum.

Resources

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Centers for Disease Control and Prevention (National Center for Chronic Disease, Prevention and Health Promotion, Division of Diabetes Translation). Mail Stop K-10, 4770 Buford Highway, NE., Atlanta, GA 30341-3717. (301) 562-1050 or (800) CDC-DIAB (800-232-3422). diabetes@cdc.gov. <http://www.cdc.gov/diabetes>.

Juvenile Diabetes Research Foundation International. 120 Wall Street, 19th floor, New York, NY 10005. (212) 785-9500 or (800) 533-2873; Fax: (212) 785-9595. info@jdrf.org. <http://www.jdrf.org>.

National Diabetes Education Program. 1 Diabetes Way, Bethesda, MD 20892-3600. (800) 438-5383. <http://ndep.nih.gov>.

National Institute of Neurological Disorders and Stroke. P.O. Box 5801, Bethesda, MD 20824. (800) 352-9424. <http://www.ninds.nih.gov>.

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Diadochokinetic rate

Definition

Diadochokinetic rate (DDK) refers to an assessment tool, used by speech-language pathologists (SLPs), that measures how quickly an individual can accurately produce a series of rapid, alternating sounds. These sounds, also called tokens, may be one syllable such as "puh," two or three syllables such as "puh-tuh" or "puh-tuh-kuh," or familiar words such as "pattycake" or "buttercup." Other names for DDK rate include maximum repetition rate and The Fletcher Time-by-Count Test of Diadochokinetic Syllable Rate, the latter of which is named for the clinician who published DKK rate data in 1972.

Purpose

Diadochokinetic rate is one means of assessing oral motor skills. DDK rate provides information about a person's ability to make rapid speech movements using different parts of his mouth. For example, the sounds "puh," "tuh," and "kuh" use the front (the lips), middle (the tip of the tongue), and back of the mouth (the soft palate), respectively. Evaluation of diadochokinetic rate usually occurs as part of an oral motor skills assessment. Other aspects of an oral motor skills assessment include examination of oral facial structures (lips, tongue, jaw, teeth, palate, and pharynx) and evaluation of velopharangeal function and breathing.

In general, DDK rates increase as children age and their motor systems mature. Some studies have shown reduced DDK rates in children and adults with speech impairments when compared to rates for individuals with typical speech. Examples of conditions that may be associated with a slower or more variable DDK rate include **ataxia**, **dysarthria**, childhood **apraxia** of speech, and **stuttering**.

Description

The task of measuring DDK rate usually occurs in a single session and takes as little as 15–20 minutes for the SLP to administer and score. Prior to administering the test, the speech-language pathologist will demonstrate the sound(s) to be repeated and allow the patient to complete several practice trials. A trial is defined by a predetermined amount of time or number of repetitions. Generally, the SLP will administer a series of tests, each of which requires the client to produce a different sound or combination of sounds.

To measure the DDK rate, a SLP will record how many times the individual repeats the sound or combination of sounds in a given period of time (usually five to 15 seconds). DDK rates are measured in terms of iterations per second (it/s) or in terms of the time required to produce a certain number of iterations of a mono-, bi-, or trisyllabic token. The rate will be calculated and compared to the published norms. The SLP may use specialized recording equipment and a computer software program to record and analyze DDK rate. The DDK rate is calculated by dividing the total number of iterations by the duration of the trial or by determining the time it took the client to make a set number of iterations. The results are scored and compared to the published normative values. For example, in

Key Terms

Ataxia Childhood apraxia of speech.

Dysarthria Stuttering.

the data published by Fletcher (1972), the norm for 20 repetitions of the syllable "puh" for a child at age 10 is 3.7 seconds.

Some clients, especially preschool age children, may have difficulty complying with the instructions or completing the DDK tasks. In such cases, real words such as "buttercup," or "pattycake" may be used to test diadochokinetic rate. Also, preliminary findings from research published by Yaruss and Logan in 2002 indicate that other means of assessing DDK productions in young children, namely, measurement of accuracy and fluency, may be more useful diagnostic tools than standard measures of DDK rate.

Resources

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American Speech Language Hearing Association (ASHA). 10801 Rockville Pike, Rockville, MD 20852-3279. (301) 897-5700 or (800) 638-8255; Fax: (301) 571-0457. actioncenter@asha.org. <http://www.asha.org>.

Dawn J. Cardeiro, MS, CGC

Diazepam

Key Terms

Benzodiazepines A class of drugs with hypnotic, antianxiety, anticonvulsive, and muscle relaxant properties, used in the treatment of anxiety or sleeping disorders, to relax muscles, or to control seizures.

Definition

Diazepam is an antianxiety medication that is also useful in the treatment of muscle spasms and some types of **seizures**. The drug belongs to the class of medications known as **benzodiazepines** that depress activity of the **central nervous system**.

Purpose

Diazepam, which is marketed under the brand names of Valium, Diastat, T-Quil, and Valrelease, is taken by millions of people to relieve feelings of anxiety. As well, the drug can lessen muscle spasms and can control some types of seizures. Diazepam is also used to therapeutically lessen the agitation caused during alcohol withdrawal by someone who is physically addicted to alcohol. Additionally, diazepam is used in the treatment of irritable bowel syndrome and to lessen the symptoms of panic attacks.

Description

Diazepam is supplied as a tablet, as a capsule that releases the active drug at a slower rate, or as a liquid. All three of these forms of the drug are taken orally. The time-release capsule should be swallowed whole. Diazepam should be stored at room temperature in a tightly closed container to avoid alteration in the compound due to excessive heat or moisture. Valium is also available in an injectable form.

Recommended dosage

Diazepam dosage is determined by a physician taking into account the nature of the problem, severity of the symptoms, and the person's response to the drug. Typical adult doses range from 2–10 mg taken two to four times a day. Children and elderly adults will typically receive 1–2 mg one to four times daily.

The dosage of diazepam typically prescribed by a physician is taken anywhere from one to four times each day, depending on the strength of the individual dose. This maintains the concentration of the drug at a therapeutic level, as diazepam is quickly absorbed from the gastrointestinal tract. Peak levels of the drug are reached within a couple of hours after administration, with levels dropping below therapeutic effectiveness within six to eight hours.

Diazepam can be taken with or without food. The liquid form can be mixed with other fluids or select foods such as applesauce.

Precautions

The recommended dosage should not be exceeded, nor should it continue to be taken after the prescribed time. Such abuse can lead to a dependence on the drug, or the establishment of tolerance. As the effectiveness of diazepam is related to its concentration, it is important to take the drug regularly. Doses should not be skipped as this could lead to a worsening of the symptoms.

Diazepam should not be taken with other central nervous system depressants such as narcotics, sleeping pills, or alcohol. The combinations could lower blood pressure and suppress breathing to the point of unconsciousness and death.

Persons taking diazepam should **exercise** extreme caution when driving or operating machinery. These activities should be avoided during periods of drowsiness associated with diazepam therapy.

Pregnant and breast-feeding woman should not take diazepam, nor should someone with **myasthenia gravis**. The drug should be used cautiously in those with **epilepsy**, as diazepam may trigger an epileptic seizure.

Side effects

Some people are allergic to diazepam. In this case, other drugs can be substituted. These include alprazolam (Xanax), chlordiazepoxide (Librium), and triazolam (Halcion).

Common side effects from diazepam include drowsiness, **dizziness**, blurred vision, **headache**, **fatigue**, muscle weakness, memory loss, skin rash, diarrhea, dry mouth, stomach upset, decreased sexual drive, and an altered appetite. Less common side effects include jaundice, decreased white blood cell count (leukopenia), insomnia, hallucinations, and irritability.

Interactions

Diazepam can interact with other prescription medicines, especially antihistamines, as well as cimetidine (Tagamet), disulfiram (Antabuse), and fluoxetine (Prozac). Additionally, interaction can occur with medications given for the relief of **depression**, **pain**, **Parkinson's disease**, asthma, and colds, and with muscle relaxants, oral contraceptives, sedatives and sleeping pills, tranquilizers, and even some vitamins. In general, the result of the interaction is to increase the drowsiness caused by diazepam.

Resources

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Brian Douglas Hoyle, PhD

Dichloralphenazone, Isometheptene, and Acetaminophen

Definition

Dichloralphenazone, isometheptene, and acetaminophen are a combination medicine indicated for the treatment of symptoms associated with vascular (tension) headaches and migraine. Dichloralphenazone is a general sedative that slows down **central nervous system** (CNS) function, causing relaxation and minor **pain** relief. Isometheptene causes narrowing of blood vessels, aiding the specific relief of **headache** pain. Acetaminophen is a general, mild pain reliever and fever reducer.

Purpose

Dichloralphenazone, isometheptene, and acetaminophen do not prevent the occurrence of regular tension headaches or migraines. Rather, they relieve symptoms, including headache, nausea, altered vision, and sensitivity to light and sound at their onset.

Description

In the United States, dichloralphenazone, isometheptene, and acetaminophen are sold under the names Amidrine, Duradrin, I.D.A , Iso-Acetazone, Isocom, Midchlor, Midrin, Migrapap, Migquin, Migratine, Migrazone, Migrend, Migrex, Mitride. The medications exert their therapeutic effects individually. Dichloralphenazone aids relaxation, isometheptene relieves the throbbing pain associated with headaches, and acetaminophen acts as a general pain reliever.

Recommended dosage

Dichloralphenazone, isometheptene, and acetaminophen are most commonly available together in capsule, tablet, or dissolving tablet form. They are prescribed by physicians in varying dosages.

Dichloralphenazone, isometheptene, and acetaminophen are not indicated for routine use or headache prevention. For the treatment of tension headaches and

Key Terms

Migraine Recurrent severe headaches generally accompanied by an aura (classic migraine), nausea, vomiting, and dizziness.

migraines, they should be taken at the onset of headache symptoms or at the first warning signs of migraine. The usual initial dose for adults is one to two capsules. Treatment including dichloralphenazone, isometheptene, and acetaminophen may be appropriate for some children, but only when advised by a physician. The maximum daily dose for anyone taking dichloralphenazone, isometheptene, and acetaminophen usually is not greater than six to eight capsules.

A double dose of dichloralphenazone, isometheptene, and acetaminophen should not be taken at one time. If one dose fails to relieve symptoms associated with tension headache or migraine, follow instructions provided by the prescribing physician for taking supplemental doses every few hours. Do not take dichloralphenazone, isometheptene, and acetaminophen for several days in a row, even if symptoms persist, unless instructed by a physician. Any persistent, severe headache should be evaluated by a physician, especially if accompanied by fever, **visual disturbances**, confusion, stiff neck, or numbness and weakness on one side of the body.

Precautions

Dichloralphenazone, isometheptene, and acetaminophen may cause drowsiness and sleepiness for several hours. Caution is necessary to determine if it is safe to drive a car or operate machinery.

It is necessary to consult a physician before taking dichloralphenazone, isometheptene, and acetaminophen with certain non-perscription medications. While taking dichloralphenazone, isometheptene, and acetaminophen, patients should avoid alcohol and CNS depressants (medicines that can make one drowsy or less alert, such as antihistimines, sleep medications, and some pain medications). They can exacerbate side effects such as drowsiness, nausea, and loss of coordination.

Avoid additional general pain relievers containing acetaminophen (such as Tylenol) while using a dichloralphenazone, isometheptene, and acetaminophen combination medicine.

Dichloralphenazone, isometheptene, and acetaminophen may not be suitable for persons with a history of asthma or other chronic lung diseases, liver disease, kidney disease, mental illness, high blood presure, **seizures**, angina (chest pain), irregular heartbeats, or other heart problems. Persons who have had a **stroke** or are obese should avoid taking dichloralphenazone, isometheptene, and acetaminophen. Patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are nursing, pregnant, or plan to become pregnant.

The effect of dichloralphenazone, isometheptene, and acetaminophen during pregnancy has not been fully established, but research demonstrates that the medications are passed into breast milk. Patients who become pregnant while taking dichloralphenazone, isometheptene, and acetaminophen should contact their physician.

Side effects

Patients and their physicians should weigh the risks and benefits of dichloralphenazone, isometheptene, and acetaminophen before beginning treatment. Most patients tolerate combination medications with dichloralphenazone, isometheptene, and acetaminophen well, but may experience a variety of mild to moderate side effects. Some possible side effects, such as upset stomach and nausea mirror the symptoms associated with migraine. Common side effects that do not usually require medical attention include:

- diziness or unsteadiness
- sleepiness or drowsiness
- feeling of warmth or heaviness
- flushing
- tingling feeling
- excessive sweating
- diarrhea

Other, less common side effects of dichloralphenazone, isometheptene, and acetaminophen may be serious. The sudden onset of some severe side efects may indicate an allergic reaction. Contact the prescribing physician immediately if any of the following symptoms occur:

- pinpoint red spots on skin
- dark stools
- rash, lumps, or hives
- redness or swelling of the face, lips, or eyelids
- change in vision
- wheezing and difficulty breathing
- chest pain or tightness in the chest
- irregular heartbeat
- faintness or loss of consciousness
- sudden or severe stomach pain
- fever

Interactions

Dichloralphenazone, isometheptene, and acetaminophen receptor agonists may have negative interactions with antibiotics, antidepressants, anticoagulants, antihistimines, asthma medications, and monoamine oxidase inhibitors (MAOIs). Patients should not take dichloralphenazone, isometheptene, and acetaminophen for several weeks after stopping treatment with MAOIs.

Dichloralphenazone, isometheptene, and acetaminophen combination medications should not be used in conjunction with other migraine treatment medications unless otherwise directed by a physician.

Resources

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ORGANIZATIONS

ACHE (American Council for Headache Education). 19 Mantua Road, Mt. Royal, NJ 08601. (856) 423-0258. <http://www.achenet.org>.

National Headache Foundation. 428 W. St. James Place, 2nd Floor, Chicago, IL 60614. (703) 739-9384 or (888) NHF-5552. <http://www.headaches.org>.

Migraine Awareness Group. 113 South Saint Asaph Street, Suite 300, Alexandria, VA 22314. (703) 739-9384. <http://www.migraines.org>.

Adrienne Wilmoth Lerner

Dichloralphenazone

Definition

Dichloralphenazone is a general sedative-hypnotic that slows **central nervous system** (CNS) function, causing relaxation and **pain** relief. It is primarily indicated as a component of a drug that is used in the treatment of tension (muscle contraction) and vascular (migraine) headaches. Additional uses for dichloralphenazone include sedation and pain relief, and treatment for symptoms associated with insomnia.

Purpose

The combination medication, including isometheptene, dichloralphenazone, and acetaminophen, is used to treat tension and vascular **headaches**. Although the combination does not prevent the occurrence of tension headaches or migraines, isometheptene, dichloralphenazone, and acetaminophen act to relieve pain at its onset. The combination also relieves some symptoms associated with migraine such as altered vision and sensitivity to light and sound.

Description

Dichloralphenazone is not indicated for routine use. The medication should be taken only at the onset of pain, tension headache symptoms, or at the first warning signs of migraine.

Recommended dosage

Dichloralphenazone is most commonly available in capsule form, and is prescribed by physicians in varying dosages. The usual dose for adults is one to two capsules. Under the supervision of a physician, treatment that includes dichloralphenazone may be appropriate for some children.

A double dose of dichloralphenazone should not be taken. If the first dose fails to relieve pain or symptoms associated with tension headache or migraine, the patient should follow instructions provided by the prescribing physician for taking supplemental doses every few hours. If pain persists for several days, this medication should not be taken without consulting the prescribing physician.

Precautions

Dichaloralphenazone may cause drowsiness and sleepiness for several hours. Extreme caution should be used when driving or operating machinery.

A physician should be consulted before taking any form of dichloralphenazone with certain non-prescription medications. Patients taking dichloralphenazone should avoid alcohol and CNS depressants, including medicines that can make one drowsy or less alert such as antihistimines, sleep medications, and some pain medications. These medicines can exacerbate the side effects of dichloraphenazone.

Dichloralphenazone may not be suitable for persons with a history of **seizures**, **stroke**, asthma or other chronic lung diseases, liver disease, kidney disease, mental illness, high blood pressure, angina (chest pain), irregular heartbeats, or other heart problems. Patients should notify their physician if they smoke, consume a large amount of alcohol, have a history of drug use, are nursing, pregnant, or

Key Terms

Migraine A recurring, severe vascular headache, often accompanied by stomach upset and visual sensitivity to light, thought to be caused by changes in blood flow and certain chemical changes in the brain.

Sedative Medications that quiet nervous system excitement, producing a relaxed state.

plan to become pregnant. The effect of dichloralphenazone during pregnancy has not been fully established. Patients who become pregnant while taking dichloralphenazone should contact their physician.

Side effects

Patients and their physicians should weigh the risks and benefits of dichloralphenazone before beginning treatment, as some forms of dichloralphenazone may be habit forming. Most patients tolerate combination medications with dichloralphenazone well. However, some people may experience a variety of mild to moderate side effects. A few possible side effects such as headache, upset stomach, and nausea mirror symptoms associated with tension headaches and migraine. Common side effects that do not usually require medical attention include:

- dizziness or unsteadiness
- sleepiness or drowsiness
- feeling of warmth or heaviness
- increased sweating
- flushing
- tingling feeling
- diarrhea

Other, less common side effects of dichloralphenazone could indicate a potentially serious condition. The sudden onset of some severe side effects may indicate an allergic reaction. If any of the following serious side effects occur, the prescribing physician should be contacted immediately:

- rash, lumps, or hives
- redness or swelling of the face, lips, or eyelids
- change in vision
- wheezing and difficulty breathing
- chest pain or tightness in the chest
- irregular heartbeat
- faintness or loss of consciousness
- sudden or severe stomach pain
- persistent fever

Interactions

Dichloralphenazone may have negative interactions with antibiotics, antidepressants, anticoagulants, antiepileptic drugs (AEDs), **anticonvulsants**, antihistimines, asthma medications, and monoamine oxidase inhibitors (MAOIs). Patients should not take dichloralphenazone for several weeks after stopping treatment with MAOIs.

Dichloralphenazone should not be used in conjunction with other migraine treatment medications unless otherwise directed by a physician.

Resources

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ACHE (American Council for Headache Education). 19 Mantua Road, Mt. Royal, NJ 08601. (856) 423-0258. <http://www.achenet.org>.

National Headache Foundation. 428 W. St. James Place, 2nd Floor, Chicago, IL 60614. (703) 739-9384 or (888) NHF-5552. <http://www.headaches.org>.

Migraine Awareness Group. 113 South Saint Asaph Street, Suite 300, Alexandria, VA 22314. (703) 739-9384. <http://www.migraines.org>.

Adrienne Wilmoth Lerner

Diencephalon

Definition

The diencephalon is a complex of structures within the brain, whose major divisions are the thalamus and hypothalamus. It functions as a relay system between sensory input neurons and other parts of the brain, as an interactive site for the central nervous and endocrine systems, and works in tandem with the limbic system.

Description

The diencephalon is composed of several structures, the whole about the size of an apricot, situated near the core center of the brain, just above the brainstem. It is made up of the medulla oblongata, pons, and midbrain, below the telencephalon, the most basal part of the cerebrum. The two major components of the diencephalon are the thalamus and the hypothalamus. Other important structures within the diencephalon complex are the epithalamus, subthalamus, third ventricle, mammillary bodies, posterior pituitary gland, and the pineal body. The diencephalon interconnects with a larger, surrounding array of structures called the limbic system, which is the seat of emotions and memory.

The diencephalon functions in the following ways:

- As a junction and relay system that receives and filters afferent (incoming) sensory information, then relays it on to other parts of the brain, mainly the cerebral cortex, but also to the **cerebellum** and brainstem.
- As an interactive site between the **central nervous system** and the endocrine system.
- As an interactive complementary to the limbic system.

The upper part of the diencephalon, making up about 80% of its mass, is the thalamus, a small pillow of neural gray matter divided into two egg-shaped lobes. The lobes' long axes run toward the front and back of the head, and are connected to each other by a small stalk, the intermediate mass. The two thalamic lobes are filled with numerous pairs of nuclei, which are concentrations of synapsing afferent, or incoming, and efferent, or outgoing, neurons. Numerous such nuclei are situated throughout the brain.

The thalamic nuclei are named and classified according to their positions within the thalamus (medial, lateral, central, etc.), by their neural connections, and by their functions. In terms of function, there are three types of thalamic nuclei: sensory, motor, and arousal.

Layered sheets of myelinated axons, the internal thalamic medullary laminae, run vertically through the lobes of the thalamus. These laminae are full of neurons that interconnect various thalamic nuclei. The edges of the internal lamina reach the surfaces of the lobes. They show as narrow, whitish, cable-like bands, running across either lobe from its posterior underside, across the top, and forward, bifurcating into two bands (two vertical layers) toward the front. The main lamina divide the lobes of the thalamus into portions containing the medial and lateral geniculate nuclei, while the anterior bifurcations enclose the anterior nuclei.

The thalamus, the basal ganglia, and the cerebellum, which is the main movement coordination center of the brain, are neurally linked to the cerebral motor cortex in reciprocal, or feedback, fashion. Together, they regulate and fine-tune motor functions. The basal ganglia, which are part of the telencephalon, are groupings of gray matter within the white matter of the cerebral hemispheres. The basal ganglia function directly with the cerebellum to modify and fine-tune body movements.

A small part of the diencephalon, the epithalamus, extends rearward from, and slightly higher than, the thalamus. It holds the habenular nuclei, the stria medullaris thalami nerve tracts, and the pineal body, or epiphysis. The habenular nuclei play a role in emotional responses to odors. They receive afferent nerves from the septum, a complex of structures within the telencephalon and limbic system, and from the lateral preoptic nuclei of the basal forebrain, which is the lowermost region of the cerebrum; the stria medullaris tracts and the basal ganglia are the conduits. The habenular nuclei send efferents to the interpeduncular nucleus of the midbrain via the habenulo-interpeduncular nerve tract.

The pea-sized, conically shaped pineal body, on a short stalk, projects rearward and downward from the epithalamus. The pineal is a gland-like organ whose functions are still only poorly understood. It is a functional, light-sensitive remnant of an ancient and much more complex system of visually oriented organs, the pineal complex. The pineal is neurally connected with the suprachiasmatic nuclei of the hypothalamus, which hold the circadian internal clock. This is located just above the optic chiasma, the point at which the optic nerves from both eyes cross. The human pineal secretes melatonin, a hormone that seems to have a calming effect on the nervous system. The pineal, in response to the level of daylight, may induce sleepiness by increasing the output of melatonin.

All sensory input, except the olfactory (smell), passes through the thalamus, where it is filtered, integrated, and passed on to proper sites in the brain, most of them within the cerebral cortex. The route is as follows:

- Impulses from the auditory organs synapse in the medial geniculate thalamic nuclei, where they are sent to the auditory centers of the cerebral cortex.
- Impulses from the eyes, via the optic nerves, synapse in the lateral geniculate thalamic nuclei, and are sent on to the calcarine cerebral cortex.
- Other sensory input synapses in the ventral posteromedial thalamic nuclei, which receive, process, and pass on somatosensory input from the head, while the ventral posterolateral thalamic nuclei do likewise with input from the rest of the body.
- The thalamic nuclei also receive input from subcortical sources and feedback from the cortical areas. These operate in tandem to filter and control input to the cortex.

Key Terms

Autonomic nervous system A complex of nerve tracts, nuclei and organs within the brain that maintain homeostasis, or the functioning of body systems at proper levels.

Hypothalamus The lowermost part of the diencephalon, containing several nuclei, nerve tracts, and the pituitary gland; it is the regulatory seat of the autonomic nervous system.

Limbic system A complex of nerve tracts and nuclei that function as the seat of memory and emotions, containing the fornix, hippocampus, amygdala, and the cingulate gyrus.

Thalamus A small mass of gray matter composing the upper structure of the diencephalon, divided into two lobes and filled with numerous thalamic.

The ventral anterior and ventral lateral thalamic nuclei, involved with motor function, receive sensory input relayed through the basal ganglia and through the superior cerebellar peduncle, the main neural tract connecting the cerebellum and the red nuclei. The ventral anterior and ventral lateral thalamic nuclei project to the premotor and motor cerebral cortex. In addition, the ventral anterior thalamic nuclei are the main relay nuclei between the thalamus and the limbic system, receiving the mammillothalamic nerve tract from the mammillary bodies in the hypothalamus and projecting to the cingulate gyrus.

The cingulate gyrus, which is not a part of the diencephalon, is the part of the cerebrum closest to the limbic system, and serves to neurally connect the thalamus and hippocampus. The cingulate gyrus associates memories and emotional responses with smells, sights, and **pain**, and allows movement of attention among objects or ideas.

The medial dorsal thalamic nuclei receive nerve tracts from the amygdala of the limbic system and send efferents to the prefrontal cerebral cortex (not part of the diencephalon), which has numerous feedback connections with the thalamus, amygdala, and other subcortical structures.

The anterior thalamic nuclei connect with the mammillary bodies of the hypothalamus, and through them, via a nerve tract, the fornix, with the hippocampus and the cingulate gyrus.

The centromedian thalamic nuclei regulate excitability levels within the cerebral cortex and thus play a major role in arousal and alertness. The centromedian thalamic nuclei receive motor-related input from the basal ganglia, cerebellum, and the reticular formation of the brainstem and midbrain, and send efferent nerves to the cerebral cortex. The reticular formation is a network of nerves running through the brainstem and hindbrain, and containing the reticular activating system, which plays a key role in inducing arousal and alertness in tune with the circadian rhythm (sleeping and waking cycles). The reticular thalamic nuclei, which receive neural input from the reticular formation, regulate general thalamic output in accordance with the circadian rhythm.

The dorsomedial thalamic nuclei are involved with emotional arousal and the expression of emotionally based behavior, as well as memory, foresight, and feelings of pleasure. These nuclei receive input from many sites and interconnect with the prefrontal cerebral cortex.

That part of the diencephalon immediately below the two lobes of the thalamus is the subthalamus. It contains several nerve tracts and the subthalamic nuclei. Small portions of the red nuclei and the substantia nigra of the midbrain reach into the subthalamus. The subthalamic nuclei are interconnected with the basal ganglia and are involved in controlling motor functions.

The hypothalamus is the lowermost structure of the diencephalon. The thalamus, epithalamus, and hypothalamus surround and define most of the third ventricle of the brain, which, like all the ventricles, is filled with cerebrospinal fluid. The third ventricle communicates with the lateral ventricles and, via the cerebral aqueduct, with the fourth ventricle.

The hypothalamus contains several nuclei, nerve tracts, and the pituitary gland. It is the regulatory seat of the autonomic nervous system, while the hypothalamus and the pituitary are the major sites in which the two regulatory systems of the body, the central nervous system and the endocrine system, interact. The hypothalamus regulates the production of pituitary hormones, influencing and being influenced by emotional states, physical appetites, autonomic functions, temperature control, and diurnal rhythms. It is thus the main control center for homeostasis, or keeping physiological maintenance systems functioning at optimal states.

Efferent nerves from the hypothalamus extend into the brainstem and the spinal cord, where they synapse with neurons of the autonomic nervous system, which regulates a number of involuntary functions, among them the rate of heartbeat, urine release, and peristalsis. The hypothalamus responds to sensations of temperature extremes, the posterior hypothalamus stimulating muscle shivering to deal with cold, via efferent neurons to motor neurons within the spinal cord, and the anterior hypothalamus producing sweating as a reaction to overheating.

The pair of globular mammillary bodies are partially embedded in the underside of the hypothalamus. They are

involved in olfactory reflexes and emotional responses to odors. Also on the underside of the hypothalamus, and toward the front, is the optic chiasma, where the two optic nerve cables of the eyes cross.

From the floor of the hypothalamus, the posterior pituitary gland, or neurohypophysis, extends forward and downward at the end of a long peduncle or stalk, the infundibulum. Efferent hypothalamic nerves extend through the infundibulum to the posterior portion of the pituitary gland, others extend to the trigeminal and facial nerve nuclei, to help control the head muscles involved in swallowing.

The posterior pituitary is an extension of the hypothalamus, but the anterior part of the pituitary is glandular tissue with an embryonic origin separate from that of the posterior pituitary. During embryonic development, the anterior and posterior lobes of the pituitary eventually meet and fuse.

The hypothalamus plays a pivotal role in regulating the endocrine system via its control of the pituitary gland's production of several hormones, while the hypothalamus is influenced in turn by hormones in the bloodstream and by nerve input. A partial list of hormones secreted by the pituitary includes cortisol, prolactin, antidiuretic hormone (ADH), oxytocin, growth hormone (GH), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), lipotropins, beta-endorphins, melanocyte stimulating hormone, luteinizing hormone, and follicle stimulating hormone.

Hormones influence functions as diverse as metabolism, growth and maturation, reproduction, dealing with stress, urine production, ion balance, sexual development, and sexual function. The hypothalamus regulates physical appetites for food, water, and sex. Afferent fibers synapsing in the hypothalamus carry input from the internal organs, the taste receptors of the tongue, the limbic system, the nipples, and the external genitalia. The hypothalamus responds to and accords with emotional states, and thus plays a major role in affecting emotions and moods, among them sexual pleasure, tranquility, rage, and fear.

The hypothalamus contributes to the regulation of the circadian rhythm via an internal clock within the suprachiasmatic nuclei. This internal clock communicates with the reticular formation of the midbrain. The reticular formation contains the reticular activating system, which plays a key role in inducing arousal and alertness, in tandem with the circadian rhythm.

The diencephalon is interconnected with a surrounding complex of brain structures, the limbic system, which functions as the center of emotional states and responses, and of memory. Besides the various structures within the diencephalon, the limbic system includes the olfactory cortex, hippocampus, amygdala, cingulate gyrus, septal nuclei, the dorsomedial nuclei of the thalamus, and the anterior nuclear complex of the thalamus.

Memories of vividly emotional experiences are recorded and kept within easy reach of consciousness within the limbic system. Connections between, and functions of, the hypothalamus and limbic system are intimately intertwined. The ventral anterior thalamic nuclei are the main relay nuclei connecting the thalamus and the limbic system, receiving the mammillothalamic tract and projecting to the cingulate gyrus.

The olfactory sense is the only one whose neurons directly connect with a processing center within the limbic system and outside the thalamus. Within the hypothalamus, relayed olfactory impulses are used to regulate appetite and sexual behavior, and to regulate autonomic reactions initiated by odors. Since the limbic system processes memory and stores important memories, the direct connection of the olfactory neurons to the limbic system helps explain why odors serve as alarms (e.g., the odor of smoke) and can trigger strong emotional responses and vivid, detailed memories of events and emotional states.

The hippocampus, the main processor of memory, is a paired structure looping over the tops of the thalamic lobes and rearwards, curving downward and forward and ending at the paired, globular, cherry-sized amygdala, below and in front of the hypothalamus. The amygdala connect with the hippocampus, the septal nuclei, the prefrontal area of the cerebrum, and the medial dorsal nucleus of the thalamus. The amygdala also send nerves to the hypothalamus via the ventral amygdalofugal pathway.

The amygdala are centers for associating strong emotions, good or bad, with memories of the experiences that triggered those emotions. Fear responses and fear-charged memories are centered in the amygdala, which can retain vivid memories of traumatic experiences, and initiate the survival fight-or-flight response.

The hippocampus sends efferents, via a cable of nerves, the fornix, to the mammillary bodies within the hypothalamus. The mammillary bodies send efferents to the anterior nuclei of the thalamus via the mammillothalamic tract.

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Society for Behavioral Neuroendocrinology. 4327 Ridge Road, Palmyra, VA 22963. srl@virginia.edu. <http://www.sbne.org>.

Kevin Fitzgerald

Diet and nutrition

Definition

Adequate nutrition and a well-balanced diet in every phase of life are essential requirements for normal development and growth, health maintenance, and disease prevention, as well as for the recovery from illness or injury. The human organism is a dynamic system, constantly using stored energy to perform physiologic functions such as blood circulation, respiration, immune surveillance and defense against infections, synthesis of proteins, hormones, and **neurotransmitters** necessary for muscle activity, sensory perception, thought processing, digestion of food and elimination of body wastes, cell and tissue detoxification, and DNA repair. Food is the main source of the micronutrients the organism utilizes to perform these vital functions, thus keeping the many physiologic systems in a state of homeostasis, or dynamic functional balance.

Description

Micronutrients are substances the body extracts from food through digestion, the process of breaking down large and complex molecules of food into more simple and smaller ones. Micronutrients are then absorbed through the walls of the small intestine into the blood vessels to be distributed to and processed by different organs and tissues. Different classes of micronutrients are used for several different purposes. For instance, some micronutrients such as vitamins are essential for cellular protection against naturally occurring metabolic toxins formed as a byproduct of cellular activity, or against toxins derived from the environment, such as pollution, chemicals, solar **radiation**, or drugs. Micronutrients are divided in the following categories: amino acids, fatty acids, sugars or carbohydrates, vitamins, and minerals.

Amino acids are the building blocks of all types of proteins that constitute cells, organs, tissues, and muscles. Some proteins are mediators of signals between cells of different organs, regulating intracellular physiology and growth. Although approximately 300 amino acids are known in nature, the human body only utilizes about 20 of them. The body itself manufactures half of the amino acids required by humans to make proteins. However, 10 of these are called essential amino acids because humans depend on their presence in food, since the body cannot adequately manufacture them. Eight of the 10 essential amino acids must be present in the diet throughout life, whereas two are necessary during development and growth, or when tissue repair is needed.

Some amino acids are created in the brain and play an important role in the regulation of mood, cognitive function, attention, and sleep pattern. The synthesis of neurotransmitters, chemical messengers in the brain that regulate neural activity, is also dependent on adequate dietary intake of essential amino acids. Examples of neurotransmitters are acetylcholine, gamma-aminobutyric acid (GABA), dopamine, and serotonin. The main source of essential amino acids is animal protein such as fish, meat, milk, and eggs. Plants are also a source of amino acids, although none contain all of the essential amino acids. It is important, therefore, to combine different types of plants within the same meal, such as nuts, beans, grains, fruits, especially in vegetarian diets.

Enzymes are another important type of protein that regulates all metabolic events. Some enzymes are responsible for the detoxification of cells and tissues, and

Key Terms

Amino acid An organic compound composed of both an amino group and an acidic carboxyl group. Amino acids are the basic building blocks of proteins. There are 20 types of amino acids (eight are "essential amino acids" that the body cannot make and must therefore be obtained from food).

Antioxidant Any substance that reduces the damage caused by oxidation, such as the harm caused by free radicals.

Free radical An unstable molecule that causes oxidative damage by stealing electrons from surrounding molecules, thereby disrupting activity in the body's cells.

Homeostasis The balanced internal environment of the body and the automatic tendency of the body to maintain this internal "steady state." Also refers to the tendency of a family system to maintain internal stability and to resist change.

Neurotransmitter A chemical messenger that transmits an impulse from one nerve cell to the next.

the activation of medications, while others are involved in the regulation of the cellular cycle during cell proliferation. Some enzymes are essential for the digestion of larger nutrients such as dietary proteins, carbohydrates, and fatty acids, and are known as digestive enzymes. Other groups of enzymes regulate the synthesis and degradation of other enzymes involved in the processing and transport of micronutrients.

Deficiency in digestive enzymes causes slow and incomplete digestion of larger nutrients, thus reducing the availability of micronutrients to the body and resulting in a nutritional deficit. Although the body manufactures some digestive enzymes, a diet rich in fruits and vegetables provides a reliable source for digestive enzymes. Papaya, pineapple, cucumber (eaten with the skin), tomatoes, and green leafy vegetables are especially good sources for digestive enzymes.

Another frequent cause of nutritional deficiency is malabsorption of nutrients in the intestinal tract due to parasite infestation, infections, or disruption of the normal intestinal microorganism balance by some medications. Normally, a mixed population of bacteria permanently lives in the intestinal mucosa, helping to break down some larger molecules such as complex carbohydrates. When this balance is disrupted, even though the daily diet contains the correct amounts of all necessary nutrients, nutritional deficiencies may occur due to the inability of the intestinal tract to absorb molecules that are not broken down by the beneficial bacteria.

Fatty acids are the components of lipids or fats that may be combined with proteins and/or sugars to form a variety of functional and structural molecules such as cholesterol, hormones, and enzymes. Fatty acids are also an important source of body energy and are stored in the adipose tissue (i.e., fat cells). Lipoproteins (such as cholesterol) are present in the structure of cell membranes and in blood plasma, and have a variety of other functions. For example, cholesterol is a precursor of bile acid and of steroid hormones such as testosterone, progesterone, and estrogen. Myelin, the white substance that involves nerve fibers as a multi-layered sheath, is constituted of lipids and proteins, and is essential for normal neural signal transmission, and muscle control and coordination. Fatty acids are present in whole milk, butter, fish, seafood, lard, meat, vegetable oils, margarine, nuts, olives, corn, soybean, and grains.

Carbohydrates encompass a variety of sugar molecules that play a multitude of roles in body physiology and are also a structural component of the cell membrane. Carbohydrates supply and store energy, aid in intercellular communication, and regulate many metabolic events in the body. The digestive process transforms carbohydrates into glucose, the main source of energy used by cells. Glucose, a simple sugar, is a component of many proteins known as glycoproteins, and is also present in the molecular structure of DNA as pentose. The central and peripheral nervous systems demand a constant supply of glucose in the blood, as does the muscular system. The body stores glucose in the form of glycogen that can be promptly mobilized when the level of glucose in the blood falls. Glycogen is mainly stored in skeletal muscles and in the liver, but it is also present in small amounts in virtually every cell of the body. Carbohydrates are present in milk, fruits, potatoes, cereals, sugar, and honey. Whole grains, lettuce, and fruits also contain a type of fibrous carbohydrate humans cannot digest, known as cellulose. Nevertheless, cellulose helps digestion because these fibers stimulate movement of the intestinal tract, preventing constipation and removing pathogenic germs.

The body needs to protect its cells and DNA from the damage oxygen and free radicals can do. Free radicals are highly reactive substances that form when oxygen interacts with other molecules during digestion or other cellular processes. To combat this damage, the body uses a defense system of antioxidant molecules that react safely with the free radicals. Some antioxidant molecules are naturally occurring enzymes. Vitamins are another important source of antioxidants.

Vitamins neutralize free radicals and protect tissue integrity and function. They are also essential for a number of other cellular functions such as tissue renewal and healing, red blood cell production, body resistance to infections, brain and muscle activity, DNA replication during cell cycle, adequate regulation of several metabolic events, recovery from disease, and prevention of chronic disease. Vitamins are divided in two categories according to their solubility: water-soluble vitamins and fat-soluble vitamins.

Vitamin C (ascorbic acid) and B-complex vitamins (thiamine, niacin, riboflavin, biotin, folic acid, cobalamin, pyridoxine, and pantothenic acid) are water-soluble vitamins. Since kidneys easily eliminate water-soluble vitamins through the urine, they must be present in the daily diet because only trace amounts are stored in the organism. The main dietary sources of vitamin C are tomatoes, green leafy vegetables, and citrus fruits such as oranges, although other fruits and vegetables do contain smaller amounts of vitamin C. Raw meat and fish also contain vitamin C that is lost in the cooking process. Vitamin C protects cells against oxidation, helps collagen formation, and the transformation of cholesterol into bile acids. The detoxification properties of vitamin C help in the elimination of the toxins and free radicals that build up in the extracellular fluids and in cells during infections.

B-complex vitamins participate as co-factors in a vast number of enzyme activities and act as co-antioxidants as well. Some B vitamins are required for red blood cell formation, while others are required for regulation of plasma cholesterol levels, energy release in tissues, amino acid synthesis, embryo development, brain development and neuronal activity, bone marrow formation, and infection resistance. Additionally, some B vitamins promote myelin sheath formation around nerve fibers and neurons during brain development in the fetus and during child growth as well. The main dietary sources of B-complex vitamins are whole milk, chicken, pork, egg, seafood, meat, liver, corn, wheat and whole grains, green leaves, and legumes. As not all B vitamins are present in each of these foods, it is important to keep a well-balanced and varied diet. Strict vegetarians, especially vegans, need supplementation of some B vitamins such as biotin and cobalamin as animal products are eliminated as a dietary source.

The fat-soluble vitamins are vitamins A, D, E, and K. The precursors of these vitamins are present in food, and are transformed by the body into the active vitamin form. Dietary precursors of vitamin A are beta-carotene and other carotenes found in carrots, yellow fruits and seeds, as well as in dark green vegetables. Retinol, found in animal products such as meat, fish, egg yolk, whole milk, and butter, is vitamin A itself. Vitamin A is essential for normal fetal development, child growth, tissue repair, healing, and renewal, vision, cell protection against free radicals, and reproduction. Beta-carotene shows several benefits of its own, independently of being converted into vitamin A by the body. Some scientific evidence shows that adequate levels of beta-carotene in the diet help to prevent chronic and degenerative diseases such as skin cancer, cardiac diseases, and cataracts. This vegetable precursor of vitamin A also has its own antioxidant activity, and enhances immune system function. Whereas excessive intake of retinol may cause liver and nerve cell toxicity, beta-carotene does not offer such a risk.

Vitamin D is, in fact, a group of molecules that function as hormones. The dietary precursor of vitamin D in plants is known as ergocalciferol. Animal products contain some preformed active molecules of vitamin D. However, the main source of vitamin D in the organism is in the form of an intermediate molecule of cholesterol that is converted into calcitriol in the skin through the action of solar radiation. Long winter months in the northern hemisphere or little exposure to sunlight sometimes lead to deficiency of vitamin D, thus requiring greater dietary intakes of animal products such as fatty fish and egg yolk. Calcitriol, one active form of vitamin D, regulates the synthesis of proteins responsible for calcium and phosphate absorption in the intestinal tract. Vitamin D also regulates the levels of calcium in blood plasma, and helps the mineralization of bones. This micronutrient is essential for normal skeletal development of infants and children, and to prevent osteoporosis in adults, especially women and elderly men.

Tocopherols are different forms of vitamin E, such as alpha and beta tocopherols, and are important antioxidants that protect cholesterol and fatty acids against peroxidation, the chemical process that transforms lipids into rancid fat. Peroxidation of circulating cholesterol causes progressive vascular obstruction, which may lead to heart attack or **stroke**. Vitamin E also protects fatty acids and lipids that are components of cell membrane structure, thus maintaining the cell's normal functionality. The best dietary sources of vitamin E are vegetable oils.

Vitamin K occurs as phylloquinone in plants, and as menaquinone in bacteria of the intestinal flora. It is essential for the right formation of clotting factors, the proteins responsible for normal blood coagulation. Dietary sources are spinach, cabbage, egg yolk, and liver, although the normal intestinal bacterial flora constitutes a regular source of the vitamin as well.

Discrete (trace) amounts of some minerals are also vital for cell metabolism, neural and muscle activity, bone development and maintenance, electro-chemical reactions, and transport of nutrients and metabolic waste through the cell membrane. The most important minerals are calcium, phosphorus, potassium, magnesium, sodium, and iron.

Calcium and phosphorus are required by a variety of body functions such as bone formation and maintenance, neural signal transmission or synapses, smooth muscle contraction, and skeletal muscle activity. They also regulate glandular and enzymatic activity. Major sources of these nutrients are milk and dairy products. Magnesium works together with calcium, regulating calcium transport into cells and to and from bones. Magnesium controls the levels of calcium transported to heart tissue, maintaining the heartbeat in a steady pace. Magnesium is also important in cells of the immune system such as lymphocytes, in skeletal muscles, and as a facilitator of oxygen delivery. Magnesium participates in the production of ATP (adenosine triphosphate), the source of energy utilized by cells.

Sodium and potassium regulate levels of fluids entering and leaving the cells, and moving between blood vessels and the lymphatic system, and are, therefore, important agents in the regulation of blood pressure. Iron is an essential component of red blood cells (hemoglobin), which transport oxygen to all tissues. Iron is stored in the plasma in proteins known as ferritin. Adequate plasma levels of ferritin are required for hematopoiesis, or blood formation. However, excess ferritin in plasma increases cholesterol peroxidation, leading to cardiovascular disease. Trace amounts of minerals are present in fruits and other vegetables, as well as in animal products such as seafood, fish, liver, milk, meat, eggs, and poultry.

Dieticians are the best advisors when a specific diet is important, such as during pregnancy, or in infancy and early childhood development, in order to prevent nutritional deficits. Physicians can refer patients to trusted dieticians. Elderly citizens and ill people also need professional nutritional guidance to meet deficiencies associated with the aging process or disease. The same is true for professional athletes and individuals working in strenuous physical and/or mental conditions. For the general population, the United States Department of Agriculture has designed the Food Guide Pyramid, illustrating the groups of foods and the daily-required variety of foods for optimum nutrition and health maintenance.

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Sandra Galeotti

Diffuse sclerosis *see* **Schilder's disease**

Diplopia *see* **Visual disturbances**

Disc herniation

Definition

Intervertebral discs are circular ring-like flat structures that function as cushions between two spinal vertebrae, allowing spinal flexibility and acting as shock absorbers. Each intervertebral disc contains a nucleus (center) surrounded by a sack of fibrocartilage (fibrous, connective tissue), rich in collagens (fibrous protein). A herniated disc occurs when the outer sack partially ruptures and the interior of the sack expands, pushing part of the disc into the spinal canal near to where the spinal cord and other nerve roots are located. This causes either chronic or acute **pain** in the back or in the neck, and movement restriction of the affected area due to pressure exerted on the spinal nerve roots. This condition is also known as a slipped disc, an intervertebral disc hernia, a herniated intervertebral disc, and a herniated nucleus pulposus.

Description

Intervertebral disc disease is among the most common causes of neck and **back pain**. Cervical disc herniations (in the neck region) are less common than lumbar (lower back) herniations. Lumbar disc herniations affect an estimated four out of five patients complaining of back pain. Several factors may contribute to a herniated disc, such as poor posture, work-related strain, traumatic injuries due to falls or blows in the back, improper weight lifting, obesity, and sport-related muscular strain. Disc herniation may also occur because of age-related degenerative processes that cause progressive loss of disc elasticity.

Key Terms

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

Spinal cord The elongated nerve bundles that lie in the spinal canal and from which the spinal nerves emerge.

Other risk factors associated with disc hernias are lack of regular physical exercises, inadequate nutrition, smoking, and genetic factors.

Demographics

Herniated disc is a common problem, with approximately one in 32, or 8.4 million people in the United States affected each year.

Causes and symptoms

Degenerative disc disease, usually related to aging, is more common in the lumbar area, where much of the wear-and-tear of a lifetime of activity is exerted, resulting in chronic back pain. However, in the cervical area the disc degenerative process usually starts with a traumatic twisting of the disc space that leads to chronic inflammatory pain in the neck, and may result in arm pain and numbness. The degenerative process may also be associated with occupational repetitive movements such as those required in construction, farming, mining, and other professional activities where workers are required to handle heavy loads.

Herniated discs sometimes cause pain that is incapacitating, and the condition accounts for a major cause of work disability and health care expense in the United States. Lumbar disc hernias are commonly associated with **sciatica** (inflammation of the sciatic nerve in the lower back) due to disc protrusion or herniation that compresses the spinal nerve root radiating to the femoral or sciatic nerve. A sensation of sharp, painful electric-like shock is felt during acute sciatica both in the back and along the involved limb. Other symptoms are a burning pain in the back, numbness or tingling sensation in the related leg, and weakness in one or both legs.

Growing scientific evidence also points to genetic factors in disc herniation, especially in families with a history of predisposition to early-onset sciatica and disk herniation. The causation factor seems to be a mutation in one of the three genes (COL9A1, COL9A2, and COL9A3), which are related to the formation of collagen.

Diagnosis

A clinical record of chronic back pain and progressive leg pain points to the possibility of a degenerative disc disease in progression; and physical palpation (examination by touch) by the physician may reveal whether a nerve root is affected. The straight leg-raising test (raising the leg straight, with no bend at the knee, until pain is experienced in the thigh, buttocks, and calf) can also point to nerve root irritation in the lumbosacral area due to herniated disc. X ray of the affected spinal area is the standard test for confirmation of a herniated disc. When surgery is being considered, other imaging tests are performed, such as a **magnetic resonance imaging (MRI)** scan or computed tomagraphy (**CT**) **scan,** for confirmation of the diagnosis.

Treatment team

The orthopedist is the medical specialist often first consulted, and many orthopedic clinics offer the services of physical therapists whose interventions will be prescribed by the physician. In more severe cases, the intervention of a **neurologist**, neurosurgeon, or an orthopedic surgeon, along with a pain specialist may be required.

Treatment

In most cases, conservative treatments such as over-the-counter painkillers, anti-inflammatory drugs, and muscle relaxants associated with a period of bed rest are enough to curb the acute phase. To prevent further acute pain, physical therapy and specific exercises may be recommended by the physician, along with the identification of poor postural habits and posture-correction exercises. However, in more severe cases where conservative treatment fails, further treatment may be necessary, such as injections with cortisone. Surgery is only a real necessity when a progressive loss of neurological function is experienced, leading, for instance, to bladder or bowel incontinence or limb paralysis. In cases of frequently recurrent acute pain, the person with a herniated disc chooses surgical intervention to decrease pain and improve quality of life.

Prognosis

The vast majority of people (more than 90%) treated for herniated disc experience improvement with pain and mobility. About 5% of people who have experienced a herniated disc will eventually have recurring pain, and another 5% will experience a herniated disc at another vertebral site.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). 1 AMS Circle, Bethesda, MD 20892-3675. (301) 495-4484 or (877) 22-NIAMS; Fax: (301) 718-6366. niamsinfo@mail.nih.gov. <http://www.niams.nih.gov/>.

Sandra Galeotti

Dizziness

Definition

Dizziness is a general term that describes sensations of imbalance and unsteadiness, such as vertigo, mild turning, imbalance, and near **fainting** or fainting. Feelings of dizziness stem from the vestibular system, which includes the brain and the parts of the inner ear that sense position and motion, coupled with sensory information from the eyes, skin, and muscle tension.

Description

Because dizziness is a general term for a variety of feelings of instability, it spans a large range of symptoms. These symptoms range from the most dramatic, vertigo, to the least severe, imbalance. Included in these feelings is fainting, which results in a loss of consciousness.

Vertigo is an acute feeling of violent rotation. People with vertigo often feel as if they are tilting or falling through space. Vertigo is most often caused by problems with the vestibular system of the inner ear. Symptoms can be brief, or may last for extended periods of time and may be accompanied by changes in pulse and blood pressure, perspiration, nausea, and a type of rapid eye movement called nystagmus.

Mild turning is a less violent type of vertigo. People with mild turning are still able to function in normal daily routines. However, a feeling of turning may continue for weeks. Mild turning is usually a symptom of inner ear dysfunction. It may also result from **transient ischemic attack**, or a lack of blood flow to the brain. People who have suffered from strokes may feel mild turning for periods of time. Mild turning may also be associated with **multiple sclerosis**, **AIDS**, or head trauma.

Imbalance is a feeling of instability or floating. It is associated with many general medical problems such as the flu or infection. Imbalance can also be associated with arthritis, especially in the neck, or another neurological problem.

Fainting is a sudden loss of consciousness and near fainting is a feeling of extreme light-headedness with a sinking or falling feeling. Vision usually becomes hazy or dimmed and the extremities become weak. Both fainting and near fainting are caused by lack of blood flow to the brain. Anything that causes a rapid drop in blood pressure, such as a heart attack or an insulin reaction in a diabetic, can result in fainting or near fainting. Panic attacks that cause a person to exhale a lot of carbon dioxide can cause fainting or near fainting.

Vestibular system

The vestibular system is the sensory system located in the inner ear that helps the body to maintain balance. Balance in the human body is coordinated by the brainstem, which, with speed and precision, collects information from other parts of the brain and sensory organs throughout the body. It is the brainstem that sends neurological instructions to the muscles and joints. The sensory organs that play critical roles relaying information to the brainstem include the skin, eyes, muscles and joints, and the vestibular system in the inner ear. Dizziness may result with dysfunction in any of these components or in the nerves that connect them.

Brain

The **cerebellum**, which is responsible for coordination and the cerebral cortex, provides neurological information to the brainstem. For example, the cerebellum is the organ that informs the body how to shift weight when going down a flight of stairs and how to balance on a bicycle. These processes are accomplished without conscious thinking.

In order to maintain balance, the brainstem depends on input from sensory organs including the eyes, muscles, joints, skin and ears. This information is relayed to the brainstem via the spinal cord. The combined neurological receptor system, which involves the brainstem, spinal cord, and sensory organs, is called the proprioceptive system. Proprioceptive dysfunction may result in dizziness, and people with problems with their proprioceptive system may fall often. Additionally, as people age, problems with proprioception become more common.

Key Terms

Auditory nerve A bundle of nerve fibers that carries hearing information between the cochlea the brain.

Benign positional paroxysmal vertigo (BPPV) A common cause of dizziness thought to be caused by debris that has collected within a part of the inner ear.

Brainstem The part of the brain extending from the base to the spinal cord, responsible for controlling basic functions such as respiration and breathing.

Cerebral cortex The surface gray matter of the cerebral hemispheres (cerebrum) of the brain, responsible for receiving sensory information, for conscious thought, and for movement.

Cerebellum Area of the brain lying below and behind the cerebrum, responsible for maintaining balance, and coordinating and controlling voluntary muscle movement.

Mèniére's disease An inner ear disorder that can affect both hearing and balance, and can cause vertigo, hearing loss, along with ringing and a sensation of fullness in the ear.

Otolith organs Organs in the vestibular apparatus that sense horizontal and vertical movements of the head.

Semicircular canals A set of three fluid-filled loops in the inner ear that are important to balance.

Vertigo Extreme dizziness.

Vestibular system The sensory system located in the inner ear that allows the body to maintain balance.

Sensory organs

Visual information is of particular importance to maintaining balance. The visual systems most involved are the optokinetic and pursuit systems. The optokinetic system is the motor impulse responsible for moving the eyes when the head moves, so that the field of vision remains clear. The pursuit system allows a person to focus on a moving object while the head remains stationary. Both of these systems feed information about the person's position relative to the surroundings to the brainstem. A specific type of eye movement called nystagmus, which is repetitive jerky movements of the eye, most often in the horizontal direction, may cause dizziness. Nystagmus may indicate that neurologic signals from the optokinetic or pursuit systems are not in agreement with the other balance information received by the brain.

Sensory information from muscles, joints, and skin plays a key role in balance. The muscles and joints of the human body are lined with sensory receptors that send neurological information about the position of the body to the brainstem. For example, receptors in the neck muscles tell the brain which way the head is turned. The skin, in particular the skin of the feet and buttocks, is covered with pressure sensors that relay information to the brain regarding what part of the body is touching the ground.

Peripheral vestibular system

The ear, particularly the inner ear, plays a critical role in maintaining balance. The inner ear contains two major parts: the cochlea, which is mostly used for hearing, and the vestibular apparatus, also known as the peripheral vestibular system, which is important in balance. A set of channels connects the two parts of the ear and therefore any disease that affects hearing may also affect balance, and vice versa.

The peripheral vestibular system consists of a series of canals and chambers, all of which are made of membranes. This membrane system is filled with a fluid called endolymph. The peripheral vestibular system is further embedded in the temporal bone of the skull. In the space between the temporal bone and the membranes of the peripheral vestibular system resides a second fluid called perilymph. Endolymph and perilymph each have a different chemical makeup consisting of varying concentrations of water, potassium, sodium, and other salts. Endolymph flows out of the peripheral vestiubular system into an endolymphatic sac and then diffuses through a membrane into the cerebrospinal fluid that bathes the brain. Perilymph flows out of the peripheral vestibular system and directly into the cerebrospinal fluid. When the flow pressures or chemical compositions of the endolymph and perilymph change, feelings of dizziness can occur. These types of changes may be related to Mèniére's disease.

The vestibular apparatus is made up of two types of sensory organs: otolith organs and semicircular canals. The otolith organs sense the direction of gravity, while the semicircular canals sense rotation and movement of the head.

Two otolith organs in each ear are called the saccule and the utricle. The saccule is oriented in a vertical direction when a person is standing and, best senses vertical motion of the head. The utricle is nearly horizontal when a person is standing, so it best senses horizontal motion of

the head. Each organ consists of calcium carbonate crystals embedded in a gel. Special hair-producing cells extend into the gel from below. As the head moves, gravity and inertia cause the crystals to bend the hairs, which are in contact with nerves. Information on the position and motion of the head is thus relayed to the brain. If the hairs or the crystals in the otolith organs are damaged, feelings of dizziness may result.

In each ear, there are also three semicircular canals that lie on planes that are perpendicular to each other. The canals are connected together by a main chamber called a vestibule. The canals and the vestibule are filled with endolymph fluid. Near its connection to the vestibule, one end of each of the canals widens into a region called the ampulla. One side of the ampulla is lined with specialized sensory cells. These cells have hairlike structures that extend into a gelatinous structure called a cupula. As the head moves in a given plane, the endolymph inside the semicircular canal in that plane remains stationary due to inertia. The cupula, however, moves because it is attached to the head. This puts pressure on the cupula, which in turn moves the hairlike structures. The bending of the hairlike structures stimulates nerves, alerting the brain that the head is moving in a particular plane. By integrating information from all three planes in which the semicircular canals lie, the brain reconstructs the three-dimensional movement of the head. If information from one of the semicircular canals does not agree with that of another, or if the information generated by semicircular canals in one ear does not agree with the information produced by the other ear, feelings of dizziness may result.

All of the signals from the peripheral vestibular system travel to the brain along the eighth cranial nerve, also called the vestibular nerve. Damage to this nerve, either through head trauma or the growth of tumors, can also cause feelings of dizziness. Neurological information from the semicircular canals seems be more important to the brain than information from the otolith structures. If the eighth cranial nerve on one side of the head is damaged, but the other side remains intact, the brain learns to compensate over time; however, the mechanics involved in this process are not well understood.

Demographics

Dizziness is an extremely common symptom occurring in people of all ages, ethnicities, and socioeconomic backgrounds. Balance disorders increase with age, and by age 75, dizziness is one of the most common reasons for visiting a doctor. In the general population, dizziness is the third most common reason that patients visit doctors. According to the National Institutes of Health (NIH), about 42% of the population of the United States will complain of dizziness at some point in their lives. In the United States, the cost of medical care for patients with symptoms of imbalance is estimated to be more than $1 billion per year.

Diseases associated with dizziness

Because it involves so many different parts of the body, the balance system may exhibit signs of dysfunction for a variety of reasons. Dizziness may be caused by problems with the **central nervous system**, the vestibular system, the sensory organs, including the eyes, muscles and joints, or more systemic disorders such as cardiovascular disease, bacterial and viral diseases, arthritis, blood disorders, medications, or psychological illnesses.

Central nervous system dysfunction

Any problem that affects the nerves leading to the brain from vestibular or sensory organs, the spinal cord, the cerebellum, the cerebral cortex, or the brainstem may result in dizziness. In particular, tumors that affect any of these organs are of concern. In addition, disorders that affect blood supply to the central nervous system, such as transient ischemic attacks, **stroke**, migraines, **epilepsy**, or multiple sclerosis, may result in feelings of dizziness.

BRAIN TUMORS Although rare, acoustic neuroma is a benign tumor growing on the vestibulo-cochlear nerves, which reach from the inner ear to the brain. It may press as well on blood vessels that flow between the peripheral vestibular system and the brain. Symptoms included ringing in one ear, imbalance, and hearing loss. Distortion of words often becomes increased as the tumor grows and disturbs the nerve. Treatment requires surgical removal of the tumor, which nearly always returns the sense of balance to normal, although some residual hearing loss may occur.

Other brain tumors may also cause feelings of dizziness. These include tumors that originate in the brain tissue, such as meningiomas (benign tumors) and gliomas (malignant tumors). Sometimes tumors from other parts of the body may metastasize in the brain and cause problems with balance.

CEREBRAL ATROPHY Age causes atrophy (deterioration) of brain cells that may result in slight feelings of imbalance. More severe forms of dizziness may result from other neurological disorders.

BLOOD SUPPLY DISORDERS If the blood flow and oxygenation to the cerebellum, cerebral cortex, or brainstem is not adequate, feelings of dizziness can result. Such symptoms can result from several types of disorders, including anemia, transient ischemic attacks (TIAs), and stroke.

TIAs are temporary loss of blood supply to the brain, often caused by arteriosclerosis (hardening of the arteries). In addition to a brief period of dizziness or vertigo, symptoms include a transient episode of numbness on one side

of the body, and slurred speech and/or lack of coordination. If the loss of blood supply to the brain is due to a blockage in one of the arteries in the neck, surgery may correct the problem.

Strokes, or cerebrovascular accidents (CVA), occur in three major ways. A thrombotic stroke occurs when a fatty deposit forms a clot in an artery, blocking blood supply to the brain. An embolic stroke occurs when part of a clot from another part of the body breaks off and obstructs an artery leading to the brain. A hemorrhagic stroke occurs when blood vessels in the brain hemorrhage, leaving a blood clot in the brain.

PERIPHERAL VESTIBULAR SYSTEM DYSFUNCTION When balance problems are brief or intermittent, the peripheral vestibular system is usually the cause. Many different problems may be at the root of vestibular disorder.

BENIGN PAROXYSMAL POSITIONAL VERTIGO (BPPV) Benign paroxysmal positional vertigo occurs following an abrupt change in position of the head. Often, onset of vertigo occurs when patients roll from their back onto the side, and it usually subsides in less than a minute. BPPV can result from head trauma, degeneration of the peripheral vestibular system with age, infection of the respiratory tract, high blood pressure, or other cardiovascular diseases. Those who suffer from an infection of their vestibular system, causing severe vertigo that lasts up to several days, can develop BPPV any time within the next eight years. BPPV is also associated with migraine **headaches**.

Two theories on the cause of BPPV currently exist. One suggests that BPPV will occur when the calcium carbonate crystals in the otolith organs (the saccule and the utiricle) are displaced and become lodged in the cupula of the semicircular canals due to head trauma, infection, or degeneration of the inner ear canals. This displacement will stimulate the nerves from the semicircular canals when the head rotates in a particular position, indicating to the brain that the person is spinning. However, the rest of the sensory organs in the body report that the body is stationary. This conflicting information produces vertigo. The calcium carbonate crystals dissolve after a brief time, and the symptom is rectified. The second theory suggests that cellular debris accumulates into a mass that moves around the semicircular canals, exerting pressure on the cupula and causing vertigo. When the mass dissolves, the symptoms subside.

INNER EAR INFECTIONS Inner ear infection, or vestibular neuronitis, occurs some time after a person has suffered from a viral infection. Onset includes a violent attack of vertigo, including nausea, vomiting, and the inability to stand or walk. Symptoms subside in several days, although feelings of unsteadiness may continue for a week or more. A swelling of the vestibular nerve following a viral infection causes vestibular neuronitis.

Photographic representation of vertigo. *(© 1993 J. S. Reid/Custom Medical Stock Photo. Reproduced by permission.)*

Sometimes the inflammation can recur over several years. A viral infection affecting the inner ear, but not the vestibular nerve, is called viral labyrinthitis. Labyrinthitis can cause hearing loss, but all other symptoms are similar to vestibular neuronitis.

Severe bacterial infections can also cause inflammation of the inner ear. These cases include risk of deafness, inflammation of the brain, and meningitis (inflammation of the membranes surrounding the brain and spinal cord). Otitis occurs when fluid accumulates in the middle ear, causing feelings of imbalance, mild turning, or vertigo. When the infection reaches the inner ear, the disease is called acute suppurative labyrinthitis. Treatment for any bacterial infection in the ear is critical to prevent long-term damage to hearing and balance organs.

PERILYMPH FISTULA Perilymph fistulas are openings that occur between the middle ear and the inner ear. This allows a hole through which perilymph can flow, changing the pressure of perilymph flowing into the brain and causing dizziness. Fistulas often form as a result of head

trauma or abrupt changes in pressure. Symptoms may also include hearing loss, ringing in the ears, coordination problems, nystagmus, and headaches. Most fistulas heal with time; however, in severe cases, surgical procedures are used to close the hole, using a tissue graft.

MÈNIÉRE'S DISEASE In 1861, French physician Prosper Mèniére described Mèniére's disease as having four particular symptoms: vertigo lasting for an hour or more, but less than 24 hours; ringing or buzzing sounds in the ear; feeling of pressure or fullness in the ear; and some hearing loss. Some people are affected in both ears; others just one ear. Onset of Mèniére's may be related to stress, although not in all cases. Nystagmus is usually associated with the attacks.

Mèniére's disease is thought to be caused by an accumulation of endolymph within the canals of the inner ear, a condition called endolymphatic hydrops. This causes produces a swelling in the canals containing endolymph, which puts pressure on the parts of the canals containing perilymph. The result affects both hearing and balance. In severe cases, it is feared that the endolymphatic compartments may burst, disrupting both the chemical and pressure balances between the two fluids.

The cause of the accumulation of endolymph is unknown, although it can be related to trauma to the head, infection, degeneration of the inner ear, or some other regulatory mechanism. Syphilis is often associated with Mèniére's disease, as are allergies and leukemia. Some suggest that Mèniére's disease is an autoimmune dysfunction. There may be a genetic predisposition to Mèniére's disease.

Mèniére's disease is usually treated with meclizine (Antivert), antihistamines, and sedatives. Diuretics can be used to rid the body of excess endolymph. Salt-free diets can also help to prevent the accumulation of fluid in the ears.

Systemic disorders

Dizziness may be a symptom of a disorder that affects the whole body, or systems within the body. Dizziness may also be the result of systemic toxicity to substances such as medications and drugs.

POSTURAL HYPOTENSION The major symptom of postural hypotension, also called orthostasis, is low blood pressure. When a person stands up from a prone position, blood vessels in the legs and feet must constrict to force blood to the brain. When blood pressure is low, the blood vessels do not constrict quickly or with enough pressure and the result is a lag before blood reaches the brain, causing dizziness. Postural hypotension can be treated with an increase in fluid intake or with blood pressure medication.

HEART CONDITIONS A variety of heart conditions can cause feelings of dizziness. In particular, arrhythmia, a dysfunction of the heart characterized by an irregular heartbeat, decreases blood supply to the brain in such a way as to cause balance problems. In most cases, symptoms of dizziness associated with arrhythmia result from problems with heart valves, such as narrowing of the aorta and mitral valve prolapse.

INFECTIOUS DISEASES Influenza and flu-like diseases can cause dizziness, especially if accompanied by fever. The virus herpes zoster oticus causes painful blisters and **shingles**. If the virus attacks the facial nerve, it may result in vertigo. Several bacterial diseases can result in dizziness, including tuberculosis, syphilis, meningitis, or encephalitis. One of the major symptoms of **Lyme disease**, which is caused by infection of a microorganism resulting from a deer tick bite, is dizziness.

BLOOD DISORDERS A variety of diseases of the blood result in feelings of dizziness. These diseases include anemia, or a depletion of iron in the blood, sickle-cell anemia, leukemia, and polycythemia.

DRUGS AND OTHER SUBSTANCES A variety of substances ingested systemically to prevent disorders of diseases can result in feelings of dizziness. In particular, overdose of aspirin and other anti-inflammatory drugs can cause problems with balance. Antibiotics taken for extended periods of time are also known to cause dizziness. Streptomycin is known to damage the vestibular system, if taken in large doses. Medicines that are used to treat high blood pressure can lower blood pressure so much as to cause feelings of light-headedness. Quinine, which is taken to treat malaria, can cause dizziness, as can antihistamines used to prevent allergy attacks. Chemotherapy drugs are well known to have various side effects, including dizziness. Alcohol, caffeine, and nicotine are also known to cause dizziness, when taken in large doses.

Diagnosis

Because maintaining posture integrates so many different parts of the body, diagnosing the actual problem responsible for dizziness often requires a battery of tests. The cardiovascular system, the neurological system, and the vestibular system are all examined.

Blood pressure is one of the most important cardiovascular measurements made to determine the cause of imbalance. Usually the physician will measure blood pressure and heart rate with the patient lying down, and then again after the patient stands up. If blood pressure drops significantly and the heart rate increases more than five beats per minute, this signals the existence of postural

hypotension. Dizziness in people suffering from diabetes or on blood pressure medicine may be caused by postural hypotension.

Neurological tests

Because the central nervous system is integral to maintaining balance, neurological tests are often performed on patients with symptoms of dizziness. A test of mental status is often performed to ascertain that mental function is healthy. Physicians may test tendon reflexes to determine the status of peripheral and motor nerves, as well as spinal cord function. Nerves in different parts of the body may also be evaluated. In addition, physicians may test muscle strength and tone, coordination, and gait.

Neurologists may also perform a variety of computerized scans that determine if tumors or acoustic neuromas are present. These tests include **magnetic resonance imaging (MRI)**, computerized tomography (**CT**), and electroencephalogram (EEG).

Tests of the vestibular system

Most often performed by a otolaryngologist, the battery of tests performed to determine the health of the vestibular system include the Dix-Halpike test, electrostagmography, hearing tests, rotation tests, and posturography.

DIX-HALPIKE TEST The Dix-Halpike test, also called the Halpike test, is performed to determine if a patient suffers from benign paroxysmal positional vertigo (BPPV). The patient is seated and positioned so that his or her head hangs off the edge of the table when lying down. The patient's head is moved 45 degrees in one direction. The patient is then asked to lie down, without moving his or her head. The same procedure will be repeated on the other side. If feelings of vertigo result from this movement, BPPV is usually diagnosed.

ELECTRONYSTAGMOGRAPHY (ENG) Considered one of the most telling diagnostic tests to determine the cause of dizziness, electronystagmography consists of a series of evaluations that test the interactions between the vestibular organs and the eyes, also called the vestibulo-ocular reflex. Results from this test can inform the physician whether problems are caused by the vestibular system or by the central nervous system.

The most common diagnostic feature observed during ENG is nystagmus, an involuntary movement of the pupils that allows a person to maintain balance. In healthy persons, nystagmus consists of a slow movement in one direction in response to a change in the visual field and quick corrective movement in the other direction. In persons with disorders of the vestibular organs, nystagmus will produce quick movements in the horizontal direction. People with neurologic disorders will show signs of nystagmus in the vertical direction or even in a circular pattern.

In most of the ENG tests, electrodes taped to the patient's head record nystagmus as the patient is exposed to a variety of moving lights or patterns of stripes that stimulate the vestibular system. The patient may be asked to stand and lie in various positions for the tests. Also, included in the ENG is a caloric test in which warm water and cool water are circulated through the outer ear. This causes a slight expansion or contraction of the endolymph in the inner ear and simulates movement cues to the brain.

HEARING TESTS Because the cochlea and the vestibular organs are adjacent to one another, hearing dysfunction can often be related to problems with dizziness. Audiograms include tests for both hearing and interpreting sounds, and can determine whether or not problems exist in the middle ear, the inner ear, or the auditory nerve.

ROTATION TESTS Rotation tests evaluate the vestibulo-ocular reflex and provide important information when the dysfunction is common to both ears. Electrodes are usually taped to the face to monitor eye movement, and the patient is placed in a chair. The chair rotates at different speeds through different arcs of a circle. The audiologist may also ask the patient to focus on different objects as the chair is rotated.

POSTUROGRAPHY During posturography tests, a patient stands on a platform that measures how weight is distributed. During the test, the patient will close and open his or her eyes or look into a box with different visual stimuli. The platform is computer controlled so that it can gently tip forward or backward or from side to side. Posturography measures how much the patient sways or moves in response to the stimuli. This provides information on the function of the proprioceptive system, as well as the vestibular system.

Treatment

If symptoms of dizziness are found to be associated with systemic diseases such as diabetes, hypotension, or other infectious diseases, or with neurological disorders, treatment for the dizziness is usually successful.

In many patients, dizziness caused by vestibular dysfunction tends to dissipate with time and with little treatment. However, available and common treatments for vestibular problems include physical therapies, medications, and surgeries. In addition, low-salt diets, relaxation techniques, and psychological counseling may be used as treatment.

Exercises and therapy

The physical therapies to decrease dizziness fall into two major groups. Compensation therapies help train the patient's brain to rely on the sensory information it receives to maintain balance, and to ignore information from damaged organs. Exercises in a compensation program are designed to focus on the movements that cause dizziness so that the brain can adapt to these behaviors. In addition, exercises that teach the patient how to keep the eye movements separate from head movements and to practice balancing in various positions are used.

Specific exercises aimed at relieving benign paroxysmal positional vertigo (BPPV), called canalith repositioning procedures, have recently been developed. By turning the head to one side and moving from a sitting to lying position in a certain sequence, BPPV can be quickly relieved. The movements in the canalith repositioning procedures are intended to move calcium carbonate crystals from the semicircular canals back to the utricle. The success rate with these exercises can be up to 90%.

Medications

A variety of medications are used to treat vertigo. These include vestibular suppressants, which seem to work by decreasing the rate of firing of nerve cells. Common vestibular suppressants are meclizine (Antivert, Bonine, and Vetrol). Also prescribed are anti-nausea medications such as promethazane (Phenergan) and antihistamines (Benadryl, Dramamine). For dizziness brought on by anxiety attacks, anti-anxiety drugs such as **diazepam** (Valium) and lorazepam (Ativan) may be used. These drugs all have side effects and are seldom prescribed for long periods of time.

Surgery

Surgery is usually the last step in the treatment of dizziness, only used after therapy and medications have failed. One of the more common surgical procedures for treating vestibular disorders is patching perilymph fistulas, or tears, at the tops of the semicircular canals. Surgery may also be used to drain excess fluid from the endolymphatic canals to relieve endolymphatic hydrops. Cutting the vestibular nerve just before it joins with the auditory nerve to form the eighth cranial nerve can also be performed to alleviate severe problems with dizziness. Finally, the entire labyrinth can be destroyed in a procedure called a labyrinthectomy, although this is usually only performed when hearing has been completely lost as well.

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Vestibular Disorders Association. P.O. Box 4467, Portland, OR 97208. (503) 229-7705 or (800) 837-8428. <http://www.vestibular.org>.

Juli M. Berwald, PhD

Donepezil *see* **Cholinesterase inhibitors**

Dopamine receptor agonists

Definition

Dopamine receptor agonists are a class of drugs with similar actions to dopamine, a neurotransmitter that occurs naturally in the brain. A neurotransmitter is a chemical that allows the movement of information from one nerve cell (neuron) across the gap between the adjacent neuron. Dopaminergic receptors are protein complexes on the surface of certain neurons of the sympathetic autonomic nervous system that bind to dopamine.

Purpose

Dopamine stimulates the heart, increases the blood flow to the liver, spleen, kidneys, and other visceral organs, and controls muscle movements and motor coordination through an inhibitory action over stimuli response. Abnormal low levels of dopamine are associated with

tremors, muscular rigidity, low blood pressure, and low cardiac input. Therefore, dopamine and dopaminergic agonist drugs are administered to treat shock and congestive heart failure and to improve motor functions in patients with **Parkinson's disease** and other **movement disorders**. The balance between two neurotransmitter levels, acetylcholine and dopamine, is essential for motor and fine movement coordination. The balance is frequently found altered in movement disorders, due to a dopamine deficiency that results in excessive stimulation of skeletal muscles. In Parkinson's disease, either dopamine levels or the number of dopamine receptors are progressively decreased, resulting in tremors, slowness of movements, muscle rigidity, and poor posture and gait (manner of walking). Symptoms of Parkinson's disease are treated with anticholinergic drugs and/or dopamine receptor agonists. Dopaminergic agonist drugs such as levodopa (L-dopa) along with carbidopa, bromocriptine mesylate, cabergoline, pergolide mesylate, pramipexole, and ropinirole hydrochloride are prescribed to treat the symptoms of Parkinson's disease, either alone or in combinations.

Key Terms

Dopamine A neurotransmitter in the brain involved in regulating nerve impulses associated with muscle movement, blood pressure, mood, and memory.

Dyskinesia Difficulty in moving, or a movement disorder.

Neurotransmitter A chemical that is released during a nerve impulse that transmits information from one nerve cell to another.

Description

L-dopa (levodopa) is a precursor of dopamine, i.e., is converted into dopamine by the body. Levodopa thus increases dopamine levels in the motor areas of the **central nervous system** (CNS), especially in the initial stages of the disease. However, as the disease progresses, the drug loses its efficacy (effectiveness). When administered with carbidopa, levodopa's effects are enhanced because carbidopa increases L-dopa transport to the brain and decreases its gastrointestinal metabolism. Therefore, two beneficial effects are achieved: better results with lower doses of levodopa (4–5 times lower doses than in L-dopa therapy alone); and reduction or prevention of levodopa side effects, such as nausea, anorexia, vomiting, rapid heart rate, low blood pressure, mood changes, anxiety, and **depression**.

Bromocriptine mesylate is a derivative of ergotamine that inhibits the production of prolactin hormone by the pituitary gland. It is used in association with levodopa, in order to allow lower doses of the latter, especially in long-term therapy. Bromocriptine is also used to treat some menstrual disorders and infertility. This drug shows poor results in patients who do not respond to levodopa.

Pergolide mesylate has an action similar to that of bromocriptine, also inhibiting prolactin secretion. Also used in Parkinson's in association with L-dopa and carbidopa, pergolide is eliminated from the body through the kidneys. Cabergoline also inhibits prolactin secretion and is used to decrease abnormally high levels of this hormone, whether due to endocrine dysfunction or due to an existing pituitary tumor. The drug is also prescribed to regulate the menstrual cycle in cases of polycystic ovaries, and to control symptoms in Parkinson's disease.

Pramipexole and ropinirole are dopaminergic agonists that show good results in controlling Parkinson's symptoms in patients still in the initial stages of the disease and not yet treated with L-dopa, thus postponing the need of levodopa administration to a later phase. They work as well in those patients with advanced Parkinson's symptoms already taking levodopa.

Precautions

Levodopa may worsen psychotic symptoms when administered to psychiatric patients and anti-psychotic drugs should not be taken with this medication. L-dopa is also contraindicated to patients with glaucoma, because it increases pressure within the eye. Patients with cardiac disorders must be carefully monitored during levodopa administration due to the risk of altered heart rhythms.

Bromocriptine is contraindicated (not advised) for children under 15 years old, in pregnancy, severe cardiac disease, and severely decreased kidney or liver function. Alcoholic beverages are contraindicated during bromocriptine use as well as the administration of diuretics or anti-psychotic drugs. Psychiatric disorders may worsen with the administration of this drug.

Pergolide is contraindicated in women who are breast-feeding or those with preexisting movement disorders or a psychotic condition. Patients with heart rhythm disturbances should be not take this medication.

Cabergoline is not indicated in cases of severe or uncontrolled hypertension (high blood pressure) or for women who are breast-feeding, and requires careful monitoring in patients with significant kidney or liver dysfunction. Pregnant women who are at risk for eclampsia should not take this medication as well.

Pramipexole and ropinirole are eliminated through the kidneys, and the simultaneous use of medications that decrease kidney function (such as cimetidine) requires medical monitoring. Patients with reduced kidney function also require careful follow up and dosage adjustments.

Side effects

Bromocriptine may cause gastrointestinal discomfort, constipation, abdominal cramps, **fatigue**, anxiety, urinary incontinence or retention, depression, insomnia, hypotension, anorexia (loss of appetite), and rapid heart rate.

Pergolide side effects include **dizziness** when rising, increased heart rate, hallucinations, mood and personality disorders, **ataxia** (loss of coordination), muscle rigidity, blurred vision, anorexia, diarrhea, depression, insomnia, **headache**, confusion, numbness, gastritis, fluid retention, and swelling of the hands, face, and feet.

Cabergoline side effects include gastrointestinal irritation, gases, abdominal **pain**, digestive difficulties, dry mouth, loss of appetite, depression, mood changes, anxiety, insomnia, depression, increased sex drive, low blood pressure, fatigue, body weight changes.

Both pramipexole and ropinirole may cause **hallucination** (especially in elderly patients), dizziness and low blood pressure when rising, nausea, and gastrointestinal discomfort such as nausea and constipation. Pramipexole may also cause general swelling, fever, anorexia, and difficulty swallowing, decreased sex drive, amnesia and mental confusion, as well as insomnia and vision abnormalities. Ropinirole sometimes causes dizziness and **fainting**, with or without a slow heart rate.

Interactions

Pyridoxine (vitamin B_6) interferes with the transport of levodopa to the central nervous system by increasing its metabolism in the gastrointestinal tract. Dopamine antagonists (i.e., inhibitors of dopamine), such as metoclopramide and phenothiazines interfere with levodopa and other dopaminergic agonists, thus decreasing its effectiveness. The simultaneous concomitant use of phenelzine and dopamine agonists may induce severe high blood pressure.

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National Parkinson Foundation. 1501 N.W. 9th Avenue, Bob Hope Research Center, Miami, Fl 33136-1494. (305) 243-6666 or (800) 327-4545; Fax: (305) 243-5595. mailbox@parkinson.org. <http://www.parkinson.org/>.

Sandra Galeotti

Dural sinuses *see* **Cerebral circulation**

Dysarthria

Definition

Dysarthria is a speech diagnostic term that can be used to classify various types of neuromuscular speech disturbances. Dysarthria results from notable degrees of one or more abnormalities involving speech musculature, including weakness, paralysis, incoordination, sensory deprivation, exaggerated reflex patterns, uncontrollable movement activities, and excess or reduced tone. Generally speaking, the dysarthrias are considered motor speech disorders because speaking difficulties are largely due to breakdowns in movement control of one or more muscle groups that compose the speech mechanism. The name of each dysarthria subtype is partially derived from the basic characteristics of the overlying movement disturbances. Notably, normal speech production involves the integration and coordination of five primary physiological subsystems: respiration (breath support); phonation (voice production); articulation (pronunciation of words); resonation (nasal versus oral voice quality); and prosody (rate, rhythm, and inflection patterns of speech).

Description

The pioneering works of Darley, Aronson, and Brown in 1975 led to the general model of dysarthria classification that continues to be used to date. These clinical researchers from the Mayo Clinic studied individuals with different neurological disorders for the primary purpose of identifying and describing in detail the various speech

problems that they exhibited. These analyses helped to formulate predictable subtypes of speech abnormalities in individuals with specific kinds of neuropathologies. Besides the six primary forms of dysarthria identified, a seventh type has been added to the differential diagnostic scheme in the past decade. The seven dysarthria subtypes are spastic, unilateral upper motor neuron, ataxic, hypokinetic, hyperkinetic, flaccid, and mixed.

Demographics

There are no known figures regarding the overall incidence of the various dysarthrias in the general population. Moreover, because numerous possible neuropathological conditions can result in dysarthria, it is unproductive to speculate about either the specific or overall demographics of this multi-varied disorder.

Causes and symptoms

Spastic dysarthria

Spastic dysarthria is caused by damage to the primary voluntary motor pathways, which originate in the frontal lobes of the brain and descend to the brainstem and spinal cord. These central tracts constitute the pyramidal or upper motor neuron (UMN) system. Virtually all individuals with spastic dysarthria present with a broad spectrum of speech disturbances, including:

- abnormally excessive nasal speech quality
- imprecise articulation behaviors such as slurred sound productions and periods of speech unintelligibility
- slow-labored rate of speech
- strained or strangled voice quality
- limited vocal pitch and loudness range and control
- incoordinated, shallow, forced, uncontrolled, and overall disruptive speech breathing patterns

Individuals with spastic dysarthria often suffer from co-occurring weakness and paralysis of all four limbs. This occurs because the nerve tracts that supply movement control to these structures run in close parallel to those that regulate muscles of the speech mechanism, thereby making them equally susceptible to damage. The specific combination and severity of these features tend to vary from person to person based on the extent of associated UMN damage. In general, people with spastic dysarthria struggle with these speech difficulties because of widespread involvement of the tongue, lip, jaw, soft palate, voice box, and respiratory musculature. Problems with emotional breakdowns, such as unprovoked crying and laughing, also occur in many cases, due to uncontrolled releases of primitive reflexes and behaviors normally regulated, in part, by a mature and healthy UMN system. Finally, swallowing difficulties, known as dysphagia, are not uncommon in this population, because of underlying weakness and paralysis of the tongue and throat wall muscles.

The most common causes of spastic dysarthria include spastic **cerebral palsy**, **multiple sclerosis**, **amyotrophic lateral sclerosis** (ALS, or Lou Gehrig's disease), multiple strokes, and closed head injuries (particularly those that cause damage to the brainstem where the UMN tracts converge on the way to nerves that directly connect with the various muscles of the head, neck, limbs, and girdle).

Unilateral upper motor neuron (UMN) dysarthria

Unilateral UMN dysarthria is caused by damage to either the left or right UMN tract, anywhere along its course to the brainstem and spinal cord. The individual with this diagnosis generally presents with mild to moderate weakness and paralysis of the lower face, tongue, arm, and leg on the side of the body opposite the damaged UMN tract. The hemiplegia may necessitate use of a cane or wheelchair, and the facial and tongue musculature disturbances usually only result in mild speech production and swallowing difficulties because the unimpaired opposite half of the lips and tongue often compensate well for this unilateral problem.

Speech breathing and inflection patterns, voice characteristics, and nasal resonance features are not typically abnormal in the individual with unilateral UMN dysarthria. However, it is not uncommon for this person to suffer from a significant language processing disorder (i.e., **aphasia**) and/or **apraxia** in which the brain damage also involves areas of the cortex that normally regulate motor programming and language formulation abilities.

The most common causes of this dysarthria subtype are cerebral vascular accidents (i.e., strokes) and mild-to-moderate head injuries.

Ataxic dysarthria

Ataxic dysarthria is caused by damage to the **cerebellum** or its connections to the cerebral cortex or brainstem. This component of the **central nervous system** is chiefly responsible for regulating the force, timing, rhythm, speed, and overall coordination of all bodily movements. When the cerebellum is damaged the affected person may exhibit drunk-like motor patterns, characterized by a wide-based and reeling gait and slurred articulation patterns with intermittently explosive voice pitch and loudness outbursts. During purposeful movement efforts, this individual often suffers from intention **tremors**, which cause under- or overshooting of the intended target.

A speech therapist helps a young boy sound out words. *(© Photo Researchers. Reproduced by permission.)*

However, this shaking phenomenon tends to disappear at rest. Swallowing is not usually disturbed.

The most common causes of **ataxia** include cerebral palsy, multiple sclerosis, and closed head injuries.

Hypokinetic dysarthria

Hypokinetic dysarthria is caused by damage to the upper brainstem in a region that is richly composed of darkly pigmented (nigra) nerve cells. These neurons contain the neurochemical agent dopamine, which helps regulate muscle tone and smooth and complete bodily movements. When various speech muscles are involved, numerous communication deficits occur, including imprecise articulation of sounds, harsh-hoarse voice quality, and abnormal bursts of speech that sound like the individual is tripping over his or her tongue. These common dysarthric features are the result of widespread rigidity (i.e., stiffness and limited range of motion [hypokinesia]), tremors, and incoordination of the tongue, lip, jaw, and voice box musculature.

Because the most common cause of hypokinetic dysarthria is **Parkinson's disease**, patients with these types of speech problems also exhibit numerous trunk and limb disturbances such as rest tremors of the hands, stooped posture, shuffling gait, and mask-like facial expressions due to involvement of associated body musculature. Swallowing difficulties may co-occur.

Hyperkinetic dysarthria

Hyperkinetic dysarthria is generally caused by damage to nerve pathways and centers within the depths of the brain (subcortex) known as the basal ganglia. These integrated central nervous system components form complex feedback loops between one another and the cerebral cortex. The basal ganglia are largely responsible for helping to maintain posture, muscle tone, bodily adjustments, and

overall stability during gross voluntary movement patterns. Damage to these structures and their circuitry generally produces two different types of symptoms, depending upon the site(s) of injury: increased muscle tone and very slow movement, known as rigidity, as seen in patients with Parkinson's disease, or involuntary, excessive, and uncontrollable quick-jerky, slow-twisting, or trembling limb and speech musculature behaviors.

Patients with Huntington's disease and tic disorders frequently exhibit the quick and jerky forms of movement abnormalities. The slow, writhing, and twisting **movement disorders** are usually observed in patients with histories of **dystonia**, athetosis, torticolis, and **dyskinesia**. In fact, spasmodic dysphonia, characterized by strained-strangled or abnormally breathy vocal quality and episodes of periodic arrests of voice, is a form of hyperkinetic dysarthria in that dystonia involves the vocal cords. Tremors are common in patients with essential (organic) tremor disorders. In general, when tongue, lip, and jaw muscles are afflicted by such breakdowns, the articulation of speech sounds is inconsistent and imprecise, voice is hoarse-harsh in quality, the rhythm of speech is flat and irregular, and breathing patterns are sudden, forced, and shallow. All of these disturbances contribute in total to variable, but often-marked degrees of speech unintelligibility in these clinical populations.

Whereas in most cases the underlying cause of muscle hyperactivity is associated with one of the above listed disease-specific entities, occasionally severe head injuries and deep brain tumors can result in any of these types of movement control disorders. Swallowing difficulties can be a significant problem for these types of patients.

Flaccid dysarthria

Flaccid dysarthria is caused by damage to nerves that emerge from the brainstem (cranial) or spinal cord and travel directly to muscles that are involved in speech production. These nerves are generically referred to as lower motor neurons. Cranial nerves V, VII, X, and XII are of great importance because they supply the chief muscles of speech production, namely, the jaw, lips, voice box and palate, and tongue, respectively. The cervical spinal nerves innervate the diaphragm, and the thoracic spinal nerves stimulate the chest and abdominal wall muscles, all of which are involved in speech breathing activities. The types of neuromuscular problems that arise as a result of injuries to these nerves depend upon which and how many nerves are disturbed. In general, the types of abnormal muscle signs occurring in patients with damage to lower motor neurons include paralysis, weakness, reduced speed of movement, depressed tactile feedback, limited reflex behaviors, and atrophy or shrinkage of muscle tissue.

Analyses of the electrical activity of involved muscles using needle electrodes frequently reveal disturbed firing patterns or twitch-like behaviors known as fasciculations. In a structure like the tongue, which is not covered with thick overlying skin, fasciculations can sometimes be evident by shining a flashlight on the surface at rest. This pathologic feature is an important differential diagnostic sign of damage to the cranial nerve XII. Patients with limited lower motor neuron damage usually exhibit less severe flaccid dysarthria than those with more widespread damage. Additionally, the actual nerves that are damaged dictate the specific types of speech difficulties that may occur. For example, if a focal lesion involves only the cranial nerve VII, as in **Bell's palsy**, only the lip musculature will be weakened. The result in this case usually produces minimal dysarthria. However, damage to multiple cranial nerves, as often occurs in certain degenerative conditions like Lou Gehrig's disease, will likely cause severe speech difficulties. The most common speech signs observed in patients with flaccid dysarthria, regardless of the cause or severity, include articulation imprecision, hypernasal voice, hoarse and breathy vocal quality, and slow-labored speech rate.

Brain stem strokes, tumors on the brain stem or along the course of the cranial or spinal nerves, **muscular dystrophy**, and general injuries to these nerves as a result of head trauma or surgical complications are among the most frequent causes of flaccid dysarthria. If spinal nerves that supply the limbs are also damaged, as may be the case in some of these clinical populations, co-occurring paralysis of these structures is likely to complicate the rehabilitation program. Swallowing problems may occur in some cases, depending upon which and how many cranial nerves are involved.

Mixed dysarthria

Mixed dysarthria is caused by simultaneous damage to two or more primary motor components of the nervous system, such as the combined upper and lower motor neuron lesions that typically occur in Lou Gehrig's disease, or the co-occurring degeneration of the upper motor neuron and cerebellum pathways seen in patients with multiple sclerosis. In the first example, the patient usually suffers from mixed spastic-flaccid dysarthria. In the second case, the MS patient often presents with mixed spastic-ataxic dysarthria. The exact mixture of neurological damage governs the characteristic speech (and overall body) musculature difficulties.

It is not uncommon for severe head injuries to cause multi-focal nervous system lesions and nonspecific mixed dysarthrias. Many such patients also struggle with limb and trunk motor problems, as well as coexisting swallowing, cognitive, language, perceptual, and psychosocial

deficits that worsen their underlying motor speech problems and complicate the rehabilitation course. The mixture may be of two or more of the previously described single-entity dysarthrias.

Diagnosis

In addition to clinical examinations, many dysarthric patients will need to submit to various laboratory studies for a thorough appraisal of the possible underlying causes, areas of brain damage, and overall prospects for improvement with appropriate treatment. Such testing might include:

- computed tomography (**CT**) or **magnetic resonance imaging (MRI)** scans of the head, neck, and/or chest
- skull x rays
- arteriography (imaging of arterial flow dynamics)
- spinal tap for cerebral spinal fluid analysis
- electroencephalography (EEG)
- electromyography (EMG)
- videoendosocopy of the vocal cords and soft palate
- pulmonary function studies
- videofluoroscopic examinations of swallowing proficiency
- speech aerodynamic and acoustic analyses

These diagnostic tests require the cooperation of many different clinical practitioners from various fields of study.

Familiarity with the variable speech subsystem abnormalities exhibited by dysarthric patients is indispensable to differential diagnosis. Additionally, because dysarthria is only a speech diagnostic term, and the underlying cause is some form of neurological problem, a medical examination, usually performed by a clinical **neurologist**, is critical both to the overall diagnosis in any given case and for effective treatment recommendations. Family members and friends can, however, facilitate this process by cursory investigations of the speech difficulties prior to visiting with diagnosticians for formal testing. This preparatory process may involve having the patient perform several physiologic tasks, as well as noting any generalized walking, balance, and limb coordination difficulties exhibited by the affected individual. If the possible cause is understood from the outset, it may help pinpoint the speech diagnosis. The individual can be engaged in general conversation to judge overall speech intelligibility. The listener can listen for signs of poor pronunciation of sounds, excessively nasal voice, hoarseness or strained vocal quality, breath support difficulties, and limited pitch and loudness inflection patterns. Any one or more of these problems may be evident in the speech profiles of individuals with different forms of dysarthria.

Treatment team

The rehabilitation team for an individual with dysarthria often varies, depending on the severity and cause of the dysarthria and the extent of associated limb and trunk musculature disabilities and co-occurring language, cognitive, and psychosocial deficits. In general, those individuals with multi-system breakdowns require a more complex array of team constituents than those who have more focal or mild problems. Most teams consist of the clinical neurologist, speech-language pathologist, physical therapist, occupational therapist, **neuropsychologist**, nurse practitioner, and social worker. In school-age patients, teachers and guidance counselors will also play very important roles in the treatment program. Naturally, the role of the speech pathologist is usually most critical in the communication treatment plan for dysarthric patients.

Treatment

Physical and occupational therapists focus on improving limb and trunk coordination, balance, and range of motion, particularly in relation to daily living functions such as walking, self-dressing, and feeding. Neuropsychologists often facilitate memory strategies, perceptual processes, and overall organizational skills required in various work-related settings and daily social circumstances. The administration of certain medications, daily health care and personal hygiene needs, and general tracheostomy care and feeding-tube monitoring may be indicated.

The speech pathologist must design specific speech musculature exercises to improve the strength, tone, range of motion, coordination, and speed of integrated tongue, lip, jaw, and vocal musculature contractions. These general objectives are often achieved following a hierarchy of exercises that may require two or more sessions of therapy per week. In some cases, when oral speech skills fail to improve with both speech and non-speech exercises, use of an alternative or augmentative communication system is required, such as computerized speech synthesizers and/or form or picture boards. These tools are most useful for those patients who possess at least some control of an upper limb to activate a keyboard or point to a picture. In very severely affected patients, a head pointer may be devised so that head movements meet these objectives.

Prognosis

The prognosis for speech improvement in any individual with dysarthria usually depends on the severity of the problem and the underlying cause. If the speech difficulties are mild to moderate, and the cause has been

treated successfully through proper medical avenues and is non-progressive, the prognosis for notable improvements with good speech therapy is often very good. However, in the case of severe dysarthria, with a medically uncontrollable or progressively deteriorating etiology, the prognosis for significant gains, even with the best therapeutic programs possible, is almost always very guarded.

Special concerns

Depending on the cause and the severity of the dysarthria, and any coexisting motor, language, cognitive, intellectual, and psychosocial deficits, the affected individual may require many different methods of care. Formal nursing or group home settings are sometimes necessary for those individuals who are not self-sufficient or who lack home care assistance and supervision. Special education classes may be required in those cases with associated learning disabilities. Structural modifications of a wheelchair to facilitate upright head posturing and abdominal support during speech breathing efforts may be helpful for some patients, and construction of ramps in the home may also be necessary to accommodate wheelchair mobility requirements. Arrangements for use of a bell or light switch activator may be indispensable to certain patients who cannot verbally, or otherwise, get the attention of caregivers.

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James Paul Dworkin, PhD

Dysautonomia *see* **Autonomic dysfunction**

Dysesthesias

Definition

The word dysesthesias is derived from the Greek "dys," which means "bad," and "aesthesis," which means "sensation." Thus, dysesthesias are "bad sensations" and the word refers to **pain** or uncomfortable sensations, often described as burning, tingling, or numbness.

Description

Dysesthesias is a symptom of pain or abnormal sensation(s) that typically cause hyperesthesia, paresthesiae, or peripheral sensory neuropathy. Dysesthesias can be due to lesions (an abnormal change) in sensory nerves and sensory pathways in the **central nervous system** (CNS, consisting of the brain and the spinal cord). The pain or abnormal sensations in dysesthesias is often described as painful feelings of tingling, burning, or numbness. Dysesthesias can simply be described as a burning pain that is worse where touch sensation is poorest.

Dysesthesias can also be caused by lesions in peripheral nerves (the **peripheral nervous system**, or PNS, which consists of nerves that are outside the brain or spinal cord). Peripheral nerves travel to muscles and organs providing a nerve supply. Dysesthesias due to a lesion in the PNS usually occurs below the level of the lesion. There is a broad spectrum of diseases, disorders, and medications that cause dysesthesias. There are two broad categories of dysesthesias called paresthesiae and peripheral sensory neuropathy. Some of the common causes of dysesthesias within these categories will be considered.

Paresthesias

Paresthesias (abnormal neurological sensations that include numbness, tingling, burning, prickling, and increased sensitivity, or hyperesthesia) can include several conditions such as **carpal tunnel syndrome**, **thoracic outlet syndrome**, **multiple sclerosis**, strokes (cerebrovascular accidents), **Guillain-Barré syndrome**, **transverse myelitis**, and compartment syndrome/Volkmann's contracture.

Carpal tunnel syndrome

Carpal tunnel syndrome is caused by entrapment of the median nerve at the wrist. There is limited available space for the median nerve. There is a disease process (i.e. osteoarthritis) that entraps the nerve. Symptoms include paresthesiae of the first three fingers usually present overnight and typically relieved by shaking or elevating the hands. Symptoms progress to sensory loss and weakness of muscles. Treatment usually includes overnight splinting, diuretics (to reduce swelling), or surgery.

Thoracic outlet syndrome

Thoracic outlet syndrome is a condition caused by compression of nerves (and blood vessels) located between the armpit and the base of the neck. The neurologic symptoms associated with thoracic outlet syndrome include dysesthesias (numbness and tingling), weakness, and fatigability. The damage occurs in nerves leaving the spinal cord located behind the neck. Symptoms worsen with arm elevation above the level of the shoulder. Approximately 50% of persons affected report a history of a single traumatic event (i.e., motor vehicle accident) that caused a neck injury.

Multiple sclerosis/transverse myelitis

Multiple Sclerosis is an inflammatory process that involves white matter. There is focal neurologic deficit which can progress. The condition can go in remission but other attacks usually occur causing neurologic deficits. Transverse myelitis (usually associated with an inflammatory process) can cause **back pain**, leg weakness, and sensory disturbance. Transverse myelitis can occur after viral infections or may even occur as a feature of multiple sclerosis.

Stroke (cerebrovascular accident)

There are two major arteries implicated with **stroke**. These include the carotid arteries (in the neck and travels into the brain) and the basilar artery (an artery located in the base of the skull). The dysesthesias associated with carotid artery stroke consists of tingling and numbness on one side of the body. Stroke associated with the basilar artery can cause dysesthesias (tingling or numbness) in the cheeks, mouth, or gums.

Guillain-Barré syndrome

Guillain-Barré syndrome (also called acute inflammatory demyelinating polyneuropathy) is an immune mediated disorder that follows some infectious process (such as infectious mononucleosis, herpes viruses, cytomegalovirus, and mycoplasma), and is the most frequent caused of acute flaccid paralysis throughout the world. Initial symptoms consist of "pins-and-needles sensations" in the feet, lower back pain, and weakness (which develop within hours or days). Weakness is prominent in the legs. Progression of symptoms can occur abruptly and patients may have serious involvement of nerves responsible for respiration and swallowing, which may be life-threatening. The condition is serious and could cause rapid deterioration. Patients usually require hospitalization and treatment with high doses of human immunoglobulin and plasmapheresis (exchange of patient's plasma for the protein called albumin).

Key Terms

HIV Human immunodeficiency virus, which causes AIDS.

Lacinating pain Piercing, stabbing, or darting pain.

Lymphocytic meningitis Benign infection of brain coverings that protect the brain.

Radiculoneuritis Inflammation of a spinal nerve.

Rodenticide Chemical that kills rodents.

Compartment syndrome/Volkmann contracture

Compartment syndrome refers to any condition that causes a decrease in compartment size or increased compartment pressure. Compartment syndromes can be caused by crush injuries, internal bleeding, fractures, snake bites, burns, and excessive **exercise**. If a compartment (or area) is injured (i.e., a crushing injury to hand), the trauma will decrease the normal area of the hand (due to bleeding). This results in an increase in compartmental pressure which could impair blood flow to the area, causing irreversible tissue ischemia (tissue death). Compartment syndrome can occur from injuries to the upper extremity which can affect the forearm and hand since these areas have naturally occurring compartments made by anatomical structures such as muscle. Excessive swelling due to traumatic injury can cause nerves and blood vessels to be compartmentalized (in a sense, crushed against) muscle from abnormal swelling or internal bleeding. If left untreated the dead muscle and nerve tissue is replaced with fibrous tissue causing a Volkmann ischemic contracture (contractures of fingers or in severe cases the forearm). In severe cases there is a loss of nerve tissue. Damage shows signs in 30 minutes and measurable functional loss after 12 to 24 hours.

Peripheral neuropathy

Peripheral neuropathies are conditions that cause injury to nerves that supply sensation to the legs and arms. This category of dysesthesias can include conditions such as amyloidosis, **Charcot-Marie-Tooth** syndrome, diabetes, leprosy, syphilis, and **Lyme disease**.

Amyloid neuropathies/hereditary neuropathies

There are several types of amyloid neuropathies, and they are all associated with diseases that deposit a protein (amyloid) in nerves and even other tissues (like blood vessels). Sensory nerves are damaged causing dysesthesias.

These disorders are inherited, occur in midlife, and represent the most relevant inherited neurologic diseases. These include Charcot-Marie-Tooth disease and amyloid neuropathies. Charcot-Marie-Tooth disease refers to inherited disease that causes nerve degeneration usually in the second to fourth decades of life. Patients exhibit impairment of sensory function, and the nerves of the toes and feet are affected (can lead to foot drop.)

Diabetes (metabolic neuropathy)

The most frequent neuropathy world wide is diabetes. **Peripheral neuropathy** can be detected in approximately 70% of long-term diabetics. The cause of nerve involvement is unclear, but it is thought that a faulty mechanism (deleterious to nerve cells) is related to high blood glucose levels. The symptoms are insidious and typically include dysesthesias evoked by regular activity (i.e., bothersome tingling of toes under bed sheets). The pain can be throbbing or it may be a continuous burning type of dysesthesias. Additionally, person may describe abrupt, quick "lightning" pains which may affect the feet and legs.

Leprous neuropathy

Leprosy is an infectious disease transmitted by a bacterium called *Mycobacterium leprae.* The World Health Organization (WHO) estimates that there are 2.5 million persons affected by leprosy. The organism proliferates in coolest regions of skin (i.e., ears, face, fingers), causing a selective loss of pain sensation (dysesthesias) in cold areas of skin.

Neurosyphilis

Neurosyphilis refers to a disease caused by untreated syphilis infection that invades the central nervous system years after initial infection. In the United States the number of cases of neurosyphilis has risen from 10,000 in 1956 to over 50,000 in 1990. Approximately 28% of patients have **ataxia**, 23% have stroke, and 10% of affected persons describe "lightning" pains. Additionally 10% have headaches and 36% have cranial neuropathy. Treatment attempts include antimicrobial therapy.

Lyme disease (Boreliosis)

Lyme disease is an infection transmitted by an arthropod (a tick which harbors the infectious bacterium called *Borrelia burdorferi*). The bacteria can be transmitted to a human by the bite of infected deer ticks, and in 2002 caused 23,000 infections in the United States. After the initial symptoms ("bulls-eye" rash, fever, **fatigue**, muscle aches, and joint aches), early disease can cause neurologic symptoms such as lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy), and radiculoneuritis. Patients may also have musculoskeletal pain that includes muscle pain (myalgia) and joint aches (arthralgia). Late symptoms include **encephalopathy**, sleep disturbances, fatigue, and personality changes.

Other causes of dysesthesias

Toxic neuropathies

Toxic neuropathies can occur due to medications (used to treat illnesses), metal exposures, substance abuse, and exposure to industrial poisons/chemicals. For drug (medications) or chemical exposure induced neuropathies the cause (mechanism of damage) is usually obscure. Medications that can cause neuropathies include (but are not limited to) antivirals, chloramphenicol (antibiotic), cisplatin (anticancer), ethambutol (antituberculosis), hydralazine (antihypertensive), isoniazid (antitubercolosis), metronidazole (antifungal), phenytoin (antiepileptic), pyridoxine (vitamin B-6), gold therapy, and vincristine/vinblastin (anticancer) therapy. Metals that can cause neuropathies include arsenic, lead, mercury, and thallium (a metal in rodenticides such as Gizmo mouse killer). Heavy metals such as lead found in lead-based paint in the automobile industry and manufacture of storage batteries and printing can cause neuropathies. Lead neuropathy can occur due to drinking bootleg whiskey distilled in lead pipes, or hand mixing of lead-based paints by artists. Occupational exposure in farming to arsenic-containing sprays, pesticides, and weed killers can cause arsenic neuropathy. Accidental ingestion of arsenic-containing rodenticides can cause arsenic neuropathy.

Chemical abuse with alcohol or by glue or nitrous oxide inhalation can cause neuropathies. Severe peripheral neuropathies can result from exposure to household and industrial chemicals.

Thallium neuropathy

Thallium neuropathy can occur in manufacturers of optic glass, industrial diamonds, and prisms. Thallium is also used as an additive in internal combustion engines. Accidental ingestion of thallium and subsequent neuropathy also occurs with rodent killer substances (rodenticides).

HIV infection

Before development of **AIDS**, persons with HIV infection can develop chronic inflammatory peripheral neuropathy. However, the most prevalent neuropathy associated with HIV infection is sensory neuropathy of AIDS, which causes pain on the soles of the feet and discomfort when walking. The pain is intense and affected

persons may have motor impairment. The condition is caused by degeneration of sensory nerve fibers.

Shingles

Another condition called herpes zoster or **shingles** (caused by the varicella zoster virus which causes chicken pox) can cause a latent nerve neuropathy with localized cutaneous eruptions during periods of reactivation. There are over 500,000 cases of shingles estimated to occur annually in the United States. The abnormal skin sensations are localized and range from itching to tingling to severe pain. Treatment typically includes antiviral medications. Pain can persist for months or even years.

Bell's palsy

The cause of **Bell's palsy** is unclear. It is thought to be due to an infectious process, possibly viral, that involves a nerve in the face called the facial nerve. Pain is often sudden and patients often describe a "numbing of the face" sensation.

Biological toxins

The ingestion of a certain fish (ciguatera) and some shellfish can be the cause of acute peripheral neuropathy (paresthesia). The typical causes among ciguatera include red snapper and barracuda from waters in the West Indies, Florida and Hawaii. Shellfish, clams scallops and mussels from the waters of Alaska, New England and the west coast are also causative biologic toxins. The neuropathy is followed after a few hours from the initial symptoms of nausea and vomiting. Paresthesiae occurs around the face and spreads to limbs. The problem can quickly progress to respiratory paralysis (paralysis of the muscles responsible for respiration) which could be a life-threatening condition.

Vitamin Deficiency

Neuropathy can result due to vitamin deficiencies such as vitamin B-12, vitamin B-1 and vitamin E. Vitamin B-12 deficiency can cause dysesthesias (sensation of "pins-and-needles" and numbness) in the feet and hands. Usually patients are diagnosed since they have a blood disorder called macrocytic megaloblastic anemia. Patients who have a bowel problem called malabsorption may loose ingested fat substances in the feces undigested, causing a loss of essential vitamins and nutrients. Fat containing molecules like vitamin E may be lost causing a neuropathy with symptoms similar to vitamin B-12 deficiency. Vitamin B-1 deficiency can likely occur due to alcoholism. The neuropathy is mostly sensory and patients describe a painful hypersensitivity of the feet. In advanced cases there may be weakness in the limbs or even paralysis leading to wrist drop or **foot drop**.

Nerve root compression

Radiculopathy, commonly caused by disk herniation (nerve root compression) is generally accompanied by muscle weakness, sensory loss and absent tendon reflexes. Herpes zoster radiculopathy is a lesion in the nerve root characterized by a burning pain and skin eruptions in dermatomal distribution. The inflammatory reaction precipitates stimulation of nerves producing a burning pain that precedes and often accompanies the skin eruptions.

General Concepts of pain management: Acute vs. chronic pain

There are several key concepts for pain management. Pain is best treated early and a vigilant search for the cause is imperative. Pain scales should be utilized in order to gauge progression of pain (i.e. getting worse or better). Unrelieved pain is implicated with negative physiological and psychological conditions. For acute pain an opioid (morphine) is a suitable agent to control moderate to severe pain. Acute pain is usually a symptom of injury or illness and serves a biological purpose (i.e. to provoke treatment of the injury). Additionally, acute pain causes anxiety, has identifiable pathology (disease) and is present less than six months. In cases of chronic pain, the dysesthesias is the problem itself and serves no biological function. Chronic pain syndromes with dysesthesias are often implicated with **depression** due to chronicity (long-term illness). Chronic pain may or may not have identifiable pathology and is present for more than six months.

Management of Pain

The first step to management of patients with neuropathic pain is to gain a good explanation of the cause and origin of the pain. Tricyclic antidepressants have an important role for the treatment of neuropathic pain (especially the "burning pain" associated with diabetes). These medications seem to be effective in several "pain" syndromes. Tricyclics tend to help with "burning" type pains, lacinating pains and cutaneous hyperalgesia. Tricyclics have an analgesic effect, thought to be mediated by alterations in brain chemistry (two specific **neurotransmitters** called serotonin and norepinephrine). **Anticonvulsants** (antiepileptic medications) can help reduce lacinating pain. Topical local aesthetic preparations (i.e. EMLA cream, eutectic mixture of local anesthetics) can penetrate skin and temporarily relieve neuropathic pain. The use of long term opioid treatment is unclear and should be reserved to selective cases. The use of capsaicin (the active substance extracted from hot pepper, can relieve pain (if placed on skin) in approximately 33% of patients with painful post-herpetic neuralgia and diabetic neuropathy.

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NIH Neurological Institute. PO Box 5801, Bethesda, MD 20824. 301-496-5751 or 1-800-352-9424. <http://www.ninds.nih.gov>.

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Dysgeusia

Definition

Dysgeusia is a disorder of the sense of taste.

Description

Any condition that affects the ability to taste is referred to as dysgeusia. While dysgeusia is often used to describe any change in the sense of taste, more specific terms include ageusia (complete loss of the sensation of taste); hypogeusia (decreased sense of taste); parageusia (bad taste in the mouth); and dysgeusia (distorted sense of taste, such as a metallic taste in the mouth). A wide variety of conditions can cause a deficit in the sense of taste, including any conditions that interfere with the functioning of the taste buds (the nerve cells on the tongue that process information about taste), conditions that interrupt the taste signal that is sent to the brain, or conditions that interfere with the normal brain processing of those signals. Processes that affect the functioning of the lingual nerve or the glossopharyngeal nerve may impair the sense of taste. Furthermore, the sense of taste is frequently dulled or impaired due to dysfunction of the sense of smell.

Causes and symptoms

There are a wide variety of conditions that can cause dysgeusia, including:

- smoking
- respiratory infections (colds, sinus infections, throat infection, or pharyngitis)
- strep throat
- inflammation of the tongue (glossitis)
- gingivitis
- influenza
- dry mouth (due to medications or disorders such as Sjogren's syndrome or salivary gland disorders or infections)
- vitamin deficiencies (such as B-12 and zinc)
- Cushing's disorder
- cancer
- diabetes
- hypothyroidism
- liver or kidney failure
- head injuries
- brain tumors or other tumors that destroy or injure areas of the nose, mouth, throat, or brain responsible for taste
- nasal polyps
- **Bell's palsy**
- **multiple sclerosis**

In addition, normal aging usually includes a decrement in the sense of taste as the numbers of taste buds decrease over time. A large number of medications can affect the sense of taste; antibiotics and cancer chemotherapeutic agents are common culprits. Examples of drugs that are known to cause dysgeusia include lithium, penicillamine, procarbazine, rifampin, vinblastine, vincristine, captopril, griseofulvin, and thyroid medications. **Radiation** therapy may cause dysgeusia.

Symptoms of dysgeusia include decreased acuity of the sense of taste or the distorted perception of an odd taste. Complete loss of taste sensation is relatively rare.

Diagnosis

Diagnosis can be made by having an individual taste and smell a variety of test substances. **CT** or **MRI** imaging may reveal the disorder underlying the development of dysgeusia.

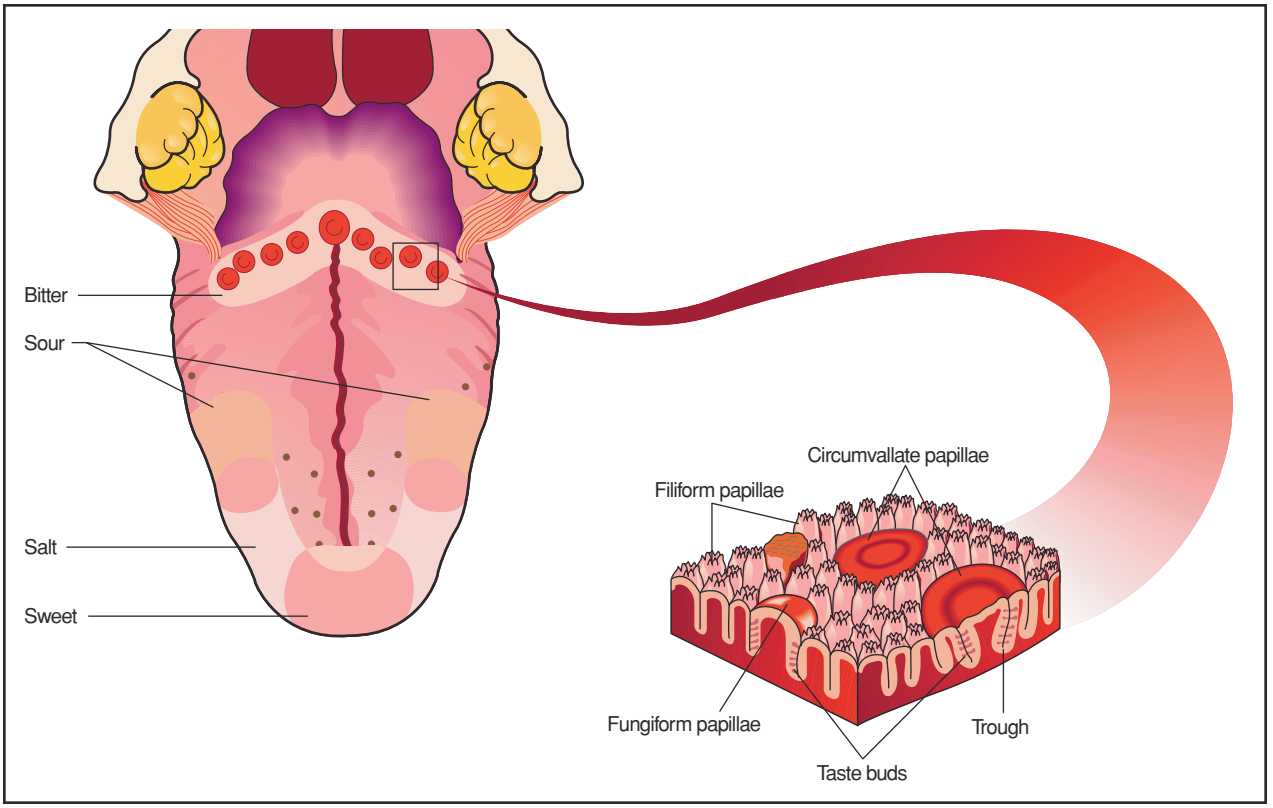

Diagram of the tongue and taste buds. *(Illustration by Electronic Illustrators Group.)*

Treatment team

Dysgeusia may be treated by a **neurologist** or by the physician who is treating the underlying condition responsible for the disorder (such as an otorhinolaryngologist for various ear, nose, or throat conditions, such as nasal polyps).

Treatment

Some types of dysgeusia resolve on their own, particularly dysgeusia that occurs due to an infection. When the infection clears, the dysgeusia usually abates and the sense of taste returns. When smokers stop smoking, their sense of taste may improve over time. Stopping some medications may also lead to an improved sense of taste. Individuals who suffer from dry mouth (xerostomia) may benefit from artificial saliva. Individuals with nasal polyps may note improved sense of taste after polyp removal.

Prognosis

Dysgeusia secondary to infection or reversible conditions like Bell's palsy may improve partially or completely with resolution of the infection or condition; dysgeusia due to medication use or smoking may also improve partially or completely when the individual stops using the medication or discontinues smoking. However, dysgeusia due to more permanent damage to the neurological apparatus responsible for taste or smell (such as head injury, multiple sclerosis, radiation treatments, or diabetes) may never improve.

Special concerns

Individuals with severely compromised taste or smell may inadvertently eat spoiled foods, leading to food-borne illness. Furthermore, without a good sense of smell or taste, there is an increased risk that an individual will not be able to protect him- or herself from exposure to other toxins, pollution, or smoke. Individuals with an impaired sense of taste may over-salt or over-sugar their food, in an attempt to compensate. They may not take in a reasonably balanced, nutritious diet with sufficient calories, because eating may become unenjoyable.

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Dyskinesia

Definition

Dyskinesias are a group of disorders characterized by involuntary movements of muscles.

Key Terms

Ataxia Failure of muscular coordination due to muscle disorder.

Chronic Over a long period of time.

Flexion (flex) To move a limb toward the body.

Kinetic Word taken from the Greek (kinesis): motion.

Neuroleptic Negative effects of thinking and behavior, creating a state of apathy and lack of initiative.

Retrocollis Muscular spasms that affect the neck muscles located in the back.

Torticollis Contracted neck muscle, causing twisting of the neck in an abnormal position.

Unilateral On one side.

Description

Dyskinesias are excessive abnormal movements that are involuntary. There are several different types of dyskinesias, and each has different clinical symptoms, causes, and treatments. Adults and children with certain chronic brain disorders often exhibit symptoms of dyskinesia. Movement can occur in the head, arms, legs, hand, feet, lips, or tongue. The dyskinesias can be categorized as **chorea**, **dystonia**, **myoclonus**, tremor, and paroxysmal tardive (late-onset type). Other forms of dyskinesia include athetosis, ballism, akathisia, tics, stereotypy, and restless legs. Dyskinesias can also be called hyperkinesia syndromes.

Chorea

Choreas are abnormal movements that are irregular, involuntary, nonrhymical, abrupt, rapid, and nonsustained jerking, which continuously flow from one body part to another. Movements are isolated, brief, and infrequent. Chorea can cause inability to maintain a sustained contraction, which causes affected persons to drop objects. Persons with chorea have an irregular dance-like gait. The cause of chorea is not completely understood.

Dystonia

Dystonia that occurs at rest may persist as the kinetic (clonic) form. Dystonias can be either focal or generalized. Focal dystonias are involuntary movements in a single body part, which commonly includes **blepharospasm** (upper facial), spasmodic torticollis (cervical), and writer's cramp. Dystonia affecting two or more body regions is called segmental dystonia. Generalized dystonia typically affects the trunk, one or both legs, and another body part. Other types of dystonias include Merge's syndrome (spasms of the jaw muscles when opening and closing of the mouth). Spasmodic dystonias can cause speech impairment due to spasms of laryngeal (throat) muscles. The intensity of muscular movements in patients with dystonia can fluctuate, and symptoms worsen during **fatigue**, stress, activity, and change in posture. In some cases, the bizarre symptoms of dystonia can be mistaken for psychological illness. Dystonias can be inherited or acquired due to another primary cause. Inherited diseases that exhibit dystonia are rare and include dopa-responsive dystonia, idiopathic tension dystonia, and x-linked dystonia-Parkinsonism (found among Ashkenazi Jews).

Myoclonus

Myoclonus refers to muscular contractions (positive myoclonus) that are brief, sudden, and severe, and shock-like movements or inhibitions (negative myoclonus). Myoclonus could be generalized or isolated. The movements consist of rhythmical irregular jerks or oscillatory jerks that occur abruptly and then fade. The abnormal jerks are associated with environmental stimuli such as light, sound, movement, and visual threat. The condition can be misdiagnosed for **epilepsy**. Myoclonus usually occurs at rest, but can also appear when the affected body part is subjected to voluntary activity, which is referred to as action myoclonus. Action myoclonus is more disabling than rest myoclonus.

Tremor

Tremors are rhythmic oscillatory movements that are regular, but may vary in rate, location, amplitude, and constancy, and depend on type and severity of the tremor.

Tremors can occur with action, at rest, and with holding a position or posture. The tremor can be so rapid it is often described as a "flicker of light." Subtypes of tremors include tremors at rest, essential tremor, which is a postural tremor at either rest or activity and may be inherited, or tremor with movement (intention "kinetic" tremor). Resting tremors are usually slow, occur during an activity, and disappear when action is initiated (e.g., **Parkinson's disease**). Essential tremor is usually benign, but can cause disability due to impairment of handwriting and limitations of activities related to daily living. Essential tremor may be inherited.

Paroxysmal dyskinesias

Paroxysmal dyskinesia is a group of disorders that includes paroxysmal kinesigenic dyskinesia, episodic **ataxia**, paroxysmal hypnogenic dyskinesia, paroxysmal exertion-induced dyskinesia, and paroxysmal non-kinesigenic dyskinesia. The paroxysmal dyskinesias are a hyperkinetic disorder characterized by intermittent involuntary movements consisting of symptoms from other **movement disorders** such as chorea, athetosis, dystonia, and ballismus. Episodes of paroxysmal dyskinesias can last from a few seconds to several days. Episodic ataxias are characterized by intermittent episodes of ataxia that can last seconds to hours. Paroxysmal dyskinesias may be triggered by prolonged exertion, sleep, stress, alcohol, coffee, tea, fatigue, sudden voluntary movement, heat, or cold.

Athetosis

Athetosis is a disorder characterized by movements that are continuous, slow, and writhing. The movements are commonly appendicular and frequently involve muscles in the face, neck, and tongue. The condition may occur at rest or when executing voluntary movement. The speed of movements in affected persons can sometimes increase and symptoms are similar to those of chorea (called choreoathetosis). Athetosis movements can blend with those of dystonia, if the muscular contractions are sustained and cause abnormal posturing.

Ballism

Ballismus are large choreic movements that are fast and usually affect the limbs. Affected individuals exhibit flinging and flailing movements. Commonly, ballismus affects one side of the body (unilateral), producing a condition called hemiballismus.

Akathisia

Akathisia refers to complex movements such as tics, compulsions, and mannerisms that are stereotypic and usually relieved when executing a motor act. Typically, when sitting, the akathitic persons may exhibit movements that include symptoms such as crossing and uncrossing the legs, squirming, pacing, stroking the scalp, or rocking the body. Patients may have burning sensations on the specific affected body part, and they may vocalize a continual moaning and groaning.

Tics

Tics can be divided into two disorders: motor tics (abnormal movements) and/or vocal tics (abnormal sounds). Children can present with a chronic disorder of both motor and vocal tics (Gilles de la **Tourette syndrome**). Movements of simple tics may be very similar to a choreic or myoclonic jerk (abrupt, single, sudden, isolated). Complex tics are movements that are distinctly coordinated patterns of sequential movements, but they may not be identical from occurrence to occurrence and they can occur in different body areas. Tics are rapid movements and, if contractions are sustained in affected body parts, they resemble dystonic movements.

One of the major clinical signs that help distinguish tics from other dyskinesias is the presence of involuntary ocular (eye) movement in persons affected with tics. The ocular manifestations of tics can include a brief jerk of the eyes or a sustained eye deviation. Two other dyskinesias, myoclonus and dystonia, can present with involuntary ocular manifestations.

With vocal tics, affected persons can exhibit grunts, throat-clearing sounds, or even the utterance of obscenities (coprolalia). Phonic tics (involving nasal and vocal muscles) can be divided into simple phonic tics such as throat-clearing or sniffing or complex phonic tics that include bark-like noises and verbalizations.

Stereotypies

Sterotypies are movements that are frequent and may last for minutes. These movements are repetitive and identical (continuous stereotypy.) The bizarre movements associated with **mental retardation**, **autism**, and **schizophrenia** are stereotypies. Continuous stereotypy is characteristic of another type of dyskinesia called tardive dyskinesia, which results from treatment with neuroleptic and antipsychotic medications.

Tardive dyskinesia

Tardive (late-onset) dyskinesia refers to a group of movement disorders that are characterized by hyperkinetic involuntary movements, consisting of mixed manifestations of orofacial dyskinesia, chorea, tics, and/or athetosis. Abnormal movement can affect muscles in the lips, face, trunk, tongue, and extremities, which can interfere with eating and dexterity. The most characteristic symptom of

tardive dyskinesia is orofacial dyskinesia, which usually starts with slow, mild tongue movements followed by exaggerated movements of lips and tongue. Affected individuals can have symptoms that may progress to chewing movements, blinking, bulging cheeks, grimacing, arching eyebrows, and blepharospasms.

Tardive dyskinesias are commonly seen in patients taking certain medications such as neuroleptics and antipsychotic medication that are prescribed for schizophrenia, schizoaffective disorder, or bipolar disorder. Other types of tardive dyskinesias include tardive akathisia, tardive dystonia, tardive myoclonus, tardive Tourettism, tardive tremor, and blepharospasm. Approximately 50% of patients taking dopamine receptor blocker medication will develop a form of tardive dyskinesia.

Tardive akathisia refers tapping, squirming, and marching movements that are repetitive. Movements associated with tardive dystonia can include a fixed posturing of face and neck, trunk, and extremities. Persons affected with tardive myoclonus, which is a rare disorder, exhibit brief jerky movements of muscles in the face, neck, trunk, arms, and legs. Symptoms of tardive Tourettism usually begins in persons older than 21 years of age and include frequent, multiple tics that are both vocal and motor. This disorder should not be confused with Tourette syndrome, which commonly presents by seven years of age.

Tardive tremors often present as involuntary rhythmical, wave-like, and persistent movements of the head, neck, limbs, or voice. Tardive tremors are present both at rest and during voluntary movement.

Early myoclonic encephalopathy

Early myoclonic **encephalopathy** is a rare disorder, in which the incidence is approximately one in 40,000 children. It is characterized by brief and abrupt myoclonic jerks (common occurrence in 90% of patients) and **seizures**. The onset of symptoms usually occurs within the first three years of life. Treatment and management depends on the underlying cause of seizures. Typically, patients receive antiepileptic medications, and improvement of symptoms is usually associated with a good prognosis. If symptoms do not improve with antiepileptic medication(s), the prognosis is not favorable.

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Dyslexia

Definition

Dyslexia is an unexpected impairment in reading and spelling despite a normal intellect.

Description

Dyslexia was first described by Hinshelwood in 1896. Orton originally hypothesized that dyslexia results from a dysfunction in visual memory and visual perception due to a delayment in maturation. Most dyslexics also display poor writing ability. Dyslexia is a classical primary reading disorder and should be differentiated from secondary disorders such as **mental retardation**, educational or environmental deprivation, or physical/organic diseases. The disorder results as a combination of genetic and environmental causes, which can induce variations in the behavioral, cognitive, and physiological measures related to reading disability. Dyslexia was previously called congenital word blindness. Dyslexia is a reading disorder, not caused by lowered motivation, inadequate learning opportunity or any overt neurological disability. Reading is a complex process which involves multiple systems to process the information cognitively and physiologically. In simple terms reading typically begins with a visual sensation stimuli and processing the text via the visual pathway in the brain (from the retina in the eye, the impulse goes in the brain to the lateral geniculate nuclei and primary visual cortex, the occipital lobe, located in the back of the head, which functions to process and integrate incoming visual

information). Input information from vision is probably integrated with other neuronal systems that include language-specific rules, learned information and symbolic images into components of language thinking related to reading. Reading-related thinking is correlated with high activity in the left-hemisphere cortical regions, and language processing centers in the brain. Additionally, learning to read is also related to the learning process, which is mediated by the **cerebellum** and on relay feedback mechanisms between related areas of the brain.

Deficits in reading may stem from disruptions of simple sensory impairments to more complex problems involving thinking related to language. There are several subtypes of dyslexias and they can be categorized as either central or peripheral dyslexias (of which there are two, attentional dyslexia and neglect dyslexia), which result from impairment to brain processes that are capable of converting letters on the page into visual word forms. There are two types of peripheral dyslexias called attentional dyslexia, and neglect dyslexia. The attentional dyslexia subtype is a rare disorder of attention control, typically correlated with damage to the left parietal lobe (located on the sides of the head). The attentional dyslexia causes an impairment of reading words in sentences, since the defect causes many words to be visible at the same time. Neglect dyslexia is usually due to brain damage, and causes an impairment of reading because the affected person misidentifies letters in certain spatial regions of either a word or a group of words. The defect for neglect dyslexia subtype is associated with the right parietal lobe. Neglect dyslexia can be further divided into left neglect dyslexia and right neglect dyslexia. In the left neglect dyslexia subtype, the affected person experiences difficulty reading initial letters of the word, which may cause a letter(s) to be substituted, omitted or added. The right neglect dyslexia subtype causes a patient to have letter errors at the end of the word.

Letter-by-letter reading (LBL, pure alexia, or pure word blindness) is another form of peripheral dyslexia causing patients to have very slow reading performance with large effects on word length and response time. There is damage to the prestriate cortex of the occipital cortex and most patients also have a dense right visual field deficit. The damage impairs the word-form system in an abnormal way so that written words seem as random letter strings.

Central dyslexias are typically caused by disruption to neuronal processes correlated with sound analysis and meaning of written words. There are two major subtypes of central dyslexias which either impair semantic reading or nonsemantic reading. Semantic reading dyslexia is also referred to as deep and phonologic dyslexia. Semantic reading is due to extensive damage to the left hemisphere which results in a deficit whereby patients can only assemble the pronunciation of a word by first assessing its meaning. Affected individuals also make visual errors when reading. Nonsemantic reading, due to damage of the left temporal lobe causes patients to have difficulty reading exception words (i.e. shove), but can read correctly words that are common and similar (i.e. love).

Key Terms

Attention deficit/hyperactivity disorder (ADHD) A disorder associated with behavioral control, due to difficulty processing neural stimuli.

Dizygotic twins Twins that share the same environment during development in the uterus but are not identical.

Lateral geniculate nuclei A structure that receives and processes impulses from the optic nerve, and sends these impulses further into the brain for more processing of information.

Monozygotic twins Twins that are genetically identical and are always of the same gender.

Occipital lobe The back part of the brain that functions as a visual interpretation center.

Parietal lobe Part of the cerebral hemisphere, located on both sides of the brain.

Phoneme The smallest meaningful segment of language (e.g., the word "cat" has 3 phonemes, "kuh," "aah," and "tuh").

Retina Area of the eye that helps process visual information to send impulses to the brain.

Temporal lobe A lobe of the brain that contains auditory and receptive (stimuli) areas.

Visual field A field of vision that is visible without eye movement.

Demographics

It is thought that dyslexia is the most common neurobehavioral disorder affecting children. The prevalence (existing cases) ranges from 5-10% of school-aged children (school and clinic identified) in the United States. However, these rates may be significantly more (up to 17.5%) in unselected populations. Research indicates that dyslexia is a chronic and persistent disorder. Evidence concerning gender predilection remains controversial. Dyslexia may also co-occur with another disorder called attention deficit/hyperactivity disorder (ADHD, 40% comorbidity). Dyslexia affects approximately 80% of children identified as manifesting a learning disorder.

Causes and symptoms

Persons affected with dyslexia have dysfunction developing an awareness of spoken and written words and segmenting smaller units of sound that are essential in an alphabetic language like English. Patients lose the ability to link and map printed symbols (letters) to sound.

Dyslexia runs in families. Studies demonstrate concordance rates of 68% for monozygotic twins and 37% for dizygote twins (Colorado Twin Study of Reading Disability). However, the genetic transmission is not simple and does not follow classical knowledge of trait heritability. Findings suggest that several genetic factors determine reading ability and the interactions of some or all factors determine the ultimate ability to read.

Evidence from neurobiological research utilizing high resolution imaging techniques, and brain measurement studies indicate differences in left temporo-parieto-occipital brain regions in dyslexic patients when compared to nonimpaired readers. Furthermore, evidence using functional brain imaging techniques in adult and children with dyslexia demonstrates a failure of normal left hemisphere posterior brain systems during reading with increased brain activation in frontal regions. This data indicates that impairment of posterior reading systems results in a disruption of the smoothly functioning and integrated reading system seen in nonimpaired persons. The impairment of posterior reading systems causes dyslexic persons to shift to ancillary neuronal systems to compensate for the deficit. It is the impairment in the posterior reading systems that prevents the development of skilled reading. Postmortem studies (confirmed in live subjects using **MRI** imaging) indicate a lack of symmetry in language-associated regions in the brain. The abnormal symmetry is associated with the common linguistic deficits that are characteristic of dyslexia.

The specific signs of dyslexia in both adults and school-aged children are similar. Patients exhibit inaccurate and labored decoding, word recognition, and text reading. They also exhibit difficulties in spelling and remain slow readers. Typical early symptoms can include difficulty playing rhyming games and problems with learning numbers and letters. Children often avoid reading independently and are unusually happy at the opportunity for parents to read to them.

Diagnosis

All cases and ages are diagnosed clinically by a combination of careful medical history, observation and psychological testing. There is no one test that is sufficient to render a definitive diagnosis. Rather, the diagnosis is made based on the results of all the clinical data attained. Dyslexia can be distinguished from other **learning disorders** by identifying the phonologic deficit. Family history and collateral data obtained from school and test results are essential. Tests to determine attention, memory, intelligence and math and language skills may be administered to establish the diagnosis.

Treatment team

The treatment team can consist of a **neurologist**, a pediatrician, and special education instructors. A clinical psychologist can perform psychological assessments (psychometric testing) to help establish the diagnosis. School and/or college counselors also comprise part of an effective and integrated treatment team.

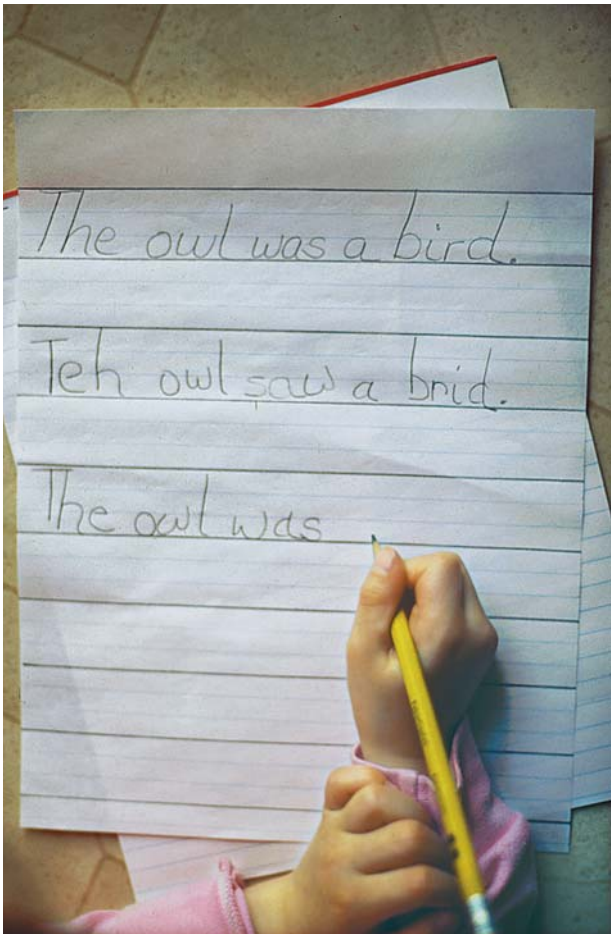
Treatment

The management for dyslexic patients is lifelong. Early identification and intervention (remediation) of reading deficits involves specialist education. Intervention programs must systematically and explicitly teach phonics ensuring a clear understanding of how letters are linked to sounds (phonemes) and spelling. Typically individualized teaching is recommended to provide a balanced remedial program providing systematic instruction on phonemic awareness, phonics, vocabulary fluency and comprehension strategies. A well-integrated treatment program also includes opportunities for writing, reading, and discussing literature. A well-executed treatment program considers each component of the reading process to improve phonemic awareness and the ability to manipulate speech sounds.

Treatment for older persons (high school, college, and graduate school) is accommodation rather than remediation. College students require extra time with examination and reading/writing assignments. Other accommodations include recorded books, tape recorders in the classroom, tutorial services, alternatives to multiple choice questions and computer availability with spelling checkers.

Recovery and rehabilitation

Rehabilitation for dyslexics is a lifelong process. Early intervention in younger patients consists of a highly structured, integrated, systematic and explicit treatment program. A balanced treatment program should include the meaning and phonetic approaches to reading to ultimately improve language development (since dyslexia is a language-based disorder.) The program should allow for personalized instruction. Older persons require accommodation in college and at work versus remediation.



A child with dyslexia, writing words incorrectly. *(Photograph by Robert Huffman. Field Mark Publications. Reproduced by permission.)*

Clinical trials

There are two current clinical research trials entitled: Comprehensive Program to Improve Reading and Writing Skills in At-Risk and Dyslexic Children; and Using MRI to Evaluate Instructional Programs for Children with Developmental Dyslexia. Information can be obtained from http://www.ClinicalTrails.com.

Prognosis

Dyslexia is a lifelong disorder, but improvement is possible. Multiple learning disabilities can be expected, since the brain connections for reading, spelling, listening, speaking, and writing are part of the linguistic system. The prognosis can ultimately depend on associated comorbidities (other disorders associated with the primary disorder), early detection and intervention, and an intensive and comprehensive treatment plan.

Special concerns

Early recognition, intervention, and family members are important. Remediation programs must be delivered by highly-trained specialists, and treatment should be individualized.

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The International Dyslexia Association. 8600 LaSalle Road, Baltimore, MD 21286-2044. 410-296-0232 or 800-ABCD123; Fax: 410-321-5069. <http://www.interdys.org>.

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Dysphagia *see* **Swallowing disorders**

Dyspraxia

Definition

Dyspraxia is a neurological disorder of motor coordination usually apparent in childhood that manifests as difficulty in thinking out, planning out, and executing planned movements or tasks. The term dyspraxia derives

from the Greek word *praxis*, meaning "movement process."

Description

The earliest description of a syndrome of clumsiness, termed "congenital maladroitness," dates back to the turn of the twentieth century. Since that time, numerous names have been given to this syndrome of impaired coordination, including dyspraxia, developmental dyspraxia, developmental coordination disorder, clumsy child syndrome, and sensory integration disorder. Some sources ascribe different meanings to these terms, while others use them interchangeably. Researchers commonly use the term developmental coordination disorder (DCD); DCD is classified by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) as a motor skills disorder.

Dyspraxia is a variable condition; it manifests in different ways at different ages. It may impair physical, intellectual, emotional, social, language, and/or sensory development. Dyspraxia is often subdivided into two types: developmental dyspraxia, also known as developmental coordination disorder, and verbal dyspraxia, also known as developmental **apraxia** of speech. Symptoms of the dyspraxia typically appear in childhood, anywhere from infancy to adolescence, and can persist into adult years. Other disorders such as **dyslexia**, learning disabilities, and attention deficit disorder often co-occur in children with dyspraxia.

Demographics

Estimates of the prevalence of developmental coordination disorder are approximately 6% in children aged 5–11. Some reports indicate a higher prevalence in the 10–20% range. Males are four times more likely than females to have dyspraxia. In some cases, the disorder may be familial.

Causes and symptoms

Developmental dyspraxia is apparent from birth or early in life. As of 2004, the underlying cause or causes for dyspraxia remain largely unknown. It is thought that any number of factors such as illness or trauma may adversely affect normal brain development, resulting in dyspraxia. Genes may also play a role in the development of dyspraxia. It is known that dyspraxia can be acquired (acquired dyspraxia) due to brain damage suffered as a result of **stroke**, an accident, or other trauma.

Symptoms of dyspraxia vary and may include some or all of the following problems:

- poor balance and coordination
- vision problems
- perceptual problems
- poor spatial awareness
- poor posture
- poor short-term memory
- difficulty planning motor tasks
- difficulty with reading, writing, and speech
- emotional and behavioral problems
- poor social skills

The symptoms of dyspraxia depend somewhat on the age of the child. Young children will have delayed motor milestones such as crawling, walking, and jumping. Older children may present with academic problems such as difficulty with reading and writing or with playing ball games.

Developmental verbal dyspraxia (DVD), a type of dyspraxia, can manifest as early as infancy with feeding problems. Children with DVD may display delays in expressive language, difficulty in producing speech, reduced intelligibility of speech, and inconsistent production of familiar words.

Diagnosis

The diagnosis of dyspraxia is based on observation of a patient's symptoms and on results of standardized tests. Findings from a neurological or neurodevelopmental evaluation may also be used to confirm a suspected diagnosis. The process of making a diagnosis of dyspraxia can be complex for a number of reasons. Dyspraxia may affect many different body functions, it can occur as a part of another syndrome, and symptoms of dyspraxia overlap with similar disorders such as dyslexia.

Diagnostic criteria

Various health professionals and organizations define the term dyspraxia differently. The Dyspraxia Foundation (England) describes it as "an impairment or immaturity of the organization of movement," and further adds that it may be associated with problems in language, perception, and thought. Other advocacy groups such as the Dyspraxia Association of Ireland and the Dyspraxia Foundation of New Zealand, Inc. offer slightly different definitions. The American Psychiatric Association lists four criteria in the DSM-IV-TR for the diagnosis of developmental coordination disorder:

- marked impairment in the development of motor coordination
- the impaired coordination significantly interferes with academic achievement or activities of daily living

- the coordination difficulties are not due to a general medical problem such as **cerebral palsy** or **muscular dystrophy** and do not meet the criteria for pervasive developmental disorder
- if **mental retardation** (MR) is present, the motor coordination problems exceed those typically associated with the MR

Treatment team

Treatment for individuals with dyspraxia is highly individualized because the manifestations vary from patient to patient. The treatment team for a child with dyspraxia may include a pediatric **neurologist**, a physical therapist, an occupational therapist, and a speech therapist, in addition to a family doctor or pediatrician. In some cases, the treatment team may also include a psychologist, a developmental optometrist, and specialists in early intervention or special education.

Treatment

Currently there is no cure for dyspraxia. Treatment mainly consists of rehabilitation through physical, occupational, and speech therapies. Other interventions such as special education, psychological therapy, or orthoptic exercises may be recommended on a case-by-case basis. The purpose of treatment for dyspraxia is to help the child to think out, plan out, and execute the actions necessary to try out new tasks or familiar tasks in novel ways.

Recovery and rehabilitation

There are specific therapies for dyspraxia. In physical therapy, a physical therapist may evaluate some or all of the following skill areas in order to formulate a plan of treatment with the patient's physician:

- muscle tone
- control of shoulders and pelvis
- active trunk extension and flexion (posture)
- hand-eye coordination (throwing a ball)
- foot-eye coordination (kicking a ball)
- midline crossing (writing)
- directional awareness (ability to move in different directions)
- spatial awareness (judge distances and direction)
- integration (moving both sides of the body simultaneously)
- knowledge of two sides/dominance of one side (knowing right from left)
- short-term memory
- motor planning (ability to plan movements needed to move from one position to another)
- self organization (dressing, eating, etc.)
- eye tracking

Physical therapy generally consists of activities and exercises designed to improve the specific skill weakness. For example, activities such as climbing, going through tunnels, and moving in and out of cones may assist a child who has poor spatial awareness. The physical therapist may also recommend that the child practice the treatment activities or exercises at home.

In occupational therapy, an occupational therapist may use standardized tests to evaluate the child's sensory integration skills. A therapeutic technique known as sensory integration may be recommended. Sensory integration techniques help a child to sort, store, and integrate information obtained by the senses so that it may be used for learning.

In speech therapy, a speech therapist may assist the child with areas such as muscle control, planning language, and forming concepts and strategies in order to communicate. The therapist may use language tests to assess language comprehension and production in order to develop a plan of treatment

Clinical trials

As of 2004, there was one clinical trial recruiting patients with a form of dyspraxia known as verbal dyspraxia. The aim of the study, entitled "Central Mechanisms in Speech Motor Control Studied with H2150 **PET**," is to use radioactive water (H2150) and **positron emission tomography (PET)** scan to measure blood flow to different areas of the brain in order to better understand the mechanisms involved in speech motor control. Information on this trial can be found at <http://www.clinicaltrials.gov> (see study number 92-DC-0178) or by contacting the National Institute on Deafness and Other Communication Disorders (NIDCD) patient recruitment and public liaison office at (800) 411-1010.

Prognosis

The prognosis for dyspraxia varies. Some children "outgrow" their condition, whereas others continue to have difficulties into adulthood. Though early diagnosis and prompt treatment may improve the outcome for a given patient, the precise factors that influence prognosis are not well understood. For example, it remains unclear how factors such as a child's specific deficits and the underlying cause for the disorder influence rehabilitation potential. Also, the prognosis for dyspraxia is situational; it depends on the age of the patient and the demands of a given setting or environment.

Special concerns

A child with a diagnosis of dyspraxia or developmental coordination disorder may be eligible to have an individual education plan (IEP). An IEP provides a framework from which administrators, teachers, and parents can meet the educational needs of a child with dyspraxia. Depending upon severity of symptoms and the presence of other problems such as learning difficulties, children may be best served by special education classes or by a private educational setting.

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American Speech Language Hearing Association (ASHA). 10801 Rockville Pike, Rockville, MD 20852-3279. (301) 897-5700 or (800) 638-8255; Fax: (301) 571-0457. actioncenter@asha.org. <http://www.asha.org>.

The Dyspraxia Foundation. 8 West Alley, Hitchin, Hertfordshire SG5 1EG, United Kingdom. +44 (0) 14 6245 5016 or +44 (0) 14 6245 4986; Fax: +44 (0) 14 6245 5052. dyspraxia@dyspraxiafoundation.org.uk. <http://www.dyspraxiafoundation.org.uk/>.

The Dyspraxia Support Group of New Zealand, Inc. The Dyspraxia Centre, P.O. Box 20292, Bishopdale, Christchurch, New Zealand. +64 3 359 7072; Fax: +64 3 359 7074. praxisnz@xtra.co.nz. <http://www.dyspraxia.org.nz/>

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Dyssynergia cerebellaris myoclonica *see* **Ramsey-Hunt syndrome type II**

Dystonia

Definition

Dystonia is a disabling movement disorder characterized by sustained contraction of muscles leading to twisting distorted postures. Dystonia may affect various parts of the body and has multiple causes, making classification and diagnosis challenging. The etiology behind the various forms of dystonia is unknown, although abnormal functioning of the cerebral cortex and basal ganglia and other pathways involved in movement are presumed. Clinical and basic science research on humans and primates, and identification of multiple genes causing dystonia have improved the understanding and treatment of this debilitating disorder.

Description

Dystonia as a term was first coined by Oppenheim in 1911 in reference to a childhood-onset syndrome he termed dystonia musculorum deformans. This entity, known as idiopathic torsion dystonia today, was noted to run in families, and although presumably inherited, was only recently proven to be of genetic cause. There is a wide range of variability in the manifestation of clinical symptoms of dystonia. Due to its various causes, dystonia is seen as a syndrome rather than a disease.

Dystonia can be classified by age of onset, cause, or by distribution of the body parts affected. Dystonia localized to a single body part such as the hand or neck is referred to as focal. Among body parts affected in focal dystonia, the eyelids, mouth, muscles controlling the voice, neck, hand, or arm may be affected. Dystonia localized to two contiguous body parts is referred to as segmental. Dystonia affecting body parts that are not next to each other is referred to as multifocal. Dystonia affecting one segment and another body part is classified as generalized. It may also affect only one half of the body and be called hemidystonia. Dystonia with a known environmental cause is referred to as secondary. The cause of primary or idiopathic dystonias is unknown or genetic.

The course and severity of dystonic symptoms may change over the duration of the illness. Symptoms may

initially involve one body part and then spread to other body parts. The likelihood of spread often depends on the age and site of onset of symptoms. Early onset dystonia may start in a limb but tends to become generalized. Adult onset dystonia may start in the neck or face muscles and tends not to spread. Dystonia may first occur only with voluntary movements, but in time, occur at rest as well.

Demographics

Dystonia follows **Parkinson's disease** and essential tremor as the most frequent movement disorder. Prevalence is estimated as 3.4 per 100,000 for generalized forms and 29.5 per 100,000 for focal dystonia. Early onset dystonia may be more frequent in patients of Jewish ancestry, especially from Eastern Europe or Ashkenazi background.

Causes and symptoms

Causes

The exact cause of dystonia is unknown. Ongoing research on dystonia is directed at examining the abnormal brain activity in different parts of the brain such as the basal ganglia and cerebral cortex. The basal ganglia are a collection of nerve cells that are part of the brain pathways important for regulating aspects of normal movement. Abnormalities in the processing of information in these pathways are thought to underlie the various **movement disorders** such as Parkinson's disease, Huntington's disease, tremor, and dystonia. There is evidence for abnormalities in the spinal cord and peripheral nerves as well, suggesting that dystonia may involve abnormalities at multiple levels of the nervous system. Patients with dystonia may have abnormal touch perception and sensation, and theories propose that there may be defects in the preparation of movement as well as the translation of sensation to movement. Dystonia can be classified by cause into primary and secondary forms. Primary or idiopathic dystonia is presumed to be of genetic or unknown cause, whereas secondary dystonias are due to an attributable cause.

Primary dystonia

Primary or idiopathic dystonias have no identifiable etiology and are presumed to be genetic in cause. There are currently at least 13 different genetic dystonia syndromes, although only a few genes have actually been isolated. The only identified gene for primary dystonia is DYT1 on chromosome 9. DYT1 dystonia tends to occur in childhood and starts in a limb only to generalize. The appearance of the dystonia may differ in individuals with the same genetic abnormality, suggesting that there are environmental factors involved as well. Primary genetic dystonias may appear in multiple family members, but most are due to new mutations in genes and referred to as sporadic. Primary dystonias tend to develop gradually over the course of months to years.

Secondary dystonia

Secondary dystonia can be caused by a structural abnormality of the brain such as a **stroke** or infection, drugs or various toxins or metabolic abnormalities. These tend to occur over the course of days to weeks due to the nature of an inciting insult. Dystonia may occur after birth trauma and may be delayed in onset for up to a decade or later. Some may occur as part of a larger disease process affecting other parts of the body such as Wilson's disease, a defect of metabolism of copper that causes abnormal liver function and movement problems such as dystonia or tremor. Usually an abnormality will be found on brain imaging studies such as **MRI** or **CT scan**. Patients taking medications for psychiatric diseases such as **schizophrenia** or psychosis may develop dystonia as a drug reaction. Dystonia may be feigned as part of a psychiatric disorder and is then known as psychogenic.

Other dystonias

Dystonia may also be associated with other neurologic disorders. These are classified as dystonia-plus syndromes. Dystonia may be associated with Parkinson's disease or **myoclonus**, another movement disorder which consists of muscle jerking. Dystonia may be part of a larger syndrome of neurodegenerative disorders, a group of diseases which are caused by degeneration of nerve cells in certain portions of the brain. Such disorders include Huntington's disease and Parkinson's disease.

Symptoms

The symptoms of dystonia depend on the body part affected. Dystonia localized to the face may involve repetitive blinking, tongue protrusion, or jaw clenching. Blinking can become so severe that the patient can not see due to inability to open the eyes. Dystonia affecting the neck may lead to sustained flexion, extension, or twisting postures of the neck known as torticollis. Some dystonias are task-specific and only arise during the performance of certain tasks such as writing, typing, or playing instruments. The progression of these symptoms can lead to severe disability and inability to perform daily work. Generalized dystonia, the most severe form, can present as twisting movements of the head, trunk, and arms, completely disabling the affected individual. Dystonia can often be associated with a tremor in the affected body part.

All forms of dystonia impair normal movement and daily function to some degree. Dystonia can be worsened by stress and anxiety, whereas it may be relieved with relaxation and sleep. Symptoms may be improved by touching various parts of the body in a phenomenon called a "sensory trick."

Diagnosis

The diagnosis of dystonia is clinical and is usually made by a **neurologist** who may have expertise with movement disorders. Investigation of dystonia will usually involve a physical examination and medical history taken by the neurologist to look for secondary causes such as drug exposure or stroke or other family members affected, suggesting a genetic cause. An MRI of the brain may be performed to look for a structural abnormality causing the symptoms. Laboratory testing may reveal abnormalities of copper metabolism associated with Wilson's disease. Genetic testing for the DYT1 gene is not performed unless the dystonia is early in onset or there is a family history of similar symptoms.

Treatment team

Treatment for dystonia involves the interaction between a neurologist, psychiatrists, and physical and occupational therapists. Treatment may involve a neurosurgeon for symptoms that do not respond to medical management. Dystonia of childhood onset is treated by a pediatric neurologist cooperating with pediatricians and pediatric therapists.

Treatment

Treatment for dystonia is usually directed towards management of the symptoms and depends on the type of dystonia. Dystonia that is associated or caused by known etiologies such as drugs, Wilson's disease, or dopa-responsive dystonia may be improved by treating the underlying disease with resolution of symptoms. The various treatments available may be grouped into oral medications, **botulinum toxin** injections, and surgical modalities.

Medications

Various oral medications are available for the symptomatic treatment of dystonia. Among these are various medications that affect different neurochemical systems thought to be important in causing dystonia. Some patients with symptoms of early onset may have dystonia that responds dramatically to levodopa. **Anticholinergics**, dopamine depleting agents, **benzodiazepines**, baclofen, or atypical antipsychotics may be tried as well.

Botox

Chemical denervation using botulinum toxin has been used for many movement disorders including dystonia. Botulinum toxin blocks the transmission of nerve impulses to the muscle and paralyzes the overactive muscles involved. Focal forms of dystonia are more amenable to treatment due to the ease of localizing injectable muscles and less extensive involvement. Botox may be used in generalized dystonia to facilitate improvement in select muscles needed for daily function such as the arms and legs.

Surgical treatment

Selective destruction or high frequency stimulation of nerve centers involved in causing dystonia has been useful in treating selected patients with disabling symptoms. Patients with generalized dystonia or hemidystonia may benefit due to the widespread nature of symptoms, limiting the efficacy of medications and botox injections. Surgical lesioning of nerve cells in the globus pallidus or stimulation of cells in the globus pallidus or subthalamic nucleus have been shown to be effective in treating the symptoms of dystonia. The long-term benefit of surgical therapies on symptoms of dystonia has yet to be validated.

Recovery and rehabilitation

Symptoms of dystonia may fluctuate over the course of years. The course of disease in any given individual can not be predicted. Some may improve spontaneously, whereas others may progress and spread to involve other body parts. Physical therapists may aid in the treatment of symptoms of dystonia. Treatment is focused on maintaining or improving the patient's ability to walk. Occupational therapy may be helpful in improving hand use.

Clinical trials

Several **clinical trials** are currently in effect for treatment of dystonia. The National Institutes of Health (NIH) and National Institutes of Neurological Diseases and Stroke (NINDS) are recruiting patients for trials examining the effect of different medications, botulinum toxin treatment, and surgical treatment for patients with dystonia. Studies are also ongoing to study the effect of electrical stimulation of the brain and nerves with magnetic fields to treat dystonia. Updated information on clinical trials can be found at the National Institutes of Health clinical trials website at www.clinicaltrials.org.

Prognosis

The prognosis for dystonia depends on the distribution and the cause. The initial site of symptoms may predict the prognosis. Patients with symptoms that start in the

leg have a higher likelihood (90%) of progression to involve other body parts and become generalized. Patients with symptoms starting in the neck and later in onset have a much lower likelihood of spread. Most focal dystonias respond to medications or botulinum toxin. Refractory and generalized dystonia may require surgical management. Most patients have a normal life expectancy although with continued disabling symptoms.

Special concerns

Educational and social needs

Dystonia in many cases is a chronic illness and due to the physical limitations and often disfiguring symptoms, may lead to feelings of **depression** or anxiety. These feelings may require treatment by a psychiatrist if severe enough. It is important for patients with dystonia to continue to be involved in community activities and social events.

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ORGANIZATIONS

Dystonia Medical Research Foundation. 1 East Wacker Drive, Suite 2430, Chicago, IL 60601-1905. (312) 755-0198; Fax: (312) 803-0138. dystonia@dystonia-foundation.org/ <http://www.dystonia-foundation.org>.

Worldwide Education & Awareness for Movement Disorders (WE MOVE). 204 West 84th Street, New York, NY 10024. (212) 875-8312 or (800) 437-6682; Fax: (212) 875-8389. wemove@wemove.org. <http://www.wemove.org>.

Peter T. Lin, MD

E

Edrophonium *see* **Cholinergic stimulants**

Electric personal assistive mobility devices

Definition

Electric personal assistive mobility devices are power-assisted devices for mobility such as wheelchairs, scooters, and more recent innovations such as the Segway™ Human Transporter. These devices make everyday life easier for someone who is partially or completely immobile.

Description

Currently there are approximately 160,000 people who use electric powered wheelchair and scooters in the United States alone. Of these, some 100,000 utilize wheelchairs and 60,000 use powered scooters. As baby boomers become senior citizens and mobility becomes more of a concern for this large population, the market for these aids is expected to increase. Industry estimates show the powered assistive device market as growing by about 7% each year through 2007. By 2007, sales of manual- and electric-powered wheelchairs and powered scooters is estimated to be $2.7 billion in the United States.

Wheelchairs

Electric wheelchairs appeared in the 1950s. Then, the less sophisticated mechanics of the chair produced a rougher and more jarring ride. Today's models are better described as electronic chairs rather than electric chairs. Electronic circuitry allows for a control of speed and a precise control of direction. Many of today's sophisticated powered wheelchairs conform to two basic styles. The first is called the traditional style and consists of a power source mounted behind or underneath the seat of the wheelchair. As the name implies, the traditional unit looks very much like a manual wheelchair.

The second design is known as a platform chair. In this design, the seating area, which can often be raised or lowered, sits on top of the power source. There are several groups of powered wheelchairs, based on the intended use. Wheelchairs designed strictly for indoor use have a smaller area between the wheels, allowing them to negotiate the tighter turns and more confined spaces of the indoor world. Other designs allow the electric wheelchair to be used both indoors and outdoors, on sidewalks, driveways, and hard, even surfaces. Finally, some electric wheelchairs are able to negotiate more rugged terrain such as uneven, stony surfaces.

Wheelchairs meant for indoor and indoor/outdoor use conserve weight by reducing the size of the rechargeable batteries that deliver the power to the device. Outdoor models deliver more power, more speed, and can operate for a longer period of time, at the cost of a heavier wheelchair. Electric wheelchairs can also be classified according to the location of the wheels that drive the device. Rear-wheel, mid-wheel, and front-wheel drive models are available. In a rear-wheel chair, the big wheels that drive the unit are positioned behind the rider's center of gravity. This is the traditional chair design.

In the mid-wheel design, the large wheels are positioned directly under the rider's center of gravity. This offers a shorter turning radius, which can be useful in tight places. However, sudden stops can cause the chair to rock or pitch forward. Finally, the front-wheel drive chair has the large wheels in front of the rider's center of gravity. This allows for a tight turning radius and even to climb over obstacles such as curbs.

For people who are immobile, some wheelchairs are capable of adjusting the person's position. Some chairs can recline and/or can tilt people back while they are still in the sitting position. Changes of position relieve pressure and can help lessen the development of skin irritation.

Roslyn Cappiello, a quadriplegic and president of the Omaha chapter of Mothers Against Drunk Driving. *(AP/Wide World Photos. Reproduced by permission.)*

Changing position can also help some people breathe more easily.

Some powered wheelchairs are also capable of raising or lowering a person. This can make life easier by allowing the person to retrieve fallen objects and to reach higher-placed objects. Some wheelchairs can even raise the person to a standing position. This increases the range of tasks a person can accomplish. A wheelchair-bound person can wash dishes, clean windows, work at a counter, and put dishes away in a cupboard, as a few examples, thus reducing the need to modify a home.

The controls to electric-powered wheelchairs vary depending on the mobility of the user. For those with arm function, a joystick can be used to propel the chair forwards or backwards, and to steer. Those who are paralyzed are able to perform these functions using a sip-and-puff setup via a straw. Some manufacturers even make voice-activated and -responsive wheelchairs.

This ability of fully paralyzed people to independently operate a wheelchair offers great potential in reducing the barriers that have prevented wheelchair users from participating fully in society.

Innovations in electric-powered wheelchairs

Construction materials used in wheelchair frames have reduced the weight of the chairs. Aluminum, stainless steel, and steel tubes are some of several materials that produce strength without excess weight.

In 1993, a new powered wheelchair marketed as the Hoveround was launched. It has features of both a wheelchair and a scooter. The most unique features are the round base and single rear wheel, which allow the chair to be turned in a full circle on the spot. A relatively recent innovation is known as the pushrim-activated power-assisted wheelchair (PAPAW). This design uses motors and an electric battery to supply forward thrust or braking capabilities that complement similar manual actions of the user. A PAPAW is best suited to a user who can manually operate a wheelchair, but not very efficiently due to **pain**, insufficient arm strength, heart and/or lung trouble, or inability to maintain effective posture.

User demand is driving new designs for mobility devices that do not look like wheelchairs. Indeed, newer designs for wheelchairs are more similar to scooters than to the traditional design of the wheelchair. The impetus for this new design has been people's desire for more independence and mobility, to the point of being able to mount curbs and travel over rough ground.

The Independence 3000 IBOT Transporter (IBOT) can change the way it moves in response to varying terrain. The two pairs of large rear wheels can operate at different height, allowing for actions like the mounting of curbs. In fact, the front pair of wheels can ride up the rear set, enabling the two pairs of wheels to balance vertically on each other.

Scooters

Scooters are designed for people who are able to walk, but have difficulty walking significant distances. Examples include people with milder forms of **cerebral palsy**, **multiple sclerosis**, postpolio syndrome, and those who have had a **stroke** or who suffer from arthritis. Scooters are not designed for those who are absolutely immobile. Scooters consist of a seat mounted on a movable platform. The rider uses handle bars to maintain balance and to steer, although some scooters use electronics that control the steering instead of the operator. The seats are typically removable to allow the scooter to be easily transported in car, truck, or other vehicle.

Scooters represent a hybrid between a manual and electric wheelchair. They appeal to those who do not have

the physical capability to power a manual wheelchair, but who do not need the electronic controls and various seating configurations that can be selected in some electric wheelchairs. For users who have the upper arm and body strength necessary to use one and also to hold themselves in a sitting position for a prolonged time, a scooter can represent a more economical alternative to a powered wheelchair.

The basic setup of a scooter is known as the base unit. This consists of a frame made of steel or aluminum attached to a platform. Some units also have a windscreen as part of the unit. The seat post can be a permanent part of the frame, or may be detachable for easy transport.

Scooters can be front-wheel drive or rear-wheel drive. The scooters with rear-wheel drive, which has a larger motor and a longer distance between the front and rear wheels, typically supply more power and so are useful for tasks like climbing hilly terrain. Front-wheel drive scooters have a smaller motor and so are more maneuverable in tight places such as indoor use. They can also be used outside on flat, paved surfaces. The choice of scooter depends on the user's needs. Three- and four-wheeled scooters are also available. These provide more stability for users whose balance is faulty.

Other personal transport devices

For many years, golf cart-style vehicles have provided transportation for elderly people. In retirement communities, carts can be an everyday part of the landscape, being used even on the roads of gated communities. As the population ages and decreased physical mobility affects more people, the popularity of electric carts may well grow.

The Segway™ Human Transporter was introduced in the 1990s. It offers increased mobility for those with disabilities, but could also aid some persons who are unable to walk long distances. The machine operates on a principle called dynamic stabilization. Essentially, this means that the machine works in a manner similar to people's sense of balance. When people standing on the machine shift their center of gravity forward, the machine moves forward. Shifting the center of gravity backward stops the machine. There is no accelerator or brake.

While more of a curiosity than practical means of transport as of 2004, the transporter is an example of how increased mobility is possible in environments such as sidewalks and factories.

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Worldwide Education & Awareness for Movement Disorders (WE MOVE). 204 West 84th Street, New York, NY 10024. (212) 875-8312 or (800) 437-MOV2 (6682); Fax: (212) 875-8389. Wemove@wemove.org. <http://www.wemove.org>.

Brian Douglas Hoyle, PhD

Electroencephalography

Definition

Electroencephalography, or EEG, is a neurological test that involves attaching electrodes to the head of a person to measure and record electrical activity in the brain over time.

Purpose

The EEG, also known as a brain wave test, is a key tool in the diagnosis and management of **epilepsy** and other seizure disorders. It is also used to assist in the diagnosis of brain damage and diseases such as strokes, tumors, encephalitis, **mental retardation**, and sleep disorders. The results of the test can distinguish psychiatric conditions such as **schizophrenia**, paranoia, and **depression** from degenerative mental disorders such as Alzheimer's and Parkinson's diseases. An EEG may also be used to monitor brain activity during surgery to assess the effects of anesthesia. Additionally, it is used to determine brain status and brain death.

Precautions

There are few adverse conditions associated with an EEG test. Persons with seizure disorders may experience **seizures** during the test in reaction to flashing lights or by deep breathing.

Description

Before an EEG begins, a nurse or technologist attaches approximately 16–21 electrodes to a person's scalp using an electrically conductive, washable paste. The electrodes are placed on the head in a standard pattern based on head circumference measurements. Depending on the purpose for the EEG, implantable, or invasive, electrodes are occasionally used. Implantable electrodes include sphenoidal electrodes, which are fine wires inserted under the zygomatic arch, or cheekbone. Depth electrodes, or subdural strip electrodes, are surgically implanted into the brain and are used to localize a seizure focus in preparation for epilepsy surgery. Once in place, even implantable electrodes do not cause **pain**. The electrodes are used to measure the electrical activity in various regions of the brain over the course of the test period.

For the test, a person lies on a bed, padded table, or comfortable chair and is asked to relax and remain still while measurements are being taken. An EEG usually takes no more than one hour, although long-term monitoring is often used for diagnosis of seizure disorders. During the test procedure, a person may be asked to breathe slowly or quickly. Visual stimuli such as flashing lights or a patterned board may be used to stimulate certain types of brain activity. Throughout the procedure, the electroencephalography unit makes a continuous graphic record of the person's brain activity, or brain waves, on a long strip of recording paper or computer screen. This graphic record is called an electroencephalogram. If the display is computerized, the test may be called a digital EEG, or dEEG.

The sleep EEG uses the same equipment and procedures as a regular EEG. Persons undergoing a sleep EEG are encouraged to fall asleep completely rather than just relax. They are typically provided a bed and a quiet room conducive to sleep. A sleep EEG lasts up to three hours, or up to eight or nine hours if it is a night's sleep.

In an ambulatory EEG, individuals are hooked up to a portable cassette recorder. They then go about normal activities and take normal rest and sleep for a period of up to 24 hours. During this period, individuals and their family members record any symptoms or abnormal behaviors, which can later be correlated with the EEG to see if they represent seizures.

An extension of the EEG technique, called quantitative EEG (qEEG), involves manipulating the EEG signals with a computer using the fast Fourier transform algorithm. The result is then best displayed using a colored gray scale transposed onto a schematic map of the head to form a topographic image. The brain map produced in this technique is a vivid illustration of electrical activity of the brain. This technique also has the ability to compare the similarity of the signals between different electrodes, a measurement known as spectral coherence. Studies have shown the value of this measurement in diagnosis of Alzheimer's disease and mild closed-head injuries. The technique can also identify areas of the brain having abnormally slow activity when the data are both mapped and compared to known normal values. The result is then known as a statistical or significance probability map (SPM). This allows differentiation between early **dementia** (increased slowing) or otherwise uncomplicated depression (no slowing).

Key Terms

Encephalitis Inflammation of the brain.

Fast Fourier transfer A digital processing of the recorded signal resulting in a decomposition of its frequency components.

Ictal EEG An EEG done to determine the type of seizure characteristic of a person's disorder. During this EEG, seizure medicine may be discontinued in an attempt to induce as seizure during the testing period.

Sphenoidal electrodes Fine wire electrodes that are implanted under the cheek bones, used to measure temporal seizures.

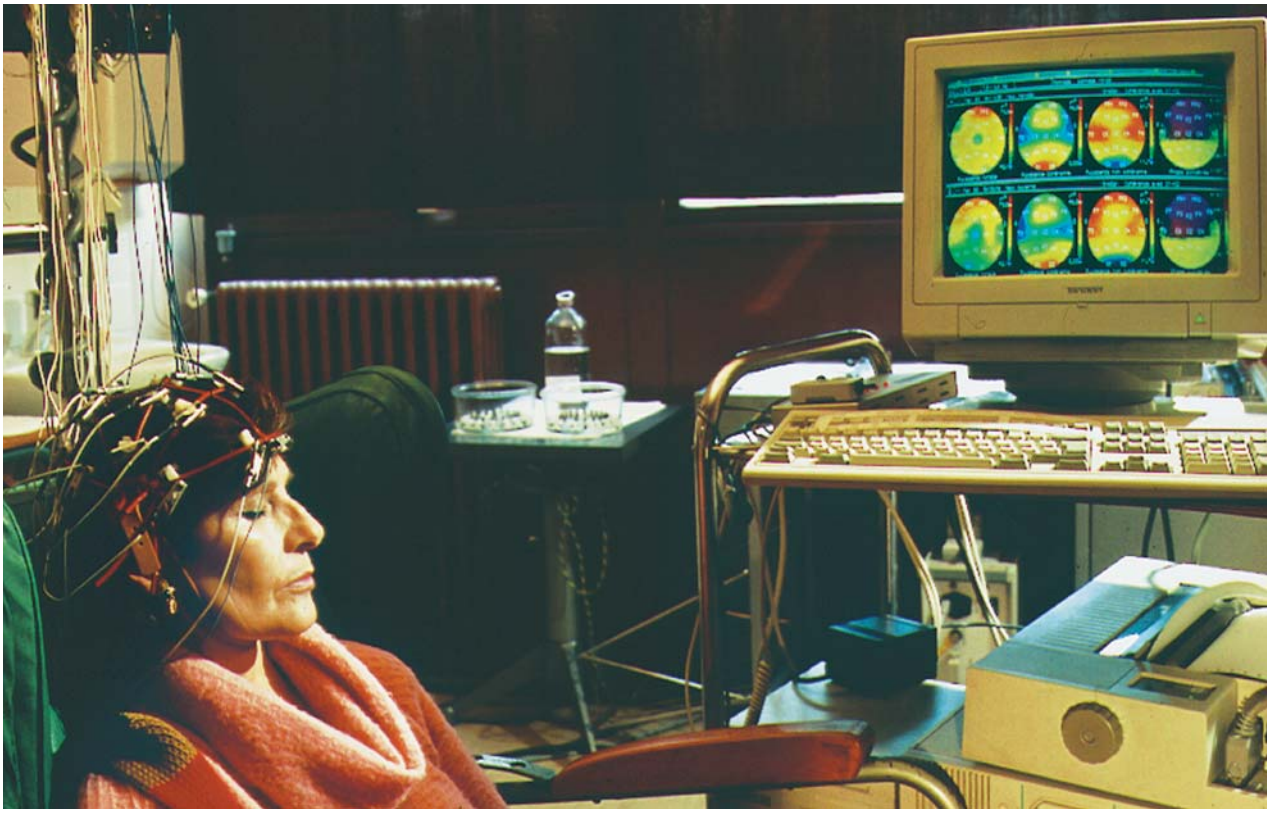
Subdural electrodes Strip electrodes that are placed under dura mater (the outermost, toughest, and most fibrous of the three membranes [meninges] covering the brain and spinal cord). They are used to locate foci of epileptic seizures prior to epilepsy surgery.

Preparation

An EEG is generally performed as one test in a series of neurological evaluations. Rarely does the EEG form the sole basis for a particular diagnosis.

Full instructions should be given to individuals receiving an EEG when they schedule their test. Typically, individuals taking medications that affect the **central nervous system**, such as **anticonvulsants**, stimulants, or antidepressants, are told to discontinue their prescription for a short time prior to the test (usually one or two days). However, such requests should be cleared with the treating physician. EEG test candidates may be asked to avoid food and beverages that contain caffeine, a central nervous system stimulant. They may also be asked to arrive for the test with clean hair that is free of spray or other styling products to make attachment of the electrodes easier.

Individuals undergoing a sleep EEG may be asked to remain awake the night before their test. They may be given a sedative prior to the test to induce sleep.



Woman undergoing an electroencephalogram (EEG). *(Photograph by Catherine Pouedras. Science Photo Library, National Audubon Society Collection/Photo Researchers, Inc. Reproduced by permission.)*

Aftercare

If an individual has suspended regular medication for the test, the EEG nurse or technician should advise as to when to begin taking it again.

Risks

Being off certain medications for one to two days may trigger seizures. Certain procedures used during EEG may trigger seizures in persons with epilepsy. Those procedures include flashing lights and deep breathing. If the EEG is being used as a diagnostic tool for epilepsy (i.e., to determine the type of seizures an individual is experiencing), this may be a desired effect, although the person needs to be monitored closely so that the seizure can be aborted if necessary. This type of test is known as an ictal EEG.

Normal results

In reading and interpreting brain wave patterns, a **neurologist** or other physician will evaluate the type of brain waves and the symmetry, location, and consistency of brain wave patterns. Brain wave response to certain stimuli presented during the EEG test (such as flashing lights or noise) will also be evaluated.

The four basic types of brain waves are alpha, beta, theta, and delta, with the type distinguished by frequency. Alpha waves fall between 8 and 13 Hertz (Hz), beta are above 13 Hz, theta between 4 and 7 Hz, and delta are less than 4 Hz. Alpha waves are usually the dominant rhythm seen in the posterior region of the brain in older children and adults, when they are awake and relaxed. Beta waves are normal in sleep, particularly for infants and young children. Theta waves are normally found during drowsiness and sleep and are normal in wakefulness in children, while delta waves are the most prominent feature of the sleeping EEG. Spikes and sharp waves are generally abnormal; however, they are common in the EEG of normal newborns.

Different types of brain waves are seen as abnormal only in the context of the location of the waves, a person's age, and one's state of consciousness. In general, disease typically increases slow activity such as theta or delta waves, but decreases fast activity such as alpha and beta waves.

Not all decreases in wave activity are abnormal. The normal alpha waves seen in the posterior region of the brain are suppressed merely if a person is tense. Sometimes the addition of a wave is abnormal. For example, alpha

rhythms seen in a newborn can signify seizure activity. Finally, the area where the rhythm is seen can be telling. The alpha coma is characterized by alpha rhythms produced diffusely, or, in other words, by all regions of the brain.

Some abnormal beta rhythms include frontal beta waves that are induced by sedative drugs. Marked asymmetry in beta rhythms suggests a structural lesion on the side lacking the beta waves. Beta waves are also commonly measured over skull lesions such as fractures or burr holes, in an activity known as a breach rhythm.

Usually seen only during sleep in adults, the presence of theta waves in the temporal region of awake, older adults has been tentatively correlated with vascular disease. Another rhythm normal in sleep, delta rhythms, may be recorded in a wakeful state over localized regions of cerebral damage. Intermittent delta rhythms are also an indication of damage of the relays between the deep gray matter and the cortex of the brain. In adults, this intermittent activity is found in the frontal region, whereas in children it is in the occipital region.

The EEG readings of persons with epilepsy or other seizure disorders display bursts, or spikes, of electrical activity. In focal epilepsy, spikes are restricted to one hemisphere of the brain. If spikes are generalized to both hemispheres of the brain, multifocal epilepsy may be present. The EEG can be used to localize the region of the brain where the abnormal electrical activity is occurring. This is most easily accomplished using a recording method, or montage, called an average reference montage. With this type of recording, the signal from each electrode is compared to the average signal from all the electrodes. The negative amplitude (an upward movement) of the spike is observed for the different channels, or inputs, from the various electrodes. The negative deflection will be greatest as recorded by the electrode that is closest in location to the origin of the abnormal activity. The spike will be present but of reduced amplitude as the electrodes move farther away from the site producing the spike. Electrodes distant from the site will not record the spike occurrence.

A final variety of abnormal result is the presence of slower-than-normal wave activity, which can either be a slow background rhythm or slow waves superimposed on a normal background. A posterior dominant rhythm of 7 Hz or less in an adult is abnormal and consistent with **encephalopathy** (brain disease). In contrast, localized theta or delta rhythms found in conjunction with normal background rhythms suggest a structural lesion.

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American Association of Electrodiagnostic Medicine. 421 First Avenue SW, Suite 300 East, Rochester, MN 55902. (507) 288-0100; Fax: (507) 288-1225. aaem@aaem.net. <http://www.aaem.net/>.

American Board of Registration of EEG and EP Technologists. PO Box 891663, Longwood, FL 32791. (407) 788-6308. <http://www.abret.org/index.htm>.

American Society of Electroneurodiagnostic Technologists Inc., 204 W. 7th Carroll, IA 51401. (712) 792-2978. <http://www.aset.org/>.

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L. Fleming Fallon, Jr., MD, DrPH

Electromyography

Definition

Electromyography (EMG) is an electrical recording of muscle activity that aids in the diagnosis of neuromuscular disease, which affects muscle and peripheral nerves.

Purpose

Muscles are stimulated by signals from nerve cells called motor neurons. This stimulation causes electrical activity in the muscle, which in turn causes contraction. A needle electrode inserted into the muscle and connected to a recording device detects this electrical activity. Together, the electrode and recorder are called an electromyography machine. EMG can determine whether a particular muscle is responding appropriately to stimulation, and whether a muscle remains inactive when not stimulated.

EMG is performed most often to help diagnose different diseases causing weakness. Although EMG is a test of the motor system, it may help identify abnormalities of nerves or spinal nerve roots that may be associated with **pain** or numbness. Other symptoms for which EMG may be useful include atrophy, stiffness, fasciculation (muscle twitching), cramp, deformity, and **spasticity**. EMG results can help determine whether symptoms are due to a muscle disease or a neurological disorder, and, when combined with clinical findings, usually allow a confident diagnosis.

EMG can help diagnose many muscle and nerve disorders, including:

- muscular dystrophy
- congenital myopathies
- mitochondrial myopathies
- metabolic myopathies
- myotonias
- peripheral neuropathies
- radiculopathies
- nerve lesions
- amyotrophic lateral sclerosis
- polio
- spinal muscular atrophy
- Guillain-Barré syndrome
- ataxias
- myasthenias
- inflammatory myopathies

Precautions

No special precautions are needed for this test. Persons with a history of bleeding disorder should consult with their treating physician before the test. If a muscle **biopsy** is planned as part of the diagnostic workup, EMG should not be performed at the same site, as it may affect the microscopic appearance of the muscle. Also, persons on blood thinners should relay this information to the physician performing the EMG.

Description

During an EMG test, a fine needle is inserted into the muscle to be tested. This may cause some discomfort, similar to that of an injection. Recordings are made while the muscle is at rest, and then during the contraction. The person performing the test may move the limb being tested, and direct the patient to move it with various levels of force. The needle may be repositioned in the same muscle for further recording. Other muscles may be tested as well. A typical session lasts from 30–60 minutes, with individual muscles usually studied for a period of two to five minutes.

A slightly different test, the "nerve conduction velocity test," is often performed at the same time with the same equipment. In this test, stimulating and recording electrodes are used and small electrical shocks are applied to measure the ability of the nerve to conduct electrical signals. This test may cause mild tingling and discomfort similar to a mild shock from static electricity. Evoked potentials may also be performed for additional diagnostic information. Nerve conduction velocity and evoked potential testing are especially helpful when pain or sensory complaints are more problematic than weakness.

Preparation

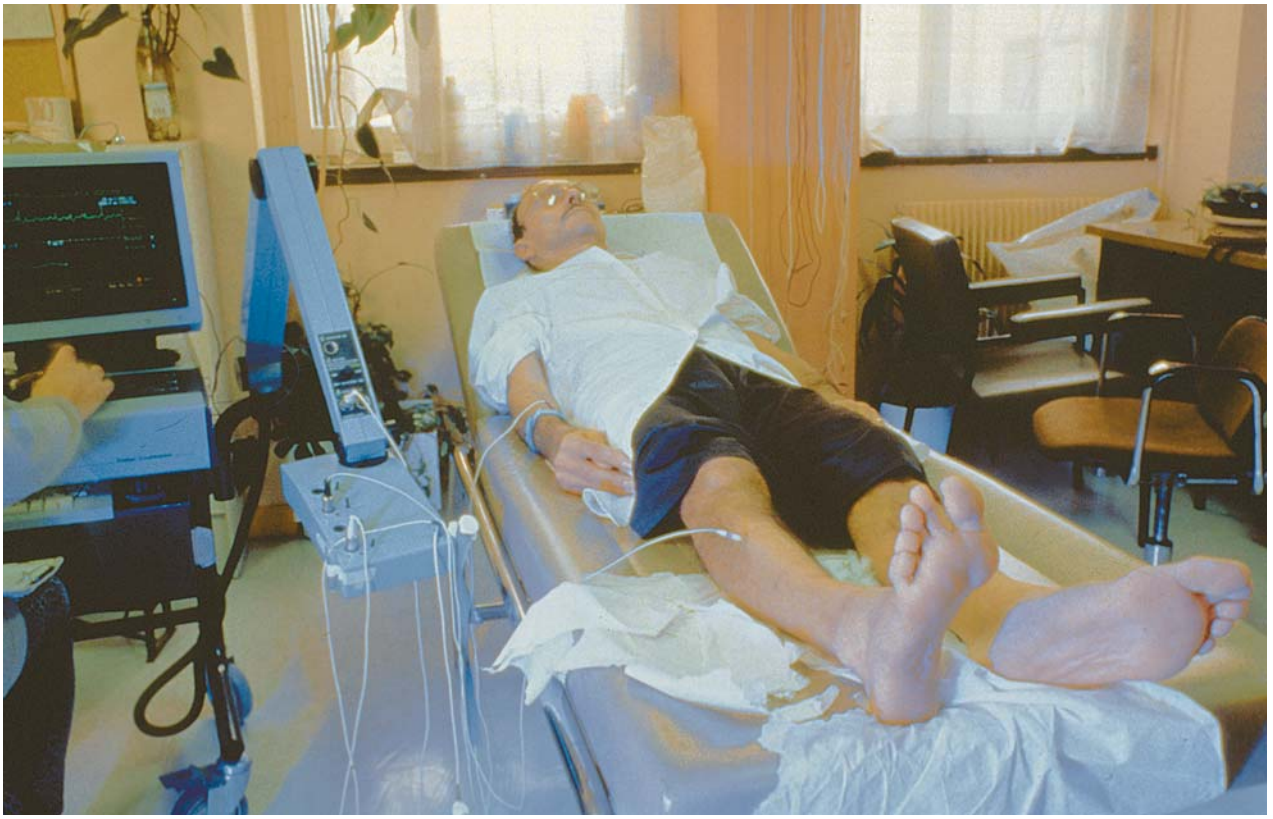
No special preparation is needed. The doctor supervising and interpreting the test should be given information about the symptoms, medical conditions, suspected diagnosis, neuroimaging studies, and other test results.

Aftercare

Minor pain and bleeding may continue for several hours after the test. The muscle may be tender for a day or two.

Risks

There are no significant risks to this test, other than those associated with any needle insertion (pain, bleeding, bruising, or infection).



Patient undergoing electromyography. *(Custom Medical Stock Photo. Reproduced by permission.)*

Key Terms

Motor neurons Nerve cells that transmit signals from the brain or spinal cord to the muscles.

Motor unit action potentials Spikes of electrical activity recorded during an EMG that reflect the number of motor units (motor neurons and the muscle fibers they transmit signals to) activated when the patient voluntarily contracts a muscle.

Normal results

There should be some brief EMG activity during needle insertion. This activity may be increased in diseases of the nerve and decreased in long-standing muscle disorders in which muscle tissue is replaced by fibrous tissue or fat. Muscle tissue normally shows no EMG activity when at rest or when moved passively by the examiner. When the patient actively contracts the muscle, spikes (motor unit action potentials) should appear on the recording screen, reflecting the electrical activity within. As the muscle is contracted more forcefully, more groups of muscle fibers are recruited or activated, causing more EMG activity.

The interpretation of EMG results is not a simple matter, requiring analysis of the onset, duration, amplitude, and other characteristics of the spike patterns.

Electrical activity at rest is abnormal; the particular pattern of firing may indicate denervation (for example, a nerve lesion, **radiculopathy**, or lower motor neuron degeneration), myotonia, or **inflammatory myopathy**.

Decreases in the amplitude and duration of spikes are associated with muscle diseases, which also show faster recruitment of other muscle fibers to compensate for weakness. Increases in the amplitude and duration of the spikes are typical of nerve diseases in which some degree of reinnervation (repair by new nerve connections to muscle) has occurred. Recruitment is reduced in nerve disorders.

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Richard Robinson

Empty sella syndrome

Definition

Empty sella syndrome is the appearance, by radiograph (x ray) of the skull, that the sella turcica, which normally contains the pituitary gland, is empty.

Description

Sella turcica is Latin for "Turkish saddle," which roughly describes the U–shaped appearance of this bony pocket when seen by x ray. It is a concavity in the middle of the sphenoid bone measuring about $1.5 \times 1.0 \times 0.5$ cm. The sphenoid bone forms a portion of the base of the skull just behind the eyes, at about the midpoint and just below the cerebral hemispheres.

The pituitary gland has a bulbous shape, extending on a stalk below the hypothalamus. The pituitary normally completely fills the sella turcica. The subarachnoid space, filled with cerebrospinal fluid (CSF), surrounds the pituitary stalk. The dura mater (see **Meninges**) normally extends away from the bony upper portion of the sella turcica forming a barrier between the subarachnoid space and the pituitary gland below. This barrier formed by the dura mater surrounding the top of the pituitary gland is known as the diaphragma sella.

In most cases when an empty sella is seen by x ray, the sella turcica is not truly empty. In fact, CSF has entered the space normally occupied by the pituitary and has compressed the gland against the wall of the sella. A truly empty sella, i.e., missing pituitary gland, is rare.

Demographics

The true incidence of empty sella syndrome in the population is not known. However, statistics collected from autopsies have shown that an empty sella is found as an incidental finding in anywhere from 5% to 25% of cases. These do not include cases in which the pituitary gland was surgically removed or irradiated.

Most cases of empty sella syndrome are seen in middle–aged, obese women, who often have hypertension. Children with empty sella syndrome are more often symptomatic, which most often manifests as growth hormone deficiency. About half of children with growth hormone deficiency are found to have an empty sella, but only 2% of children with normal pituitary function have the finding.

Causes and symptoms

Primary empty sella syndrome is thought to be congenital (present at birth) in most cases, and is caused by a failure or opening of the diaphragma sella. This may be an accidental occurrence, with no known triggering or causative factors. In some cases the sella turcica may grow larger than normal.

Secondary empty sella (acquired) may be caused by a medical procedure, such as surgery or **radiation** for a pituitary tumor. Disease or trauma may also reduce the size of the pituitary, or eliminate it completely. Abnormally low production of one or more pituitary hormones is known as hypopituitarism. A specific type of acquired empty sella syndrome associated with hypopituitarism, known as Sheehan's syndrome, is caused by infarction (loss of blood supply) of the pituitary brought on by shock or hemorrhage after labor and delivery. In cases of acquired empty sella, the condition is a byproduct of some other process.

Probably less than 10% of individuals with primary empty sella syndrome have some symptoms of hypopituitarism. Symptoms related to secondary empty sella syndrome would be those of the underlying cause, except in the case of empty sella syndrome due to trauma.

Hypopituitarism can result in one or more of the following:

- Hypothyroidism. Decreased production of the thyroid gland, which can result in diminished metabolism, intolerance of cold temperatures, **fatigue**, mental and physical sluggishness, constipation, muscle aches, dry skin, and dry hair.
- Hypogonadism. Decreased production of sex hormones, which can result in loss of pubic hair, decreased sex drive, impotence in men, and amenorrhea (absence of menstrual cycle) in women.

Key Terms

Cerebrospinal fluid The clear, normally colorless fluid that fills the brain cavities (ventricles), the subarachnoid space around the brain, and the spinal cord and acts as a shock absorber.

Hypopituitarism A condition characterized by underactivity of the pituitary gland.

Pituitary gland The most important of the endocrine glands (glands that release hormones directly into the bloodstream), the pituitary is located at the base of the brain. Sometimes referred to as the "master gland," it regulates and controls the activities of other endocrine glands and many body processes including growth and reproductive function. Also called the hypophysis.

- Hypoadrenalism. Decreased production of the adrenal gland, which can result in low blood pressure and hypoglycemia (low blood sugar).

Diagnosis

Other than those cases detected directly at autopsy (usually incidentally), empty sella syndrome is always diagnosed by some type of imaging study of the brain (x ray, **CT scan**, or **MRI**). Again, in many of these cases the empty sella is detected as a coincidental finding on an imaging study ordered for some other reason. Only occasionally is the diagnosis made because empty sella syndrome was suspected from some type of endocrinological abnormality suggesting hypopituitarism.

Treatment

Treatment of symptomatic empty sella syndrome would typically involve replacement therapy for any deficient hormones. For instance, hypothyroidism would require treatment with synthetic thyroid hormone, hypoadrenalism could be treated with steroids (cortisol), and hypogonadism might require sex hormone replacement therapy. Treatment of endocrinological dysfunction can be especially difficult because of the complicated way in which the many hormones of the body interact with and affect each other. In addition, all treatments for empty sella syndrome would be symptomatic treatments; there is no method to restore the pituitary gland to its normal size.

Prognosis

In most cases in which hypopituitarism accompanies empty sella syndrome, treatment for the symptoms would be lifelong. In all cases in which disease or medical intervention has reduced or eliminated the pituitary gland, there is no method of completely restoring normal pituitary function. Replacement therapies are effective when well-managed. However, even someone with optimum therapy is unlikely to feel completely "well," in relation to normal pituitary function, all of the time.

Special concerns

Symptoms of empty sella syndrome may be subtle, and may mimic other conditions. Since an accurate diagnosis of empty sella syndrome requires imaging studies of the brain, there is a risk that the condition could be misdiagnosed, or go undiagnosed.

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Encephalitis and meningitis

Definition

Encephalitis is an acute inflammatory process that affects brain tissue and is almost always accompanied by inflammation of the adjacent **meninges** (tissues lining the brain). There are many types of encephalitis, most of which are caused by viral infections.

Meningitis is an inflammation of the membranes (meninges) that surround the brain and spinal cord. Meningitis may be caused by many different viruses and bacteria, or by diseases that can cause inflammation of tissues of the body without infection (such as systemic **lupus** erythematosus). Viral meningitis is sometimes called aseptic meningitis to indicate it is not the result of a bacterial infection.

Description

Encephalitis can be divided into two forms, primary and secondary encephalitis, according to the two methods by which the viruses infect the brain. Primary encephalitis occurs when a virus directly invades the brain and spinal cord. Primary encephalitis can happen to people at any time of the year (sporadic encephalitis), or can be part of an outbreak (epidemic encephalitis). Secondary, or post-infectious encephalitis occurs when a virus first infects another organ and secondarily enters the brain.

Meningitis is an inflammation of the membranes that surround the brain and spinal cord, and may be caused by many different viruses and bacteria, or by non-infectious inflammatory diseases. Encephalitis is a distinct disease from meningitis, although, clinically, the two often share signs and symptoms of inflammation of the meninges.

Demographics

Determining the true incidence of encephalitis in the United States is difficult because reporting policies are neither standardized nor rigorously enforced. Several thousand cases of viral encephalitis are reported yearly. HSE (herpes simplex encephalitis), the most common cause of sporadic encephalitis in other western countries, is still relatively rare in the United States, with an overall incidence of two cases per one million persons per year.

Arboviruses (viruses transmitted to humans by blood-sucking insects such as mosquitoes and ticks) are the most common causes of episodic encephalitis. These statistics may be misleading because most people bitten by arbovirus-infected insects do not develop clinical disease, and only 10% of those develop overt encephalitis. Among less common causes of viral encephalitis, varicella-zoster encephalitis (a complication of the condition commonly known as **shingles**) has an incidence of one in 2000 infected people.

Internationally, Japanese virus encephalitis (JE), occurring principally in Japan, Southeast Asia, China, and India, is the most common viral encephalitis outside the United States.

In 1995, there were 5755 cases of bacterial meningitis reported in United States. This is a dramatic decrease from the 12,920 cases reported in 1986, probably due to the decrease in *Haemophilus influenzae* meningitis since the introduction of the Hib vaccine. The occurrences by infectious agents in 1995 are as follows:

- *Streptococcus pneumoniae*: 1.1 per 100,000 persons
- *Neisseria meningitides*: 0.6 per100,000 persons
- *Streptococcus*: 0.3 per 100,000 persons
- *Listeria monocytogenes*: 0.2 per 100,000 persons
- *Haemophilus influenzae*: 0.2 per 100,000 persons

The incidence of meningitis in newborns has shown no significant change in the last 25 years. Viral meningitis is the most common form of aseptic meningitis and, since the introduction of the mumps vaccine, is caused by enteroviruses in up to 85% of cases. The incidence of encephalitis is more difficult to estimate because of difficulty in establishing the diagnosis. One report estimates an incidence of one in 500–1,000 infants and in the first six months of life.

Causes and symptoms

Causes

The causes of encephalitis are usually infectious, but may also be due to some noninfectious causes. Three broad categories of viruses—herpes viruses, viruses responsible for childhood infections, and arboviruses (viruses harbored by mosquitoes and ticks, and transferred through their bite)—typically trigger encephalitis.

ENCEPHALITIS AND HERPES VIRUSES Some herpes viruses that cause common infections may also cause encephalitis. These include:

- Herpes simplex virus. There are two types of herpes simplex virus (HSV) infections. HSV type 1 (HSV-1) causes cold sores or fever blisters around the mouth. HSV type 2 (HSV-2) causes genital herpes. HSV is the most common cause of sporadic encephalitis, with HSV-1 being the more common culprit. When untreated, the mortality rate from herpes simplex encephalitis is between 60–80%. That number drops to 15–20% with treatment.
- Varicella-zoster virus. This virus is responsible for chicken pox and shingles. It can cause encephalitis in adults and children, but the cases tend to be mild.
- Epstein-Barr virus. This herpes virus causes infectious mononucleosis. If encephalitis develops, it's usually mild, but more severe forms can result in death in up to 8% of cases.

ARBOVIRUSES The mosquito season varies according to geographic location. Arbovirus transmission, therefore, also varies according to season, the cycle of viral transmission, and local climatic conditions. Six encephalitis disease groups caused by arboviruses are monitored by the United States Centers for Disease Control (CDC) and include:

- St. Louis encephalitis
- West Nile encephalitis

Key Terms

Arboviruses Viruses harbored by arthropods (mosquitoes and ticks) and transferred to humans by their bite. Arboviruses are one cause of encephalitis.

Electroencephalogram A procedure that uses electrodes on the scalp to record electrical activity of the brain. Used for detection of epilepsy, coma, and brain death.

Encephalitis Inflammation of the brain.

Meningitis Inflammation of the meninges, the membranes that surround the brain and spinal cord.

Pathogen A disease-causing organism.

Seizure A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

- Powassan encephalitis
- Eastern equine encephalitis
- Western equine encephalitis
- California serogroup viral encephalitis, which includes infections with the following viruses: La Crosse, Jamestown Canyon, snowshoe hare, trivittatus, Keystone, and California encephalitis viruses.

OTHER CAUSES OF ENCEPHALITIS Bacterial pathogens (disease-causing organisms), such as rickettsial disease, mycoplasma, and cat scratch disease, are rare, but often involve inflammation of the meninges. Encephalitis can be due to parasites and fungi. Insects, such as mosquitoes in the eastern and southeastern United States can also spread encephalitis.

CAUSES OF MENINGITIS Viral meningitis is the most common infection of the **Central Nervous System** (CNS). It most frequently occurs in children younger than one year of age. Enteroviruses (viruses that causes infections of the gastrointestinal tract) are the most common causative agent and are a frequent cause of febrile illnesses in children. Other viral pathogens include paramyxoviruses, herpes, influenza, rubella, and adenovirus. Meningitis may occur in up to half of children younger than three months with enteroviral infections. Enteroviral infections can occur any time during the year, but are normally associated with outbreaks in the summer and fall. Viral infections cause an inflammatory response, but to a lesser degree than bacterial infections. Damage from viral meningitis may be due to an associated encephalitis and increased intracranial pressure.

Bacterial meningitis is fairly uncommon, but can be extremely serious. There are two main types of bacterial meningitis, which cause most of the reported bacterial cases: meningococcal and pneumococcal. *Haempohilus influenzae* type b (Hib), which was recently a major cause of bacterial meningitis, has now been almost eliminated by the vaccination of infants. The most common causative organisms in the first month of life are *Escherichia coli* and group B streptococci. *Listeria monocytogenes* infection also occurs in patients in this age range and accounts for 5–10% of cases. In people older than two months, *S. pneumoniae* and *N. meningitides* currently cause the majority of the cases of bacterial meningitis. *H. influenzae* may still occur, especially in children who have not received the Hib vaccine.

Symptoms

Symptoms of encephalitis include sudden fever, **headache**, vomiting, heightened sensitivity to light, stiff neck and back, confusion and impaired judgment, drowsiness, weak muscles, a clumsy and unsteady gait (manner of walking), bulging in the soft spots (fontanels) of the skull in infants, and irritability. More severe or late symptoms include loss of consciousness, **seizures**, muscle weakness, or sudden severe **dementia**.

Symptoms of meningitis, which may appear suddenly, often include high fever, severe and persistent headache, stiff neck, nausea, and vomiting. Changes in behavior such as confusion, sleepiness, and difficulty waking up are extremely important symptoms and may require emergency treatment.

In infants, symptoms of meningitis may include high-pitched cry, moaning cry, whimpering, dislike of being handled, fretfulness, arching of the back, neck retraction, blank, staring expression, difficulty in waking, lethargia, fever, cold hands and feet, refusing to feed or vomiting, pale, blotchy skin color. In adults, symptoms of meningitis may include vomiting, headache, drowsiness, seizures, high temperature, joint **pain**, stiff neck, and aversion to light.

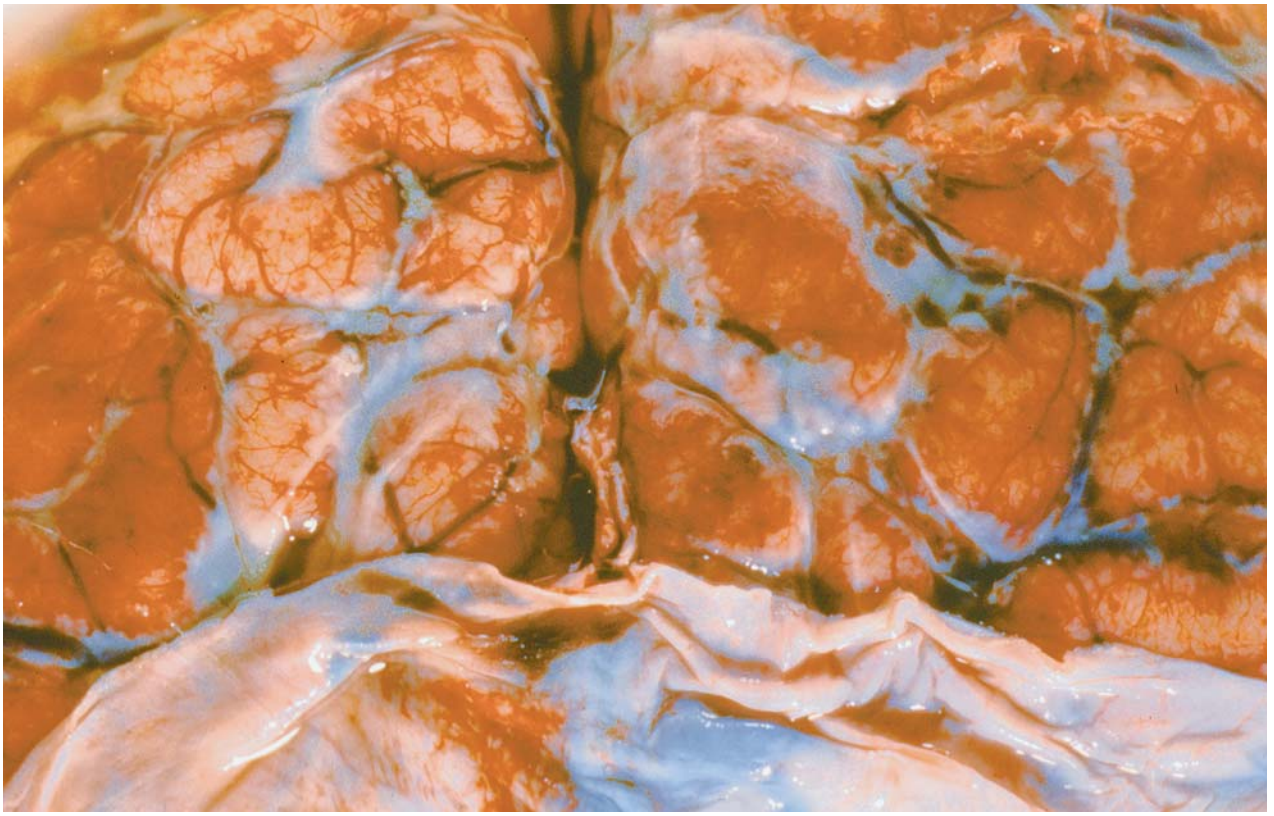
Arboviral infections may be asymptomatic or may result in illnesses of variable severity. Arboviral meningitis is characterized by fever, headache, and stiff neck. Arboviral encephalitis is characterized by fever, headache, and altered mental status that ranges from confusion to coma. Signs of brain dysfunction such as numbness or paralysis, cranial nerve palsies, visual or hearing deficits, abnormal reflexes, and generalized seizures may also be present.

Diagnosis

Encephalitis or meningitis is suspected by a physician when the symptoms described above are present. The physician diagnoses encephalitis or meningitis after a careful examination and testing. The examination includes special maneuvers to detect signs of inflammation of the membranes that surround the brain and spinal cord (meninges). Tests that are used in the evaluation of individuals suspected of having encephalitis or meningitis include blood counts, blood cultures, coagulation studies, bacterial antigen studies of urine and serum, brain scanning, and spinal fluid analysis.

The most common method of diagnosing encephalitis and meningitis is to analyze the cerebrospinal fluid surrounding the brain and spinal cord. A needle inserted into lower spine extracts a sample of fluid for laboratory analysis, which may reveal the presence of an infection or an increased white blood cell count, a signal that the immune system is fighting an infection. The cerebrospinal fluid may also be slightly bloody if small hemorrhages have occurred. Diagnosis of herpes simplex encephalitis can be difficult, but advances using sensitive DNA methods have allowed detection of the virus in spinal fluid.

Electroencephalography (EEG) measures the waves of electrical activity produced by the brain. It is often used



Occipital lobes of brain with acute meningitis. Dura mater has been reflected from surface of brain, revealing intensely discolored red (hyperemic) arachnoid mater and subarachnoid pus (white-gray purulent material). The patient, a three-and-a-half-year-old boy, was well except for an upper respiratory infection with cough one day prior to death. *(Joseph R. Siebert. photograph. © Custom Medical Stock Photo. Reproduced by permission.)*

to diagnose and manage seizure disorders. A number of small electrodes are attached to the scalp. The patient remains still during the test and at times may be asked to breathe deeply and steadily for several minutes or to stare at a patterned board. At times, a light may be flashed into eyes. These actions are meant to stimulate the brain. The electrodes pick up the electrical impulses from brain and send them to the EEG machine, which records the brain waves on a moving sheet of paper. An abnormal EEG result may suggest some of diseases, but a normal result does not rule them out.

Brain imaging, using computed tomography (CT) or **magnetic resonance imaging (MRI)** may reveal swelling of brain. These techniques may reveal another condition with signs and symptoms that are similar to encephalitis, such as a concussion.

Rarely, if diagnosis of herpes simplex encephalitis isn't possible using DNA methods or by CT or MRI scans, a physician may take a small sample of the brain tissue, or **biopsy**, for analysis to determine if the virus is present. Physicians usually attempt treatment with antiviral medications before suggesting brain biopsy.

Blood testing can confirm the presence of West Nile virus in the body by drawing a sample of blood for laboratory analysis. When infected with West Nile virus, an analysis of blood sample may show a rising level of an antibody against the virus, a positive DNA test for the virus or a positive virus culture.

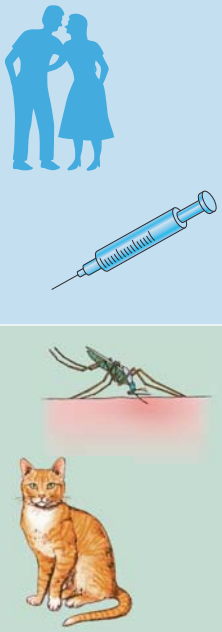
Treatment team

The treatment team may include a pediatrician or a general practitioner, an infectious disease specialist and/or a critical care specialist, a neurosurgeon, a **neurologist** or a neonatologist. Others professionals may give support during hospitalization for intravenous antibiotics or other specific procedures.

Treatment

Treatment for meningitis depends on the cause and on the symptoms. Antiviral medications may be used if a virus is involved. Antibiotics are prescribed for bacterial infections. If the causative organism is unknown, antibiotic regimes can be based on the child's age. In infants

Causes of Encephalitis	How Spread
Enteroviruses	Contact with body fluids
Herpes simplex virus	Person to person contact
HIV (human immunodeficiency virus)	When an infected person's blood or body fluids are introduced into the bloodstream of a healthy person
Arboviruses	Bites from mosquitoes that pick up the virus from infected birds, chipmunks, squirrels, or other animals
Animal-borne illnesses	Bites from infected animals such as cats, dogs, and bats



(Illustration created by Frank Forney.)

aged 30 days or younger, ampicillin is usually prescribed along with an aminoglycoside or a cephalosporin (cefotaxime) medication. In children aged 30–60 days, ampicillin and a cephalosporin (ceftriaxone or cefotaxime) can also be used. However, since *S. pneumoniae* occasionally occurs in this age range, vancomycin should be part of treatment instead of ampicillin. In older children, cephalosporin or ampicillin plus chloramphenicol can be used. Often, rifampicin is given (in meningococcal bacterial meningitis cases) as a preventative measure to roommates, close family members, or others who may have come in contact with an infected person.

In addition, anticonvulsant medications may be used if there are seizures. Corticosteroids may be needed to reduce brain swelling and inflammation. Dexamethasone is usually indicated for children with suspected meningitis who are older than six weeks and is recommended for treatment of infants and children with *H. influenzae* meningitis. Sedatives may be needed for irritability or restlessness and over-the-counter medications may be used for fever and headache.

Until a bacterial cause of CNS inflammation is excluded, the treatment should include parenteral (given by injection) antibiotics. Treatment with a third-generation cephalosporin antibiotic, such as cefotaxime sodium (Claforan) or ceftriaxone sodium (Rocephin), is usually recommended. Vancomycin (Lyphocin, Vancocin, Vancoled) should be added in geographic areas where strains of *S. pneumoniae* resistant to penicillin and cephalosporins have been reported.

Encephalitis can be difficult to treat because the viruses that cause the disease generally don't respond to many medications. The exceptions are herpes simplex virus and varicella-zoster virus, which respond to the antiviral drug acyclovir, and is usually administered intravenously in the hospital for at least ten days.

Treatment is available for many symptoms of encephalitis. Patients with headache should rest in a quiet, dark environment and take analgesics. Narcotic therapy may be needed for pain relief; however, medication induced changes in level of consciousness should be avoided. Anticonvulsant medication and anti-inflammatory drugs to reduce swelling and pressure within the skull are usually prescribed. Otherwise, treatment mainly consists of rest and a healthy diet including plenty of liquids.

Recovery and rehabilitation

As opposed to many untreatable neurological conditions, encephalitis and meningitis are diseases that, given the adequate treatment described above, often resolve with

complete recovery. It is very important that the disease's cause is promptly identified and treated before any complication is irreversibly established. Physical and speech therapy are often helpful when neurological deficits remain, as are occupational therapists and audiologists.

Clinical trials

The National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Neurological Disorders and Stroke (NINDS) support and conduct research on encephalitis and meningitis. Much of this research is aimed at learning more about the cause(s), prevention, and treatment of these disorders. Ongoing **clinical trials** as of early 2004 include:

- Valacyclovir for long-term therapy of Herpes simplex encephalitis; IVIG—West Nile encephalitis: Safety and Efficacy; Structure of the Herpes Simplex Virus Receptor; sponsored by National Institute of Allergy and Infectious Diseases
- Natural History of **West Nile Virus Infection**; Omr-IgG-am™ for Treating Patients with or at High Risk for West Nile Virus Disease; sponsored by Warren G. Magnuson Clinical Center
- Intrathecal Gemcitibine to Treat Neoplastic Meningitis; Intrathecal Gemcitabine in Treating Patients with Cancer and Neoplastic Meningitis; sponsored by Baylor College of Medicine

Updated information on clinical trials can be found at the National Institutes of Health clinical trials website at www.clinicaltrials.org.

Prognosis

The prognosis for encephalitis varies. Some cases are mild, short and relatively benign and patients have full recovery. Other cases are severe, and permanent impairment or death is possible. The acute phase of encephalitis may last for one to two weeks, with gradual or sudden resolution of fever and neurological symptoms. Neurological symptoms may require many months before full recovery. Prognosis for people with viral meningitis is usually good.

With early diagnosis and prompt treatment, most patients recover from meningitis. However, in some cases, the disease progresses so rapidly that death occurs during the first 48 hours, despite early treatment. Permanent neurological impairments including memory, speech, vision, hearing, muscle control, and sensation difficulties can occur in people who survive severe cases of meningitis and encephalitis.

The prognosis for appropriately treated meningitis has improved, but there is still a 5% mortality rate and significant morbidity (lasting impairment). The prognosis varies with the age of the person, clinical condition, and infecting organism.

Special concerns

A person's exposure to mosquitoes and other insects that harbor arboviruses can be reduced by taking precautions when in a mosquito-prone area. Insect repellents containing DEET provide effective temporary protection form mosquito bites. Long sleeves and pants should be worn when outside during the evening hours of peak mosquito activity. When camping outside, intact mosquito netting over sleeping areas reduces the risk of mosquito bites. Communities also employ large-scale spraying of pesticides to reduce the population of mosquitoes, and encourage citizens to eliminate all standing water sources, such as in bird baths, flower pots, and tires stored outside to eliminate possible breeding grounds for mosquitoes.

Although large epidemics of meningococcal meningitis do not occur in the United States, some countries experience large, periodic outbreaks. Overseas travelers should check to see if meningococcal vaccine is recommended for their destination. Travelers should receive the vaccine at least one week before departure, if possible. A vaccine to prevent meningitis due to *S. pneumoniae* (also called pneumococcal meningitis) can also prevent other forms of infection due to *S. pneumoniae.* The pneumococcal vaccine is not effective in children under two years of age, but it is recommended for all individuals over 65 years of age and younger people with certain chronic medical conditions.

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ORGANIZATIONS

Meningitis Foundation of America, Inc. 7155 Shadeland Station Suite 190, Indianapolis, Indiana 46256-3922. (317) 595-6383 or (800) 668-1129; Fax: (317) 595-6370. support@musa.org. <http://www.musa.org/>.

National Institute of Allergy and Infectious Diseases (NIAID). 31 Center Drive, Rm. 7A50 MSC 2520, Bethesda, Maryland 20892-2520. (301) 496-5717. <http://www.niaid.nih.gov/>.

Centers for Disease Control and Prevention (CDC), Division of Vector-Borne Infectious Diseases. P.O. Box 2087, Fort Collins, Colorado 80522. (800) 311-3435. dvbid@cdc.gov. <http://www.cdc.gov/ncidod/dvbid/index.htm>.

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Encephalitis lethargica

Definition

Encephalitis lethargica is an inflammation of the brain caused by two trypanosomes (microscopic protozoan parasites). The illness, which can be fatal, is transmitted from one infected person to another by the tsetse fly. While it can occur globally, encephalitis lethargica is especially prevalent in Africa.

Description

Encephalitis lethargica is a vector-borne disease, meaning it is transmitted to a susceptible person by a living creature. The tsetse fly lives in moist vegetation near lakes and rivers and in grassy areas. People living near these regions are most susceptible the bite of a tsetse fly infected with the trypasosomes that cause encephalitis lethargica. The disease is also known as African trypanosomiasis, sleeping sickness, sleepy sickness, and von Economo's disease. Another form of the trypanosome-borne disease that occurs in North, Central, and South America is called Chagas disease.

Other subspecies of the trypanosome parasite can infect animals such as cattle, who can also harbor the trypanosomes that are infectious to humans.

Demographics

The form of encephalitis lethargica known as African trypanosomiasis occurs only in the sub-Saharan area of Africa. Tsetse flies are endemic in this region. However, for as yet unknown reasons, there are regions where tsetse flies are found, but the disease is absent. There have been several epidemics in Africa in the nineteenth and twentieth centuries. From 1896–1906, Uganda and the Congo basin were affected. A more wide-ranging epidemic occurred in 1920. Finally, an epidemic that began in 1970 is still occurring.

The latest epidemic is a result of the relaxed surveillance for the disease that happened with the near-eradication of the disease in the 1960s. As of 2004, the disease is a threat to more than 60 million people in 36 sub-Saharan African countries. In 1999, nearly 45,000 cases were reported, according to the World Health Organization (WHO). These cases represent individuals who were able to seek treatment and receive a definitive diagnosis at local health care centers. The actual number of cases was likely much higher, with estimates ranging from 300,000–500,000 cases actually occurring. In Africa, the disease occurs primarily in rural areas, where health care is least available. Poverty and encephalitis lethargica are associated with one another.

Causes and symptoms

The disease is caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense.* The first species is found in central and West Africa. The infection is chronic; it persists for months or years with no display of symptoms. When they do emerge, the disease is at an advanced stage and the symptoms are more severe. *T. brucei rhodesiense* is found primarily in southern and eastern Africa. It causes an infection whose symptoms appear quickly (acute infection). This disease is more severe. Fortunately, the rapid appearance of symptoms offers more of a chance for quick detection.

Both trypanosomes are transferred to the tsetse fly when the fly obtains a blood meal from an infected person. The trypanosomes then multiply in the blood of the fly, and can be transferred to a susceptible person on whom the fly subsequently feeds.

The early symptoms of the disease include fever, severe **headache**, joint **pain**, and swelling of the lymph nodes. These symptoms can disappear and reoccur. Later, symptoms of what is called the neurological phase emerge and often include the characteristic symptoms of the disease: extreme weakness, paralysis of eye muscles, sleepiness, disruption of the sleep cycle, and a lapse into a deep and fatal coma. Transmission of the trypanosomes across the placenta from a pregnant woman to the fetus can occur. Typically this causes spontaneous abortion or death of the fetus.

Diagnosis

The most useful diagnostic sign is swollen cervical glands. This indicates the presence of the parasite. Populations can be screened for clinical signs of the disease (the

Key Terms

Encephalitis Inflammation of the brain, usually caused by a virus. The inflammation may interfere with normal brain function and may cause seizures, sleepiness, confusion, personality changes, weakness in one or more parts of the body, and even coma.

Parasite An organism that lives and feeds in or on another organism (the host) and does nothing to benefit the host.

Vector-borne disease A disease that is delivered from one host to another by a vector or carrier organism.

early phase symptoms) and the use of tests that detect antibodies to the parasite in the blood. An early diagnostic sign of the bite of the tsetse fly is the appearance of a painful red sore (chancre) at the site of the bite.

A type of diagnosis called phase diagnosis can be used to help determine the level of advancement of the disease. Cerebro-spinal fluid is obtained by the technique of lumbar puncture and analyzed. Phase diagnosis requires medical and laboratory staff, and is typically done in a clinic. The long period, symptom-free period of a Trypanosoma brucei gambiense infection can complicate and delay diagnosis.

Treatment team

Physicians and nurses are the primary team involved in treating encephalitis lethargica. Additionally, public health workers in Africa and other areas affected with the tsetse fly receive help from health agencies throughout the world, who provide aid and strategies to reduce populations of the fly, educate local peoples to bite prevention methods, and treat affected individuals. Warring factions, with resulting political instability and hunger in the Sub-Saharan region of Africa have led to difficulty in controlling the spread of the tsetse fly and the disease.

Treatment

The choice of treatment depends on whether the disease is detected earlier or later in the infection. Early-stage infections can be treated using two drugs; suramine and pentamidine. An agreement between the World Health Organization and the drug's manufacturer (Aventis) has guaranteed continued production of the compounds.

Treatment of the later, neurological symptoms requires a drug that can cross the blood-brain barrier to reach the parasite. Currently only one drug (melarsoprol) is commercially available. The drug causes harsh side effects and itself has a fatal complication rate approaching 10%. As well, resistance of the trypanosomes to the drug is increasing. A second drug (eflornithine) exists, but is not commercially available. It is active only against *Trypanosoma brucei gambiense.* There is no vaccine for the disease.

Recovery and rehabilitation

Recovery from the early stage of the disease can be complete. Recovery from the neurological stage is typically incomplete, with varying degrees of impaired brain function often resulting. Once the person reaches the stage of coma, the disease is invariably fatal.

Clinical trials

As of early 2004, there were no **clinical trials** in progress for the study of encephalitis lethargica. Rather, efforts to increase screening of susceptible populations and to increase the supply of drugs is the identified priority for scientists working with the disease.

Prognosis

If treated early, a person with encephalitis lethargica can be cured. If not treated early, the prognosis is much less favorable due to resulting brain damage. Encephalitis lethargica is fatal if untreated.

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Centers for Disease Control and Prevention (CDC). 1600 Clifton Road, Atlanta, GA 30333. (404) 639-3311 or (800) 311-3435. <http://www.cdc.gov>.

World Health Organization (WHO). Avenue Appia 20, 1211 Geneva, Geneva, Switzerland. +41 22 791 21 11; Fax: +41 22 791-3111. info@who.int. <http://www.who.int>.

Brian Douglas Hoyle, PhD

Key Terms

Cerebrospinal fluid A clear fluid that is produced in the ventricles of the brain and circulates around and within the brain and spinal cord.

Neural tube defect A birth defect caused by abnormal closure or development of the neural tube, the embryonic structure that gives rise to the central nervous system.

Teratogen A substance that has been demonstrated to cause physical defects in the developing human embryo.

Encephaloceles

Definition

Encephaloceles refers to defects in the development of a fetal structure called the neural tube. The tube fails to close completely during development of the fetus, resulting in portions of the brain and its surrounding membranes that protrude from the skull in sac-like formations. Often, normal brain function is impaired and children with encephaloceles experience delays in development.

Description

In normal fetal development, the neural tube forms by the closure of the neural structure. When this does not occur in the case of an encephalocele, the result is a groove. The groove can form down the middle region of the upper part of the skull, or between the forehead and the nose, or down the back of the skull. The incomplete closure also creates areas where the brain and its overlaying membrane can bulge outward in sac-like protrusions. The larger deformities, in particular those that occur at the back of the skull, are readily evident and are recognized very soon after birth. These deformities are also associated with abnormal structure and functioning of the brain. Some encephaloceles are less evident, even to the point of being undetectable at birth. Defects in the region of the forehead and nose are examples.

Demographics

Encephaloceles occur rarely. At a rate of one per 5,000–10,000 live births, an encephalocele is less common than **spina bifida**, another neural tube defect. Geographical differences occur with respect to the type of encephalocele. Malformation of the back portion of the head is more common in Europe and North America, whereas involvement of the front portion of the head occurs more frequently in Southeast Asia, Malaysia, and Russia.

Causes and symptoms

The exact cause of encephaloceles is not yet known. The disorder is passed on from generation to generation, and is more prevalent in families where there is a history of spina bifida. It is clear that one or more genetic abnormalities lie at the heart of the condition. However, fetal development is an extremely complex process, with interactions between various genes, and influence of the external environment determining which genes are activated at which time. Thus, pinning down the crucial genes whose expression or changed activity produces abnormal neural tube formation is a difficult task.

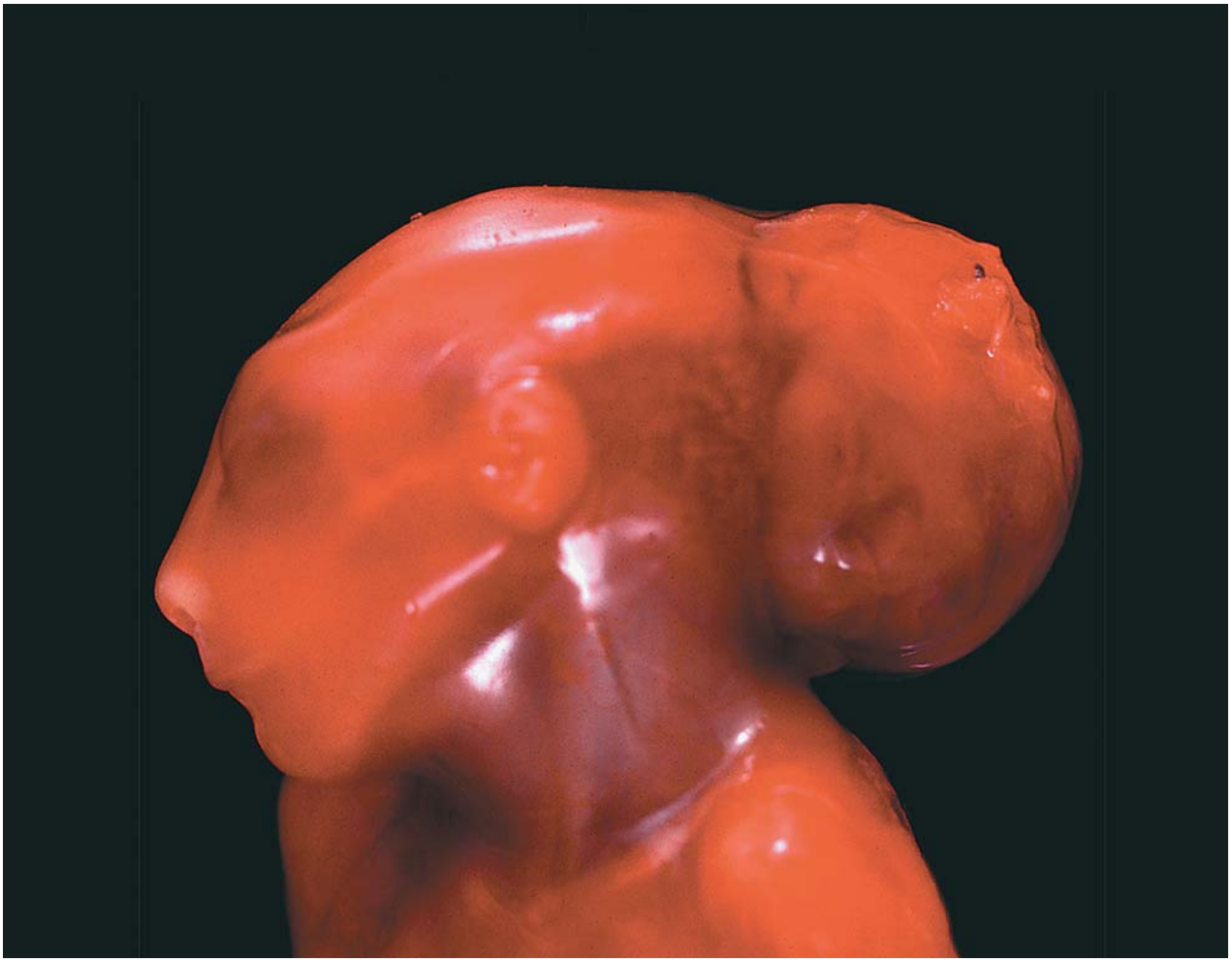
Research using animal models has shown that teratogens, compounds like x rays, trypan blue, and arsenic, which can damage the developing fetus, cause encephaloceles in the animals. Whether exposure of a human fetus to such agents contributes to encephalocele formation in humans is not known.

Most often, the symptoms of encephaloceles are not difficult to recognize. These include the excessive build-up of cerebrospinal fluid in the brain (a condition called **hydrocephalus**), paralyzed arms and legs (spastic quadriplegia), an abnormally small head (**microcephaly**), difficulty in tasks like walking and reaching because of a lack of coordination (**ataxia**), delayed or impaired mental and physical development (although intelligence is not always affected), problems with vision, and **seizures**.

If the bulging portion contains only cerebrospinal fluid and the overlaying membrane, the malady can also be called a cranial meningocele or a meningocele. If brain tissue is also present, the malady can also be referred to as an encephalomeningocele.

Diagnosis

Diagnosis is based at the discovery of the physical abnormalities at birth or sometime later, and on the failure to attain the various physical and mental developmental milestones that are a normal part of early life.



Encephalocele, a brain formation growing outside the skull, on a 16-week-old fetus. *(© Siebert/Custom Medical Stock Photo. Reproduced by permission.)*

Treatment team

Medical treatment involves family physicians, neurosurgeons, and nurses. Special education professionals, physical therapists, and caregivers are also an important part of the treatment team, as an affected person may require assistance in everyday activities throughout life.

Treatment

Treatment typically involves surgery. The surgery is usually accomplished soon after birth, and re-positions the bulging brain back into the skull, removes any of the sac-like protrusions, and corrects the skull deformities. Often, shunts are placed during surgery to drain excess cerebrospinal fluid from the brain. While delicate, the operation typically relieves the pressure that would otherwise impede normal brain development. Other treatment involves dealing with specific symptoms and producing as comfortable and satisfying everyday life as is possible.

Recovery and rehabilitation

Prospects for recovery are difficult to predict prior to surgery. Nonetheless, if surgery is successful, and other developmental difficulties have not occurred, an individual can develop normally. Where neurological and developmental damage has occurred, the focus shifts from recovery to maximizing mental and physical abilities.

Clinical trials

As of April 2004, no clinical trails for specific study of encephaloceles were being conducted. However, research is underway to more clearly define the mechanisms of brain development, and several **clinical trials** related to

neural tube defects are recruiting participants. Updated information can be found at the National Institutes of Health clinical trials website at: http://clinicaltrials.gov.

Prognosis

As for recovery and rehabilitation, the prognosis is varies and cannot be predicted beforehand. In general, when the bulging material consists of mainly cerebrospinal fluid, a complete recovery can occur 60–80% of the time. However, the presence of brain tissue in the protruding material can reduce the chances of a complete recovery considerably.

Special concerns

Folic acid, a B vitamin, has been shown to help prevent neural tube defects when taken before and in early pregnancy. The March of Dimes organization and the United States Public Health Service recommend that all women who may become pregnant take a multi-vitamin that contains 400 micrograms of folic acid every day.

Resources

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ORGANIZATIONS

Birth Defect Research for Children. 930 Woodcock Road, Suite 225. Orlando, FL 22808. (407) 895-0802 or (800) 313-2232; Fax: (407) 895-0824.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605. (914) 428-7100 or (888) 663-4637; Fax: (914) 428-8203. askus@marchofdimes.com. <http://www.marchofdimes.com>.

National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD, 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders. 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Brian Douglas Hoyle, PhD

Encephalopathy

Definition

Encephalopathy is a condition characterized by altered brain function and structure. It is caused by diffuse brain disease.

Description

Encephalopathy may be caused by advanced and severe disease states, infections, or as a result of taking certain medications. The three main causes of encephalopathy are liver disease, kidney disease, and lack of oxygen in the brain. The associated symptoms can include subtle personality changes, inability to concentrate, lethargy, progressive loss of memory and thinking abilities, progressive loss of consciousness, and abnormal involuntary movements. Symptoms vary with the severity and type of encephalopathy.

Encephalopathy may vary in severity from only subtle changes in mental state to a more advanced state that can lead to deep coma. Cerebral edema is a common manifestation of severe encephalopathy, which causes an increase in intracranial pressure. The major related causes of death include sepsis, circulatory collapse, and brain failure related to a syndrome encompassing cerebral edema, damaged blood-brain-barrier, increased intracranial pressure, brainstem herniation, and/or neurotoxins leaking into the brain and killing brain cells. Additionally, patients with severe encephalopathy usually develop intracranial hypertension, which can produce cerebral ischemia injury and cerebral herniation.

Demographics

There is no statistical information available for encephalopathy per se. Encephalopathy can occur at any age and there seems to be no gender or racial predilection, because encephalopathy is a manifestation of a primary illness.

Causes and symptoms

Causes

There is a wide variety of conditions that cause encephalopathy. Encephalopathy can be caused by infections (bacteria, viruses, or prions); lack of oxygen to the brain; liver failure; kidney failure; alcohol/drug overdose; prolonged exposure to toxic chemical (solvents, paints, industrial chemicals, drugs, **radiation**); metabolic diseases; brain tumor; increased intracranial pressure; and poor nutrition.

HYPOXIC ENCEPHALOPATHY Hypoxic encephalopathy refers to a lack of oxygen to the entire brain, which

Key Terms

Cerebral herniation Movement of the brain against the skull.

Cerebral ischemia Lack of oxygen to the brain, which may result in tissue death.

Encephalogram Machine that detects brain activity by measuring electrical activity in the brain.

Intracranial hypertension Increase in pressure in the brain.

typically results in brain damage. Cerebral **hypoxia** can be caused by drowning, low blood pressure, birth injuries, cardiac arrest, strangulation, asphyxiation caused by smoke inhalation, severe hemorrhage, carbon monoxide poisoning, high altitudes, choking, tracheal compression, complications of anesthesia, paralysis of respiratory muscles, and respiratory failure.

Cardiac arrest is the most common condition that causes cerebral hypoxia. When the heart stops pumping, oxygen-rich blood cannot be delivered to vital organs such as the brain. Hypoxia to the brain causes irreversible brain damage after two minutes.

HEPATIC ENCEPHALOPATHY Hepatic encephalopathy refers to a condition of brain and nervous system damage caused by liver (hepatic) failure. Diseases that damage the liver causing impairment of the detoxification and functional capabilities of the liver can cause hepatic encephalopathy. Examples of disorders that decrease liver function are hepatitis or cirrhosis. Impairment in the detoxification capabilities of the liver causes accumulation of toxic chemicals in the blood such as ammonia, in addition to many other impurities that all collectively cause damage to the nervous system.

KIDNEY FAILURE The main function for the kidneys is to eliminate excess fluid and waste material from the blood. When the kidneys lose the ability to filter the blood, dangerous levels of waste products accumulate in the body. Chronic renal failure can be caused by diabetes, analgesic nephropathy (due to long-term use of aspirin or nonsteroidal anti-inflammatory drugs), kidney diseases (polycystic kidney disease, pyelonephritis, and glomerulonephritis), renal artery stenosis (a narrowing of the artery that supplies blood to the kidneys), and lead poisoning.

SEVERE INFECTIONS Severe infections, especially those that affect the brain, can cause encephalopathy. Infections that specifically target the brain are encephalitis, which is inflammation of the brain, typically caused by a virus, or meningitis, which is inflammation of the tissue that surrounds and protects the brain.

CHRONIC ALCOHOL USE Long-term use of alcohol not only causes destruction of brain cells but can cause cirrhosis of the liver or hepatitis, which results in the destruction of liver cells. Chronic alcoholism leads to progressive destruction of liver cells, which can cause end-stage liver failure. A subtype of hepatitis infection called hepatitis C typically causes progressive destruction to liver cells.

UREMIC ENCEPHALOPATHY Uremia describes the final stage of progressive renal insufficiency, which culminates in end-stage kidney failure with neurologic involvement. This is called uremic encephalopathy. The cause is unknown and no single metabolite or toxin is responsible for symptoms, but rather it is an accumulation of several chemicals/toxins in the blood that causes symptoms of encephalopathy.

Symptoms

The hallmark of encephalopathy is altered mental state. In mild cases, hypoxia can cause an altered mental state, which includes symptoms such as motor incoordination, poor judgment, and inattentiveness. Mild cases have no lasting effects. Patients who have severe hypoxia or anoxia (total lack of oxygen delivery, usually from cardiac arrest) lose consciousness within seconds. Other symptoms of encephalopathy include lethargy, nystagmus (rapid, involuntary eye movement), tremor, **dementia**, **seizures**, **myoclonus** (involuntary twitching of a muscle or group of muscles), muscle weakness and atrophy, and loss of ability to speak or swallow. An early and characteristic feature of hepatic encephalopathy is called constitutional **apraxia**, which is inability to reproduce simple designs such as a star. Patients with liver failure may exhibit a symptom called asterixis, an involuntary jerking tremor of the hands.

Diagnosis

The diagnosis of encephalopathy depends on the presence of acute or chronic liver disease; altered mental state such as confusion, stupor, or coma; symptoms of **central nervous system** damage; and abnormal wave patterns on an encephalogram. Diagnostic tests that may be utilized to establish the diagnosis include, but are not to limited to: complete blood count; liver function tests; ammonia and glucose levels; lactate levels (often elevated due to impaired tissue perfusion and because of decreased clearance by the liver); arterial blood gases (may reveal hypoxemia); kidney function tests; blood cultures (to detect infectious agents); virology testing (for hepatitis); neuroimaging studies; and ultrasound studies.

Treatment team

The causes of encephalopathies are broad. Additionally, the symptoms are also broad, ranging from mild changes of consciousness to coma or death. Therefore, the treatment team can consist of a broad spectrum of specialists that can include, but is not limited to, an internist, oncologist, pulmonologist, critical care physician, radiologist, hepatologist (specialist in liver diseases), and surgeon. The disorder can also occur in the pediatric ages or even at birth. In these critical situations, specialists in pediatric critical care, a neonatologist, and a perinatologist (specialist in maternal-fetal health) would be involved.

Treatment

Hypoxia or anoxic encephalopathy is an emergency, and immediate measures are necessary to prevent further damage to the brain and to restore breathing and circulation. It is necessary to treat hepatic encephalopathy early to prevent long-term damage. Specific treatment for hepatic encephalopathy is aimed at eliminating toxic substances and/or treatment of the primary illness that caused encephalopathy. Elimination of toxins such as ammonia can be accomplished by decreasing absorption of protein from the gut. By giving the patient a compound called lactulose, absorption of ammonia can be decreased. Persons with hepatic encephalopathy should not consume protein, and constipation should be avoided. Uremic encephalopathy caused by chronic renal failure is treated with transplantation or dialysis.

Recovery and rehabilitation

Recovery is an emergency for all patients with severe hypoxia or anoxia. Vital functions such as breathing, cardiac function, and delivery of oxygen-rich blood to the brain should be restored within two to five minutes. If anoxia persists for more than two minutes, there will be permanent and severe damage to the brain.

Clinical trials

There are four active government-sponsored **clinical trials** that are recruiting patients. There is a phase III clinical trial concerning birth asphyxia (hypoxic-ischemic encephalopathy) in infants up to six hours old. A phase II clinical trial is investigating the neuroimaging findings associated with persistent encephalopathy caused by the tick-transmitted infection called Lyme's disease (persistent Lyme encephalopathy). A third study is investigating a genetic form of familial dementia that causes encephaolpathy due to neurodegeneration of brain tissue. A fourth study investigates a disorder called neuronal ceroid lipofuscinosis (NCLS), which is a common heritable form of encephaopathy that occurs in one of 12,500 children. Detailed information about each of these studies can be obtained online from the website <http://www.clinicaltrials.gov>.

Prognosis

The outcome for patients who present with symptoms of encephalopathy depends on the cause. If the cause can be corrected in time, the outcome can be favorable. However, if encephalopathy is a manifestation of more advanced chronic disease, or if it is part of a rapidly fulminating disorder, the outcome can be poor and death may ensue due to the primary cause.

Special concerns

Persons who present with encephalopathy have advanced disease or the beginning of an advanced disease process. Vigilance on the part of the primary care provider is necessary to take all precautions to prevent this process.

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ORGANIZATIONS

National Institute of Neurological Disorders and Stroke NIH Neurological Institute. P.O. Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

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Encephalotrigeminal angiomatosis *see* **Sturge-Weber syndrome**

Endovascular embolization

Definition

Endovascular embolization is a procedure that utilizes chemical agents or metallic coils to stop bleeding and treat **aneurysms** or brain tumors.

Purpose

The purpose is either to cut off blood supply or to fill a sac (also creating a thrombus). Endovascular embolization is a procedure used to treat hemorrhage, cranial tumors, or aneurysms. The procedure can be life saving. Bleeding can be stopped in cases of trauma, epistaxis (nosebleed), coughing up blood from the lungs (hemoptysis), gastrointestinal bleeding, hemorrhage to solid organs, and postcesarean, postoperative, or postpartum bleeding in the abdomen or pelvis. Additionally, endovascular embolization is used to cut off the blood supply to cranial tumors which eventually causes tumor cell destruction and tumor mass shrinkage from lack of oxygen and nourishment. The procedure can also be utilized for packing an aneurysm with coils, to prevent rupture and possible death from intracranial hemorrhage.

Precautions

Embolization is an indication for treatment of many clinical entities. The procedure is performed under general anesthesia and elective cases require pre-procedural evaluation with an anesthesiologist. The procedure requires a brief inpatient stay for one to two days. Dietary restrictions and medical work-up are usually indicated before elective surgery (i.e., cranial tumors). If an aneurysm or tumor cannot be safely embolized, the procedure is terminated. For bleeding, the procedure may likely be an emergency.

Description

Embolization is a useful procedure in a broad spectrum of clinical disorders. Typically embolization for any reason begins with a diagnostic **angiography** procedure to identify the source of the problem. The diagnostic angiography is usually performed in an artery. A catheter is usually inserted into the groin artery and dye is injected into the system. The catheter is wiggled through to the desired location using a television monitor. The target area may be a region where there is bleeding or it may be an aneurysm or cranial tumor. Once at the target area, chemicals or metal coils (for an aneurysm) are introduced by a microcatheter. In the case of an aneurysm, soft metal coils are placed with a microcatheter in the aneurysm until it is packed with about five to six coils. Filling the aneurysm will prevent blood flow into the aneurysm sac, since the sac is filled with coils and a thrombus after the procedure. Endovascular embolization can help to stop bleeding or rebleeding for patients who are hemorrhaging. For cranial tumors the goal is to inject emboli in blood vessels that nourish brain tumors. This causes destruction of the tumor mass due to lack of blood supply. For any reason, when a blood vessel requires embolization, coils are the instrument of choice.

Preparation

Routine blood tests are done one to two days before an elective embolization. For scheduled procedures the patient should not eat or drink liquids after midnight the night before the procedure. The procedure is usually performed in a neuroangiography unit. A nurse will shave the patient's groin area since the catheter is inserted in the groin artery (also called the femoral artery). Emergency preparation may be initiated for persons who are actively bleeding.

Aftercare

After elective embolization, patients are taken to a neurosurgical intensive care unit or a step-down unit for close monitoring and recovery. It is necessary to lie flat for eight hours after the procedure to allow the groin area (where the catheter was inserted) to heal. Usually the next day the patient will be transferred to a regular ward room and discharged to home the following day.

Risks

The risk of embolization is low. Possible complications include weakness in an arm or leg, dysesthesia, speech or visual deficits, and **stroke**.

Normal results

Normal results depend on the indications for the procedure. For bleeding the desired goal is rapid cessation of bleeding source. Aneurysm will likely develop saccular occlusion (occlusion of the aneurysm sac), reducing the risk of rupture and fatal intracranial hemorrhage. The desired effect for an intracranial tumor is obliteration of tumor vasculature, which eventually causes destruction of the tumor mass, secondary to oxygen deprivation.

Resources

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WEBSITES

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Key Terms

Aneurysm A sac formed by dilatation of an arterial wall.

Dysesthesia Painful feeling of numbness and tingling.

Endovascular Embolization of Cranial Tumors. University of North Carolina at Chapel Hill. <http://www.cs.unc.edu/Research/intel/brain.html>.

Endovascular Embolization Treatment of Aneurysms. The University of Toronto. <http://nrainavm.uhnres.utoronto.ca/malformations/content/treat_embo_aneurysm.htm>.

ORGANIZATIONS

International Radiosurgery Support Association. PO Box 5186, Harrisburg, PA 17110. (717) 260-9808; Fax: (717) 260-9809. getinfo@irsa.org. <http://www.irsa.org>.

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Epidural hematoma

Definition

An epidural hematoma is a pocket of blood that forms immediately outside the dura mater. The dura mater is the fibrous outermost sheath or membrane that encloses the brain and spinal cord. Epidural means outside the dura, and hematoma means mass of blood.

Description

Epidural hematomas usually form when a violent blow breaks a blood vessel in the space outside the dura mater, whether in the skull or in the spinal column. In the skull, the vessel most often responsible for epidural hematoma is the middle meningeal artery.

Blood from the broken vessel forms a pressurized pocket of blood, like a large, internal blood blister. The growing hematoma pushes against the rigid bone of the skull or spinal column and thus exerts pressure on the dura mater, which in turn pushes on the brain or spinal cord. This pressure may stretch and tear blood vessels or even force the brain to herniate (i.e., partially squeeze out) through the foramen magnum, the hole in the bottom of the skull through which the spinal cord enters, or through the tentorium cerebelli, the part of the dura mater that covers the **cerebellum** and supports the occipital lobes from below. Herniation of the brain is likely to be fatal.

Epidural hematomas are less common than subdural hematomas, which are the most common mechanism of fatal brain damage in head trauma. They are also distinguished from intracranial hematomas, volumes of blood that collect inside the brain rather than at its surface.

Demographics

Traumatic brain injuries such as those that can result in cranial epidural hematoma are common. About 500,000 patients are admitted to hospitals in the United States annually with head injuries that cause brain damage, and some 75,000–90,000 of these patients die. Motor vehicle accidents are the most common cause of closed-head injuries, accounting for 50–70% of such injuries. Falls are the second most common cause of closed head trauma. Alcohol is a contributing factor in about 40% of severe head injuries. Sports such as football can result in traumatic head injury, but do so relatively rarely. Three-quarters of patients with **traumatic brain injury** are male, and the risk of traumatic brain injury declines steadily with age.

Epidural hematoma occurs in about 1% of all patients with severe head injuries. The fraction of comatose head-injury patients with **subdural hematoma** is greater, but still only about 10%.

Causes and symptoms

Intracranial subdural hematoma

The most common cause of cranial epidural hematoma is head trauma, which is some kind of blow to the head. Epidural hematomas are most commonly found in the temporal or temporoparietal region, i.e., along the sides of the brain. Patients often lose consciousness due to the original head trauma, regain consciousness and undergo a period of clear-mindedness, then deteriorate neurologically.

Spinal epidural hematoma

Trauma is a common cause of spinal epidural hematoma. Non-trauma causes include anticoagulant therapy, hemophilia, liver disease, aspirin use, systemic **lupus** erythematosus, and, rarely, lumbar puncture. In 40–50% of cases of spinal epidural hematoma, no precipitating trauma or other cause is observed; these cases are considered spontaneous.

Spinal epidural hematoma causes compression of the spinal cord. Symptoms vary with the amount and location of this pressure. **Back pain** may be slight or absent. The patient may have loss of feeling (anesthesia) or less-than-normal feeling (hypoesthesia) in the legs, arm, or trunk. There may be weakening of the legs and loss of deep tendon reflexes. There may be bowel and bladder dysfunction

Key Terms

Dura mater The tough, fibrous outermost layer of the three meninges that surround the brain and spinal cord.

Hematoma A bruise or collection of blood within soft tissue that results in swelling.

(e.g., incontinence or inability to control the bladder or bowels).

Diagnosis

Neurologic assessment is the first step in determining the severity of a head injury. The patient's speech, eye-opening, and muscular responses are evaluated, along with the orientation (if conscious) to place, time, and commands to open eyes or the like. If the patient is unconscious, examination of the pupillary light reflex is important. An epidural or other hematoma increases intracranial pressure, which quickly has an effect on the third cranial nerve, which contains, among other nerve fibers, those that control constriction of the pupil. Pressure that blocks this nerve leads to fixed dilation of the pupil. Fixed pupil dilation in one or both eyes is a strong indicator that the patient may have an intracranial hematoma. To distinguish between epidural, subdural, and intracranial hematoma, computerized tomography (**CT**) or **magnetic resonance imaging (MRI)** is probably necessary. Surgeons determine if swelling on one side of the brain has shifted the midline of the brain. If a shift of more than 0.2 in (5 mm) is found, an emergency **craniotomy** (opening of the skull) may be performed.

Patients with spinal epidural hematoma may experience sudden onset of back or neck **pain** at the site of the bleed. Coughing or any other maneuver that increases pressure inside the torso may worsen the pain transiently. In children, the bleeding is more likely to be in the cervical (neck) region than in the thoracic (middle back) region.

When making the diagnosis of spinal epidural hematoma, physicians must decide whether the symptoms of spinal compression are being caused by a hematoma or by a tumor. CT or MRI are definitive in distinguishing between compression of the spinal cord caused by tumor or hematoma.

Treatment team

Treatment for hematoma is primarily surgical. A **neurologist** and a neurosurgeon will be essential members of the treatment team, as will nursing staff, in the operating room and out of it, who are specially trained in head trauma care.

Treatment

Emergency care for spinal trauma consists of immobilizing the patient and administering high-dose corticosteroids. However, the highest priority for any intracranial or spinal hematoma is relief of the pressure by surgical drainage of the hematoma.

Recovery and rehabilitation

Epidural hematoma can result in permanent paralysis or other neurological deficits. If spinal cord compression due to hematoma is alleviated within 6–12 hours, permanent symptoms may be avoided. Prevention of brain damage depends more on preventing the brain from being deformed by the pressure of the hematoma than on relieving that pressure. Rehabilitation needs will depend on how much permanent damage, if any, has been caused.

Clinical trials

As of 2004, no **clinical trials** were being conducted for epidural hematoma patients in the United States.

Resources

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Larry Gilman

Epilepsy

Definition

The words "epilepsy" and "epileptic" are of Greek origin and have the same root as the verb "epilambanein," which means "to seize" or "to attack." Therefore, epilepsy

means seizure, while epileptic means seized. In the modern understanding of epilepsy, it should not be considered a disease. Rather, it is a symptom indicating a medical condition in the brain that causes a potential for recurrent **seizures**. The condition of epilepsy has many causes and the kinds of seizures that occur can vary widely.

Key Terms

Automatisms Movements during a seizure that are semi-purposeful but involuntary.

Gelastic seizures Seizures manifesting with brief involuntary laughter.

Gray matter The portion of the brain that contains neurons, as opposed to white matter, which contains nerve tracts.

Spike wave discharge Characteristic abnormal wave pattern in the electroencephalogram that is a hallmark of an area that has the potential of generating a seizure.

Description

The word epilepsy is actually a descriptive term. It takes into account an individual's risk of recurrent seizures. However, when people are suffering from meningitis and have a seizure, they would not be considered to have epilepsy unless they had a seizure after the meningitis resolved. In this case, these individuals have a risk for recurrent seizures and, hence, epilepsy. If an individual over time does not have any seizures off medications, then it could be said that epilepsy has resolved or gone into remission.

For thousands of years, epilepsy was looked upon differently than most other medical problems. Because of this, epilepsy has been fraught with social stigmas, even up to today. The ancient Greeks knew about the condition that led to a sudden attack upon the unfortunate. Although Hippocrates, in roughly 400 B.C., referred to epilepsy as the sacred disease, he did so to emphasize the general public's superstitious view of the condition. Of course, it certainly was not an affliction sent from a deity, nor was it even a demon. Nevertheless, seizures, which manifest in unusual behaviors, mystified observers who considered this illness, from all others, as coming from another world.

The current understanding of epilepsy is a recent development. Previously, it was not even believed that the brain had electrical properties. It was not until the last few centuries that the brain was considered the seat of the mind; it was the heart or the lungs that were commonly regarded as the organ of thought. Physicians struggled with what to even call a seizure. In general, any behavior that resulted in a loss of consciousness or convulsions was labeled a seizure. It is likely that episodes of **fainting** were erroneously called seizures.

Finally, in 1873, an adequate definition for the term seizure finally came into existence. The famous English **neurologist** John Hughlings Jackson explained epilepsy as "a sudden, excessive, and rapid discharge of gray matter of some part of the brain" that would correspond to the patient's experience.

Demographics

More than 2.5 million Americans suffer from epilepsy, and more than another 50 million worldwide. Epilepsy is more common than **Parkinson's disease**, **multiple sclerosis**, **cerebral palsy**, and **muscular dystrophy** all combined. The risk of experiencing one seizure in the course of a lifetime, from any cause, is close to 10%. However, there is an approximately 1% chance of developing epilepsy in the general population before the age of 20. The risk increases to 3% by age 75. Of course, depending on the age group being studied, the cause of epilepsy will vary. The incidence of epilepsy is relatively constant among different ethnic groups and similar between genders. However, there may be variation in incidence in underdeveloped countries due to access to care and endemic illness that can cause seizures, such as neurocystercercosis in Latin American countries.

Causes and symptoms

Epilepsy has many causes that, in part, have an affect on the clinical presentation of symptoms. In order for epilepsy to occur, there must be an underlying physical problem in the brain. The problem can be so mild that an individual is perfectly normal other than seizures. The brain has roughly 50–100 billion neurons. Each neuron can have up to 10,000 contacts with neighboring neurons. Hence, trillions of connections exist. However, only a very small area of dysfunctional brain tissue is necessary to create a persistent generator of seizures and, hence, epilepsy. The following are potential causes of epilepsy:

- genetic and/or hereditary
- perinatal neurological insults
- trauma with brain injury
- **stroke**
- brain tumors
- infections such as meningitis and encephalitis
- multiple sclerosis
- ideopathic (unknown or genetic)

Any of the above conditions have the potential for causing the brain or a portion of it to be dysfunctional and produce recurrent seizures. Regardless of the exact cause, epilepsy is a paroxysmal (sudden) condition. It involves the synchronous discharging of a population of neurons. This is an abnormal event that, depending on the location in the brain, will correspond to the particular symptoms of a seizure. The International League Against Epilepsy (ILAE) issued a classification of types of seizures. The list gives the kind of seizures that can occur. Individual seizure types are based on the clinical behavior (semiology) and electrophysiological characteristics as seen on an electroencephalogram (EEG). Generalized seizures included in the list are:

- tonic-clonic seizures (includes variations beginning with a clonic or myoclonic phase)
- clonic seizures, including without tonic features and with tonic features
- typical absence seizures
- atypical absence seizures
- myoclonic absence seizures
- tonic seizures
- spasms
- myoclonic seizures
- eyelid myoclonia, including without absences and with absences
- myoclonic atonic seizures
- negative **myoclonus**
- atonic seizures
- reflex seizures in generalized epilepsy syndromes

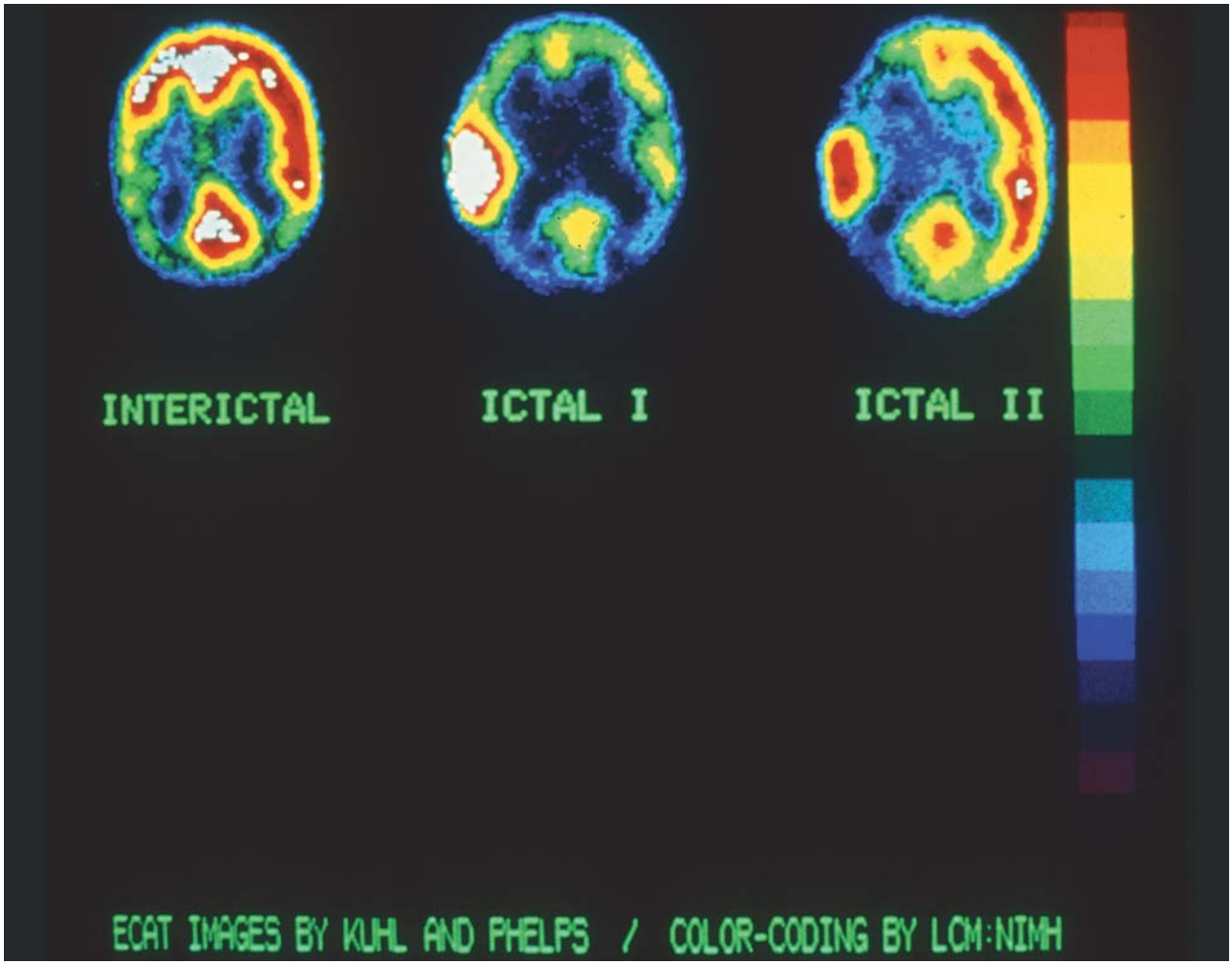
Focal seizures included in the ILAE list are:

- focal sensory seizures with elementary sensory symptoms (e.g., occipital and parietal lobe seizures) and experiential sensory symptoms (e.g., temporo-parieto-occipital junction seizures)
- focal motor seizures with elementary clonic motor signs, asymmetrical tonic motor seizures (e.g., supplementary motor seizures), typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures), hyperkinetic automatisms, focal negative myoclonus, and inhibitory motor seizures
- gelastic seizures
- hemiclonic seizures
- secondarily generalized seizures
- reflex seizures in focal epilepsy syndromes

In 1989, the International League Against Epilepsy also issued the following classification of epilepsies and epileptic syndromes:

- benign familial neonatal seizures
- early myoclonic encephalopathy
- Ohtahara syndrome
- migrating partial seizures of infancy (syndrome in development)
- West syndrome
- benign myoclonic epilepsy in infancy
- benign familial and non-familial infantile seizures
- Dravet's syndrome
- HH syndrome
- myoclonic status in nonprogressive encephalopathies (syndrome in development)
- benign childhood epilepsy with centrotemporal spikes
- early onset benign childhood occipital epilepsy (Panayiotopoulos type)
- late-onset childhood occipital epilepsy (Gastaut type)
- epilepsy with myoclonic absences
- epilepsy with myoclonic-astatic seizures
- **Lennox-Gastaut syndrome**
- Landau-Kleffner syndrome (LKS)
- epilepsy with continuous spike-and-waves during slow-wave sleep (other than LKS)
- childhood absence epilepsy
- progressive myoclonus epilepsies
- idiopathic generalized epilepsies with variable phenotypes include juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures only
- reflex epilepsies
- idiopathic photosensitive occipital lobe epilepsy
- other visual sensitive epilepsies
- primary reading epilepsy
- startle epilepsy
- autosomal dominant nocturnal frontal lobe epilepsy
- familial temporal lobe epilepsies
- generalized epilepsies with **febrile seizures** plus (syndrome in development)
- familial focal epilepsy with variable foci (syndrome in development)
- symptomatic focal epilepsies
- limbic epilepsies
- mesial **temporal lobe epilepsy** with hippocampal sclerosis
- mesial temporal lobe epilepsy defined by specific etiologies
- neocortical epilepsies
- Rasmussen syndrome

Classifying epilepsy can help in the evaluation and management of patients with seizure disorders. The combination of seizure type(s), etiology (cause), age of onset,



PET scans of a human brain during the stages of an epileptic seizure; the middle image represents the most severe period of the seizure. *(© Photo Researchers, Inc. Reproduced by permission.)*

family history, and other medical or neurological conditions can be used to identify an epilepsy syndrome. Classification helps clinicians and researchers understand the broader picture of seizure disorders. On a practical level, syndrome identification can help in planning the management of patients. Syndrome classification schemes are revised periodically as individual components of particular categories are better understood.

The term idiopathic refers to a cause that is suspected to be, if not genetic, then unknown. Cryptogenic is a term that suggests that an underlying cause is suspected, but not yet fully understood. Symptomatic is a term that is applied to epilepsies that are a result of understood underlying pathologies.

The management and prognosis vary considerably among these differing syndromes. Epilepsies that have a genetic basis can be inherited or occur spontaneously. A detailed family history can often identify other family members who have had seizures. However, because seizures are common, it is possible to have more than one family member with epilepsy, though the etiologies may not be related. To say that a particular type of epilepsy is genetic does not mean that it is necessarily transmitted by heredity. Often, disorders can have a genetic cause, but be spontaneously occurring in only one member of a family. In this case, there may simply be a random mutation in that particular person's genes.

There are several mechanisms in which epilepsies can be inherited. So-called simple Mendelian inheritance occurs with benign familial neonatal convulsions and autosomal dominant nocturnal frontal lobe epilepsy. On the other hand, complex inheritance mechanisms can involve more than one gene, or a gene mutation in combination with environmental or acquired factors such as juvenile

myoclonic epilepsy. As the genetics of the epilepsies become better understood, the classification scheme will evolve.

With epilepsy, symptoms vary considerably depending on the type. The common link among the epilepsies is, of course, seizures. The different epilepsies can sometimes be associated with more than one seizure type. This is the case with Lennox-Gastaut syndrome.

Diagnosis

Arriving at a diagnosis of epilepsy is relatively straightforward: when people suffer two or more seizures, they would be considered to have epilepsy. However, diagnosing the specific epilepsy syndrome is much more complex. The first step in the evaluation process is to obtain a very detailed history of the illness, not only from the patient but from the family as well. Since seizures can impair consciousness, the patient may not be able to recall the specifics of the attacks. In these cases, family or friends that have witnessed the episodes can fill in the gaps about the particulars of the seizure. The description of the behaviors during a seizure can go a long way to categorizing the type of seizure and help with the overall diagnosis. Moreover, in the initial visit with the physician, the entire history of the patient is obtained. In a child, this would include birth history, complications, if any, maternal history, and developmental milestones. At any age, so-called co-morbidities (other medical problems) are considered. Medications that have been taken or currently being prescribed are documented.

A complete physical examination is performed, especially a neurological exam. Because seizures are an episodic disorder, abnormal neurological findings may not be present. Frequently, people with epilepsy have a normal exam. However, in some, there can be abnormal findings that can provide clues to the underlying cause of epilepsy. For example, if someone has had a stroke that subsequently caused seizures, then the neurological exam can be expected to reveal a focal neurological deficit such as weakness or language difficulties. In some children with seizures, there can be a variety of associated neurologic abnormalities such as **mental retardation** and cerebral palsy that are themselves non-specific but indicate that the brain has suffered, at some point in development, an injury or malformation. Also, subtle findings on examination can lead to a diagnosis such as in **tuberous sclerosis**. This is an autosomal dominantly inherited disorder associated with **infantile spasms** in 25% of cases. On examination, patients have so-called ash-leaf spots and adenoma sebaceum on the skin. There can also be a variety of systemic abnormalities that involve the kidneys, retina, heart, and gums, depending on severity.

In the course of evaluating epilepsy, a number of tests are typically ordered. Usually, magnetic resonance image (**MRI**) of the brain is obtained. This is a scan that can help in finding many known causes of epilepsy such as tumors, strokes, trauma, and congenital malformations. However, while MRI can reveal incredible details of the brain, it cannot visualize the presence of abnormalities in the microscopic neuronal environment. Another test that is routinely ordered is an electroencephalogram (EEG). Unlike the MRI scan, this can be considered a functional test of the brain. The EEG measures the electrical activity of the brain. Some seizure disorders or epilepsies have a characteristic EEG with particular abnormalities that can help in diagnosis. Other tests that are frequently ordered are various blood tests that are also ordered in many medical conditions. These blood tests help to screen for abnormalities that can be a factor in the cause of seizures. Occasionally, genetic testing is performed in those instances where a known genetic cause is suspected and can be tested. A major concern in the course of an evaluation of epilepsy is to identify the presence of life-threatening causes such as brain tumors, infections, and cerebrovascular disease. Also, an accurate diagnosis can expedite the most effective treatment plan.

The symptoms of epilepsy are dependent in part on the particular seizures that occur and other medical problems that may be associated. Seizures, themselves, can take on a variety of features. A simple sustained twitching of an extremity could be a focal seizure. If a seizure arises in the occipital lobes of the brains, then a visual experience can occur. Aura is a term often used to describe symptoms that a person may feel prior to the loss of consciousness of a seizure. However, auras are, themselves, small focal seizures that have not spread in the brain to involve consciousness. Smells, well-formed hallucinations, tingling sensations, or nausea have each occurred in auras. The particular sensation can be a clue as to the location in the brain where a seizure starts. Focal seizures can then spread to involve other areas of the brain and lead to an alteration of consciousness, and possibly convulsions. In certain epilepsy syndromes such as Lennox-Gastaut, there can be more than one type of seizure experienced, such as atonic, atypical absence, and tonic-axial seizures.

Treatment

One challenge in predicting the course of epilepsy is that for any type, there can be a variable response to treatment. Sometimes, seizures may play a rather small role in the manifestation of a medical condition. For example, a severe head injury could result in seizures that readily respond to medication, but severe neurological impairments and disabilities may still be present. On the other hand, a

different head injury may result in relatively mild neurological problems, but there may be seizures that are severe and be resistant to medications.

Whatever the case, the ultimate goals when treating epilepsy are to:

- strive for complete freedom from seizures
- have little to no side effects from medications
- be able to follow an easy regimen so that compliance with treatment can be maintained

Up to 60% of patients with epilepsy can be expected to achieve control of seizures with medication(s). However, in the remaining 40%, epilepsy appears to be resistant, to varying degrees, to medications. In these cases, the epilepsy is termed medically intractable.

Generally, the choice of medication is somewhat trial and error. There are, however, a number of considerations that guide the choice of treatment. Each medication has a particular side effect profile and mechanism of action. Some medications seem to be particularly effective for certain epilepsy syndromes. For example, juvenile myoclonic epilepsy responds well to valproic acid. On the other hand, ethosuxamide is primarily used for absence seizures.

As with any medication, individuals can have very different experiences with same drug. Consequently, it is difficult to predict the efficacy of treatment in the beginning. A key concept of treatment is to first strive for monotherapy (or single drug therapy). This simplifies treatment and minimizes the chance of side effects. Sometimes, however, two or more drugs may be necessary to achieve satisfactory control of seizures. As with any treatment, potential side effects can be worse than the disease itself. Moreover, there is little point in controlling seizures if severe side effects limit quality of life. If a seizure disorder is characterized by mild, focal, or brief symptoms that do not interfere with day-to-day life, then aggressive treatments may not be justified. Epilepsy medications do not cure epilepsy; the medications can only control the frequency and severity of seizures. A list of the most commonly used medications in the management of epilepsy includes:

- phenobarbital
- phenytoin (Dilantin, Phenytek)
- clonazepam (Klonipin)
- ethosuxamide (Zarontin)
- carbamazepine (Tegretol, Carbatrol)
- divalproex sodium (Depakote, Depakene)
- felbamate (Felbatol)
- gabapentin (Neurontin)
- lamotrigine (Lamictal)
- topiramate (Topamax)
- tiagabine (Gabatril)
- zonisamide (Zonegran)
- oxcarbazepine (Trileptal)
- leviteracetam (Keppra)

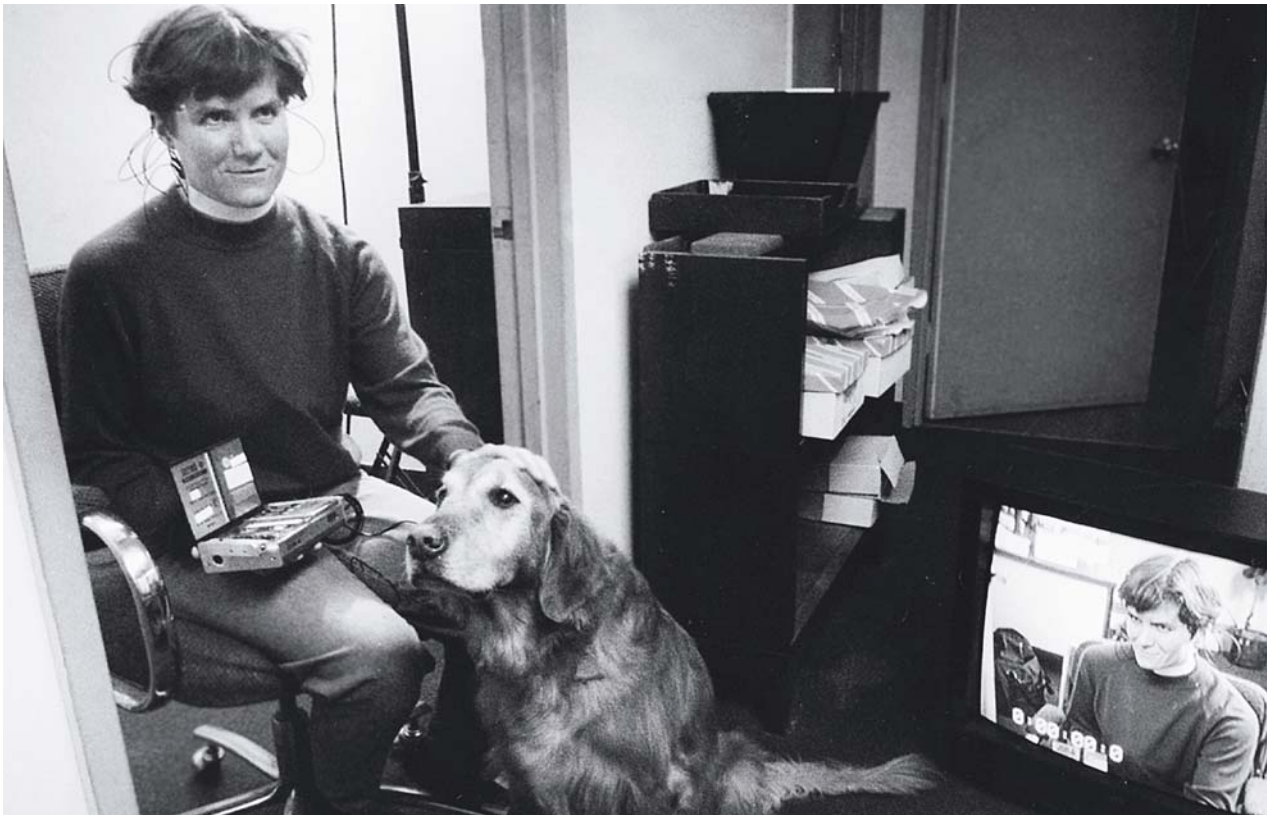
It has been found that the initial, thoughtfully chosen medication can be expected to make almost 50% of patients seizure free for extended periods of time. If the initial drug fails, another well-chosen drug may make an additional 14% of people seizure free. If that drug fails, then the likelihood of rendering someone with epilepsy seizure free is poor. This does not mean that trying more medications or combinations of them may not be successful, but rather, these statistics give the neurologist and the patient an understanding of the realities of epilepsy treatment. In cases where medications do not fully control epilepsy, it is recommended that a more extensive evaluation at a comprehensive epilepsy center be conducted where an epileptologist (a specialist in epilepsy) will more thoroughly assess the particular aspects of the seizures. When medications are clearly ineffective, the other types of therapy that can be considered are the ketogenic diet, brain surgery, and vagal nerve stimulation.

Ketogenic diet

The ketogenic diet is based on high-fat, low-carbohydrate, and low-protein meals. The ketogenic diet is named because of the production of ketones by the breakdown of fatty acids. The most common version of the diet involves long-chain triglycerides. These are present in whole cream, butter, and fatty meats.

The ketogenic diet is administered with the support of a nutritionist with experience in this treatment modality. It is mostly used in children with medically intractable epilepsy and whose diet can be controlled. The ketogenic diet can be considered a pharmacologic treatment. As such, there are potential side effects that limit its tolerance. This includes hair thinning, lethargy, weight loss, kidney stones, and possibly cardiac problems. Sugar-free vitamin and mineral supplementation is necessary. The diet may not be appropriate for certain individuals, particularly in children, who may have certain metabolic diseases.

Overall, the diet has been very helpful in the control of seizures in many patients. Roughly 50% of patients can hope to achieve complete control of seizures, 25% of the patients see improvements, and another 25% are non-responders. There are some patients who have an improvement in behavior. If the diet is well tolerated with good results, then it can be maintained for up to two years, followed by a careful gradual transition to regular meals.



Elizabeth Rudy, who suffers from epilepsy, sits hooked up to brain wave monitor. Her left hand strokes her seizure-predicting dog, Ribbon. *(A/P Wide World Photos. Reproduced by permission.)*

Epilepsy surgery

Epilepsy surgery is an option in the attempt to either cure or significantly reduce the severity of medically resistant cases. It is thought that up to 100,000 patients in the United States could be potential candidates for a surgical treatment. However, only about 5,000 cases are performed throughout the United States annually. This is likely due to several factors, including the belief that any brain surgery is a last resort, the lack of awareness or understanding of the benefits of surgery, and the false hope that some medication will come along that will be effective.

There are several kinds of surgery that are available depending on the nature of the seizure disorder. A list of operations that are utilized regularly for epilepsy include:

- lobectomy
- lesionectomy
- corpus collosotomy
- multiple subpial transection
- hemispherectomy

The type of surgery that is performed depends on the nature of the individual seizure disorder. If a seizure can be localized to a particular area in the brain, then this abnormal region can potentially be surgically removed. Epileptic brain tissue is abnormal and its removal can provide a chance of a cure. Generally, surgery should be a consideration when the risk and benefits of it outweigh the long-term risks of uncontrolled epilepsy.

The approach taken in any brain surgery for epilepsy is highly individualized and great care is taken to avoid injury to essential brain tissue. The most common epilepsy surgery performed is the temporal lobectomy. Brain tumors are frequently associated with seizures. In many cases, surgery to remove the tumor is planned so that regions that may be causing seizures are removed as well. However, in many cases, epilepsy surgery cannot be done.

Vagus nerve stimulation

Another non-medicinal approach to treating epilepsy is a novel method that became available in July 1997. The Food and Drug Administration (FDA) approved the use of the vagal nerve stimulator (VNS) as add-on therapy in patients who experience seizures of partial onset. The VNS is designed to intermittently deliver small electrical stimulations to a nerve in the neck called the vagus nerve.

There are two vagal nerves, one on each side of the neck near the carotid arteries, making a pair of cranial nerves (there are 12 different paired cranial nerves). The vagus nerve carries information from the brain to many parts of the thoracic and abdominal organs. The nerve also carries information from these same organs back to the brain. VNS takes advantage of this fact and, by intermittent stimulation, there is an effect on many brain areas that can be involved in seizures.

About 50% of patients experience at least 50% reduction in the frequency of their seizures. The responses to VNS range from complete control of seizures (less than 10% of patients) to no noticeable improvement. The device is not a substitute for epilepsy surgery and should be considered only after there is an evaluation for epilepsy surgery. The implantation of the device requires relatively minor surgery with two incisions, one in the neck and the other in the left upper chest area.

The battery in the device lasts up to eight to ten years, after which the device can be replaced. Side effects of VNS therapy include voice hoarseness that typically does not impair communication. Like any surgery, there is an initial risk of infection, bleeding, and **pain**. Recovery takes a few weeks. Individuals can return to their usual activities once the incisions have healed.

Clinical trials

The National Institute of Neurological Disorders and Stroke list a number of **clinical trials**. There are also a number of studies being conducted at a more basic science stage evaluating the role of the following in seizures and epilepsy: **neurotransmitters**, non-neuronal cells, and genetic factors. Treatment strategies including **deep brain stimulation** and intracranial early seizure detection devices are being studied at different stages.

Prognosis

The prognosis of epilepsy varies widely depending on the cause, severity, and patient's age. Even individuals with a similar diagnosis may have different experiences with treatment. For example, in benign epilepsy of childhood with centrotemporal spikes (also called benign rolandic epilepsy), the prognosis is excellent with nearly all children experiencing remission by their teens. With childhood absence epilepsy, the prognosis is variable. In this case, the absence seizures become less frequent with time, but almost half of patients may eventually develop generalized tonic-clonic seizures. Overall, the seizures are responsive to an appropriate anticonvulsant. On the other hand, the seizures in Lennox-Gastaut syndrome are very difficult to control. In this case, however, the ketogenic diet can help. In seizures that begin in adulthood, one can expect that medications will control seizures in up to 60–70% of cases. However, in some of the more than 30% of medically intractable cases, epilepsy surgery can improve or even cure the problem.

Overall, most patients have a good chance of controlling seizures with the available options of treatment. The goal of treatment is complete cessation of seizures since a mere reduction in seizure frequency and/or severity may continue to limit patients' quality of life: they may not be able to drive, sustain employment, or be productive in school.

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American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. 860.586.7505. <www.aesnet.org>.

Epilepsy Foundation of America. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <www.epilepsyfoundation.org>.

International League Against Epilepsy. Avenue Marcel Thiry 204, B-1200, Brussels, Belgium. + 32 (0) 2 774 9547; Fax: + 32 (0) 2 774 9690. <www.epilepsy.org>.

Roy Sucholeiki, MD

Erb's palsy *see* **Brachial plexus injuries**

Erb-Duchenne and Dejerine-Klumpke palsies *see* **Brachial plexus injuries**

Exercise

Definition

Exercise is physical activity that is undertaken in order to improve one's health. Physicians, physical therapists, and researchers have found that exercise plays an important role in the maintenance of brain, nerve, and muscle function in the human body. New research suggests that exercise may delay mental deterioration with age and disease, and perhaps even promote neurogenesis (nerve cell growth).

Description

Health care professionals recommend regular exercise because it increases energy, contributes to overall health, improves sleep, increases life expectancy, and enhances lifestyle. In terms of specific medical disorders, exercise has been shown to prevent or delay the onset of coronary artery disease, bone loss and osteoporosis, some types of cancer, and **stroke**.

Generally, exercise is categorized into the following four types:

- Aerobic exercise focuses on strengthening the heart, lungs, and circulatory system. Its major goal is to increase the heart rate and breathing rate. Examples of aerobic exercise include jogging, bicycling, swimming, and racket sports.
- Strength training focuses on strengthening muscles and joints. It also improves balance and increases metabolism. Weightlifting is the most common form of strength training.
- Balance exercises are used to improve stability. They stimulate the vestibular system, which includes muscles, joints, sensory organs, the inner ear, and the brain.
- Stretching exercises improve flexibility, which helps prevent injury during other forms of exercises and may decrease chronic pain. Stretching exercises include yoga, tai chi, and basic stretches.

All four types of exercises have been found to be important to maintaining brain, nerve, and muscle health.

Exercise and the brain

Exercise is particularly beneficial to the health of the brain. It has long been known that exercise causes the endocrine system to release serotonin and dopamine, hormones in the brain that produce feelings of euphoria and peacefulness. These hormones often allow people who exercise to think more clearly and perform mental tasks more easily. Exercise has also been successfully used as a treatment for **depression**, used in lieu of prescription antidepressants.

A 2003 study on mice suggests that new brain cells can grow as a result of exercise. This neurogenesis, previously thought not to occur in adult mammals, is concentrated in the hippocampus, the part of the brain responsible for learning and spatial memory. In addition, the study found that the mice subjected to an exercise regimen had stronger synapses than the mice that were sedentary. Other research shows that nerve growth factors, called neurotropins, are stimulated by exercise. Finally, exercise increases blood flow to the brain, as well as collateral circulation, enhancing mental function and nerve cell stimulation.

Exercise and aging

Aging naturally affects a variety of processes in the human body. Exercise has many positive benefits that prevent or slow the age-related deterioration of brain, nerve, and muscle functions.

In 2001, a study reported by the Mayo Clinic showed that regular exercise in older people slowed rates of mental deterioration, including Alzheimer's disease and **dementia**. On tests of mental acuity, older people who exercised regularly performed just as well as younger people who did not exercise. Another study found that regular walking greatly slowed rates of mental decline in older women.

Between the ages of 30 and 90, natural aging processes result in the loss of 15–25% of the brain tissue. In particular, losses are significant in the parts of the brain consisting of gray matter, which is associated with learning and memory. The February 2003 issue of *Journal of Gerontology: Medical Sciences* reported that this natural degradation of gray matter in older people was significantly decreased in people who exercised regularly compared to those who did not exercise. In the study, fitness levels were determined by treadmill-walking tests and tissue degradation was measured using **magnetic resonance imaging (MRI)**.

Balance is often affected as people age. Balance depends on input from the eyes, ears, and other sensory organs, all of which are affected by age. In addition, muscle strength and tone are required for balance. The natural aging process includes contraction of muscle tissue, and sedentary lifestyles only exacerbate the weakening of muscles. Joints supported by strong muscles are more stable than joints that are supported by weak muscles. Strength training, in particular, has the potential to counteract loss of muscle strength.

Physical therapy and the brain, nerves, and muscles

Therapeutic exercises have been designed to enhance a variety of aspects of physical fitness in patients suffering from diseases and dysfunctions. Goals of physical therapy include improving circulation, coordination, balance, and respiratory capacity. Exercises may be geared toward mobilizing joints and releasing contracted muscles and tendons.

Patients suffering from neurological disorders can be treated with a variety of physical therapies. For example, motor neuron damage or partial peripheral nerve damage may respond to a specific type of physical therapy called proprioceptive neuromuscular facilitation (PNF). PNF focuses on exercises that build muscle strength by applying resistance to muscle contraction. Patients who have experienced cerebrovascular accidents may undergo PNF combined with training for muscle strength, balance, and coordination. **Multiple sclerosis** is treated with PNF along with physical fitness training. Physical therapies for Parkinson disease focus on general physical fitness training, along with stretching exercises.

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Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. Division of Nutrition and Physical Activity, 4770 Buford Highway, NE, Atlanta, GA 30341-3724. (888) CDC-4NRG ((888) 232-4674). <http://www.cdc.gov>.

The President's Council on Physical Fitness and Sports. Department W, 200 Independence Ave., SW, Room 738-H, Washington, DC 20004. (202) 690-9000; Fax: (202) 690-5211. <http://fitness.gov/index.html>.

Juli M. Berwald

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.

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.

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.

Causes and symptoms

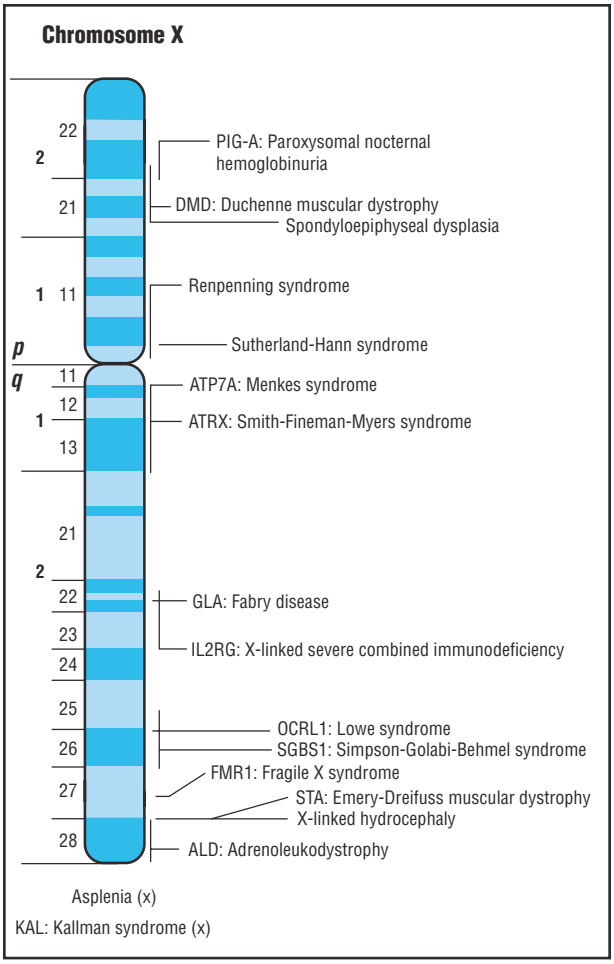
Fabry disease is caused by a change (mutation) in the GLA gene. This gene is responsible for the production of the enzyme alpha-galactosidase A. Alpha-galactosidase A normally breaks down globotriaosylceramide. Globotriaosylceramide is a natural substance in the body, made of sugar and fat. A mutation 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 buildup that inhibits normal function and leads to the symptoms associated with the disease.

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.

The signs and symptoms of Fabry disease vary. Some individuals with Fabry disease have many severe 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 age 40. 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.



Fabry disease, on chromosome X. *(Gale Group.)*

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 A 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 female carriers. 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 team

A number of specialized practitioners are necessary to care for patients with Fabry disease. Depending on the specific manifestations, these specialists may include a dermatologist to treat skin problems; a **neurologist** to treat such complications as dizziness, seizure, stroke; an ophthalmologist to treat eye problems; a nephrologist to treat kidney problems; a cardiologist to treat heart problems. A pain specialist may be helpful, as well.

Treatment

There is currently no cure for Fabry disease. Until such time as enzyme replacement therapy is proven to be safe and effective, individuals with Fabry disease must rely on traditional treatments. Pain can be treated with medications such as **carbamazepine** and dilantin. Individuals with Fabry disease are recommended to have routine evaluations of 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.

Clinical trials

A number of **clinical trials** are underway. Some are studying the specific nervous system effects of the disase. Others are giving individuals with Fabry disease the alpha-galactosidase A enzyme (Replagal) as a form of enzyme replacement therapy. If successful, this enzyme replacement therapy may reduce or eliminate the symptoms associated with Fabry disease. Clopidogrel, a blood thinner, is also being studied to see if its administration may decrease the rate/severity of such complications as stroke and heart attack.

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 continuous 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.

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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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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Facial synkinesis

Definition

Facial synkinesis is the involuntary movement of facial muscles that accompanies purposeful movement of some other set of muscles; for example, facial synkinesis may result in the mouth involuntarily closing or grimacing when the eyes are purposefully closed.

Description

Facial synkinesis occurs during recuperation from conditions or injuries that affect the facial nerve, for example during recovery from **Bell's palsy**. During recovery, as the facial nerve tries to regenerate, some new nerve twigs may accidentally regrow in close proximity to muscles that they wouldn't normally innervate (stimulate). Facial synkinesis may occur transiently, during recovery, or may become a permanent disability.

As with all facial injuries or palsies, facial synkinesis can cause considerable emotional distress. Lack of control over one's facial expressions is known to be a serious psychological stressor.

Causes and symptoms

Facial synkinesis can follow any injury or condition causing palsy or paralysis of the facial nerve. The most common associated disorder is Bell's palsy; about 40% of all individuals who are recovering from Bell's palsy will experience facial synkinesis during recovery. Other conditions that may prompt the development of facial synkinesis include **stroke**, head injury, birth trauma, head injury, trauma following tumor removal (such as acoustic neuroma), infection, **Lyme disease**, diabetes, and **multiple sclerosis**.

Facial synkinesis can cause a number of abnormalities in the facial muscles. For example, when a patient with facial synkinesis tries to close his or her eyes, the muscles around the mouth may twitch or grimace. Conversely, when the patient tries to smile, the eyes may involuntarily close. The phenomenon of purposeful mouth movements resulting in involuntary eye closing is often referred to as "jaw winking." Unfortunately, as with any facial deformity or disability, facial synkinesis carries with it a high risk of concomitant **depression**, anxiety, and disruption of interpersonal relationships and employment.

Diagnosis

Diagnosis is usually apparent on physical examination. When the patient is asked to move certain facial muscles (i.e., smile), other facial muscles will be activated (e.g., the eyes may close involuntarily). When the underlying condition is unclear, a variety of tests may be required, such as **CT** or **MRI** scanning or EMG (electromyographic) testing to evaluate the functioning of the facial nerves and muscles.

Treatment team

Facial synkinesis may be treated by neurologists or otorhinolaryngologists.

Treatment

Treatment may include:

- surgery, to remove causative tumors or other sources of pressure on and damage to the facial nerve
- steroid medications, to decrease inflammation of the facial nerve
- facial exercises
- electrical stimulation (this remains controversial, and may, in fact, worsen facial synkinesis in some patients)
- intensive video-assisted, electromyographic feedback facial muscle retraining
- injections of the paralytic agent botox into the muscle groups that are contracting involuntarily

Prognosis

The prognosis of facial synkinesis is quite variable, depending largely on the prognosis of the underlying condition that caused its development.

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Fainting

Definition

Fainting is a temporary loss of consciousness, weakness of muscles, and inability to stand up, all caused by sudden loss of blood flow to the brain. Fainting is a relatively common symptom caused by a variety of problems

relating to changes in blood pressure. The American Heart Association reports that fainting is responsible for 3% of all visits to emergency rooms and 6% of all admissions to hospitals.

Description

Fainting is a common symptom, also called syncope, vasovagal attack, neurally mediated syncope (NMS), neurocardiogenic syncope, and vasodepressor or reflex mediated syncope. Most simple faints result from an overstimulation of the autonomic nervous system that results in a drop in blood pressure and a slowed heart rate. Both of these conditions decrease blood flow to the brain, which causes a feeling of lightheadedness (presyncope) or a complete loss of consciousness (syncope). Fainting usually occurs in people who are standing or sitting upright. A person about to faint may also feel nauseated, weak, and warm. The person may experience temporary visual impairment, **headache**, ringing in the ears, shortness of breath, sensation of spinning, tingling in the extremities, and incontinence. A person experiencing presyncope may also appear pale or bluish. When consciousness is lost, a person usually falls down. This allows for more blood flow to the brain, resulting in a return to consciousness, usually within a few minutes.

Causes

Fainting is caused by a variety of factors, including stress, **pain**, overheating, dehydration, excessive sweating, exhaustion, hunger, alcohol, and drugs. Fainting may also be a side effect of some medications. A simple faint resulting from any of these factors is usually not a symptom of a neurological disorder.

Some people faint when changing positions, a condition known as postural hypotension. When people with this condition move from a lying position to a standing or sitting position, the sudden pooling of blood in the legs may cause a temporary decrease in blood circulation to the brain, causing a faint. This condition is common in elderly people who have been bedridden for some time and in people with poor muscle tone.

Some faints indicate serious disorders of the nervous or circulatory systems. Nervous system disorders that cause faints include acute or subacute dysautonomia, postganglionic autonomic insufficiency, and chronic preganglionic autonomic insufficiency. Fainting may also signal an irregular pattern of nervous stimulation such as micturition syncope (fainting while urinating), **glossopharyngeal neuralgia** (irritation of the ninth cranial nerve, causing pain in the tongue, throat, ear, and tonsils), cough syncope (fainting while coughing violently), and stretch syncope (fainting when stretching arms and neck). Faints can also indicate problems with the regulation of blood pressure and heart rate, and with disorders such as diabetes, alcoholism, malnutrition, and amyloidosis. Fainting can signal circulatory problems, particularly those that disrupt blood flow to the brain, as well as problems with the electrical impulses that control the heart, problems with the sinus node of the heart, heart arrhythmia, blood clots in the lung, a narrowing of the aorta, or other anatomical irregularities in the heart. Additionally, hyperventilation, usually associated with anxiety or panic, can result in a faint.

Diagnosis

Patients visiting a doctor because of fainting will usually have their blood pressure checked when they are lying down and then again after they stand up. If there is a significant decrease in blood pressure, it may indicate postural hypotension. A more sophisticated form of this blood pressure test is a tilt test, during which a person is strapped to a board that is rotated from the horizontal to the vertical position. Blood pressure is measured in both positions; an extreme drop indicates postural hypotension.

To test for circulatory problems, a physician may also use an electrocardiogram (EKG) to test for abnormalities of the heart beat. **Exercise** stress tests or wearing a Holter monitor for a day may also be performed to check for disorders of the heart. Fainting suspected to be caused by neurological disorders requires additional tests and evaluation by a **neurologist**.

Treatment

If a person faints while sitting, the body weight should be supported and the head positioned between the knees. If a person faints while standing, the individual should be carefully lowered to the ground and the legs elevated. Any tight clothes, including belts and collars, should be loosened. The head should be turned to the side so that the tongue does not obstruct the trachea and any vomit can be cleared from the airway. If the person stops breathing, cardiopulmonary resuscitation (CPR) should be started and a call should be placed to emergency medical services. A person who has fainted may benefit from cold compresses to the head and neck. After the person regains consciousness, he or she should remain lying or sitting for some time and should stand up only if no feeling of lightheadedness persists.

A person who faints often will be treated for the underlying condition. Often, medications are used to control fainting; however, other methods may be helpful as well. In some people, changing to a high-salt diet or wearing support hose to keep blood from pooling in the legs prevents fainting. Some people may be able to prevent fainting by keeping glucose levels at a more constant level or

Key Terms

Autonomic nervous system The part of the nervous system that controls so-called involuntary functions, such as heart rate, salivary gland secretion, respiratory function, and pupil dilation.

Postural hypotension A drop in blood pressure that causes faintness or dizziness and occurs when an individual rises to a standing position. Also known as orthostatic hypotension.

Syncope A loss of consciousness over a short period of time, caused by a temporary lack of oxygen in the brain.

by learning breathing techniques to prevent hyperventilation. Another technique for preventing faints is drinking enough fluid to keep blood volume high.

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American Heart Association National Center. 7272 Greenville Avenue, Dallas, TX 75231. (800) AHA-USA1. <http://www.americanheart.org/presenter.jhtml?identifier=1200000>.

National Heart, Blood and Lung Institute. P.O. Box 30105, Bethesda, MD 20824-0105. (301) 592-8573; Fax: (301) 592-8563. <http://www.nhlbi.nih.gov/index.htm>.

National Institute of Neurological Disorders and Stroke. P.O. Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov/>.

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Familial hemangioma *see* **Cerebral cavernous malformation**

Familial spastic paralysis *see* **Hereditary spastic paraplegia**

Fatigue

Definition

Fatigue may be defined as a subjective state in which one feels tired or exhausted, and in which the capacity for normal work or activity is reduced. There is, however, no commonly accepted definition of fatigue when it is considered in the context of health and illness. This lack of definition results from the fact that a person's experience of fatigue depends on a variety of factors. These factors include culture, personality, the physical environment (light, noise, vibration), availability of social support through networks of family members and friends, the nature of a particular fatiguing disease or disorder, and the type and duration of work or **exercise**. The experience of fatigue associated with disease will be different for someone who is clinically depressed, is socially isolated, and is out of shape, as compared to another person who is not depressed, has many friends, and is aerobically fit.

Description

Fatigue is sometimes characterized as normal or abnormal. For example, the feeling of tiredness or even exhaustion after exercising is a normal response and is relieved by resting; many people report that the experience of ordinary tiredness after exercise is pleasant. Moreover, this type of fatigue is called "acute" since the onset is sudden and the desired activity level returns after resting. On the other hand, there is fatigue that is not perceived as ordinary, that may develop insidiously over time, is unpleasant or seriously distressing, and is not resolved by rest. This kind of fatigue is abnormal and is called "chronic."

Some researchers regard fatigue as a defense mechanism that promotes the effective regulation of energy expenditures. According to this theory, when people feel tired they take steps to avoid further stress (physical or emotional) by resting or by avoiding the stressor. They are then conserving energy. Since chronic fatigue is not normal, however, it is a common symptom of some mental disorders, a variety of physical diseases with known etiologies (causes), and medical conditions that have no biological markers although they have recognizable syndromes (patterns of symptoms and signs).

Fatigue is sometimes described as being primary or secondary. Primary fatigue is a symptom of a disease or mental disorder, and may be part of a cluster of such symptoms as **pain**, fever, or nausea. As the disease or disorder progresses, however, the fatigue may be intensified by the patient's worsening condition, by the other disease symptoms, or by the surgical or medical treatment given to the patient. This subsequent fatigue is called secondary.

Risk factors

Fatigue is a common experience. It is one of the top ten symptoms that people mention when they visit the doctor. Some people, however, are at higher risk for developing fatigue. The risk for women is about 1.5 times the risk for men, and the risk for people who do not exercise is twice that of active people. Some researchers question whether women really are at higher risk, since women are more likely than men to go to the doctor with health problems; also, men are less likely to admit they feel fatigued. Other risk factors include obesity, smoking, use of alcohol, high stress levels, **depression**, anxiety, and low blood pressure. Having low blood pressure is usually considered desirable in the United States, but is regarded as a treatable condition in other countries. Low blood pressure or postural hypotension (sudden lowering of blood pressure caused by standing up) may cause fatigue, **dizziness**, or **fainting**.

Major sources of chronic fatigue

Disease

There are many diseases and disorders in which fatigue is a major symptom—for example, cancer, cardiovascular disease, emphysema, **multiple sclerosis**, rheumatic arthritis, systemic **lupus** erythematosus, HIV/AIDS, infectious mononucleosis, chronic fatigue syndrome, and fibromyalgia. The reasons for the fatigue, however, vary according to the organ system or body function affected by the disease.

Physical reasons for fatigue include:

- Circulatory and respiratory impairment. When the patient's breathing and blood circulation are impaired, or when the patient has anemia (low levels of red blood cells), body tissues do not receive as much oxygen and energy. Consequently, the patient experiences a general sense of fatigue. Fatigue is also an important warning sign of heart trouble; it precedes 30–55% of myocardial infarctions (heart attacks) and sudden cardiac deaths.
- Infection. Microorganisms that disturb body metabolism and produce toxic wastes cause disease and lead to fatigue. Fatigue is an early primary symptom of chronic, nonlocalized infections found in such diseases as acquired immune deficiency syndrome (**AIDS**), **Lyme disease**, and tuberculosis.

KEY TERMS

Biological marker An indicator or characteristic trait of a disease that facilitates differential diagnosis (the process of distinguishing one disorder from other, similar disorders).

Deconditioning Loss of physical strength or stamina resulting from bed rest or lack of exercise.

Electrolytes Substances or elements that dissociate into electrically charged particles (ions) when dissolved in the blood. The electrolytes in human blood include potassium, magnesium, and chloride.

Metabolism The group of biochemical processes within the body that release energy in support of life.

Stress A physical and psychological response that results from being exposed to a demand or pressure.

Syndrome A group of symptoms that together characterize a disease or disorder.

- Nutritional disorders or imbalances. Malnutrition is a disorder that promotes disease. It is caused by insufficient intake of important nutrients, vitamins, and minerals; by problems with absorption of food through the digestive system; or by inadequate calorie consumption. Protein-energy malnutrition (PEM) occurs when people do not consume enough protein or calories; this condition leads to wasting of muscles and commonly occurs in developing countries. In particular, young children who are starving are at risk of PEM, as are people recovering from major illness. In general, malnutrition damages the body's immune function and thereby encourages disease and fatigue. Taking in too many calories for the body's needs, on the other hand, results in obesity, which is a predictor of many diseases related to fatigue.
- Dehydration. Dehydration results from water and sodium imbalances in body tissues. The loss of total body water and sodium may be caused by diarrhea, vomiting, bed rest, overexposure to heat, or exercise. Dehydration contributes to muscle weakness and mental confusion; it is a common and overlooked source of fatigue. Once fatigued, people are less likely to consume enough fluids and nutrients, which makes the fatigue and confusion worse.
- Deconditioning. This term refers to generalized organ system deterioration resulting from bed rest and lack of exercise. In the 1950s and 1970s, the National Aeronautics and Space Administration (NASA) studied the effects

of bed rest on healthy athletes. The researchers found that deconditioning occurred rapidly (within 24 hours) and led to depression and weakness. Even mild exercise can counteract deconditioning, however, and it has become an important means of minimizing depression and fatigue resulting from disease and hospitalization.

- Pain. When pain is severe enough, it may disrupt sleep and lead to the development of such sleep disorders as insomnia or **hypersomnia**. (Insomnia is the term for having difficulty falling and/or staying asleep. Hypersomnia refers to excessive sleeping.) In general, disrupted sleep is not restorative; people wake up feeling tired, and as a result their pain is worsened and they may become depressed. Furthermore, pain may interfere with movement or lead to too much bed rest, which results in deconditioning. Sometimes pain leads to social isolation because the person cannot cope with the physical effort involved in maintaining social relationships, or because family members are unsympathetic or resentful of the ill or injured person's reduced capacity for work or participation in family life. All of these factors worsen pain, contributing to further sleep disruption, fatigue, and depression.
- Stress. When someone experiences ongoing pain and stress, organ systems and functional processes eventually break down. These include cardiovascular, digestive, and respiratory systems, as well as the efficient elimination of body wastes. According to the American Psychiatric Association, various chronic diseases are related to stress, including regional enteritis (intestinal inflammation), ulcerative colitis (a disease of the colon), gastric ulcers, rheumatoid arthritis, cardiac angina, and dysmenorrhea (painful menstruation). These diseases deplete the body's levels of serotonin (a neurotransmitter important in the regulation of sleep and wakefulness, as well as depression), and endorphins (opiate-like substances that moderate pain). Depletion of these body chemicals leads to insomnia and chronic fatigue.
- Sleep disorders. There are a variety of sleep disorders that cause fatigue, including insomnia, hypersomnia, **sleep apnea**, and **restless legs syndrome**. For example, hypersomnia may be the result of brain abnormalities caused by viral infections. Researchers studying the aftermath of infectious mononucleosis proposed that exposure to viral infections might change brain function with the effect of minimizing restorative sleep. Another common disorder is sleep apnea, in which the patient's breathing stops for at least 10 seconds, usually more than 20 times per hour. Snoring is common. People may experience choking and then wake up gasping for air; they may develop daytime hypersomnia (daytime sleepiness) to compensate. Sleep apnea is associated with aging, weight gain, and depression. It is also a risk factor for **stroke** and myocardial infarctions. Restless legs syndrome is a condition in which very uncomfortable sensations in the patient's legs cause them to move and wake up from sleep, or keep them from falling asleep. All of these disorders reduce the quality of a person's sleep and are associated with fatigue.

Fibromyalgia and chronic fatigue syndrome

Fibromyalgia (also known as myofascial syndrome or fibrositis) is characterized by painful and achy muscles, tendons, and ligaments. There are 18 locations on the body where patients typically feel sore. These locations include areas on the lower back and along the spine, neck, and thighs. A diagnostic criterion for fibromyalgia (FM) is that at least 11 of the 18 sites are painful. In addition to pain, people with FM may experience sleep disorders, fatigue, anxiety, and irritable bowel syndrome. Some researchers maintain, however, that when fatigue is severe, chronic, and persistent, FM is indistinguishable from chronic fatigue syndrome (CFS). The care that patients receive for FM or CFS depends in large measure on whether they were referred to a rheumatologist (a doctor who specializes in treating diseases of the joints and muscles), **neurologist**, or psychiatrist.

Some doctors do not accept CFS (also known as myalgic encephalomyelitis) as a legitimate medical problem. This refusal is stigmatizing and distressing to the person who must cope with disabling pain and fatigue. Many people with CFS may see a number of different physicians before finding one who is willing to diagnose CFS. Nevertheless, major health agencies such as the Centers for Disease Control (CDC) in the United States have studied the syndrome. As a result, a revised CDC case definition for CFS was published in 1994 that lists major and minor criteria for diagnosis. The major criteria of CFS include the presence of chronic and persistent fatigue for at least six months; fatigue that does not improve with rest; and fatigue that causes significant interference with the patient's daily activities. Minor criteria include such flu-like symptoms as fever, sore throat, swollen lymph nodes, myalgia (muscle pain), difficulty with a level of physical exercise that the patient had performed easily before the illness, sleep disturbances, and headaches. Additionally, people often have difficulty concentrating and remembering information and they experience extreme frustration and depression as a result of the limitations imposed by CFS. The prognosis for recovery from CFS is poor, although the symptoms are manageable.

Psychological disorders

While fatigue may be caused by many organic diseases and medical conditions, it is a chief complaint for several mental disorders, including generalized anxiety

disorder and clinical depression. Moreover, mental disorders may coexist with physical disease. When there is considerable symptom overlap, the differential diagnosis of fatigue is especially difficult.

GENERALIZED ANXIETY DISORDER

People are diagnosed as having generalized anxiety disorder (GAD) if they suffer from overwhelming worry or apprehension that persists, usually daily, for at least six months, and if they also experience some of the following symptoms: unusual tiredness, restlessness and irritability, problems with concentration, muscle tension, and disrupted sleep. Such stressful life events as divorce, unemployment, illness, or being the victim of a violent crime are associated with GAD, as is a history of psychiatric problems. Some evidence suggests that women who have been exposed to danger are at risk of developing GAD; women who suffer loss are at risk of developing depression, and women who experience danger and loss are at risk of developing a mix of both GAD and depression.

While the symptoms of CFS and GAD overlap, the disorders have different primary complaints. Patients with CFS complain primarily of tiredness, whereas people with GAD describe being excessively worried. In general, some researchers believe that anxiety contributes to fatigue by disrupting rest and restorative sleep.

DEPRESSION

In the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), the presence of depressed mood or sadness, or loss of pleasure in life, is an important diagnostic criterion for depression. Daily fatigue, lack of energy, insomnia, and hypersomnia are indicators of a depressed mood. The symptoms of depression overlap with those of CFS; for example, some researchers report that 89% of people with depression are fatigued, as compared to 86–100% of people with CFS. The experience of fatigue, however, seems to be more disabling with CFS than with depression. Another difference between CFS and depression concerns the onset of the disorder. Most patients with CFS experience a sudden or acute onset, whereas depression may develop over a period of weeks or months. Also, while both types of patients experience sleep disorders, CFS patients tend to have difficulty falling asleep, whereas depressed patients tend to wake early in the morning.

Some researchers believe that there is a link between depression, fatigue, and exposure to too much REM sleep. There are five distinct phases in human sleep. The first two are characterized by light sleep; the second two by a deep restorative sleep called slow-wave sleep; and the last by rapid eye movement, or REM, sleep. Most dreams occur during REM sleep. Throughout the night, the intervals of REM sleep increase and usually peak around 8:30 A.M. A sleep deprivation treatment for depression involves reducing patients' amount of REM sleep by waking them around 6:00 A.M. Researchers think that some fatigue associated with disease may be a form of mild depression and that reducing the amount of REM sleep will reduce fatigue by moderating depression.

Managing fatigue

The management of fatigue depends in large measure on its causes and the person's experience of it. For example, if fatigue is acute and normal, the person will recover from feeling tired after exertion by resting. In cases of fatigue associated with influenza or other infectious illnesses, the person will feel energy return as they recover from the illness. When fatigue is chronic and abnormal, however, the doctor will tailor a treatment program to the patient's needs. There are a variety of approaches that include:

- Aerobic exercise. Physical activity increases fitness and counteracts depression.
- Hydration (adding water). Water improves muscle turgor, or tension, and helps to carry electrolytes.
- Improving sleep patterns. The patient's sleep may be more restful when its timing and duration are controlled.
- Pharmacotherapy (treatment with medications). The patient may be given various medications to treat physical diseases or mental disorders, to control pain, or to manage sleeping patterns.
- Psychotherapy. There are several different treatment approaches that help patients manage stress, understand the motives that govern their behavior, or change maladaptive ideas and negative thinking patterns.
- Physical therapy. This form of treatment helps patients improve or manage functional impairments or disabilities.

In addition to seeking professional help, people can understand and manage fatigue by joining appropriate self-help groups, reading informative books, seeking information from clearinghouses on the Internet, and visiting websites maintained by national organizations for various diseases.

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MEDLINEplus Health Information. U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894. (888) 346-3656. <http://www.medlineplus.gov>.

National Chronic Fatigue Syndrome and Fibromyalgia Association. P.O. Box 18426, Kansas City, MO 64133. (816) 313-2000.

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Febrile seizures

Definition

Febrile **seizures** are the most common type of convulsions in infants or small children and are triggered by fever. It is not in the strict sense an **epilepsy** syndrome but rather a symptom of a febrile illness, and it normally affects children between three months and five years of age, mainly toddlers. During a febrile seizure, a child may lose consciousness and move or shake the limbs. The seizure itself is normally harmless and does not cause brain damage. A child who experiences a seizure in the setting of a fever should be taken to the hospital so that any serious causes of the fever can be evaluated.

Description

Febrile seizures (or convulsions) occur mainly in children between three months and five years of age and are associated with a fever of any cause. Toddlers are most commonly affected and there is a tendency for febrile seizures to run in families. These seizures are associated with fevers that rapidly rise to temperature up to or above 102°F, but they can also occur with lower temperatures.

There are two types of febrile seizures: simple (or benign) and complex. Benign febrile seizures account for 80–85% of all febrile seizures, and last less than 15 minutes. They usually do not recur within 24 hours. Complex febrile seizures, which suggest a more serious illness, account for 15–20% of all cases, last more than 15 minutes, and can recur within 24 hours.

Children with febrile seizures often lose consciousness and shake, moving limbs on both sides of the body. Less commonly, children become rigid or have twitches on only one side of the body.

Demographics

About 2–5% of all children experience a febrile seizure and about 25% of these children have a first-degree relative with history of febrile seizures. There is a slightly higher prevalence among boys, and no ethnic differences have been reported. Less than 5% of children with febrile seizures will eventually develop epilepsy.

Causes and symptoms

The exact role of the fever in the development of seizures is not clear. However, it is known that viral infections are the most common cause of fever in children with a first febrile seizure who are admitted to hospitals, mainly caused by viruses like herpes and influenza. Meningitis causes less than 1% of febrile seizures, but should be investigated to rule out this serious infection, especially in children less than one year old or those who continue to appear ill after the fever subsides. Seizures that occur after immunizations are likely to be the febrile type due to temperature elevation, particularly those after the DTP (diphtheria, pertussis, tetanus) and measles immunizations. Upper respiratory tract infections accompanied by high fever, in combination with a low seizure threshold, can often affect infants and young children and, thus, account for the most common cause of these convulsions.

In a few studies, children with febrile seizures have been found to have decreased zinc levels in both the serum and the cerebrospinal fluid, which is the fluid that bathes the brain and the spinal cord. Deprivation of zinc may play a role in the seizures. Children with iron-deficiency anemia have been shown to have febrile seizures at a higher rate than nonanemic children.

There is a positive family history in up to 31% of all cases of febrile seizures, although the exact mode of inheritance is not known and varies among families. It has long been recognized that there is a genetic component for the susceptibility to this type of seizure; this may be caused by mutations in several genes, especially the FB4 gene.

Febrile seizures typically begin with a sudden contraction of muscles on both sides of the body, usually facial muscles, trunk, arms, and legs. The force of the

Key Terms

Epilepsy A disorder of the central nervous system characterized by seizures.

Meningitis Inflammation of the meninges, the membranes that surround the brain and spinal cord.

Seizure Abnormal electrical discharge of neurons in the brain, often resulting in abnormal body movements or behaviors.

muscle contraction may cause the child to emit an involuntary cry or moan. The child falls, if standing, and may bite the tongue. Urinary incontinence and vomiting can occur. The child will not breathe, and may turn blue. Children cannot respond to any stimuli, and loss of consciousness, hallucinations, confusion, and feelings of fear or other emotions may occur. Focal seizures (those without loss of consciousness) involving only a part of the body are less common, and might become generalized, affecting the whole body.

Diagnosis

The first action of the physician is to stop the fever and find its cause(s). Physicians may ask about previous seizures without a fever, which can indicate that the child is more likely to have an underlying seizure disorder such as epilepsy rather than a febrile seizure. Physicians also consider the family history of seizures, febrile or otherwise, and must investigate any known nervous disorder in the child, such as developmental delay or severe head injury. Any medication the child has taken is suspicious, and the possibility of drug reaction or poisoning may also be considered.

It is important to rule out any infectious disease as the first cause of a seizure, especially meningitis. In the case of meningitis, the child appears particularly ill, shows neck rigidity, has an unusually long period of drowsiness after the seizure, and experiences a complex febrile seizure (often prolonged and repeated). Lumbar puncture (commonly known as a spinal tap) can be performed in this case to examine the cerebrospinal fluid for indications of meningitis. Other tests such as blood tests, urine tests, and x rays may be used in diagnosing the cause of fever.

Treatment team

A pediatrician is normally the first physician to be seen, and a **neurologist** should be considered for those cases in which a neurological disorder is thought to be the cause of the seizure rather than the fever.

Treatment

During the acute phase of the seizure, the main objective is to keep the child in a position on his or her side or stomach to avoid aspiration of saliva or vomit and avoid injuries. The child should be placed on the floor or in a safe area, and all dangerous objects must be removed. A child having a seizure should not be restrained. If the child vomits, or if saliva and mucus build up in the mouth, a side posture should be used. It is also important that parents do not force anything into the child's mouth, as this could result in breaking teeth. Also, tongue swallowing will not occur. If the child inadvertently bites the tongue, it will heal. Any tight clothing should be removed, especially around the neck. Because the seizure occurs in the setting of a fever, the main target of therapy is to bring the fever down. Removing the clothes and applying cool washcloths to the child's neck and face may help, and acetaminophen or ibuprofen suppositories, if available, may control the elevated temperature.

Rarely, a child may experience a persistent seizure, which could evolve into what is called **status epilepticus**. Airway management and anticonvulsivants are the first line of treatment during this medical emergency.

The most commonly used medication includes **benzodiazepines** such as lorazepan (Ativan) and **diazepam** (Valium). An intravenous line is usually placed in the vein because it is the fastest and most reliable means of drug administration.

Recovery and rehabilitation

Children are normally drowsy or in a state of confusion after a seizure, but become responsive within 15–30 minutes. A simple febrile seizure stops by itself within a few seconds to 10 minutes, usually followed by a brief period of drowsiness or confusion. In this case, an antiseizure medication may not be required. After a seizure, the child is twitchy, with jerks of the arms and legs.

Clinical trials

As of early 2004, there are no open **clinical trials** for febrile seizures at the National Institutes of Health (NIH). However, the National Institute of Neurological Disorders and Stroke (NINDS), a part of the NIH, often sponsors research on febrile seizures in medical centers throughout the United States.

Prognosis

About 35% of children who have had a febrile seizure will have another one with a subsequent fever. Of those who do, about 50% will have a third seizure. Few children have more than three seizure episodes. A child is more

likely to fall in the group that has more than one febrile seizure if there is a family history, if the first seizure happened before 12 months of age, or if the seizure happened with a fever below 102°F.

Seizures occur at the time the brain is sensitive to the effects of temperature and often cause parents great anxiety. As the onset is dramatic, parents are afraid their children will die or undergo brain damage. However, simple febrile seizures are harmless and they do not cause death, brain damage, epilepsy, **mental retardation**, or learning difficulties.

Special concerns

Parental anxiety or other factors may cause a child to be placed on long-term anticonvulsant medicine. This will not benefit the patient. Children with the possibility of having a second seizure should not engage in activities that are potentially harmful, such as taking unsupervised baths or climbing higher than 5 ft (1.5 m) off the ground.

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Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (301) 459-3700 or (800) 332-1000; Fax: (301) 577-2684. postmaster@efa.org. <http://www.epilepsyfoundation.org>.

Marcos do Carmo Oyama
Iuri Drumond Louro, MD, PhD

Felbamate

Definition

Felbamate is an anticonvulsant indicated for the control of **seizures** in the treatment of **epilepsy**, a neurological dysfunction in which excessive surges of electrical energy are emitted in the brain.

Purpose

Felbamate is thought to decrease abnormal activity and excitement within the **central nervous system** (CNS) that may trigger seizures. While felbamate controls some types of seizures associated with epilepsy, there is no known cure for the disorder. Felbamate has shown effectiveness in controlling partial seizures in adults when prescribed alone. When prescribed with other antiepileptic medicines, felbamate has shown effectiveness in managing the intractable (difficult to control) seizures of **Lennox-Gastaut syndrome** in children.

Description

In the United States, felbamate is sold under the brand name Felbatol and FBM. Felbamate acts to depress CNS function; however the precise mechanisms by which it exerts its therapeutic effects in the prevention of seizures is unknown.

Recommended dosage

Felbamate is taken by mouth and is available in tablet or oral suspension form. Adult patients usually take felbamate three to four times daily. The typical total daily dose for an adult or teenager over 14-years-old ranges from 1200 mg to 3600 mg. Treatment including felbamate is appropriate for some children with intractable seizures. The typical total daily dosage formula for a child is between 15 mg and 45 mg per kilogram of body weight.

Beginning a course of treatment which includes felbamate requires a gradual dose-increasing regimen. Patients typically take a reduced dose at the beginning of treatment. The prescribing physician will determine the proper beginning dosage and may raise a patient's daily dosage gradually over the course of several weeks. It may take several weeks to realize the full benefits of felbamate.

It is important to not take a double dose of felbamate. If a daily dose is missed, take it as soon as possible. However, if it is almost time for the next dose, then skip the missed dose. When ending treatment for epilepsy that includes felbamate, physicians typically direct patients to gradually taper their daily dosages. Stopping the medicine suddenly may cause seizures to return or occur more frequently.

Precautions

Prior to initiating therapy with felbamate, blood tests to check for anemia, infection, and liver function will likely be performed. Periodic blood tests are necessary to monitor liver and bone marrow function while receiving felbamate therapy, and for a period after the drug is discontinued.

Key Terms

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Seizure A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain, resulting in abnormal body movements or behaviors.

Felbamate may not be suitable for persons with a history of **stroke**, anemia, liver or kidney disease, mental illness, diabetes, high blood presure, angina (chest **pain**), irregular heartbeats, or other heart problems.

Before beginning treatment with felbamate, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant, nursing, or plan on becoming pregnant. Research in animals indicates that felbamate may inhibit fetal growth and development. Patients who become pregnant while taking felbamate should contact their physician.

Consult a physician before taking felbamate with certain non-perscription medications. Patients should avoid alcohol and CNS depressants (medicines that can make one drowsy or less alert, such as antihistimines, sleep medications, and some pain medications) while taking felbamate.

Side effects

Patients should discuss with their physicians the risks and benefits of treatment including felbamate before taking the medication. Dizziness and nausea are the most frequently reported side effects. Most mild side effects do not require medical treatment, and may diminish with continued use of the medication. Additional possible mild side effects include anorexia (loss of appetite), vomiting, insomnia, **headache**, and sleepiness. If any symptoms persist or become too uncomfortable, the prescribing physician should be consulted.

Felbamate has been implicated as the cause of serious side effects, including plastic anemia (bone marrow failure) and liver failure. It is estimated that one in every 3,600 to 5,000 patients taking felbamate will eventually develop aplastic anemia, and the fatality rate of complicating aplastic anemia is nearly 30%. For this reason, felbamate is prescribed seldomly, and only after other medications have failed to control seizures. Persons taking felbamate who experience any of the following symptoms should immediately contact a physician:

- rash or purple spots on skin
- nosebleed
- yellow tint to eyes or skin
- bruising easily
- signs of infection
- weakness and fatigue

Interactions

Felbamate should be used with other other seizure prevention medications (**anticonvulsants** or anti-epileptic drugs [AEDs]), only if prescribed by a physician. Felbamate increases blood levels of phenytoin (Dilantin) and valproic acid (Depekene), while reducing blood levels of **carbamazepine** (Tegretol).

Felbamate, like many other anticonvulsants, may decrease the effectiveness of oral contraceptives (birth control pills) or contraceptives containing estrogen.

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Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

Adrienne Wilmoth Lerner

Fisher syndrome

Definition

Fisher syndrome is a rare, acute neurological disorder characterized by a triad of clinical manifestations that includes brain-damage associated abnormal coordination (**ataxia**), a condition that involves the paralysis of the eyes called ophthalmoplegia, and a generalized absence of reflexes (areflexia).

Description

Fisher syndrome is also known as Miller Fisher syndrome, as was described in 1956 by Canadian physician Charles Miller Fisher. It is an acute, rare nerve disease that is considered to be a variant of **Guillain-Barré syndrome**. In both syndromes, the associated nerve disease can be acquired after viral illness. Once the disorder is diagnosed and treated, the physical and mental effects can be minimal or absent, thus emphasizing the importance of medically identifying affected individuals and treating them accordingly.

Fisher syndrome is also known as acute idiopathic ophthalmologic neuropathy syndrome of ophthalmoplegia, ataxia, and areflexia. Related conditions include disorders called Bickerstaff's brainstem **encephalopathy** and acute ophthalmoparesis.

Demographics

Fisher syndrome is an extremely rare disorder. It is reported to affect persons between the ages of 38 and 65 years old. The related Guillain-Barré syndrome is more common than Fisher syndrome. Age is not a factor, and anyone who produces specific antibodies can acquire it.

Causes and symptoms

The majority of affected individuals with Fisher syndrome produce an antibody by their immune system that is related to the susceptibility to develop the disease following a viral illness; it is unclear how. It is thought that the antibody anti-GQ1b IgG is associated with paralysis of the eye, or ophthalmoplegia. The cause of Fisher syndrome and Guillain-Barré syndrome in both cases is due to an autoimmune disease whereby antibodies produced by the body's immune system mistakenly attack a nerve insulator and impulse carrier called the myelin sheath. This causes inflammation and damage to the nervous system. Guillain-Barré syndrome differs from Fisher syndrome in that different nerve groups are targeted and paralysis in the former begins with the legs and moves upward. Fisher syndrome, on the other hand, begins in the head (paralysis of the eyes) and moves in the direction toward the neck and arms. Although the direct cause is unknown, 65% of cases are thought to be linked to herpes-related viral illness (although viruses other than herpes can also be involved).

The first symptoms appear to be related to a virus and include a **headache**, fever, and pneumonia. The characteristic triad of symptoms that result in individuals who acquire Fisher syndrome is in addition to generalized muscle atrophy (weakness) and respiratory complications that can involve respiratory failure if untreated. It is uncommon to observe a patient with Fisher syndrome that does not have some degree of generalized weakness. Damage to motor function is believed to be associated with damage sustained by the cranial nerves of the brain, with sensory nerve damage extending to the patient's arms and legs. In cases that also include abnormalities in the brainstem, it is more likely to be due to a related disorder called Bickerstaff's syndrome.

Diagnosis

Diagnosis is made clinically by detecting manifestations involving the characteristic trio of symptoms usually following a viral infection: paralysis of the eyes (ophthalmoplegia), abnormal coordination (ataxia), and absence of reflexes (areflexia).

Treatment team

Patients are usually treated by a physician that specializes in infectious diseases, and a **neurologist**. Diagnosis and treatment are usually made by these professionals.

Treatment

Treatment for Fisher syndrome involves removing the plasma from affected individuals, a procedure called plasmapheresis. In doing so, antibodies that cause the disease are also removed. In the alternative, patients can be treated with an intravenous injection of immunoglobulin (IVIg) to boost the immune system. Untreated patients can experience double vision, nausea, difficulty walking, and sensitivity to light that can continue for several months.

Recovery and rehabilitation

Once Fisher syndrome is identified, treatment can lead to recovery in as soon as two to four weeks after the symptoms are initially acquired. After six months, the symptoms are usually almost completely resolved. Although some individuals have secondary complications and relapses occur in 3% of cases, most individuals have a nearly complete recovery.

Clinical trials

As most affected individuals who are treated have a good prognosis, **clinical trials** to treat the disorder are not currently being investigated. There is research being conducted to find better ways to diagnose and ultimately cure the neurological damage that sometimes occurs in Fisher syndrome.

Prognosis

The prognosis is good for individuals who are detected and treated soon after the onset of symptoms. In these cases, affected individuals have a favorable prognosis and (on average) should expect to have a normal lifespan. This disorder is seldom life-threatening.

Key Terms

Areflexia Absence of a reflex; a sign of possible nerve damage.

Ataxia Loss of coordinated movement caused by disease of nervous system.

Ophthalmoplegia Paralysis of the motor nerves of the eye.

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Guillain-Barré Syndrome Foundation International. P.O. Box 262, Wynnewood, PA 19096. (610) 667-0131; Fax: (610) 667-7036. info@gbsfi.com. <http://www.gbsfi.com>.

Bryan Richard Cobb, PhD

Floppy infant syndrome *see* **Hypotonia**

Foot drop

Definition

Foot drop is a weakness of muscles that are involved in flexing the ankle and toes. As a result, the toes droop downward and impede the normal walking motion.

Description

The use of the term foot drop can make it seem as if the condition is rather simple and inconsequential. This is not the case. Foot drop can be a consequence of injury to muscles that are known as dorsiflexor muscles, injury to certain nerves, a **stroke**, brain injury, toxic effect of drugs, and even diabetes. Foot drop is likely not a new malady. Historical descriptions that match foot drop date back over 2000 years.

Foot drop can also be described as drop foot, steppage gait, and as equinovarus deformity.

Demographics

Foot drop affects both males and females. However, it is more common in males (the male to female ratio is approximately 2.8:1). Both feet are equally as prone to develop the problem. Some forms of foot drop occur in mid-aged people who put stress on that area of the body during athletics. Surgery to the knee or leg can lead to nerve damage that then leads to the development of foot drop. For example, approximately 0.3–4% of people who have a surgical procedure called a total knee arthroplasty develop foot drop. People who undergo surgery to the tibia (a leg bone) subsequently experience foot drop at a rate of 3–13%.

Causes and symptoms

Foot drop is caused by weakness that occurs in specific muscles of the ankle and the foot. The affected muscles participate in the downward and upward movement of the ankle and the foot. The specific muscles include the anterior tibialis, extensor hallucis longus, and the extensor digitorum longus. The normal function of these muscles is to allow the toes to swing up from the ground during the beginning of a stride and to control the movement of the foot following the planting of the heel towards the end of the stride. Abnormal muscle function makes it difficult to prevent the toes from clearing the ground during the stride. Some people with foot drop walk with a very exaggerated swinging hip motion to help prevent the toes from catching on the ground. Another symptom of foot drop, which occurs as the foot is planted, is an uncontrolled slapping of the foot on the ground.

There are three general causes of the muscle weakness. Damage to nerves can affect the transmission of impulses that help control muscle movement and function. **Motor neuron diseases** such as **amyotrophic lateral sclerosis** (ALS) or **post-polio syndrome**, tumors in the brain or spinal cord, or diseases of the nerve roots of the lumbar spine are all neurological conditions that may produce foot drop. Second, the muscles themselves may be damaged. Third, there can be some skeletal or other anatomical abnormality that affects the movement of the ankle or foot. A combination of these factors can also be involved, as is the case with the drop foot malady known as Charcot foot.

Diagnosis

Diagnosis of foot drop is based on the visual appearance of the altered behavior of the foot. Analysis of blood can be done to look for a metabolic cause, such as diabetes, alcoholism, or presence of a toxin. Among the tests

Key Terms

Gait Body position during and manner of walking.

Orthotic A device applied to or around the body to aid in positioning or mobility, commonly used to control foot mechanics.

commonly performed are fasting blood sugar, hemoglobin determination, and determination of the levels of nitrogen and creatinine.

Visual examination of the foot can include routine photographs, **magnetic resonance imaging** or magnetic resonance neurography (both of which are useful in visualizing areas surrounding damaged nerves). An electromyelogram can be useful in distinguishing between the different types of nerve damage that can be responsible for foot drop.

Treatment team

Treatment can involve the family physician, family members, and physical therapists. Physical therapists guide exercises that assist in maximizing muscular strength.

Treatment

Foot drop that cannot be treated by surgery is often treated using a special orthotic device that provides normal range of motion to the foot and ankle during walking. Other people with foot drop can benefit from the stimulation of the affected nerves. The stimulation is applied as the foot is raised during a stride and is stopped when the foot touches down on the ground.

When the cause of foot drop is a muscular or nerve difficulty, surgery can be beneficial. Surgery can relieve the pressure on a compacted nerve, repair a muscle, and even restore a normal gait by lengthening the Achilles tendon or replacing a defective tendon.

Recovery and rehabilitation

Depending on the nature of the cause of foot drop, recovery can be partial or complete. Physical therapy and an ankle foot orthotic device worn in the shoe are important aspects of rehabilitation.

Clinical trials

As of mid-2004, there were no **clinical trials** recruiting participants for the study or treatment of foot drop, although the National Institute of Neurological Disorders and Stroke supports research into many of the neurological conditions that may result in foot drop.

Prognosis

When foot drop is due to a compressed nerve, corrective surgery can produce a complete recovery within several months. If the cause is a skeletal problem or other neurological problem, the prognosis for complete recovery is not as certain.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

National Institutes of Health. Bldg. 31, Rm. 4C05, Bethesda, MD 20892. (301) 496–8188; Fax: (540) 862–9485. ncpoa@cfw.com. <http://www.niams.nih.gov/index.htm>.

Brian Douglas Hoyle, PhD

Fourth nerve palsy

Definition

The sole function of the fourth nerve is innervation of the superior oblique muscle, which is one of the six muscles of eye movement. Fourth nerve palsy or trochlear nerve palsy is a neurological defect resulting from dysfunction of the fourth cranial nerve. Double vision, also known as diplopia, may occur because of the inability of the eyes to maintain proper alignment.

Description

Trochlear nerve palsy has been described since the mid-1800s. Bielchowsky was first to describe it as the leading cause of vertical (two images appearing one on top of the other or at angles) double vision.

Injury to the fourth cranial nerve can stem from congenital or acquired causes with one or both nerves being affected. It is unclear whether the congenital variant of this disorder is due to developmental abnormalities of the nerve itself or nucleus, which is an area of the brain where

the nerve begins and receives signals for proper functioning. In addition the muscle and its tendon may also display abnormal laxity and muscle fiber weakness. Most cases of acquired fourth nerve palsy results from dysfunction of the nerve itself, although cerebrovascular accidents (**stroke**) may directly injure the nucleus.

Demographics

Fourth nerve palsies have no predilection for males or females. It is difficult to accurately predict the occurrence of congenital palsies since some go unnoticed throughout a person's life. Acquired nerve palsies are more likely to occur in older patients with diabetes or vascular disease versus the general population.

Causes and symptoms

Causes of fourth nerve palsy can be broadly classified as congenital or acquired. Isolated congenital palsies may be heralded by head-tilting to the opposite side of the affected nerve in early childhood. In others a congenital palsy may go unnoticed because of a compensatory mechanism allowing for alignment of the eyes when focusing on an image.

Isolated acquired trochlear nerve palsies can be the result of numerous disorders. Most commonly an underlying cause cannot be found and this is known as an idiopathic palsy. Due to its long course within the brain, the fourth nerve is susceptible to injury following severe head trauma. Depending on the site of **nerve compression** during trauma one or both nerves may be affected. **Aneurysms** or brain tumors may directly compress or result in an increase of intracranial pressure (the pressure within the skull) resulting in nerve palsies.

Disorders such as **myasthenia gravis**, diabetes, meningitis, microvascular disease (atherosclerotic vascular disease) or any cause of increased intracranial pressure may result in trochlear nerve palsy. A congenital palsy that has gone undetected may manifest itself in adulthood when the compensatory mechanism for ocular alignment is lost. Additionally the removal of a cataract may restore clear vision to both eyes allowing the patient to become aware of their double vision.

A child with a congenital palsy may be found doing a head tilt by his or her parents or relatives. Children will very rarely complain of double vision.

Adults with a new onset fourth nerve palsy will note two images, one on top of the other or angled in position when both eyes are open. Covering of one eye, no matter which one is covered, will resolve their diplopia. Their double vision will worsen when looking down or away from the affected side. If both nerves are affected he or she may experience a horizontal diplopia (two images side by side) when looking downward. If a decompensated palsy is suspected, one should review old photographs to document a pre-existing head tilt to support the diagnosis.

Key Terms

Diplopia Visual sensation of seeing two images of the same object, resulting from a failure of the eyes to properly align. Also known as double vision.

Superior oblique muscle One of six extraocular muscles concerned with eye movement. The superior oblique muscle pushes the eye down, turns it inward and rotates it outward.

Myasthenia gravis An autoimmune disease characterized by fluctuating weakness of voluntary muscles from antibodies which block neurochemical transmission at the neuromuscular junction.

Diagnosis

Diagnosing a fourth nerve palsy is for the most part a clinical diagnosis. Careful history taking and examination is the key to diagnosis. The Bielchowsky head-tilt test is one commonly used and reliable technique to diagnose isolated trochlear nerve palsies. Review of patient's old photographs can prove indispensable in diagnosing a decompensated palsy, obviating the need for additional testing.

Computed tomography or **magnetic resonance imaging** may be needed if the palsy is thought to be due to a structural brain lesion. Blood work or a lumbar puncture may be ordered if myasthenia gravis, meningitis or other systemic disorders are considered as potential causes.

Treatment team

Ophthalmologists, neuro-ophthalmologists, optometrists and neurologists are medical specialists who can evaluate and diagnose a patient with a fourth nerve palsy. Usually an optometrist or ophthalmologist will initially see a patient complaining of diplopia or displaying stigmata of trochlear nerve palsy. A referral will then likely be made to a **neurologist** or neuro-ophthalmologist for evaluation and workup.

Treatment

Since most fourth nerve palsies are idiopathic, treatment is conservative given the high rate of spontaneous resolution. Monitoring a patient for six months to one

year for improvement can prove to be frustrating and disabling for the patient. A prism may resolve or greatly reduce a patient's diplopia during this period, allowing for return to normal daily activities, such as driving, shopping or reading.

Botulinum toxin used to weaken muscles that overact, causing ocular misalignment, in the presence of a trochlear nerve palsy has been disappointing thus far. Surgery aimed at weakening or strengthening one or more of the extraocular muscles has proven useful in many cases of persistent palsies. Indications for surgery include worsening diplopia, head-tilt resulting in neck **pain** and poor cosmetic appearance. Procedures performed include the Knapp, Plager or Harada-Ito techniques and are chosen based on the amount and type of ocular misalignment found on examination. These procedures weaken or strengthen extraocular muscles by relocating their attachments to the eye. Muscles may also be weakened by cutting across or removing a portion of the muscle.

Recovery and rehabilitation

A six-month to one-year waiting period is warranted to observe for spontaneous improvement. During this period the patient may benefit from prismatic lenses to eliminate or reduce their diplopia. Eye movement exercises have not proved useful for improving or expediting recovery.

Clinical trials

As of November, 2003 no **clinical trials** regarding trochlear nerve palsies were underway.

Prognosis

The prognosis for trochlear nerve palsies is dependent upon the underlying cause. Most cases of idiopathic or microvascular nerve palsies resolve within a several weeks to six-month time period without treatment. Traumatic nerve palsies may take up to one year to resolve, with less than half regaining any improvement. Palsies secondary to brain masses or aneurysms have the least likelihood of any recovery and may take up to one year to improve. If present, proper treatment of myasthenia gravis or other underlying systemic disease, excluding a cerebrovascular accident usually results in complete recovery in the vast majority of cases.

Special concerns

Patients afflicted with a fourth nerve palsy should refrain from driving unless an eye patch is used. In addition certain types of employment may warrant a medical leave or temporary change of duties.

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Adam J. Cohen, MD

Friedreich ataxia

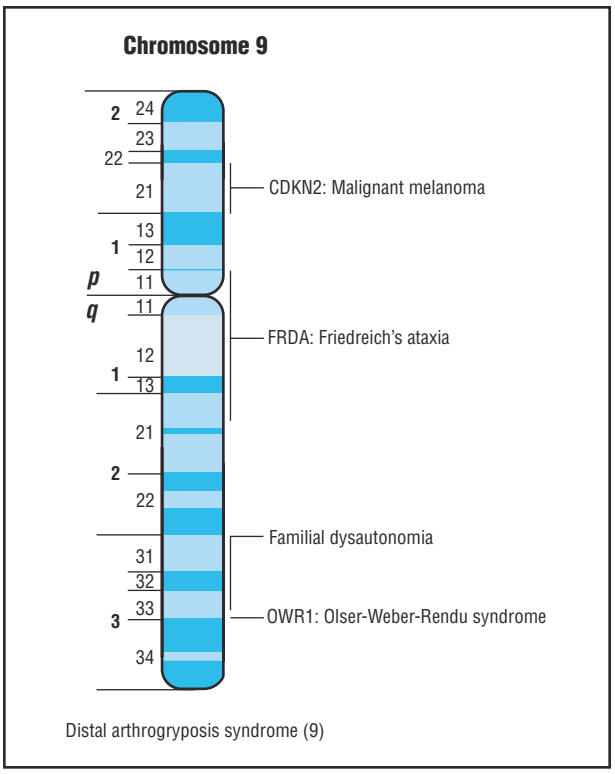
Definition

Friedreich **ataxia** (FRDA or FA) is an inherited, degenerative nervous system disorder that results in muscle weakness and inability to coordinate voluntary muscle movements.

Description

Onset of FDRA is usually in childhood or early adolescence. The disorder is characterized by unsteady gait, slurred speech, absent knee and ankle jerks, Babinski responses, loss of position and vibrations senses, leg muscle weakness, loss of leg muscle mass, scoliosis, foot deformities, and heart disease. FRDA is a slowly progressive condition associated with a shortened life span, most often due to complications of heart disease.

FRDA is named for Nikolaus Friedreich, the German doctor who first described the condition in 1863. The most common form of the disorder, found in about three–quarters of patients, is referred to as "classic" or "typical" FDRA. Atypical forms of FDRA include: late onset Friedreich ataxia (LOFA), very late onset Friedreich ataxia (VLOFA), Friedreich ataxia with retained reflexes (FARR), Acadian type (Louisiana form), and spastic paraparesis without ataxia.



Friedreich ataxia, on chromosome 9. *(Gale Group.)*

Demographics

FRDA is the most common inherited ataxia and affects between 3,000–5,000 people in the United States. The prevalence of FDRA in the Caucasian population is approximately one in 50,000 to one in 25,000. Prevalence appears to be highest in French Canadians from Quebec, Acadians from Louisiana, and among certain populations in southern Italy and Cyprus. Approximately 1% of Caucasian individuals carry one defective copy of the gene responsible for FRDA, known as FRDA1. FRDA is rare in people of Asian or African descent.

Causes and symptoms

FRDA is an autosomal recessive condition, which means that an affected individual has two altered or nonfunctioning FRDA1 genes, one from each parent. The FRDA1 gene is located on chromosome 9 and codes for a protein called frataxin. The most common gene alteration (or mutation), which is found in greater than 95% of affected individuals, is a triplet repeat expansion. The triplet repeat is a sequence of DNA bases called GAA. Normally the GAA sequence is repeated five to 33 times but in people with FRDA, it is repeated between 66 to 1700 times. Longer GAA triplet repeats are associated with more severe disease, but the severity of disease in a given individual cannot be predicted from the repeat length. About 4% of patients have the triplet repeat expansion in one copy of the FDRA1 gene and a different type of mutation, a point mutation, in the other FRDA1 gene. There have been a few patients with classic FDRA in which the FRDA1 gene on chromosome 9 has been shown not to be the cause.

FRDA1 gene mutations lead to loss of function of the gene and subsequently to decreased production of frataxin. Frataxin plays a role in the balance of iron in the mitochondria, the cellular energy structures. Frataxin insufficiency leads to a number of effects including excessive iron accumulation in the mitochondria and, eventually, the production of chemicals called free radicals that can damage and kill the cell. The cells most affected in FRDA are those in the brain, spinal cord, nerves, heart, and pancreas.

FRDA is a slowly progressive, unremitting, ataxia. There is variability in age of onset, presence of symptoms, rate of progression, and severity. Although onset of FRDA usually occurs before age 25, symptoms may appear as early as age two or as late as 30 to 40 years. Gait ataxia, or difficulty walking, is often the first sign of the disease. For example, an affected child might trip frequently over low obstacles. The ataxia eventually spreads to the arms within several years, resulting in decreased hand-eye coordination. Unsteadiness when standing still and deterioration of position sense is common. Other symptoms that appear early in the course of the disease are loss of knee and ankle tendon reflexes and **dysarthria** (slowness and slurring of speech). Over time, individuals with FRDA experience loss of sensation that begins in their hands and feet and may spread to other parts of the body. Abnormal muscle control and tone leads to problems such as scoliosis (curvature of the spine) and foot deformities such as *pes cavus* (high-arched feet) with extensor plantar response. Arm weakness, if it occurs, develops later in the course of the disorder. Loss of muscle control eventually necessitates use a wheelchair.

Heart disease represents a potentially significant complication of FRDA. Heart muscle enlargement with or without an abnormal heartbeat is present in about two–thirds of cases and represents a major cause of death. About one–third of patients develop diabetes, most of whom will require insulin. Other medical findings in FRDA include optic nerve atrophy, nystagmus (eye tremor), tremor, amyotrophy (loss of muscle mass), hearing loss, difficulty swallowing, and incontinence.

Diagnosis

A diagnosis of FDRA is based on clinical findings and results of genetic testing. The clinical diagnosis of Friedreich ataxia is made through physical exam and medical history. The presence of progressive ataxia, loss of position and/or vibration sense, and loss of lower limb

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 for analysis. 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 to draw out a sample of the chorionic membrane. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome A microscopic thread-like structure found within each cell of the human body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Chromosomes contain the genetic information necessary to direct the development and functioning of all cells and systems in the body. They pass on hereditary traits from parents to child (like eye color) and determine whether the child will be male or female.

DNA Deoxyribonucleic acid; 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.

tendon reflexes in a child or adolescent is suspicious of the diagnosis. Tests that may aid in diagnosis include **electromyography**, nerve conduction studies, an electrocardiogram, an echocardiogram, **magnetic resonance imaging (MRI)**, computed tomography (CT) scan, a spinal tap, and glucose analysis of blood and urine. Genetic testing is recommended for all individuals in whom the diagnosis of FRDA is suspected.

Genetic testing is accomplished by counting the number of GAA repeats in the FRDA gene to see if there is an expansion (66 or more repeats). For those cases in which only one FRDA gene has a triplet repeat expansion, 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 chorionic villus sampling (CVS) or amniocentesis.

Treatment team

Management of FRDA requires a multidisciplinary approach. In addition to the patient's primary health care professionals, medical professionals involved in the care of patients with FRDA generally include a **neurologist**, a cardiologist, an orthopedic surgeon, an ophthalmologist, a speech therapist, a physical therapist, an occupational therapist, and a physiatrist. Additional specialists in endocrinology and urology may be needed. Some patients with FRDA may receive comprehensive services through a **muscular dystrophy** association (MDA) clinic and/or a Shriner's Hospital for Children. A genetic specialist, such as a clinical geneticist or a genetic counselor, may be helpful to the patient and family, especially at the time of diagnosis or prior to genetic testing. Psychological counseling and support groups may also assist families in coping with this condition.

Treatment

As of 2003, there is no cure for FRDA. The purpose of treatment, which is largely supportive, is to help patients optimize function and to manage any associated medical complications of the disorder. Treatment includes most if not all of the following options:

- Orthopedic intervention. Braces or surgery may be necessary to treat scoliosis and foot deformities. For example, a surgical procedure known as spinal fusion may be considered in patients with significant curvature.
- Medications. Some antioxidants (chemicals that capture free radicals) have shown benefits in patients with FRDA. Vitamin E and coenzyme Q10, which are naturally occurring substances, may be prescribed. Patients should discuss the current recommendations with their physician.
- Cardiac and diabetes care. Since cardiac disease is the most common cause of death, proper cardiac care is essential. For those cases in which there is heart disease,

medications can be effective for many years. Of those individuals with diabetes mellitus, most will require insulin therapy.

Recovery and rehabilitation

Rehabilitation for Friedreich ataxia consists of speech, physical, and occupational therapy. The goal of these therapies is to make full use of the patient's existing muscular functions. For example, physical therapy can help stretch muscles to improve or maintain flexibility. Speech therapy can help to retrain certain muscles in order to improve speech and swallowing. Occupational therapy can teach patients to use adaptive techniques and devices that may help compensate for loss of coordination and strength. For example, prostheses, walking aids, and wheelchairs may be recommended to help the individual with FRDA to remain ambulatory or mobile.

Clinical trials

Research studies of idebenone, a synthetic antioxidant, have shown it to reduce hypertrophy (overgrowth) of the left ventricle of the heart in patients with FRDA. A phase I clinical trial will be conducted in the United States to establish the maximum tolerated dose of idebenone in children, adolescents, and adults with Friedreich's ataxia; as of November 2003, active patient recruitment was underway. Information on this trial can be found at <http://www.clinicaltrials.gov> or by contacting the National Institute of Neurological Disorders and Stroke patient recruitment and public liason office at 1-800-411-1222. Another substance that is being researched is an antioxidant known as mitoquinone or "MitoQ" which is a synthetic form of coenzyme Q10 that has the potential to protect the mitochondria from free radical damage. As of 2003, mitoquinone was in the developmental phase of study and not yet available to patients.

Prognosis

The rate of progression of FRDA varies. Most patients lose the ability to walk within 15 years of symptom onset, and 95% require a wheelchair for mobility by age 45. Shortened life span from FRDA 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.

Special concerns

A child with a diagnosis of Friedreich ataxia is eligible to have an Individual Education Plan (IEP). An IEP provides a framework from which administrators, teachers, and parents can meet the educational needs of a child with FRDA.

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Friedreich's Ataxia Research Alliance (FARA). 2001 Jefferson Davis Highway, Suite 209, Arlington, VA 22202. (703) 413-4468; Fax: (703) 413-4467. fara@frda.org. <http://www.frda.org>.

Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717; Fax: (520) 529-5300. mda@mdausa.org. <http://www.mdausa.org>.

National Ataxia Foundation (NAF). 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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G

Gabapentin

Definition

Gabapentin is a prescription drug that was initially approved to help manage **epilepsy**. The Food and Drug Administration (FDA) has also approved gabapentin for treatment of the nerve **pain** that sometimes accompanies herpes infections. Gabapentin is available in the United States under the trade name Neurontin.

Purpose

Although the FDA has only approved gabapentin for managing epilepsy and treating nerve pain associated with herpes infections, doctors often prescribe the medication for managing other conditions, including **tremors** associated with **multiple sclerosis**, nerve pain, bipolar disorder, and migraine prevention.

Description

As an antiepileptic drug, gabapentin may be used in conjunction with other drugs to prevent partial **seizures**. Partial seizures are caused by brief abnormal electrical activity in localized areas of the brain. Partial seizures usually do not cause unconsciousness, but may cause rhythmic contractions in one area of the body or abnormal numbness or tingling sensations.

Although gabapentin was originally approved by the FDA in 1993, it is still not understood how gabapentin prevents seizures. However, the drug is related to gamma-aminobutyric acid (GABA), a neurochemical that possesses inhibitory properties. In brain cells, these inhibitory actions prevent excitatory electrical impulses from spreading to neighboring cells. As a result, gabapentin probably prevents the spread of abnormal excitatory activity in the brain at least in part, by mimicking the actions of GABA.

By preventing excitatory communication between cells, gabapentin may also inhibit the electrical impulses involved in pain conduction. This may account for the drug's ability to alleviate pain, especially nerve pain.

When gabapentin is used along with other therapies for managing epileptic partial seizures, improvements should be observed within 12 weeks. On the other hand, pain relief may be evident within one week when the drug is used for pain associated with herpes infections.

Recommended dosage

For adults, the initial dose of gabapentin is 300 mg taken by mouth three times each day. The dosage may be increased if necessary. Dosages as high as 800–1,200 mg three times daily have been well tolerated.

In children three to 12 years of age, the starting dose should be 10–15 mg/2.2 lb (1 kg)/day given in three equal doses. This dose can be increased until an effective dosage is reached, typically 25–40 mg/2.2 lb (1 kg)/day. Lower dosages are required for patients that have kidney disease.

Precautions

In children, gabapentin may cause behavioral and emotional disorders. The drug should be used cautiously and the dosage should be reduced in those with severe kidney disease. In experimental animals, gabapentin caused tumors to develop; however, it is not known if this occurs in humans.

Patients should take gabapentin only as prescribed. The drug should never be stopped abruptly because doing so increases the likelihood of having a seizure. Since gabapentin can cause **dizziness** and **fatigue**, patients should avoid driving or operating complex machinery until they know whether the drug adversely affects their reaction time or impairs their judgment.

Side effects

The most common side effects that cause adults to stop taking gabapentin are dizziness, sleepiness, fatigue, shaky movements, difficulty walking, or swelling in the ankles.

Key Terms

Antiepileptic A drug that prevents or limits the spread of epileptic seizures.

Bipolar disorder A mental illness that causes episodes of depression and mania; also known as manic-depressive illness.

Epilepsy A chronic nervous system disorder that typically causes temporary behavior changes, uncontrolled shaking, loss of attention, or unconsciousness.

Gamma-aminobutyric acid (GABA) The major inhibitory neurotransmitter in the brain.

Herpes A virus that causes cold sores, sexually transmitted diseases, shingles, or chicken pox.

Kilogram (kg) One thousand grams, or about the equivalent of 2.2 pounds (lb).

Migraine A recurrent headache, often accompanied by vomiting, that typically affects just one side of the head.

Milligram (mg) One-thousandth of a gram, or about the equivalent of 0.035 ounces (oz).

Multiple sclerosis A chronic disease of the central nervous system in which the tissues surrounding the brain and spinal cord are damaged.

Neurotransmitter A chemical in the brain that transmits messages between neurons or nerve cells.

Partial seizures Brief, temporary alterations in movement or sensory nerve function cause by abnormal electrical activities in localized regions of the brain.

In children, the side effects the drug may cause include emotional problems, hostility, and hyperactivity.

Interactions

Unlike many other drugs that are used to treat epilepsy, there are few drug interactions associated with gabapentin. It is recommended, however, that antacids not be used sooner than two hours after gabapentin to avoid compromising gabapentin's effectiveness.

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Kelly Karpa, PhD, RPh

Galantamine *see* **Cholinesterase inhibitors**

Gaucher disease

Definition

Gaucher disease is a rare, inherited disorder in which a deficient or missing enzyme causes an abnormal buildup of a fatty substance called glucosylceramide throughout the body. Abnormal accumulations of this substance are toxic to organs and tissues, resulting in progressive, permanent damage.

Description

Gaucher disease belongs to a group of conditions called lipid storage diseases. Lipids are fatty substances used throughout the body. In lipid storage diseases, enzymes that would ordinarily break down lipids so that they can be appropriately used are absent. This results in the progressive accumulation of large quantities of these lipids.

In Gaucher disease, the specific type of lipid that accumulates is called a glucosylceramide. Deficient activity of an enzyme called beta-glucosidase results in glucosylceramide accumulation throughout the body and damage to normal tissues and organs.

There are three types of Gaucher disease. Type 1 is the most common. Each type has a characteristic age of onset and constellation of symptoms.

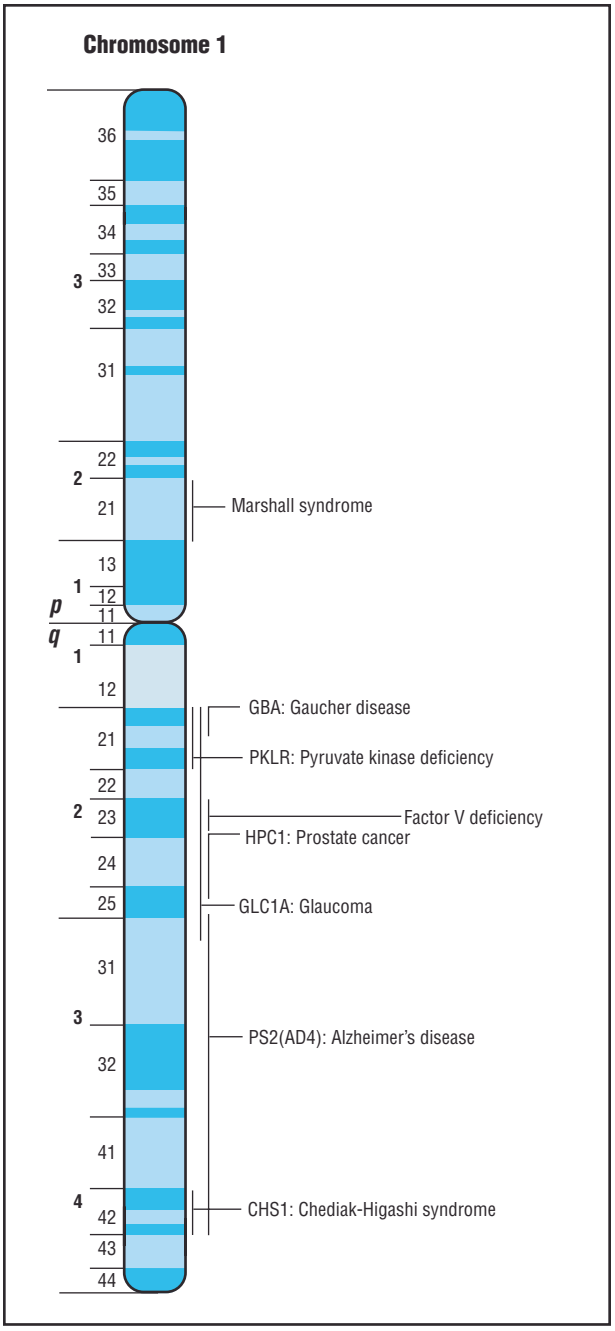
Demographics

In the general population, one in 50,000–100,000 develop Gaucher disease. However, Gaucher type 1 disease is considerably more common among Jewish people from eastern and central Europe (Ashkenazi Jews), affecting one in 500–1,000 individuals.

Causes and symptoms

Gaucher disease is an inherited disease, caused by a defective GBA gene. The disease is recessive, meaning that a child has to inherit a defective gene from both the mother and the father in order to have the actual condition.

Type 1 affects both children and adults. Its major manifestations include easy bruising, anemia, **fatigue**,



Gaucher disease, on chromosome 1. *(Gale Group.)*

liver and/or spleen enlargement, bone and joint **pain**, joint problems, and increased risk of bone fractures.

Type 2 usually begins to show symptoms during infancy. This type causes many of the same symptoms seen in type 1 (easy bruising, anemia, liver and/or spleen enlargement), but it also results in severe and progressive neurological problems. Damage to the **central nervous system** results in **seizures**, difficulty walking, paralyzed eye muscles, and progressive **dementia**. Most patients with type 2 disease die by about age two.

Type 3 causes the same kinds of symptoms seen in type 2, but the neurological involvement is more mild and the progression is more gradual.

Diagnosis

Diagnosis of Gaucher disease can be made by performing a bone marrow examination, and identifying specific "Gaucher cells" within the specimen. Other cells can be examined to demonstrate decreased activity of the enzyme beta-glucosidase. DNA testing can also reveal the specific mutation responsible for the disease, particularly within Ashkenazi Jewish populations.

Treatment team

The treatment team may vary, depending on the patient's specific symptoms. Early in the diagnostic phase, a geneticist may be helpful. If neurological problems predominate, a **neurologist** will be necessary. A hematologist may be consulted to handle the blood-related complications such as anemia. Other specialists may include an ophthalmologist, orthopedic surgeon, physical and occupational therapists, and speech and language therapist.

Treatment

Symptomatic treatment may include blood transfusions to treat anemia, removal of the enlarged spleen, and joint replacement. Some patients have been cured via bone marrow transplant, but this procedure carries a very high risk of complications and death, and requires a carefully matched donor, which can be difficult to find.

Newer treatments include enzyme replacement therapy. While not curative, intravenous enzyme replacement can decrease the severity of, or reverse, many of the complications of type 1 disease, including liver/spleen enlargement, anemia, neurologic problems, and bone abnormalities. Severe brain damage cannot be reversed, however.

Clinical trials

A variety of **clinical trials** on Gaucher disease are being conducted, including testing of a medicine called OGT918 that may slow or decrease the accumulation of lipids, hopefully with improved neurological outcomes. Other clinical trials are evaluating the outcome of treatment with enzyme replacement therapy in Gaucher disease types 2 and 3, the effect of alendronate sodium on bone disease in Gaucher disease, and the short- and longer-term outcome of bone marrow or umbilical cord blood transplantation in children with Gaucher disease.

Key Terms

Beta-glucosidase An enzyme responsible for breaking down glucosylceramide.

Glucosylceramide A chemical substance composed of glucose (sugar) and lipid (fat).

Lipid A fatty substance in use throughout the body.

Prognosis

The prognosis of Gaucher disease depends on the specific type. Because type 1 has no neurologic manifestations, it has the best prognosis. Lifespan depends on the severity of the complications, but some patients live into the 70s or 80s. Type 2 is universally fatal, generally by about age two. Patients with type 3 generally survive until about age 20 or 30.

Special concerns

Carriers of the defective gene may be identified during genetic counseling, and prenatal diagnosis is also possible.

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Children's Gaucher Research Fund. PO Box 2123, Granite Bay, CA 95746. (916) 797-3700; Fax: (916) 797-3707. research@childrensgaucher.org. <http://www.childrensgaucher.org>.

National Gaucher Foundation. 5410 Edson Lane, Suite 260, Rockville, MD 20852-3130. (301) 816-1515 or 800-GAUCHER (428-2437); Fax: (301) 816-1516. ngf@gaucherdisease.org. <http://www.gaucherdisease.org>.

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Gene therapy

Definition

Classic gene therapy is the direct use of genetic material in the treatment of disease. This usually involves inserting a functional gene or DNA fragment into key cells to mitigate, or cure, a disease. A broader definition of gene therapy includes all applications of DNA technology to treat disease. For people with certain neurological conditions such as **Parkinson's disease** and **Canavan disease**, initial gene therapy trials have shown promise. Developing gene therapies for treating disorders of the nervous system poses unique challenges, such as how to introduce the therapeutic gene across the blood-brain barrier or how to target the therapeutic gene to one specific area of the brain.

Purpose

Genes play a role in every function of the human body. Defects or mutations within a gene can lead to malfunction or disease of cells, tissues, and/or organs. Although standard drug therapy is usually effective in treating the symptoms of a disorder, a patient may be required to take the drugs for an extended time and there may be serious or unpleasant side effects. However, a patient may be cured with few negative consequences if treatment can be targeted directly at the specific cause of the disease (the gene defect), or if that cause can be neutralized or reversed. Therefore, gene therapy provides an attractive alternative to drug therapy as it seeks to provide treatment strategies that will be more complete and less toxic to the patient. Furthermore, gene therapy may provide a way of treating diseases that cannot be managed by standard therapies.

Description

There are many diverse approaches to gene therapy since the biological basis of each disease is unique, presenting a different set of parameters and challenges. However, in each case, a basic set of criteria must be met. First,

it is essential to fully understand the disease to be treated. The cells or tissues associated with the disease must be well defined and accessible. The gene and the specific mutation or mutations causing the disease must be known, and it must be possible to isolate or synthesize a normal, functional copy of that gene and to incorporate it into a vector. The vector then transfers the new gene to the target cells where, hopefully, the gene will become fully active. The most common roles for the expressed gene include replacing a defective gene, inhibiting or degrading a deleterious DNA, RNA, or protein, or directly or indirectly killing the cell.

Single gene disorders resulting in a loss of gene function in one specific target tissue provide the easiest options for gene therapy, though strategies for many types of mutations have been investigated. A broad spectrum of diseases has been considered for gene therapy, including:

- neurological disorders, e.g., Parkinson disease, Huntington disease
- muscular dystrophies
- immunological disorders, e.g., severe combined immunodeficiency syndrome (SCIDS)
- blood abnormalities, e.g., thalassemias, hemophilia
- cancer

Unfortunately, many of the more commonly occurring disorders, including heart disease, diabetes, and high blood pressure, result from defects in multiple genes making them unlikely candidates for gene therapy using existing technologies.

For each disease, it must be determined if *ex vivo* or *in vitro* technology is the best approach. In *ex vivo* technology, patient cell samples are collected and cultured in the laboratory. The new gene is incorporated into the growing cells, and these are subsequently transferred back into the patient. Not all of the cultured cells will include the new gene, and not all will survive the transfer. The hope is that a sufficient number of the modified cells will be functional in the patient such that the therapy will reverse the disease. *In vitro* therapy involves injecting the new gene directly into the target tissue where the individual cells must pick it up. Of the two, this method is technically easier and cheaper, but it is harder to determine how many of the target cells actually acquire the new gene. *Ex vivo* therapy is more expensive and time consuming, but allows greater control of the conditions.

Both processes require the use of a vector to get the new gene across the cell membrane and into a cell. Viruses have proven to be highly effective as vectors since these are biological entities with a natural function of infecting host cells. DNA technology allows viruses to be manipulated to replace the normal payload of disease-causing genetic material with therapeutic genes. The virus will retain its ability to infect a host cell but, instead of causing a disease, it will deposit the new gene into the cell.

Other mechanisms of gene transfer have also been investigated. Artificial chromosomes have been developed, but these are often too large to move across cell membranes. Liposomes, structures with lipid membranes, that encompass genetic material can be successfully used as vectors if the liposome is absorbed by the cell or if its membrane fuses with the cell membrane releasing the new gene inside the cell.

Once the gene enters the cell, one of two things occurs. It may be degraded and lost, which is an unfavorable outcome. Preferably, the gene will stably incorporate into the DNA of the target cell so that it can be processed as a normal part of that genome. If the gene therapy is designed to replace a defective gene, the best-case scenario is for the new gene to integrate into a completely renewable cell such as a stem cell. Theoretically, in this situation, the gene will be permanently incorporated into the patient's body and no further therapy will be required. Alternatively, if the gene integrates into a genome of a cell with a finite lifespan, the beneficial effects of the gene will only exist while that cell lives, requiring the gene therapy to be repeated at a later time.

One of the early successes of gene therapy was for a four-year-old girl with adenine deaminase (ADA) deficiency. This is a form of SCIDS that results in malfunction of the immune system and can lead to death as a result of severe infection. Conventional treatment had failed for this patient, making her a candidate for gene therapy. A normal ADA gene was incorporated into a retroviral vector that transferred the gene into the patient's lymphocytes *in vitro*. The modified cells were returned to her circulation by transfusion. After five months, her levels of ADA activity had risen from less than 1% to 50%. With additional therapies over the next two years, her health improved as the enzyme activity stabilized, and she was able to begin a normal life. Twelve years later, she still demonstrates reasonable levels of ADA activity, but the gene therapy was not a cure as she must continue to receive the standard enzyme replacement therapy to maintain her health.

Acquired diseases can also be treated with gene therapy as demonstrated by a novel strategy for treating brain cancer. The thymidine kinase (TK) gene from the herpes simplex virus (HSV) has an enzymatic property that converts the drug ganciclovir into a toxic substance that can kill human cells. It was postulated that this could be used as a targeted killing tool. To investigate, cloned HSV TK

Key Terms

DNA Deoxyribonucleic acid; 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.

Mutation A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease. This change can be transmitted to offspring.

Recombinant DNA DNA that has been altered by joining genetic material from two different sources. It usually involves putting a gene from one organism into the genome of a different organism.

RNA Ribonucleic acid, a nucleic acid that transmits messages in the DNA to other elements in the cell.

Severe combined immunodeficiency syndrome (SCIDS) 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.

Vector A carrier organism (such as a fly or mosquito) that serves to deliver a virus (or other agent of infection) to a host. Also refers to a retrovirus that had been modified and is used to introduce specific genes into the genome of an organism.

Virus A small infectious agent consisting of a core of genetic material (DNA or RNA) surrounded by a shell of protein. A virus needs a living cell to reproduce.

genes were injected into brain tumors. In the brain, only the tumor cells are dividing, so these are the only cells that will be infected by the viral vector, and are thus the only cells that will receive the HSV TK gene. When the patient is subsequently treated with ganciclovir, the tumor cells that have incorporated the HSV TK gene will be selectively killed. **Clinical trials** proved that tumor cells could be selectively eliminated by demonstrating a reduction in the size of the brain tumors in seven of nine patients.

A completely different set of therapies is possible if the idea of gene therapy includes the use of DNA for patient treatment in ways other than inserting new genes into cells. One example is the drug Gleevec that was approved in 2001 for use in patients with chronic myelogenous leukemia (CML). Gleevec is a substance that binds to the defective protein produced in CML, blocking that protein's activity and alleviating the symptoms of the disease. This is a targeted therapy that affects only the cells with the CML mutation, so there are very few side effects. Recombinant DNA technology has also been utilized to generate genetically engineered copies of vaccines (Recombivax HB), antibodies, and normal gene products (insulin).

Aftercare

If the new DNA can be stably incorporated into the proper regenerative target cells, the patient may be cured of disease. No additional care should be required, although periodic monitoring of the patient is appropriate.

For gene therapies in which the new DNA is inserted into cells with a finite lifespan, the therapeutic effect will be lost when those cells die. In these situations, the patient will require continuing treatments. Monitoring of patients who receive drugs and substances arising from recombinant DNA technology is the same as standard drug therapy.

Precautions

Currently classic gene therapy is still experimental. Although many patients have shown significant improvement following their treatment, at least two individuals have died as a result of this type of therapy. Therefore, experts carefully review all protocols before any studies are undertaken. Initial research is done in an animal model system, and any problems detected are carefully evaluated before the same treatments are attempted in humans.

Risks

A patient who is receiving gene therapy may face a number of potential problems. The viral vectors used may cause infection and/or inflammation of tissues, and artificial introduction of viruses into the body may initiate other disease processes. Functional gene therapy relies on stable incorporation of a new gene into an individual's own DNA. As the integration is random, occasionally the new gene may insert within another normally functioning gene, causing its damage or inactivation. This, in turn, could lead to cancer or other disease. It is also critical that the new

gene have the proper regulatory controls so that the gene product is produced in the proper amount. Over-expression of certain genes can have deleterious results. Any of these problems could render the gene therapy ineffective, or, at worst, cause the death of the subject.

Normal results

Classic gene therapy seeks to treat or cure a defined disease by incorporating a functional gene or gene product into target cells of an affected individual.

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Constance K. Stein

Gerstmann-Straussler-Scheinker disease

Definition

Gerstmann-Straussler-Scheinker disease is a progressively disabling and ultimately fatal brain infection caused by a unique protein particle called a prion. Gerstmann-Straussler-Scheinker disease is an inherited disorder, and occurs in familial clusters.

Description

Gerstmann-Straussler-Scheinker disease belongs to a group of diseases originally known as slow virus infections. Currently, slow virus infections are classed together as transmissible spongiform encephalopathies (TSE), or **prion diseases**. Other TSEs include **kuru**, **Creutzfeldt-Jakob disease**, and fatal familial insomnia. The TSE called new variant Creutzfeldt-Jakob disease (also known colloquially as "Mad Cow Disease") has received a great deal of public attention. The TSEs, including Gerstmann-Straussler-Scheinker disease, involve abnormal clumps of protein that accumulate throughout the brain, destroying brain tissue and leaving spongy holes.

Demographics

About 10% of all transmissible spongiform encephalopathies are inherited. Gerstmann-Straussler-Scheinker disease occurs worldwide, but because of its pattern of familial transmission, cases tend to occur in specific geographic clusters. Only a few families have been identified as carrying the mutation that causes Gerstmann-Straussler-Scheinker disease.

Gerstmann-Straussler-Scheinker disease is caused by a genetic mutation caused by an infectious protein particle called a prion, which stands for proteinaceous infectious particle. A prion is similar to a virus, except that it lacks any nucleic acid, which prevents it from reproducing. Prions are abnormal versions of proteins that are found in the membranes of normal cells. These abnormal proteins can be passed directly to individuals through the ingestion of prion-infected tissue or when open sores on the recipient's skin are exposed to prion-infected tissue. In addition to being transmissible (as are other infectious agents like viruses or bacteria), prions are unique because they can also be acquired through genetic inheritance. This is the case with Gerstmann-Straussler-Scheinker disease.

In Gerstmann-Straussler-Scheinker disease, one of several possible specific gene mutations is present, leading to the abnormal deposition of tangled masses of a protein called amyloid throughout the brain. The spinocerebellar tracts (nerves that run from the brain's **cerebellum** throughout the spinal cord) become increasingly atrophied (shrunken) and dysfunctional over time.

Symptoms of Gerstmann-Straussler-Scheinker disease tend to begin in later middle age, usually between the ages of 40 and 55. Early symptoms include unsteady gait and difficulty walking, discoordination, clumsiness. As the disease progresses, the individual experiences difficulty speaking; abnormal, involuntary, rapid darting eye movements; paralyzed eye movement; deafness; blindness; and **dementia**. Death often occurs within five to 10 years of the initial symptoms.

Diagnosis

Diagnosis of Gerstmann-Straussler-Scheinker disease is arrived at through characteristic abnormalities found on the electroencephalogram (EEG), a test of brain waves and electricity. **MRI** studies and biopsies (tissue samples) from the brain may also show changes that are characteristic of

Key Terms

Classic Creutzfeldt-Jakob disease A rare, progressive neurological disease that is believed to be transmitted via an abnormal protein called a prion.

Fatal familial insomnia A rare, progressive neurological disease that is believed to be transmitted via an abnormal protein called a prion.

Gerstmann-Sträussler-Scheinker syndrome A rare, progressive neurological disease that is believed to be transmitted via an abnormal protein called a prion.

New variant Creutzfeldt-Jakob disease A more newly identified type of Creutzfeldt-Jakob disease that has been traced to the ingestion of beef from cows infected with bovine spongiform encephalopathy. Known in the popular press as Mad Cow Disease.

Transmissible spongiform encephalopathy A term that refers to a group of diseases, including kuru, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and new variant Creutzfeldt-Jakob disease. These diseases share a common origin as prion diseases, caused by abnormal proteins that accumulate within the brain and destroy brain tissue, leaving spongy holes.

prion disease. Like certain forms of CJD, Gerstmann-Straussler-Scheinker disease can be analyzed with DNA testing; specifically, the white blood cells are examined in order to identify one of the mutations associated with the disease.

Treatment team

Diagnosis of slow virus infection is usually made by a **neurologist**.

Treatment

There are no available treatments for Gerstmann-Straussler-Scheinker disease. It is relentlessly progressive, incurable, and fatal. Supportive care for the patient and his or her family is the only treatment.

Prognosis

Gerstmann-Straussler-Scheinker disease is always fatal.

Special Concrns

Gerstmann-Straussler-Scheinker disease is unique among transmissible spongiform encephalopathies, because mutations can be identified through DNA analysis of a sufferer's white blood cells. This allows other family members to be counseled regarding their personal risk of disease inheritance, projected age of disease onset, and potential illness duration. While some mutations sentence an individual to certain disease, other locations of mutations have only a 50% chance of leading to actual disease. Additionally, in families known to carry a mutation of Gerstmann-Straussler-Scheinker disease, amniocentesis can identify fetuses affected by the mutation, allowing families to make decisions about whether or not to continue a pregnancy.

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Rosalyn Carson-DeWitt, MD

Gerstmann syndrome

Definition

Gerstmann syndrome is a cluster of neurological symptoms that includes difficulty writing (dysgraphia or agraphia), difficulty with arithmetic (dyscalculia or acalculia), an inability to distinguish left from right, and difficulty identifying fingers (finger **agnosia**).

Description

Two types of Gerstmann syndrome have been identified: an acquired form that occurs in adults who have suffered brain injury through **stroke** or trauma, and a developmental form that has been noted in children.

The brain area that seems to be primarily responsible for the deficits seen in Gerstmann syndrome appears to be the parietal lobe, which is located behind the frontal lobe. Current research has not identified a tendency for the developmental form of Gerstmann syndrome to be inherited.

Although both adults and children with Gerstmann syndrome may have considerable impairment, they do not necessarily have abnormal intelligence.

Demographics

Gerstmann syndrome is usually identified in adult patients who have a history of brain injury or stroke. A very small group of children have also been identified as having the developmental form of the condition. Although the diagnosis tends to be made in school-aged children (usually at the point when writing and calculating become central classroom tasks), the condition may well be congenital. There are no reports clarifying the frequency or incidence of either the acquired or the developmental forms of Gerstmann syndrome.

Key Terms

Acalculia The inability to perform basic calculation (addition, subtraction, multiplication, division).

Agraphia The inability to write.

Angular gyrus A particular ridge (outfolding) in the parietal lobe of the brain.

Aphasia Difficulty using or understanding language.

Apraxia Difficulty performing a voluntary movement, although the muscles necessary are all functional.

Constructional apraxia Difficulty or inability to copy a drawing.

Dyscalculia Difficulty with basic arithmetic and calculations.

Dysgraphis Difficulty writing.

Finger agnosia Inability to identify a particular finger.

Parietal lobes The brain lobes on top of the brain, behind the frontal lobes.

Causes and symptoms

In adults, Gerstmann syndrome may be acquired when bleeding into the brain during a stroke or after a traumatic head injury occurs in an area of the left parietal lobe called the angular gyrus. A few adult cases of Gerstmann syndrome have also been described after viral encephalitis, tumor, or toxic exposure has caused injury to this same area of the brain. A specific cause for developmental Gerstmann syndrome has not been identified, although the fact that both parietal lobes are affected suggests that the problem occurs some time during early brain development.

The core symptoms in Gerstmann syndrome include:

- dysgraphia or agraphia: an inability or impairment in the ability to express oneself through the written word.
- dyscalculia or acalculia: an inability to perform basic calculations.
- left-right confusion: difficulty identifying the left or right of one's body or of other objects.
- finger agnosia: an inability to identify one's own or someone else's finger on the basis of a verbal command to hold up a particular finger.

Adults with Gerstmann syndrome may also display some degree of **aphasia**, which is an impaired ability to communicate verbally, to understand verbal communication, and to understand written language. Children with developmental Gerstmann syndrome may also exhibit poor handwriting, difficulty spelling, reading problems, and difficulty copying simple drawings (called constructional **apraxia**).

Diagnosis

Diagnosis is through a comprehensive neurological exam and through psychoeducational testing.

Treatment team

The treatment team may include a **neurologist**, behavioral pediatrician, psychologist, psychiatrist, occupational therapist, physical therapist, and educational specialist.

Treatment

There is no cure for Gerstmann syndrome. Neither children nor adults with this disorder will recover completely from its effects. Instead, supportive therapy may teach some skills, but will also help identify bypass strategies that can be used. For example, if the arithmetic facts cannot be learned, then the use of calculators and other resources should be encouraged. Word processing programs

on computers, including those that have voice-recognition capability, can greatly assist someone with Gerstmann syndrome with the tasks of writing. Classroom accommodations for children with Gerstmann syndrome can help assure success.

Prognosis

Gerstmann syndrome is a permanent disorder. It will last an individual's lifetime. However, the prognosis can be very good if the patient is helped to understand his or her deficits, supported in using effective bypass strategies, and encouraged to continue developing his or her areas of strength.

Special concerns

Good diagnosis and support is necessary so that individuals with Gerstmann syndrome can maintain the strongest possible self-esteem. Care must be taken not to suggest that the individual's failed efforts are due to laziness or lack of caring. Instead, the neurological basis of the disorder should be clearly explained, and reasonable bypass strategies should be immediately identified and implemented.

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Giant cell arteritis *see* **Temporal arteritis**

Giant cell inclusion disease *see* **Cytomegalic inclusion body disease**

Gilles de la Tourette syndrome *see* **Tourette syndrome**

Globoid cell leukodystrophy *see* **Krabbe disease**

Glossopharyngeal neuralgia

Definition

Glossopharyngeal neuralgia is a chronic **pain** syndrome that causes intense, shooting pains in the back of the tongue and throat, tonsillar areas, and middle ear.

Description

Glossopharyngeal neuralgia may be due to inflammation or compression of either the glossopharyngeal nerve or the vagus nerve, another nerve that innervates (stimulates) the same basic areas. The condition usually comes on quite suddenly, and may wax and wane in severity over time. This condition may occur in conjunction with **trigeminal neuralgia** (a pain syndrome affecting the face).

Demographics

Glossopharyngeal neuralgia usually strikes people over the age of 40. It is a relatively rare condition, affecting about 0.7/100,000 individuals per year.

Causes and symptoms

The cause of glossopharyngeal neuralgia is not completely understood, although it seems that conditions (tumors, infections, injuries, or blood vessels located close to the glossopharyngeal nerve) that put pressure on the glossopharyngeal nerve may sometimes be responsible for its development. Individuals with diabetes or **multiple sclerosis** may also develop glossopharyngeal neuralgia. Episodes of pain may be brought on by swallowing, sneezing, chewing, clearing the throat, eating spicy foods, drinking cold liquids, speaking, laughing, or coughing.

Glossopharyngeal neuralgia causes sudden, intense pains in the throat, mouth, tongue, jaw, ear, and neck. The pains have been described as excruciating and electric shock-like, and usually last from seconds to several minutes. Because the glossopharyngeal nerve also affects heart rate and blood pressure, some patients experience

abnormal heart rhythms during episodes of pain. The heart rate may become so slow, in fact, that the patient faints.

Diagnosis

The diagnosis is usually strongly suspected from the patient's characteristic description of the pain episodes. Often, the doctor can trigger an episode by gently touching the back of the throat with a cotton swab. The test is then repeated after application of a topical anesthetic has been used to numb the throat. If the pain episodes are caused by glossopharyngeal neuralgia, touching the back of the anesthetized throat with a cotton swab will not trigger an episode of pain.

CT or **MRI** may reveal inflammation of the glossopharyngeal nerve or the presence of an abnormality (such as a tumor) that is exerting pressure on the nerve. **Angiography** involves introducing dye into the vascular system, in order to take x-ray, CT, or MRI images that may reveal the location of a blood vessel that is exerting pressure on the glossopharyngeal nerve.

Treatment team

Neurologists and otorhinolaryngologists treat glossopharyngeal neuralgia.

Treatment

Carbamazepine, phenytoin, **gabapentin**, baclofen, and tricyclic antidepressants may be used to ameliorate the pain of glossopharyngeal neuralgia. When a blood vessel is identified as compressing the glossopharyngeal nerve, surgery may be performed to move the vessel or to position a Teflon felt pad between the blood vessel and the nerve, in order to attempt to mitigate any pressure that is exerted on the nerve. In severe cases of glossopharyngeal neuralgia that don't respond to other treatments, surgery that severs the glossopharyngeal nerve may be the only treatment that relieves the sufferer's pain.

Prognosis

The prognosis of glossopharyngeal neuralgia varies, depending on the underlying cause of the disorder. Some individuals are completely relieved of the pain episodes after surgery; others continue to have periodic exacerbations throughout their lives.

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Rosalyn Carson-DeWitt, MD

Glucocorticoids

Definition

Glucocorticoids are naturally-produced steroid hormones, or synthetic compounds, that inhibit the process of inflammation.

Purpose

The target of glucocorticoids: inflammation

Glucocorticoids are used to stop the inflammation process. The inflammatory process has evolved in the body for a useful purpose; namely as a defensive reaction to the damage or injury to tissue. By a series of reactions, inflammation is designed to isolate whatever is causing the irritation, help eradicate the presumed invader, and help repair the surrounding damaged tissue.

The hallmarks of inflammation are redness, heat, swelling, and **pain**. These reactions arise from the various steps in the inflammation pathway. The inflammatory response begins with the expansion of the capillaries, which allows more blood to flow to the target site. Various proteins from the blood then exit the blood and gather at the target site. Ultimately, white blood cells called leukocytes also accumulate at the site of injury. When these processes occur in response to an invader such as a microorganism, this is beneficial for the body, as it can rid the body of a potential problem. However, sometimes the inflammatory response can persist long after the actual problem is gone, or can be maintained if an infection itself becomes chronic, or can be activated by some malfunction in the body's defense mechanisms. Chronic inflammation of this type can cause damage to host tissue. Examples of processes that can produce chronic inflammation are tuberculosis, inflammatory bowel diseases such as ulcerative

Key Terms

Osteoporosis A disorder involving loss of calcium and density in the bones, resulting in brittle bones and changes in posture.

Steroid A naturally-occurring hormone, and a large class of drugs that chemically resemble cholesterol. Among the more common types of steroids, anabolic steroids are sometimes used illegally in athletics, and glucocorticoid steroids are used to reduce inflammation.

colitis and Crohn's disease, silicosis, and the continued presence of a foreign body in a wound.

Glucocorticoids can be prescribed to dampen or stop entirely this chronic inflammatory chain of events. Depending on the particular glucocorticoid that is used, inflammation can be affected at different points in the inflammatory pathway.

Description

Some of the various glucocorticoids can be naturally produced in the body. Chemically, these are steroid hormones. They are different from the infamous anabolic steroids that some athletes use to increase muscle mass and strength. Rather, glucocorticoids are catabolic steroids, meaning they are designed to break down compounds. Natural glucocorticoids are produced in the adrenal glands located immediately above the kidneys (the word adrenal derives from "ad," meaning top of, and "renal," meaning kidney). The region of the adrenal glands called the cortex is the site of glucocorticoid manufacture.

Glucocorticoids can also be artificially made, and are usually referred to as glucocorticoid drugs. Examples of glucocorticoids are prednisone, prednisilone, methylprednisilone, dexamethasone, and hydrocortisone. Glucocorticoids are usually taken orally as tablets, capsules, syrup, and liquid, with the exception of hydrocortisone (which is applied as a cream). Most can also be used in cream form, and some can be applied as drops to relieve eye irritations.

Prednisone is the commonly prescribed glucocorticoid because of its high activity. In the body prednisone is transformed by the liver into prednisolone. Prednisolone is equally as effective and is often prescribed by physicians instead of prednisone. Dexamethasone can be prescribed in higher doses than the other glucocorticoids. A common use for this compound is the reduction of nerve swelling following nerve damage or neurosurgery. Depending on the manufacturer, dexamethasone is marketed as Decadron, Dexameth, Dexone, and Hexadrol.

Glucocorticoids and metabolism

As well as affecting the inflammatory process, glucocorticoids have an effect on the utilization of compounds in the body (metabolism). Indeed, the designation glucocorticoid arose from observations that the hormones played a role in the utilization of glucose. In an absence of food, which can be broken down to supply glucose, glucocorticoids act to increase and maintain the normal levels of glucose in the blood. They accomplish this by stimulating glucose production by cells, particularly in the liver, and by enhancing the breakdown of fat in fat tissue. As well, glucocorticoids curb the storage of glucose in cells of the body, which leaves the sugar ready for use.

Glucocorticoids and inflammation

Glucocorticoids are global in their inhibition of the inflammatory response. That is, they act at different stages in the process, and affect all types of inflammatory responses no matter what stimulated the response. The action of glucocorticoids has to do with their structure. Their shape permits them to move across the membrane that surrounds cells in the body, and to be recognized by molecules inside the cell called glucocorticoid receptors. Binding of the particular glucocorticoid to a receptor forms a complex between the two molecules. This complex can enter the nucleus of the cell (the zone where the genetic material is located, and where the two-step process whereby nucleic acid forms the blueprint for the manufacture of the protein building blocks of the cell takes place). Within the nucleus, the complex affects the manufacture of the proteins. The production of some proteins is enhanced while the manufacture of other protein species is diminished. The latter are proteins involved in inflammation and in the release of a normally membrane-bound molecule that acts as a signal for inflammation to begin. The end result is the suppression of inflammation.

Recommended dosage

The prescribed dosages of glucocorticoids vary depending on the compound used and the nature of the patient's condition. Depending on the glucocorticoid, the dose may be taken once a day, over the course of several doses spaced evenly throughout the day, or even every other day.

Precautions

As with any prescription drug, the recommended daily dosage and schedule for the drugs should not be changed independent of a physician's notification. As well, side effects associated with the long-term use of glucocorticoids can occur.

Side effects

Prolonged use of glucocorticoids may cause a number of adverse effects. These include the suppression of the immune system (which makes the person more susceptible to infections), osteoporosis, shifts in the body's fluid balance, skin changes, changes in brain chemistry, and altered behavior.

Dexamethasone can cause loss of appetite, weight loss, stomach upset, vomiting, drowsiness, **headache**, confusion, fever, joint pain, and peeling skin. Not all side effects will be present in everyone taking dexamethasone.

More severe side effects of glucocorticoid use include development of diabetes (which can occur transiently even with short-term use of the drugs), glaucoma, cataract formation, peptic ulcer, convulsions, and inhibited growth of children. A physician determines whether the potential risks of the particular glucocorticoid outweigh the advantages of its use, and prescribes the minimum dose necessary to achieve the desired effect.

Interactions

Interactions between glucocorticoids and other medications can occur. These include anticoagulants (such as aspirin), digoxin, estrogen, oral contraceptives, **phenobarbital**, some antibiotics, and even some vitamins.

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Brian Douglas Hoyle, PhD

Guillain-Barré syndrome

Definition

Guillain-Barré syndrome (GBS) is an inflammation of the covering that surrounds nerve cells of the brain and spinal cord. The basis of the inflammation is not conclusively known, but is generally considered to arise from a malfunctioning immune system that recognizes host tissues as being foreign. The inflammation reaction damages the nerves of the brain and spinal cord, producing weakness in the muscles, loss of sensation (such as the sense of touch in the fingers), or outright paralysis.

GBS is termed a syndrome rather than a disease because there is no conclusive evidence to support the possibility that a specific disease-causing agent such as a bacteria or a virus is the direct cause of the malady. Infections may be a trigger to the development of GBS, however.

Description

The syndrome is named after George Charles Guillen and Jean-Alexandre Barré, French co-authors of a classic paper on the syndrome that was published in 1916. A third author, André Strohl, was not subsequently associated with the syndrome that was the subject of the paper.

GBS is a rare and acute disorder. An acute disorder displays a rapid appearance of symptoms, and a rapid worsening of the symptoms. In the case of GBS, symptoms typically appear over just a single day. Most often, symptoms are first noticed in the feet and legs. The symptoms often progress to involve different parts of the body over the next several days to several weeks. In addition, during that time other more severe symptoms can appear. In more than 90% of cases, the symptoms reach their peak by four weeks.

The syndrome is an inflammatory disorder, in which a person's own immune system attacks the nerves outside the brain and the spinal cord. These nerves are known as peripheral nerves. The nerve inflammation that occurs can damage the nerve cells. The covering (sheath) of a fatty material called myelin that surrounds the cells can be lost. This loss is called demyelination.

Additionally, the elongated portion of the nerve cell called the axon can be killed. This phenomenon is called denervation. The axon conveys electrical impulses to more distant areas of muscles, and from one nerve cell to another. Demyelination and denervation bring about muscle weakness, loss of sensation, or paralysis because the affected nerves cannot transmit signals to muscles. This loss of signal transmission inhibits the muscles from being able to respond to nerve signals. As well, the brain receives fewer signals and the person can become unable to feel heat, cold, or **pain**.

GBS is also known as Landry-Guillain-Barré syndrome, acute idiopathic polyneuritis, infectious polyneuritis, and acute inflammatory demyelinating polyneuropathy (AIDP). Another malady called chronic inflammatory demyelinating polyradicalneuropathy is possibly related to GBS. It is far less common than GBS (which itself is rare) and persists longer.

Demographics

GBS can occur at any age. However, the syndrome tends to be more prevalent in men and women aged 15–35 years and 50–75 years (a bimodal pattern of age distribution), respectively. Males are slightly more susceptible than females (the ratio of those affected is approximately 1.5 male per female). There is no known racial group that is any more susceptible to GBS, nor any known geographical localization of the syndrome.

In the United States, the syndrome is rare. For example, the annual incidence of GBS in the United States ranges from 0.6 to 2.4 cases per 100,000 people. Nonetheless, GBS is the most common cause of neuromuscular paralysis among Americans.

Causes and symptoms

Causes

The exact cause of GBS is not known. However, bacterial or viral infections may be a trigger for its development. Almost 70% of those who develop GBS have had an infectious illness in the preceding two to four weeks. Examples of infections include sore throat, cold, flu, and diarrhea. Bacteria that have been associated with the subsequent development of GBS include chlamydia, *Mycoplasma pneumoniae*, and *Campylobacter jejuni.*

The suspected involvement of Campylobacter is noteworthy, as this bacterium is a common contaminant of poultry. Inadequate cooking can allow the microbe to survive and cause an infection in those who consume the food. Thus, there may be a connection between GBS and food quality. The form of GBS that may be associated with the presence of Campylobacter may be particularly severe. For reasons that are unclear, the peripheral nerves can themselves be directly attacked, rather than just the myelin sheath around the nerves.

Usually, infections such as those caused by Campylobacter have abated before the onset of GBS. As well, chronic infection with the viruses responsible for mononucleosis, herpes, and acquired immunodeficiency syndrome can prelude the appearance of GBS. The latter is also known as HIV-1 associated acute inflammatory demyelinating polyneuropathy.

Other possible associated factors include vaccination (rabies, swine flu, influenza, Group A streptococci), surgery, pregnancy, and maladies such as Hodgkin's disease and systematic **lupus** erythematosus.

Whether there is direct (causal) connection between infections and maladies and the subsequent development of GBS, or whether the events are only coincidental, is not known. For example, vaccination of Americans against the swine flu in 1976 increased the rate of GBS by less than one case per 100,000 people. Whether this increase was directly due to the vaccine is impossible to determine. Furthermore, more than 99% of people suffering from GBS who have been surveyed by the United States Centers for Disease Control and Prevention (CDC) have not recently been vaccinated. According to the CDC, the chance of developing GBS as a result of vaccination is remote.

It is conceivable that the infections or illnesses disrupt the body's immune system such that autoimmune destruction of nerve cell components occurs. Although this intriguing possibility is favored among many scientists, it remains unsubstantiated.

There is no evidence to indicate that GBS is an infection or that it is a genetically linked (heritable) disorder.

Symptoms

The initial sensation of weakness or paralysis in the toes spreads upward within days to a few weeks to the arms and the central part of the body. In medical terminology, this represents an ascending pattern of spread. The weakness and paralysis can also be accompanied by a tingling sensation, and a cramping or more constant pain in the feet, hands, thighs, shoulders, lower back, and buttocks. Use of the hands and feet can become impaired. More serious development of paralysis can make breathing difficult, even to the point that mechanical ventilation becomes necessary.

Other, less typical symptoms include blurred vision, clumsiness, difficulty in moving facial muscles, involuntary muscle contractions, and a pronounced heartbeat. Symptoms that are indicative of an emergency include difficulty in swallowing, drooling, breathing difficulty, and **fainting**.

Progression from the early symptoms to the more severe symptoms can occur very quickly (i.e., 24–72 hours). Typically, the exacerbated condition persists for several weeks. Recovery then typically occurs gradually, and can take anywhere from days to six months or more.

In very mild cases, an individual may just have a general feeling of weakness. As the symptoms abate after a few weeks, the person may dismiss the incident as a viral infection, without ever knowing the true nature of the illness.

Diagnosis

GBS is suspected if a patient displays muscle weakness or paralysis that has been increasing in severity, especially if an illness has occurred recently. Loss of reflexes such as the knee jerk reaction can be an early clue to a clinician.

Clinical data can be useful in diagnosis. For example, a hormone that is involved in maintaining the proper chemical balance of urine can be affected in GBS. The result is

Key Terms

Autonomic nervous system The part of the nervous system that is concerned with the control of involuntary bodily functions such as breathing, sweating, blinking, and the heartbeat.

Axon The long, hairlike extension of a nerve cell that carries a message to a nearby nerve cell.

Demyelination Loss of the myelin (a fatty substance) sheath that surrounds and insulates the axons of nerve cells and is necessary for the proper conduction of neural impulses.

Neuropathy A disorder of the nervous system or a nerve.

called the syndrome of inappropriate antidiuretic hormone. Antibodies to nerve cells may be present as a result of the body's immune reaction against its own constituents.

Another clue to the diagnosis of GBS can be the finding of muscle weakness by neurological examination. One such test is known as nerve conduction velocity. In this test, the selected nerve is stimulated, usually with surface electrodes contained in a patch that is applied to the surface of the skin. The nerve can be stimulated using a very mild electrical current put out from one electrode, and the resulting electrical activity is recorded by the other electrodes in the patch. The nerve conduction velocity is calculated knowing the distance between electrodes and measuring the time it takes for the impulses to travel from the generating to the measuring electrodes. A person with GBS whose nerves have usually lost some or most of the myelin sheath will display a slower conduction velocity than that displayed by an unaffected person. Electrical impulses travel along the damaged nerve slower than along an undamaged nerve.

Muscle response to electrical stimulation can also be measured by **electromyography** (EMG). In this test, a needle electrode is inserted through the skin into the muscle. When the muscle is stimulated, for example, by contracting it, the resulting visual or audio pattern carries the information about the muscle's response. The characteristic pattern of wavelengths produced by a healthy muscle (the action potential) can be compared to a muscle in someone suspected of having GBS.

When paralysis of the heart muscle is suspected, an electrocardiogram can be used to record the electrical activity of the heart. GBS muscle paralysis can alter the normal pattern of the heartbeat.

Finally, an examination of the cerebrospinal fluid by means of a spinal tap (also known as a lumbar puncture) may detect a higher-than-normal level of protein in the absence of an increase in the number of white blood cells (WBCs). An increase in WBCs is a hallmark of an infection.

Treatment team

Neurologists, immunologists, physical therapists, occupational therapists, and nurses figure prominently in GBS treatment. The assistance of support groups such as the Guillen-Barré Syndrome Foundation International can also be a useful adjunct to treatment.

Treatment

As recently as the 1980s, treatment for GBS consisted of letting the syndrome run its course. While most people recovered completely with time, some people were not as lucky. Those who develop severe symptoms such as breathing difficulty are routinely hospitalized.

One medical procedure that can be useful in the treatment of GBS is called plasmaphoresis. It is also known as plasma exchange. In plasmapheresis, antibody-laden blood plasma (the liquid portion of the blood) is removed from the body. Red blood cells are separated and put back into the body with antibody-free plasma or intravenous fluid. The treatment can lessen the symptoms of GBS and hasten recovery time. As of December 2003, it is not known why plasmapheresis works. It is suspected that the removal of antibodies may lessen the effects of the body's immune attack on the nerve cells.

Another procedure that produces similar results involves the administration of intravenous immune globulin (IVIG). Both treatments have been shown to speed up recovery time by up to 50%. IVIG has been shown to be an effective treatment for immune-system-related neuropathies in general. IVIG may act by reducing the amount of anti-myelin antibodies through the binding of the defective antibodies by healthy antibodies contained in the IVIG solution, and in suppressing the immune response.

Other treatments are designed to prevent or lessen complications of GBS. For example, choking during eating, because of throat muscle weakness or paralysis, can be prevented using a feeding tube, and formation of blood clots can be lessened by the use of chemicals that thin the blood. The pain associated with GBS can be treated with anti-inflammatory drugs or, if necessary, stronger-acting narcotic medication. For patients who have breathing difficulties, clinicians may first need to supply oxygen, install a breathing tube (intubation), and/or use a mechanical device that helps in breathing.

Physical therapy is helpful. Caregivers can move a patient's arms and legs to help maintain the flexibility

and strength of the muscles. Later in recovery, sessions in a whirlpool (hydrotherapy) can help restore function to arms and legs. Often, therapists will design a series of exercises to be performed when the patient returns home.

Recovery and rehabilitation

More than 95% of people afflicted with GBS survive. In about 20% of people, however, muscle weakness and **fatigue** may remain. Some people find that wearing highly elastic gradient compression stockings beneficial. The stockings produce the greatest compression at the toes, with a tapering-off upwards to the thigh. The effect is to reduce the volume of veins, which increases the rate of blood flow through the veins. The increased blood flow can reduce the feeling of numbness in the toes.

Clinical trials

As of early 2004, three **clinical trials** were recruiting patients, including:

- Assessment of chronic Guillain-Barré syndrome improvement with use of 4-aminopyridine. The study, funded by the United States Food and Drug Administration Office of Orphan Products Development, seeks to assess the potential of 4-aminopyridine in increasing the transmission of impulses in damaged nerves. It is hoped that increased nerve activity could restore some lost muscle activity, as has occurred using the drug with those afflicted with **multiple sclerosis**. The contact is the Spain Rehabilitation Center, University of Alabama at Birmingham, 35249-7330; Jay Meythaler, M.D. (205) 934-2088, (email: Jmeythal@uab.edu).
- Safety, tolerability, and efficacy of rituximab in patients with anti-glycoconjugate antibody-mediated demyelinating neuropathy: a double-blind placebo-controlled randomized trial. While not directly related to GBS, the study concerns the loss of the myelin sheath of nerves and so is relevant. The study, sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), is designed to evaluate the usefulness of rituximab in preventing the antibody damage to nerves. The contact is the National Institutes of Health Patient Recruitment and Public Liaison Office, Building 61, 10 Cloister Court, Bethesda, MD, 20892-4754; (800) 411-1222; prpl@mail.cc.nih.gov.
- Diagnostic evaluation of patients with neuromuscular diseases. This NINDS-sponsored study is designed to screen patients for other studies and to help train clinicians in the diagnosis of maladies including GBS. The contact information is the same as the above item.

Prognosis

Most of those afflicted with GBS recover completely, although the recovery can in some cases be slow (months to years). Complete recovery usually occurs when the symptoms fade within three weeks of appearing. The typical scenario is for a patient to experience the most weakness from 10–14 days after the appearance of symptoms, with complete recovery occurring within weeks or a few months. In contrast, a poor prognosis can be associated with a rapid appearance of symptoms, use of assisted ventilation for a month or more, severe nerve damage, and with advancing age.

While recovery is complete for most of those afflicted with GBS, in 10–20% of cases the symptoms reappear, in 15–20% the neurologic complications can persist and can cause a long-term disability, and 5–10% of those who are afflicted die. The main cause of death historically was from respiratory failure due to muscle paralysis. With mechanical ventilation, respiratory failure in GBS is less often fatal. Currently the main cause of death is malfunctioning of the autonomic nervous system, which controls involuntary processes such as heart rate, blood pressure, and body temperature.

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Guillain-Barré Syndrome Foundation International. P.O. Box 262, Wynnewood, PA 19096. (610) 667-0131; Fax: (610) 667-7036. info@gbsfi.com. <http://www.gbsfi.com>.
National Institutes of Health. 9000 Rockville Pike, Bethesda, MD 20892. (301) 496-4000. NIHInfo@od.nih.gov. <http://www.nih.gov>.
National Institute for Neurological Disorders and Stroke. P.O. Box 5801, Bethesda, MD 20824. (301) 496-5761 or (800) 352-9424. <http://www.ninds.nih.gov>.

Brian Douglas Hoyle, PhD

H

Hallervorden-Spatz disease *see* **Pantothenate kinase-associated neurodegeneration (PKAN)**

Hallucination

Definitions

A hallucination is a sensory perception without a source in the external world. The English word "hallucination" comes from the Latin verb *hallucinari*, which means "to wander in the mind." Hallucinations can affect any of the senses, although certain diseases or disorders are associated with specific types of hallucinations.

It is important to distinguish between hallucinations and illusions or delusions, as the terms are often confused in conversation and popular journalism. A hallucination is a distorted sensory experience that appears to be a perception of something real even though it is *not* caused by an external stimulus. For example, some elderly people who have been recently bereaved may have hallucinations in which they "see" the dead loved one. An illusion, by contrast, is a mistaken or false interpretation of a real sensory experience, as when a traveler in the desert sees what looks like a pool of water, but in fact is a mirage caused by the refraction of light as it passes through layers of air of different densities. The bluish-colored light is a real sensory stimulus, but mistaking it for water is an illusion. A delusion is a false belief that a person maintains in spite of evidence to the contrary and in spite of proof that other members of their culture do not share the belief. For example, some people insist that they have seen flying saucers or unidentified flying objects (UFOs) even though the objects they have filmed or photographed can be shown to be ordinary aircraft, weather balloons, satellites, etc.

Description

It would be difficult to describe a "typical" hallucination, as these experiences vary considerably in length of time, quality, and sense or senses affected. Some hallucinations last only a few seconds; however, some people diagnosed with Charles Bonnet syndrome (CBS) have reported visual hallucinations lasting over several days, while people who have taken certain drugs have experienced hallucinations involving colors, sounds, and smells lasting for hours. Albert Hoffman, the Swiss chemist who first synthesized lysergic acid diethylamide (LSD), experienced nine hours of hallucinations after taking a small amount of the drug in 1943. In 1896, the American **neurologist** S. Weir Mitchell published an account of the six hours of hallucinations that followed his experimental swallowing of peyote buttons.

There is not always a close connection between the cause of a person's hallucinations and the emotional response to them. One study of patients diagnosed with CBS found that 30% of the patients were upset by their hallucinations, while 13% found them amusing or pleasant. The environment in which LSD and other hallucinogens are taken may affect an individual's psychological constitution and personal reactions. The writer Peter Matthiessen, for example, noted that his 1960s experiences with LSD "were magic shows, mysterious, enthralling," while his wife "... freaked out; that is the drug term, and there is no better.... her armor had cracked, and all the night winds of the world went howling through." In contrast to those who take hallucinogens, however, a majority of patients with **narcolepsy**, alcoholic hallucinosis, or post-traumatic disorders finds their hallucinations frightening.

Demographics

The demographics of hallucinations vary depending on their cause; however, many researchers think that they are underreported for several reasons:

• Fear of being thought "crazy" or mentally ill

- Gaps in research. For example, some types of hallucinations are associated with disorders that primarily affect the elderly, who are often underrepresented in health surveys
- Fear of being reported to law enforcement for illegal drug use

In 2000, one of the few studies of hallucinations in a general Western population reported the following statistics:

- Of a total sample of 13,000 adults, 38.7% reported hallucinations: 6.4% had hallucinations once a month, 2.7% once a week, and 2.4% more than once a week.
- Of the subjects, 27% reported having hallucinations in the daytime. In this group, visual (3.2%) and auditory (0.6%) hallucinations were closely associated with diagnoses of psychotic or anxiety disorders.
- Of the subjects, 3.1% reported haptic (tactile) hallucinations; most of these subjects were current drug users.

There is currently no evidence that hallucinations occur more frequently in some racial or ethnic groups than in others. In addition, gender does not appear to make a difference. The demographics of hallucinations associated with some specific age groups, conditions, or disorders are as follows:

- Children. Hallucinations are rare in children below the age of eight. About 40% of children diagnosed with **schizophrenia**, however, have visual or auditory hallucinations.
- Eye disorders. About 14% of patients treated in eye clinics for glaucoma or age-related macular degeneration report visual hallucinations.
- Alzheimer's disease (AD). About 40–50% of patients diagnosed with AD develop hallucinations in the later stages of the disease.
- Drug use. Hallucinogens are the third most frequently abused class of drugs (after alcohol and marijuana) among high school and college students. Various surveys report that about 7% of people in the United States over the age of 12 have taken LSD at least once; that 5% of high school seniors admit to using MDMA (Ecstasy); and that 20–24% of college students use MDMA. The highest rate of hallucinogen abuse is found in Caucasian males between the ages of 18 and 25.
- Normal sleep/wake cycles. Sleep researchers in Great Britain and the United States have reported that 30–37% of adults experience hypnagogic hallucinations, which occur during the passage from wakefulness into sleep, while about 10–12% report hypnopompic hallucinations, which occur as a person awakens. Hallucinations related to ordinary sleeping and waking are not considered an indication of a mental or physical disorder.
- Migraine headaches. About 10% of patients diagnosed with migraine headaches experience visual hallucinations prior to the onset of an acute attack.
- Adult-onset schizophrenia. According to the National Institute of Mental Health (NIMH), about 75% of adults diagnosed with schizophrenia experience hallucinations, most commonly auditory or visual. The auditory hallucinations may be command hallucinations, in which the person hears voices ordering him or her to do something. For example, the man who killed a Swedish politician in September 2003 told the police that voices in his head told him "to attack."
- Temporal lobe **epilepsy** (TLE). About 80% of patients diagnosed with TLE report gustatory and olfactory hallucinations as well as auditory and visual hallucinations.
- Narcolepsy. Frequent hypnagogic hallucinations are considered one of four classic symptoms of narcolepsy, and are experienced by 60% of patients diagnosed with the disorder.
- Post-traumatic stress disorder (PTSD). Studies of combat veterans diagnosed with PTSD have found that 50–65% have experienced auditory hallucinations. Visual, olfactory, and haptic hallucinations have been reported by survivors of rape and childhood sexual abuse.

Causes

The neurologic causes of hallucinations are not currently completely understood, although researchers have identified some factors in the context of specific disorders, and have proposed various hypotheses to explain hallucinations in others. There does not appear to be a single causal factor that accounts for hallucinations in all people who experience them.

Sleep deprivation

Research subjects who have undergone sleep deprivation experiments typically begin to hallucinate after 72–96 hours without sleep. It is thought that these hallucinations result from the malfunctioning of nerve cells within the prefrontal cortex of the brain. This area of the brain is associated with judgment, impulse control, attention, and visual association, and is refreshed during the early stages of sleep. When a person is sleep-deprived, the nerve cells in the prefrontal cortex must work harder than usual without an opportunity to recover. The hallucinations that develop on the third day of wakefulness are thought to be hypnagogic hallucinations that occur during "microsleeps," or short periods of light sleep lasting about one to ten seconds.

Key Terms

Amygdala An almond-shaped brain structure in the limbic system that is activated in stressful situations to trigger the emotion of fear. Hallucinations related to post-traumatic stress are thought to be caused by the activation of memory traces in the amygdala that have not been integrated and modified by other parts of the brain.

Auditory Pertaining to the sense of hearing.

Charles Bonnet syndrome (CBS) A disorder characterized by visual hallucinations following a sudden age-related deterioration in a person's vision, most commonly glaucoma or macular degeneration. CBS is named for a Swiss doctor who first described it in his visually impaired grandfather in 1780.

Command hallucination A type of auditory hallucination in which the person hears voices ordering him or her to perform a specific act.

Corollary discharge A mechanism in the brain that allows one to distinguish between self-generated and external stimuli or perceptions.

Delusion A false belief that a person maintains in spite of obvious proof or evidence to the contrary.

Flashback A vivid sensory or emotional experience that happens independently of the initial event or experience. Flashbacks resulting from the use of LSD are sometimes referred to as hallucinogen persisting perception disorder, or HPPD.

Gustatory Pertaining to the sense of taste.

Hallucinogen A drug or other substance that induces hallucinations.

Haptic Pertaining to the sense of touch; sometimes called tactile hallucinations.

Hippocampus A part of the brain that is involved in memory formation and learning. The hippocampus is shaped like a curved ridge and belongs to an organ system called the limbic system.

Hypnagogic Pertaining to drowsiness; refers to hallucinations that occur as a person falls asleep.

Hypnopompic Persisting after sleep; refers to hallucinations that occur as a person awakens.

Illusion A false interpretation of a real sensory image or impression.

Irritative hallucinations Hallucinations caused by abnormal electrical activity in the brain.

Lysergic acid diethylamide (LSD) The first synthetic hallucinogen, discovered in 1938.

Neuroleptic Another name for an antipsychotic medication.

Neurotransmitters Chemicals that carry nerve impulses from one nerve cell to another.

Olfactory Pertaining to the sense of smell.

Psychosis A severe mental disorder characterized by loss of contact with reality. Hallucinations are associated with such psychotic disorders as schizophrenia and brief psychotic disorder.

Release hallucinations Hallucinations that develop after partial loss of sight or hearing, and represent images or sounds formed from memory traces rather than present sensory input. They are called "release" hallucinations because they would ordinarily be blocked by incoming sensory data.

Post-traumatic memory formation

Hallucinations in trauma survivors are caused by abnormal patterns of memory formation during the traumatic experience. In normal situations, memories are formed from sensory data, organized in a part of the brain known as the hippocampus, and integrated with previous memories in the frontal cortex. People then "make sense" of their memories through the use of language, which helps them to describe their experiences to others and to themselves. In traumatic situations, however, bits and pieces of memory are stored in the amygdala, an almond-shaped structure in the brain that ordinarily attaches emotional significance to memories, without being integrated by the hippocampus and interpreted in the frontal cortex. In addition, the region of the brain that governs speech (Broca's area) often shuts down under extreme stress. The result is that memories of the traumatic event remain in the amygdala as a chaotic wordless jumble of physical sensations or sensory images that can re-emerge as hallucinations during stressful situations at later points in the patient's life.

Irritative hallucinations

In 1973, a British researcher named Cogan categorized hallucinations into two major groups that he called "irritative" and "release" hallucinations. Irritative hallucinations result from abnormal electrical discharges in the

brain, and are associated with such disorders as migraine **headaches** and epilepsy. Brain tumors and traumatic damage to the brain are other possible causes of abnormal electrical activity manifesting as visual hallucinations.

Hallucinations have also been reported with a number of infectious diseases that affect the brain, including bacterial meningitis, rabies, herpes virus infections, **Lyme disease**, HIV infection, toxoplasmosis, Jakob-Creuzfeldt disease, and late-stage syphilis.

Release hallucinations

Release hallucinations are most common in people with impaired eyesight or hearing. They are produced by the spontaneous activity of nerve cells in the visual or auditory cortex of the brain in the absence of actual sensory data from the eyes or ears. These experiences differ from the hallucinations of schizophrenia in that those patients experiencing release hallucinations are often able to recognize them as unreal. Release hallucinations are also more elaborate and usually longer in duration than irritative hallucinations. The visual hallucinations of patients with CBS are an example of release hallucinations.

Neurotransmitter imbalances

Neurotransmitters are chemicals produced by the body that carry electrical impulses across the gaps (synapses) between adjoining nerve cells. Some neurotransmitters inhibit the transmission of nerve impulses, while others excite or intensify them. Hallucinations in some conditions or disorders result from imbalances among these various chemicals.

NARCOLEPSY Narcolepsy is a disorder characterized by uncontrollable brief episodes of sleep, frequent hypnagogic or hypnopompic hallucinations, and sleep paralysis. Between 1999 and 2000, researchers discovered that people with narcolepsy have a much lower than normal number of hypocretin neurons, which are nerve cells in the hypothalamus that secrete a neurotransmitter known as hypocretin. Low levels of this chemical are thought to be responsible for the daytime sleepiness and hallucinations of narcolepsy.

PRESCRIPTION MEDICATIONS Hallucinations have been reported as side effects of such drugs as ketamine (Ketalar), which is sometimes used as an anesthetic but has also been used illegally to commit date rape; paroxetine (Paxil), an SSRI antidepressant; mirtazapine (Remeron), a serotonin-specific antidepressant; and zolpidem (Ambien), a sleep medication. Ketamine prevents brain cells from taking up glutamate, a neurotransmitter that governs perception of **pain** and of one's relationship to the environment. Paroxetine alters the balance between the neurotransmitters serotonin and acetylcholine.

Hallucinations in patients with Alzheimer's disease are thought to be a side effect of treatment with neuroleptics (antipsychotic medications), although they may also result from inadequate blood flow in certain regions of the brain. The antiretroviral drugs used to treat HIV infection may also produce hallucinations in some patients.

HALLUCINOGENS AND DRUGS OF ABUSE Like the hallucinations caused by prescription drugs, hallucinations caused by drugs of abuse result from disruption of the normal balance of neurotransmitters in the brain. Hallucinations in cocaine and amphetamine users, for example, are associated with the overproduction of dopamine, a neurotransmitter associated with arousal and motor excitability. LSD appears to produce hallucinations by blocking the action of the neurotransmitters serotonin (particularly serotonin-2) and norepinephrine. Phencyclidine (PCP) acts like ketamine in producing hallucinations by blocking the reception of glutamate.

People who have used LSD sometimes experience flashbacks, which are spontaneous recurrences of the hallucinations and other distorted perceptions caused by the drug. Some doctors refer to this condition as hallucinogen persisting perception disorder, or HPPD.

There are two types of alcohol withdrawal syndromes characterized by hallucinations. Alcoholic hallucinosis typically occurs after abrupt withdrawal from alcohol after a long period of excessive drinking. The patient hears threatening or accusing voices rather than "seeing things," and his or her consciousness is otherwise normal. **Delirium** tremens (DTs), on the other hand, is a withdrawal syndrome that begins several days after drinking stops. A patient with the DTs is disoriented, confused, depressed, feverish, and sweating heavily as well as hallucinating, and the hallucinations are usually visual.

MOOD DISORDERS Visual hallucinations occasionally occur in patients diagnosed with **depression**, particularly the elderly. These hallucinations are thought to result from low levels of the neurotransmitter serotonin. The hallucinations that occur in patients with **Parkinson's disease** appear to result from a combination of medication side effects, depressed mood, and impaired eyesight.

Schizophrenia

The auditory hallucinations associated with schizophrenia may be the end result of a combination of factors. These hallucinations have sometimes been attributed to unusually high levels of the neurotransmitter dopamine in the patient's brain. Other researchers have noted abnormal patterns of brain activity in patients with schizophrenia. In particular, these patients suffer from dysfunction of a mechanism known as corollary discharge, which allows people to distinguish between stimuli outside the self and

internal intentions and thoughts. Electroencephalograms (EEGs) of patients with schizophrenia that were taken while the patients were talking showed that corollary discharges from the frontal cortex of the brain (where thoughts are produced) failed to inform the auditory cortex (where sounds are interpreted) that the talking was self-generated. This failure would lead the patients to interpret internal speech as coming from external sources, thus producing auditory hallucinations. In addition, the brains of patients with schizophrenia appear to suffer tissue loss in certain regions. In early 2004, some German researchers reported a direct correlation between the severity of auditory hallucinations in patients with schizophrenia and the amount of brain tissue that had been lost from the primary auditory cortex.

Diagnosis

The differential diagnosis of hallucinations can be complicated, but in most cases taking the patient's medical history will help the doctor narrow the list of possible diagnoses. If the patient has been taken to a hospital emergency room, the doctor may ask those who accompanied the patient for information. The doctor may also need to perform a medical evaluation before a psychiatric assessment of the hallucinations can be made. The medical evaluation may include laboratory tests and imaging studies as well as a physical examination, depending on the patient's other symptoms. If it is suspected that the patient is suffering from delirium, **dementia**, or a psychotic disorder, the doctor may assess the patient's mental status by using a standard instrument known as the mini-mental status examination (MMSE) or the Folstein (after the clinician who devised it). The MMSE yields a total score based on the patient's appearance, mood, cognitive skills, thought content, judgment, and speech patterns. A score of 20 or lower usually indicates delirium, dementia, schizophrenia, or severe depression.

Hallucinations in elderly patients may require specialized evaluation because of the possibility of overlapping causes. The American Association for Geriatric Psychiatry lists hallucinations as an indication for consulting a geriatric psychiatrist. In addition, elderly patients should be routinely screened for visual or hearing impairments.

Treatment

Hallucinations are treated with regard to the underlying disorder. Depending on the disorder, treatment may involve antipsychotic, anticonvulsant, or antidepressant medications; psychotherapy; brain or ear surgery; or therapy for drug dependence. Hallucinations related to normal sleeping and waking are not a cause for concern.

Prognosis

The prognosis of hallucinations depends on the underlying cause or disorder.

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American Psychiatric Association (APA). 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901. (703) 907-7300. apa@psych.org. <http://www.psych.org>.

National Institute of Mental Health (NIMH) Office of Communications. 6001 Executive Boulevard, Room 8184, MSC 9663, Bethesda, MD 20892-9663. (301) 443-4513 or (866) 615-NIMH; Fax: (301) 443-5158. nimhinfo@nih.gov. <http://www.nimh.nih.gov>.

National Schizophrenia Foundation. 403 Seymour Avenue, Suite 202, Lansing, MI 48933. (517) 485-7168 or (800) 482-9534; Fax: (517) 485-7180. inquiries@nsfoundation.org. <http://www.nsfoundation.org>.

National Sleep Foundation (NSF). 1522 K Street NW, Suite 500, Washington, DC 20005. (202) 347-3471; Fax: (202) 347-3472. nsf@sleepfoundation.org. <http://www.sleepfoundation.org>.

Rebecca Frey, PhD

Head injury *see* **Traumatic brain injury**

Headache

Definition

Headache is a **pain** in the head and neck region that may be either a disorder in its own right or a symptom of an underlying medical condition or disease. The medical term for headache is cephalalgia. Headaches are one of the most common and universal human ailments, described in the Bible as well as in medical writings from ancient Egypt, Babylonia, Greece, Rome, India, and China. Severe chronic headaches were once treated by the oldest known surgical procedure, known as trepanning or trephining, in which the surgeon drilled a hole as large as 1–2 in diameter in the patient's skull without benefit of anesthesia. Evidence of trepanning has been found in skulls from Cro-Magnon people that are about 40,000 years old.

Description

Contemporary doctors divide headaches into two large categories, primary and secondary, according to guidelines established by the International Headache Society (IHS) in 1988 and revised for republication in 2004. Primary headaches are those that are not caused by an underlying medical condition. There are three types of primary headaches: migraine, cluster, and tension headaches. More than 90% of all headaches are primary headaches. Secondary headaches are caused by disease or medical condition; they account for fewer than 10% of all headaches.

Primary headaches

MIGRAINE HEADACHES Migraine headaches are characterized by throbbing or pulsating pain of moderate or severe intensity lasting from four hours to as long as three days. The pain is typically felt on one side of the head; in fact, the English word "migraine" is a combination of two Greek words that mean "half" and "head." Migraine headaches become worse with physical activity and are often accompanied by nausea and vomiting. In addition, patients with migraine headaches are hypersensitive to lights, sounds, and odors.

The two most common types of migraines are known as classic and common migraine, respectively. Classic migraine, which accounts for 10–20% of the cases of migraine, is distinguished by a brief period of warning symptoms 10–60 minutes before an acute attack. This prodrome, which is known as an aura, may include such symptoms as seeing flashing lights or zigzag patterns, temporary loss of vision, difficulty speaking, weakness in an arm or leg, and tingling sensations in the face or hands. Common migraine is not preceded by an aura, although some patients experience mood changes, unusual tiredness, or fluid retention shortly before an attack. An attack

of common migraine may include diarrhea and frequent urination, as well as nausea and vomiting.

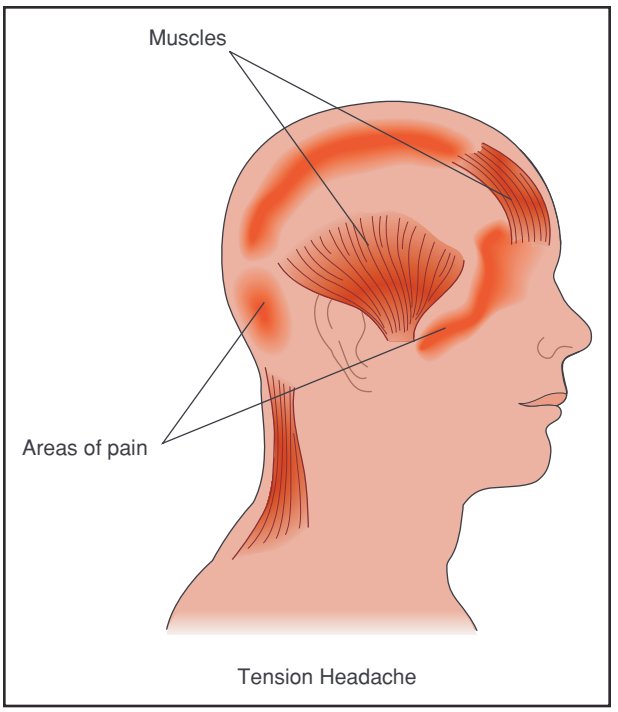
Less common types of migraines include hemiplegic migraine, characterized by temporary paralysis on one side of the body; ophthalmoplegic migraine, in which the pain is felt in the area around the eye; basilar artery migraine, which involves a major artery at the base of the brain and primarily affects young women; and headache-free migraine, which is characterized by the gastrointestinal and visual symptoms of classic migraine, but does not involve head pain.

CLUSTER HEADACHES Cluster headaches are recurrent brief attacks of sudden and severe pain on one side of the head, usually most intense in the area around the eye. Other names for these headaches include histamine cephalalgia, Horton neuralgia, or erythromelalgia. Cluster headaches may last between five minutes and three hours; they may occur once every other day or as often as eight times per day. The IHS classifies cluster headaches as either episodic or chronic. Episodic cluster headaches occur over periods lasting from seven days to one year, with the clusters separated by headache-free intervals of at least two weeks. The average length of a cluster ranges between two weeks and three months. Chronic cluster headaches occur over a period longer than a year without a headache-free interval, or with pain-free intervals that are shorter than two weeks.

The pain of a cluster headache is excruciating; some patients describe it as severe enough to make them consider suicide. Patients with cluster headaches are restless; they may pace the floor, weep, rock back and forth, or bang their heads against a wall in desperation to stop the pain. In addition to severe pain, patients with cluster headaches often have a runny or congested nose, watery or inflamed eyes, drooping eyelids, swelling in the area of the eyebrows, and heavy facial perspiration. Because of the nasal symptoms and the relative rarity of cluster headaches, these episodes have sometimes been misdiagnosed as sinusitis.

TENSION HEADACHES Tension headaches are the most common headaches in the general population; other names for them include muscle contraction headache, ordinary headache, psychomyogenic headache, and stress headache. The IHS classifies tension headaches as either episodic or chronic; episodic tension headaches occur 15 or fewer times per month, whereas chronic tension headaches occur on 15 or more days per month over a period of six months or longer.

Tension headaches rarely last more than a few hours; 82% resolve in less than a day. The patient will usually describe the pain of a tension headache as mild to moderate in severity. The doctor will not find anything abnormal in the course of a general physical or neurological examination, although sore or tense areas (trigger points) in the muscles of the patient's forehead, neck, or upper shoulder area may be detected.



Tension headaches are caused by severe muscle contractions triggered by stress or exertion. Tension headaches usually occur in the front of the head, although they may also appear at the top or the back of the skull. *(Illustration by Electronic Illustrators Group.)*

REBOUND HEADACHES Rebound headaches, which are also known as analgesic-abuse headaches, are a subtype of primary headache caused by overuse of headache drugs. They may be associated with medications taken for tension and migraine headaches.

Secondary headaches

Secondary headaches, which are caused by diseases or disorders, are categorized as either traction or inflammatory headaches. Traction headaches result from the pulling, stretching, or displacing of structures that are sensitive to pain, as when a brain tumor presses on the outer layer of nerve tissue that covers the brain. Inflammatory headaches are caused by infectious diseases of the ears, teeth, sinuses, or other parts of the head.

Major causes of secondary headaches include the following:

- Brain tumors. Headaches associated with brain tumors usually begin as episodic nighttime headaches that are accompanied by projectile vomiting. The headaches may become continuous over time, and usually get worse if the patient coughs, sneezes, bears down while using the

toilet, or does something else that increases the pressure inside the head.

- Meningitis. Meningitis is an inflammation of the **meninges**, the three layers of membranes that cover the brain and spinal cord. Meningitis is usually caused by bacteria or viruses, and may produce chronic headaches.
- Head trauma. Patients may complain of headaches as well as memory problems, general irritability, and **fatigue** for months or even years after a head injury. These symptoms are sometimes grouped together as post-concussion syndrome. In some cases, a blow on the head may cause some blood vessels to rupture and produce a hematoma, or mass of blood that displaces brain tissue, and can cause **seizures** or weakness as well as headaches.
- **Temporal arteritis**. First described in 1890, temporal arteritis is an inflammation of the temporal artery that most commonly affects people over 50. In addition to headache, patients with temporal arteritis may have fever, loss of appetite, and blurring or loss of vision. Temporal arteritis is treated with steroid medications.
- **Stroke**. Headaches may be associated with several conditions that may lead to stroke, including high blood pressure and heart disease. Headaches may also result from completed stroke or from the mini-strokes known as transient ischemic attacks, or TIAs.
- Lumbar puncture. About 25% of patients who undergo a lumbar puncture (spinal tap) develop a headache from the lowered cerebrospinal fluid pressure around the brain and spinal cord. Lumbar puncture headaches usually go away on their own after a few hours.
- Sinus infections. Acute sinusitis is characterized by fluid buildup inside sinus cavities inflamed by a bacterial or viral infection. Chronic sinusitis usually results from an allergic reaction to smoke, dust, animal fur, or similar irritants.
- Referred pain. This type of pain is felt in a part of the body at a distance from the injured or diseased area. Headache pain may be referred from diseased teeth; disks in the cervical spine that have been damaged by spondylosis (degeneration of the spinal vertebrae caused by osteoarthritis); or the temporomandibular joint, the small joint in front of the ear where the lower jaw is attached to the skull.
- Idiopathic intracranial hypertension. Also known as **pseudotumor cerebri**, this disorder is caused by increased pressure inside the skull in the absence of any abnormality of the **central nervous system** or blockage in the flow of the cerebrospinal fluid. In addition to headache, patients with this disorder experience diplopia (seeing double) and other visual symptoms.

Demographics

Headaches in general are very common in the adult population in North America. The American Council for Headache Education (ACHE) estimates that 95% of women and 90% of men in the United States and Canada have had at least one headache in the past 12 months. Most of these are tension headaches. Tension headaches may begin in childhood in some patients, but most commonly start in adolescence or the early 20s. The gender ratio for episodic tension headaches is about 1.4 F:1 M; for chronic tension headaches, 1.9 F:1 M.

Migraine and cluster headaches have distinctive demographic patterns. Migraine headaches are less common than tension headaches, affecting about 11% of the population in the United States and 15% in Canada. Several studies done in the United Kingdom and the United States, however, indicate that doctors tend to underdiagnose migraine headache; thus the true number of patients with migraine may be considerably higher than the usual statistics indicate. Migraines are a major economic burden; it is estimated that the annual cost of time lost from work due to migraines in the United States alone is $17.2 billion. Most people who experience migraines have their first episode in childhood or adolescence, although some experience their first migraine after age 20. Migraines occur most frequently in adults between the ages of 25 and 55; the gender ratio is about 3 F:1 M. Although migraine headaches occur in people of all races and ethnic groups, they are thought to affect Caucasians more often than African or Asian Americans.

Currently, migraine is the only type of primary headache known to run in families. A child with one parent affected by migraines has a 50% chance of developing migraines as an adult; if both parents are affected, the risk rises to 70%. Although geneticists think that a number of different genes are involved in transmitting a susceptibility to migraine, they have recently identified two specific loci on human chromosomes 1 and 14, respectively, that are linked to migraine headaches. The locus on chromosome 1q23 has been linked to familial hemiplegic migraine type 2, while the locus on chromosome 14q21 is associated with common migraine.

Cluster headaches are the least common type of primary headaches, affecting about 0.4% of adult males in the United States and 0.08% of adult females. The gender ratio is 5–7.5 M:1 F. Cluster headaches occur most commonly in adults between the ages of 20 and 40. It is not currently known whether cluster headaches are more common in some racial or ethnic groups than in others; however, many patients with cluster headaches have a history of face or head trauma.

The demographics of secondary headaches vary depending on the disease or disorder that causes the headache.

Key Terms

Analgesic A medication that relieves pain without causing loss of consciousness; over-the-counter analgesics include aspirin and NSAIDs.

Aura A group of visual or other sensations that precedes the onset of a migraine attack.

Cephalalgia The medical term for headache.

Dura mater The outermost and toughest of the three membranes or meninges that cover the brain and spinal cord. The arteries that supply the dura mater and the portion of the dura mater at the base of the skull are sensitive to pain.

Endodontist A dentist who specializes in the treatment of diseases and injuries that affect the tooth root, dental pulp, and the tissues surrounding the tooth root.

Idiopathic Of unknown cause or spontaneous origin. Some headaches are considered idiopathic.

Neurotransmitter Any of a group of chemicals that transmit nerve impulses across the gap (synapse) between two nerve cells.

Nociceptor A specialized type of nerve cell that senses pain.

Open-label study A type of study in which both the researchers and the subjects are aware of the drug or therapy that is being tested.

Pathophysiology The changes in body functions associated with a disorder or disease.

Primary headache A headache that is not caused by another disease or medical condition.

Prodrome A symptom or group of symptoms that appears shortly before an acute attack of illness. The term comes from a Greek word that means "running ahead of."

Projectile vomiting Forceful vomiting that is not preceded by nausea. It is usually associated with increased pressure inside the head.

Prophylaxis A measure taken to prevent disease or an acute attack of a chronic disorder. Migraine prophylaxis refers to medications taken to reduce the frequency of migraine attacks.

Rebound headache A type of primary headache caused by overuse of migraine medications or pain relievers. It is also known as analgesic abuse headache.

Secondary headache A headache that is caused by another disease or disorder.

Somatoform disorders A group of psychiatric disorders in the DSM-IV classification that are characterized by external physical symptoms or complaints related to psychological problems rather than organic illness.

Spondylosis A general medical term for degenerative changes in the spinal vertebrae caused by osteoarthritis.

Status migrainosus The medical term for an acute migraine headache that lasts 72 hours or longer.

Temporomandibular joint (TMJ) The small joint in front of the ear in humans where the mandible (lower jaw) is attached to the skull.

Causes and symptoms

Causes

PHYSICAL A person feels headache pain when specialized nerve endings known as nociceptors are stimulated by pressure on or injury to any of the pain-sensitive structures of the head. Most nociceptors in humans are located in the skin or in the walls of blood vessels and internal organs; the bones of the skull and the brain itself do not contain nociceptors.

The specific parts of the head that are sensitive to pain include:

- the skin that covers the skull and cervical spine
- the 5th, 9th, and 10th cranial nerves and the nerves that supply the upper part of the neck
- the venous sinuses inside the head
- the large arteries at the base of the brain
- the large arteries that supply the dura mater, which is the outermost of the three meninges (membranes) that cover the brain and spinal cord
- the portion of the dura mater at the base of the skull

Tension headaches typically result from tightening of the muscles of the face, neck, and scalp as a result of emotional stress; physical postures that cause the head and neck muscles to tense (e.g., holding a phone against the ear with one's shoulder); **depression** or anxiety; temporomandibular joint dysfunction (TMJ); or degenerative arthritis of the neck. The tense muscles put pressure on the walls of the blood vessels that supply the neck and head,

which stimulates the nociceptors in the tissues that line the blood vessels. In addition, the nociceptors in patients with chronic tension headaches appear to be abnormally sensitive to stimulation.

The pathophysiology of migraine headaches has been debated among doctors since the 1940s. Some researchers think that migraines are the end result of a magnesium deficiency in the brain or of hypersensitivity to a neurotransmitter known as dopamine. Another theory holds that certain nerve cells in the brain cortex become unusually excitable and depolarize (lose their electrical potential) spontaneously, releasing potassium and glutamate, an amino acid. These substances then depolarize nearby nerve cells, resulting in a chain reaction known as cortical-spreading depression (CSD). CSD then leads to changes in the amount of blood flowing through the blood vessels and stimulation of their nociceptors, resulting in severe headache. More recently, the discovery of specific genes associated with migraine indicates that genetic mutations are responsible for the abnormal excitability of the nerve cells in the brains of patients with migraine.

Little is known about the causes of cluster headaches or changes in the central nervous system that produce them.

PSYCHOLOGICAL Chronic headaches are often associated with anxiety, depression, or a specific group of mental disorders known as somatoform disorders. These disorders include hypochondriasis and pain disorder; they are characterized by physical symptoms (frequently headache) that suggest that the patient has a general medical condition, but there is no diagnosable disease or disorder that fully accounts for the patient's symptoms. The relationship between psychological and physical factors in headaches is complex in that headaches may be either the cause or result of emotional disturbances, or both. Some patients find that chronic headaches disappear completely after a stressful family- or job-related situation has been resolved.

Warning symptoms

Most headaches are not associated with serious or life-threatening illnesses. Patients should, however, immediately call their primary physician if they have any of the following symptoms:

- three or more headaches per week
- need for a pain reliever every day or almost every day
- need for greater than recommended doses of over-the-counter medications (OTCs)
- stiff neck or fever accompanying the headache
- shortness of breath, hearing problems, blurry vision, or severe sore throat
- dizziness, weakness, slurred speech, mental confusion, or drowsiness
- headache following a head injury that is not relieved by OTCs
- headache triggered by **exercise**, coughing, sexual activity, or bending over
- persistent or violent vomiting
- change in the character of the headaches—for example, persistent severe headaches in a person who has previously had only mild headaches of brief duration
- recurrent headaches in a child
- recurrent severe headaches, beginning after age 50

Diagnosis

Patient history

The differential diagnosis of headaches begins with a complete patient history, including a family history. In many cases, a primary care physician can make the diagnosis on the basis of the history. The doctor will ask the patient about head injuries or surgery on the head; eye problems or disorders; sinus infections; dental problems or extensive oral surgery; and medications that the patient is taking regularly.

After taking the history, the doctor will ask the patient to describe the location and type of pain that he or she experiences during the headache. People who have tension headaches will typically describe the pain as "viselike," "tightening," "pressing," or as a steady or constant ache. Patients with migraine headaches, on the other hand, will usually say that the pain has a "throbbing" or "pulsating" character, while patients with cluster headaches describe the pain as "penetrating" or "piercing." About 85% of patients with tension headaches experience pain on both sides of the head, most commonly in the area around the forehead and temples. Patients with migraine or cluster headaches, however, are more likely to feel pain on only one side of the head.

Some primary care physicians give the patient a printed questionnaire that consists of 50–55 brief yes/no questions that cover such matters as the timing and frequency of the headaches; whether other family members have the same type of headache; whether the patient feels depressed; whether the headaches are related to changes in the weather; and so on. The answers to the questions will usually fall into a pattern that tells the doctor whether the patient has migraines, tension headaches, cluster headaches, or headaches with other causes. The doctor may also ask the patient to keep a headache diary to help identify foods, stress, lack of sleep, weather, and other factors that may trigger headaches.

It is possible for patients to have more than one type of headache. For example, patients with chronic tension headaches often have migraine headaches as well.

Physical examination

The physical examination helps the doctor identify other symptoms and signs that may be relevant to the diagnosis, such as fever; difficulty breathing; nausea or vomiting; stiff neck; changes in vision or hearing; watering or inflammation of the nose and eyes; evidence of head trauma; skin rashes or other indications of an infectious disease; and abnormalities in the structure or alignment of the patient's spinal column, teeth or jaw. In some cases, the doctor may refer the patient to a dentist, oral surgeon, or endodontist for a more detailed evaluation of the patient's mouth and jaw.

Special studies

Some laboratory tests are useful in identifying headaches caused by infections or by such disorders as anemia or thyroid disease. These tests include a complete blood count (CBC); erythrocyte sedimentation rate (ESR); and blood serum chemistry profile.

Patients who report **visual disturbances** and other neurologic symptoms may be given visual field tests and have the pressure of the fluid inside their eyes (intraocular pressure) tested to check for glaucoma. A lumbar puncture (spinal tap) may be done to confirm a diagnosis of idiopathic intracranial hypertension.

Imaging studies may include x rays of the sinuses to check for sinus infections; and CT or **MRI** scans, which are done to rule out brain tumors and cerebral **aneurysms**.

Patients whose symptoms cannot be fully explained by the results of physical examinations and tests may be referred to a psychiatrist for evaluation of psychological factors related to their headaches.

Treatment

Medical

TENSION HEADACHES Episodic tension headaches are usually relieved fairly rapidly by such over-the-counter analgesics as aspirin (300–600 mg every four hours), acetaminophen (650 mg every four hours), or another nonsteroidal anti-inflammatory drug (NSAID), usually ibuprofen (Advil) or naproxen (Naprosyn, Aleve). The doctor may prescribe a tricyclic antidepressant or benzodiazepine tranquilizer in addition to a pain reliever for patients with chronic tension headaches. A newer treatment for chronic tension headaches is **botulinum toxin** (Botox type A), which appears to work very well for some patients. As of 2003, however, Botox has not yet been evaluated in controlled multicenter studies as a treatment for chronic headaches; the data obtained so far are derived from case reports and open-label studies.

MIGRAINE HEADACHES Medications can be prescribed to prevent migraines as well as to treat the symptoms of an acute attack. Drugs that are given for migraine prophylaxis (to prevent or lower the frequency of migraine attacks) include tricyclic antidepressants, beta-blockers, and anti-epileptic drugs, which are also known as **anticonvulsants**. As of 2003, sodium valproate (Epilim) is the only anticonvulsant approved by the Food and Drug Administration (FDA) for prevention of migraine. Such newer anticonvulsants as **gabapentin** (Neurontin) and **topiramate** (Topamax) are presently being evaluated as migraine preventives. Moreover, a new study reported that three drugs currently used to treat disorders of muscle tone are being explored as possible preventives for migraine—Botox, baclofen (Lioresal), and tizanidine (Zanaflex). Early results of open trials of these medications are positive.

Nonsteroidal anti-inflammatory drugs acetaminophen (Tylenol), ibuprofen (Motrin), and naproxen (Aleve) are helpful for early or mild migraines. More severe or unresponsive attacks may be treated with dihydroergotamine; a group of drugs known as triptans; beta-blockers and calcium channel-blockers; antiseizure drugs; antidepressants (SSRIs); meperidine (Demerol); or metoclopramide (Reglan). Some of these are also available as nasal sprays, intramuscular injections, or rectal suppositories for patients with severe vomiting. Sumatriptan and the other triptan drugs (zolmitriptan, rizatriptan, naratriptan, almotriptan, and frovatriptan) should not be taken by patients with vascular disease, however, because they cause narrowing of the coronary arteries.

About 40% of all migraine attacks do not respond to treatment with triptans or any other medication. If the headache lasts longer than 72 hours—a condition known as status migrainosus—the patient may be given narcotic medications to bring on sleep and stop the attack. Patients with status migrainosus are often hospitalized because they are likely to be dehydrated from severe nausea and vomiting.

CLUSTER HEADACHES Medications that are given as prophylaxis for cluster headaches include verapamil (Calan, Isoptin, Verelan), which is a calcium channel blocker, and methysergide (Sansert), which is a derivative of ergot. A new study indicates that topiramate (Topamax), an anticonvulsant, is also effective in preventing cluster headaches. Sumatriptan (Imitrex) or indomethacin (Indameth, Indocin) may be prescribed to suppress an attack.

REBOUND HEADACHES Continued use of some pain relievers or **antimigraine** drugs can lead to rebound headaches, which may be frequent or chronic and often occur in the early morning hours. Rebound headache can be avoided by using antimigraine drugs or analgesics under a doctor's supervision, using only the minimum dose necessary to treat symptoms. Tizanidine (Zanaflex) has been reported to be effective in treating rebound headaches when taken together with an NSAID; Botox has also been used successfully in some patients.

Diet and lifestyle modifications

One measure that people can take to lower the risk of episodic tension headaches is to get enough sleep and eat nutritious meals at regular times. Skipping meals, using unbalanced fad diets to lose weight, and having insufficient or poor-quality sleep can bring on tension headaches. In fact, the common association of tension headaches with hunger, lack of sleep, heat, and sudden temperature extremes has led some researchers to suggest that headaches developed over the course of human evolution as an internal protective response to stress from the environment.

Changes in diet may be helpful to some patients with migraine, although some experts think that the role of foods in triggering migraines has been exaggerated. Women with migraines, however, often benefit by switching from oral contraceptives to another method of birth control or by discontinuing estrogen replacement therapy.

Patients with cluster headaches are advised to quit smoking and minimize their use of alcohol, because nicotine and alcohol appear to trigger cluster headaches. Currently, the precise connection between these chemicals and cluster attacks, however, is not completely understood.

Surgical

Headaches that are caused by brain tumors, post-injury hematomas, dental problems, or disorders affecting the spinal disks usually require surgical treatment. Surgery may also be used to treat cases of idiopathic intracranial hypertension that do not respond to treatment with steroids, repeated lumbar punctures, or weight reduction.

Some plastic surgeons have reported success in treating patients with chronic migraines by removing some muscle tissue near the eyebrows, cutting a branch of the trigeminal nerve, and repositioning the soft tissue around the temples.

Psychotherapy

Psychotherapy may be helpful to patients with chronic headaches by interrupting the "feedback loop" between emotional upset and the physical symptoms of headaches. One type of psychotherapy that has been shown to be effective is cognitive restructuring, an approach that teaches people to reframe the problems in their lives—that is, to change their conscious attitudes and responses to these stressors. Some psychotherapists teach relaxation techniques, biofeedback, or other approaches to stress management as well as cognitive restructuring.

Complementary and alternative (CAM) treatments

There are a number of different CAM treatments for headache, but most fall into two major groups: those intended as prophylaxis or pain relief, and those that reduce the patient's stress level.

CAM therapies intended to prevent headaches or relieve discomfort include:

- Feverfew (*Tanacetum parthenium*). Feverfew is an herb related to the daisy that is traditionally used in England to prevent migraines. Published studies indicate that feverfew can reduce the frequency and intensity of migraines. It does not, however, relieve pain once the headache has begun.
- Butterbur root (*Petasites hybridus*). Petadolex is a natural preparation made from butterbur root that has been sold in Germany since the 1970s as a migraine preventive. Petadolex has been available in the United States since December 1998.
- Brahmi (*Bacopa monnieri*). Brahmi is a herb used in Ayurvedic medicine to treat headaches related to anxiety.
- **Acupuncture**. Studies funded by the National Center for Complementary and Alternative Medicine (NCCAM) have found that acupuncture is an effective treatment for headache pain in many patients.
- Naturopathy. Naturopaths include dietary advice and nutritional therapy in their approach to treatment, which is often effective for patients with episodic or chronic tension headaches.
- Chiropractic. Some patients with tension or migraine headaches find spinal manipulation effective in relieving their pain; however, no controlled studies of the long-term effectiveness of chiropractic in treating headaches have been done as of 2003.

CAM therapies that are reported to be effective in reducing emotional stress related to headaches include:

- yoga and t'ai chi
- prayer and meditation
- aromatherapy
- hydrotherapy, particularly whirlpool baths
- Swedish massage and shiatsu
- pet therapy
- humor therapy
- music therapy

Clinical trials

As of late 2003, there were three National Institutes of Health (NIH) trials recruiting patients with headaches: a study evaluating a new intranasal drug (civamide) for cluster headaches; a study of the effectiveness of biofeedback and relaxation training in patients with chronic migraine or tension headaches; and a study of migraine headaches in children.

Prognosis

The prognosis of primary headaches varies. Episodic tension headaches usually resolve completely in less than a day without affecting the patient's overall health. According to NIH statistics, 90% of patients with chronic tension or cluster headaches can be helped. The prognosis for patients with migraines, however, depends on whether the patient has one or more of the other disorders that are associated with migraine. These disorders include Tourette's syndrome, **epilepsy**, ischemic stroke, hereditary essential tremor, depression, anxiety, and others. For example, migraine with aura increases a person's risk of ischemic stroke by a factor of six.

The prognosis of secondary headaches depends on the seriousness and severity of their cause.

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American Academy of Neurology (AAN). 1080 Montreal Avenue, Saint Paul, MN 55116. (651) 695-2717 or (800) 879-1960; Fax: (651) 695-2791. memberservices@aan.com. <http://www.aan.com>.

American Council for Headache Education (ACHE). 19 Mantua Road, Mt. Royal, NJ 08061. (856) 423-0258; Fax: (856) 423-0082. achehq@talley.com. <http://www.achenet.org>.

International Headache Society (IHS). Oakwood, 9 Willowmead Drive, Prestbury, Cheshire SK10 4BU, United Kingdom. +44 (0) 1625 828663; Fax: +44 (0) 1625 828494. rosemary@ihs.u-net.com. <http://216.25.100.131>.

National Headache Foundation. 820 North Orleans, Suite 217, Chicago, IL 60610. (773) 525-7357 or (888) NHF-5552. <http://www.headaches.org>.

NIH Neurological Institute. P. O. Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

Rebecca J. Frey, PhD

Hearing disorders

Definition

Hearing disorders range from a temporary, partial loss of hearing to the permanent loss of hearing known as deafness.

Description

The variety of hearing disorders includes a loss or decrease in the ability to discern certain frequencies of sound, a ringing or other noise that is unrelated to any actual external sound, damage due to physical trauma or infection, and genetically determined structural malformation.

Demographics

Hearing disorders occur worldwide in all races. The hearing loss that occurs with age is very common, affecting an estimated 30% of Americans over 60 years of age and 50% of those older than 75.

Tinnitus, a ringing or noisy sensation in the ears, is quite common with an estimated 20% of people affected worldwide. In the United States alone, some 36 million people experience tinnitus.

For hearing loss caused by otosclerosis, middle-aged Caucasian women are more prone than others, perhaps as a consequence of hormonal changes. In otosclerosis, abnormal bone development occurs in the middle ear, resulting in progressive hearing loss. Sudden hearing loss happens more often to people ages 30–60 for unknown reasons.

Causes and symptoms

Presbycusis

Presbycusis (or sensorineural hearing loss) is the loss of hearing that occurs with age. The condition results from the long-term assault on the ear structures, particularly on the inner ear, from a lifetime of noise, ear infections, or growths on bones of the outer or middle ear. The inner ear is where the vibrational sound waves are converted to electrical signals, courtesy of thousands of tiny hairs that are in a fluid-enclosed space called the cochlea. The hairs are connected to nerve cells, which send the electrical signals to the brain.

Most age-related hearing loss is due to damage to the cochlea. The tiny hairs can bend or even break, and the attached nerve cells can degenerate. The resulting less-efficient transmission of the electrical signal, particularly of higher-pitched tones, causes hearing loss.

Symptoms of presbycusis typically include increased difficulty in making out sounds of a certain volume or tone, especially when background sounds are present.

Conductive hearing loss

In conductive hearing loss, sound is not transmitted efficiently through the outer and middle ears. These regions house the eardrum, ear canal, and the trio of tiny bones (ossicles) in the middle ear that transmits sound energy to the inner ear. The hearing loss can be due to malformation of structures like the canal or the ossicles, dense buildup of ear wax, or fluid in the ear due to colds, allergies, or infections like otitis media. Symptoms include a decreased ability to detect fainter sounds and a general lowering of the sound level that can be detected.

Otitis media

Otitis media is an inflammation in the middle ear that is usually accompanied by fluid buildup. The condition may be transient in some children, but persistent in others to the point of requiring surgical correction. In developed countries, otitis media is second to the common cold as the most common health problem in preschool-aged children. Hearing loss occurs because of the fluid accumulation and the resulting suppression of sound waves moving to the inner ear.

Central auditory processing disorders

Central auditory processing disorders result in hearing loss when the areas of the brain involved in hearing are damaged. Sources of damage include disease, injury, and tumor growth. Consistent with the variety of causes, the symptoms of the disorders include the inability to hear certain sounds, inability to tell one sound from another, and the inability to recognize a pattern such as speech in sounds.

Congenital hearing loss

Congenital hearing loss is present from birth and is caused by a genetic defect or disturbance during fetal development. Genetic factors cause more than half of all such disorders. Depending on the nature of the genetic defect, the occurrence of the hearing loss may be common or rare. For example, if both parents have a genetically determined hearing deficiency, the chance of passing the trait to their children is high. In other cases, people who have normal hearing carry a second, defective copy of a crucial gene. The chance of passing on the hearing loss is 25%.

Hearing loss at birth can also be caused by pre-birth infections such as measles, cytomegalovirus, or herpes simplex virus.

Otosclerosis

The abnormal growth of the bone of the middle ear prevents the ossicles, particularly the last of the trio of bones (the stapes), from properly transmitting sound

Key Terms

Cochlear implant A device used for treating deafness that consists of one or more electrodes surgically implanted inside or outside the cochlea, an organ in the inner ear that transforms sound vibrations in the inner ear into nerve impulses for transmission to the brain.

Ossicles Tiny bones in the middle ear, the incus, malleus, and stapes, that convey sound impulses from the eardrum to the inner ear.

Otitis media Inflammation, usually with infection, of the middle ear.

Otosclerosis Abnormal bone development in the middle ear, resulting in progressive hearing loss.

Presbycusis Loss of hearing that gradually occurs because of age-related changes in the inner or middle ear.

Tinnitus Ringing or noisy sensations in the ears when no external sound is present, often associated with hearing impairment and excess noise exposure.

waves to the inner ear in otosclerosis. The cause(s) of otosclerosis are not clear, although observations that the disorder spans family generations make a genetic source likely.

The diminished hearing that occurs is not sudden. Rather, the change is gradual and is usually recognized when the person becomes aware that she or he can no longer hear a low-pitched sound such as a whisper.

Other genetically based hearing losses

Usher syndrome affects both the ears and eyes. The defective genes that are at the heart of the malady are passed from parents to children. Depending on the nature of the syndrome, children can be born with moderate to severe hearing loss, or can be totally deaf. Others begin life essentially normal, with hearing loss progressively worsening to deafness by the teenage years.

Waardenburg syndrome affects both the ears and the color of the skin, eyes, or hair. Eyes can be different colors and hair can have a patch of white or become prematurely gray. Hearing can range from normal to severely impaired. At least four genes can produce the syndrome when they undergo mutation.

Ménière's disease

Ménière's disease is a change in the volume of the inner ear that produces swelling, pressure, **pain**, intermittent hearing loss, **dizziness**, and tinnitus. Swelling may be so pronounced that membranes like the eardrum can rupture. As well, some people report that their voice sounds louder than normal. The disease may be caused by a viral or bacterial infection.

Tinnitus

Tinnitus is a ringing noise or other sound that occurs in the absence of an external source of sound. For some, tinnitus is an infrequent occurrence. Others are very inconvenienced by near-constant tinnitus. The noises experienced in tinnitus range in description and include electronic noise, hissing steam, chirping crickets, bells, breaking glass, buzzing, and even the noise of a chainsaw. The noises can be constant or may rise and fall in volume with head motion or with the planting of feet during running.

Tinnitus has various known triggers. Foods such as red wine, cheese, and chocolate have been implicated. Over-the-counter drugs such as ibuprofen and extra-strength aspirin, and prescribed drugs, including oral contraceptives and aminoglycoside antibiotics, can cause tinnitus. Drug-related tinnitus disappears when the dosage is reduced or the drug stopped. The growth of certain tumors can cause tinnitus.

The aging of the inner ear is also a factor in tinnitus. As nerve cells deteriorate and the many hairs in the cochlea that transmit sound waves to the nerves become damaged and broken with time, the signaling of sound impulses to the brain becomes faulty. Nerves may fire when there has been no stimulus. The brain interprets the signal as actual noise.

Sudden deafness or sudden sensorineural hearing loss

This rapid decrease or complete loss of hearing can occur within minutes or over the course of several days. The hearing loss typically affects one ear and often resolves with time. Sudden deafness is much more serious and should be treated as a medical emergency requiring immediate medical attention. Causes are unclear and may involve an infection, head injury, reaction to a drug, problems with circulation, and other disorders such as **multiple sclerosis**.

Deafness

The complete loss of hearing can be due to genetically determined developmental difficulties, a trauma such as a loud noise, physical damage to structures in the ear, nerves, or relevant areas of the brain, and infection during pregnancy (such as rubella). In a great many cases, deafness is permanent. Childhood deafness typically becomes apparent when a child appears inattentive and fails to meet language milestones.

A mother and young daughter communicate with sign language. *(© Custom Medical Stock Photo. Reproduced by permission.)*

Diagnosis

Presbycusis is usually first detected by a family physician. Diagnosis is subsequently made by a hearing specialist or an audiologist, and involves a hearing test in which sounds of differing frequencies and gradually decreasing volume are sent to one ear at a time.

Tinnitus is self-evident, as the ringing or other sensation is impossible to ignore. In contrast, otitis media can be difficult to diagnose, as it is often not accompanied by pain or a fever. Fluid in the ear can be a sign of otitis media. Also, changes in children's behavior such as playing the television louder, misunderstanding directions, and pulling at the ears can all be indicators of otitis media.

Imaging of the inside of the ear using the technique of **magnetic resonance imaging (MRI)** can be useful in diagnosing Ménière's disease. Usher syndrome is diagnosed by the simultaneous appearance of ear and eye problems.

Treatment team

The varied treatment can involve the family physician and more specialized doctors, including audiologists and otolaryngologists (specialists in ear, nose, and throat disorders). As well, speech-language pathologists can be involved in the treatment of hearing loss-related speech disorders in children.

Treatment

Treatment for presbycusis can be as simple as keeping the ear canals free from sound-muffling wax buildup. Another fairly common treatment for older people is the use of a hearing aid, which amplifies sound and directs the sound into the ear canal. About 20% of those with age-related hearing loss can benefit from an aid. More severe presbycusis can be treated using a cochlear implant. The device actually compensates for the nonworking parts of the inner ear. Conductive hearing loss can usually be fully corrected by medication or surgery. Similarly, when tinnitus is caused by overmedication, the condition is alleviated by modifying or eliminating the dosage of the drug.

Ménière's disease and Usher syndrome cannot be cured, however, the symptoms can be greatly relieved by release of the buildup of pressure in the inner ear and the use of hearing aids or implants, respectively. Coping strategies and increased knowledge of the conditions can then help a person lead an essentially normal life.

Otosclerosis that is more pronounced can be treated by a surgical procedure called a stapedectomy, in which the damaged portion of the middle ear, the stapes, one of the three bones of the middle ear, is bypassed by an implanted device that routes sound to the inner ear. Milder otosclerosis may be lessened by the use of a hearing aid.

Recovery and rehabilitation

Some conditions that can be addressed by surgery or the use of a hearing aid or an implant have varying levels of recovery. Other conditions involving permanent deafness cannot be cured.

Clinical trials

As of April 2004, at least eight **clinical trials** were active in the United States. Most focus on deafness, in particular the determination of the genetic factors that contribute to or cause deafness. Updated information on these studies can be found at the National Institutes of Health Web site for clinical trials at <http://www.clinicaltrials.gov>.

Prognosis

Age-related hearing loss can be partially or almost completely compensated for by a change in lifestyle and the development of coping skills (listening to the radio at higher volume, different conversational behavior in crowds, use of hearing aids or implants). Otitis media can cause delayed speech development, if undiagnosed, because of the child's impaired ability to hear. Sudden hearing loss usually resolves on its own within a few days to several weeks. However, in about 15% of cases, the condition worsens with time.

Special concerns

The various surgeries that can be performed all carry some risk, and the quality of sound that is provided by cochlear implants varies greatly among recipients.

Additionally, tinnitus can be caused by the buildup of cholesterol in arteries around the ear, high blood pressure, and by malformed arteries or veins. Tinnitus, therefore, may be an indication of a more serious health problem.

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ORGANIZATIONS

American Academy of Audiology. 8300 Greensboro Drive, Suite 750, McLean, VA 22102. (703) 790-8466 or (800) 222-2336; Fax: (703) 790-8631. info@audiology.org. <http://www.audiology.org>.

American Speech-Language-Hearing Association. 10801 Rockville Pike, Rockville, MD 20852. (301) 638-8255 or (800) 638-8255; Fax: (301) 571-0457. actioncenter@asha.org. <http://www.asha.org>.

American Tinnitus Association. PO Box 5, Portland, OR 97207-0005. (503) 248-9985 or (800) 634-8978; Fax: (503) 248-0024. tinnitus@ata.org. <http://www.ata.org>.

Deafness Research Foundation. 1050 17th Street NW, Suite 701, Washington, DC 20036. (202) 289-5850. <http://www.drf.org>.

National Center on Deafness. 18111 Nordhoff Street, Northridge, CA 91330-8267. (818) 677-2145; Fax: (818) 677-7693. ncod@csun.edu. <http://ncod.csun.edu>.

National Institute on Deafness and Other Communication Disorders, National Institutes of Health. 31 Center Drive, MSC 2320, Bethesda, MD 20892-2320. (301) 496-7243 or (800) 241-1044; Fax: (301) 402-0018. nidcdinfo@nidcd.nih.gov. <http://www.nidcd.nih.gov>.

Brian Douglas Hoyle, PhD

Hemianopsia

Definition

Hemianopsia is a term that describes a loss of vision that affects half of the visual field of one eye or both eyes.

Description

Hemianopsia prevents an individual from seeing objects in half of the visual field of a particular eye. As a result, an individual suffering from hemianopsia will not see objects that are in the affected visual field.

Causes and symptoms

Conditions or injuries that affect the optic nerve can cause hemianopsia. The sequelae (aftereffects) of **stroke**, brain aneurysm, occlusion of the optic artery, brain tumors, or traumatic head injuries can all result in hemianopsia. Occasionally, individuals who suffer from

migraine headaches may experience hemianopsia during a migrainous episode or as part of the prodromal aura that precedes the actual **headache**; this type of hemianopsia resolves completely upon resolution of the headache. Transient hemianopsia can result from bouts of extremely high blood pressure (as occurs in eclampsia) or during or after a seizure. Other rare causes of hemianopsia include infections, such as encephalitis, brain abscess, **progressive multifocal leukoencephalopathy**, and **Creutzfeldt-Jakob disease**.

Symptoms of hemianopsia involve the inability to see objects in half of the visual field of one or both eyes, which may be manifested by reading difficulties, problems walking through crowded areas, frequent accidents (bumping into objects that are located in the lost visual field), or being startled at what seems to be the sudden emergence of people or objects in the visual field.

Diagnosis

Diagnosis is usually evident when basic testing reveals a blind area in half of the visual field of one or both eyes. Further testing will be necessary to uncover the underlying causative condition: CT or **MRI** scanning may reveal the presence of a stroke, aneurysm, or brain tumor.

Treatment team

Neurologists, ophthalmologists, and neuroophthalmologists all work with patients with hemianopsia. Occupational therapists and vision rehabilitation specialists can be integral in teaching the individual how to compensate for their vision loss.

Treatment

Treatment includes therapy to practice techniques that may help an individual overcome the obstacles of hemianopsia. For example, changing reading techniques (looking at the last part of the word, rather than the first) may improve an individual's ability to read and enjoy reading. Special scanning techniques may be taught, using a machine called a Dynavision, which will help an individual learn how to turn the head in certain ways to scan the environment and compensate for the lost visual field.

Special glasses lenses, some with mirrors or prisms incorporated, may allow an individual with hemianopsia to view a greater visual field.

Prognosis

Recovery of vision after stroke or head injury is usually maximal within the first three to six months; hemianopsia persisting after that point is usually permanent.

Special concerns

Driving can be a particular concern for people with hemianopsia. By learning new techniques for scanning the environment, some individuals can safely return to driving; others will not be able to drive safely, and will no longer be able to obtain a driver's license. This can result in significant changes in an individual's lifestyle, independence, and employability.

Resources

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ORGANIZATIONS

Lighthouse International. 111 East 59th Street, New York, NY 10022. 212-821-9200 or 800-829-0500. info@lighthouse.org. <http://www.lighthouse.org/Default.htm>.

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Hemifacial spasm

Definition

A hemifacial spasm is an involuntary contraction of the muscles of facial expression, resulting in eyelid closure and upturning of the corner of the mouth and accompanied by facial weakness.

Description

Hemifacial spasm results in involuntary contraction of the facial muscles limited to one side of the face. The eyelids are involved, and upturning of the corner of the mouth is observed. The patient may have facial twitching during periods of sleep. If left untreated, the twitching may worsen and extend to other facial muscles.

Demographics

Females are affected more than males, regardless of race. Typically, patients afflicted with hemifacial spasm are in their 40s or 50s.

Causes and symptoms

The cause of hemifacial spasm has been linked to overactivity of the seventh cranial nerve nucleus that signals facial muscle movement. In other instances, hemifacial spasm may be caused by compression by a mass or

abnormal blood vessel or by a lack of blood supply (ischemia) of the seventh cranial nerve at its origin or by the nucleus itself. It is thought that compression by a convoluted cerebral artery is the most common cause. In some patients, no underlying cause can be detected, which is termed an idiopathic hemifacial spasm. In younger patients, **multiple sclerosis** may be the cause.

Patients will usually report involuntary twitching of one side of the face (hemifacial), lasting seconds to minutes. Family members may observe facial twitching while the patient sleeps. **Pain** or numbness is usually not reported.

Diagnosis

When a clinical diagnosis has been established, imaging of the brain is required to rule out ischemia, mass lesions, or abnormal vasculature. **Magnetic resonance imaging (MRI)** of the brain, with and without contrast, as well as MRI-angiography, are advised. Blood tests are not required for patients believed to have hemifacial spasm.

Treatment team

Ophthalmologists, neuro-ophthalmologists, and neurologists are physicians who can diagnose and treat hemifacial spasm. If surgery is indicated as a form of treatment, it is usually performed by a neurological surgeon.

Treatment

The mainstay of treatment is injection of **botulinum toxin** to the face, which results in temporary paralysis of selected muscles of facial expression. Botulinum toxin, commonly known as Botox (Allergen Inc.), is a neurotoxin produced by the bacterium, *Clostridium botulinum*. This toxin weakens facial muscles by inhibiting the release of a neurotransmitter, acetylcholine, which results in temporary and partial muscle paralysis. Botulinum toxin has become an accepted and widely used treatment for hemifacial spasm. Although its use is relatively safe and easily injected, the effect of botulinum toxin is temporary, lasting approximately six months. This necessitates the need for re-injection or increased doses of the toxin, depending on the patient's response.

If botulinum toxin fails to be effective or the patient does not tolerate it well, decompression of the seventh cranial nerve can be attempted. This procedure, performed by a neurosurgeon, entails placing a sponge between the seventh nerve and the vessel compressing the nerve.

Other treatment options include severing branches of the seventh nerve, destruction of eyelid and facial musculature, and oral anti-seizure medications. However, oral medications have proven to be limited in their efficacy and have significant side effects.

Recovery and rehabilitation

There is usually no recovery period following the injection of botulinum toxin. The maximal effects are usually seen four to seven days following injection.

Clinical trials

Currently there are no clinical trials scheduled to study this disorder.

Prognosis

The vast majority of patients responds favorably to injections with a low rate of complications. A small percentage of patients improves spontaneously, and benefits from psychotherapy, surgery, or oral medications.

Special concerns

Support groups and information for patients and families are excellent resources that may improve treatment outcomes and psychosocial ramifications.

Resources

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ORGANIZATIONS

Hemifacial Spasm Association. <http://www.hfs-assn.org>.

Adam J. Cohen, MD

Hemiplegia alterans *see* **Alternating hemiplegia**

Hereditary spastic paraplegia

Definition

Hereditary spastic paraplegia (HSP) is a hereditary degenerative disorder affecting the corticospinal tracts (long never fibers that supply the upper and lower limbs)

within the spinal cord. The disease frequently results in progressive **spasticity** (involuntary movement) of leg muscles with varying degrees of stiffness and weakness of other muscle groups in the thighs, lumbar spinal area, and muscles responsible for up and down feet movements. The extent of degeneration and severity of symptoms varies among the affected people, even those among the same family group. The age of onset for the disease also varies. Some families show a pattern of disease, with symptoms developing earlier in each new generation. In most individuals, however, the disease onset occurs between the second and the fourth decades of life, with a few cases beginning later, or as early as infancy and early childhood.

Key Terms

Ataxia A condition marked by impaired muscular coordination, most frequently resulting from disorders in the brain or spinal cord.

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.

Corticospinal tract A tract of nerve cells that carries motor commands from the brain to the spinal cord.

Neurodegenerative disease A disease in which the nervous system progressively and irreversibly deteriorates.

Neuropathy A disease or abnormality of the peripheral nerves (the nerves outside the brain and spinal cord). Major symptoms include weakness, numbness, paralysis, or pain in the affected area.

Spinal cord The elongated nerve bundles that lie in the spinal canal and from which the spinal nerves emerge.

Description

Other names of this disorder are hereditary spastic paraparesis, Strumpell-Lorrain syndrome, Strumpell disease, familial spastic paraparesis, spastic spinal familial paralysis, and Troyer syndrome. When the only manifested symptom is progressive spasticity, HSP is also known as Pure Hereditary Spastic Paraplegia.

HSP presents three forms of inheritance: autosomal dominant HSP, autosomal recessive HSP, and X-linked HSP. Autosomal dominant HSP requires the presence of an inherited mutation in only one copy of the gene responsible for the disease, whereas autosomal recessive HSP requires mutation in the two copies (maternal and paternal) to manifest the disease. X-linked HSP is rare and the mutated gene is located in the X chromosome, which is transmitted by the mother. HSP is also divided into two categories, uncomplicated HSP and complicated HSP.

Demographics

As usually happens with other rare neurological diseases, the HSP symptoms may overlap or be mistaken with other neurodegenerative disorders. Consequently, HSP incidence is only estimated, with approximately three cases out of 100,000 individuals as an average estimate for the United States and Europe. Ninety percent of HSP cases are uncomplicated and do not affect life expectancy.

Causes and symptoms

Hereditary spastic paraplegia (HSP) belongs to a group of neurodegenerative (progressive nervous system dysfunction) disorders with common symptoms of progressive and usually severe weakness and spasticity of the lower limbs. However, mutations in different genes may result in HSP, a phenomenon known as genetic heterogeneity. For instance, uncomplicated HSP may be inherited as an autosomal dominant mutation in about 70% of cases; but the involved mutated gene may be a different one, located in a different chromosome, from one family to another. Any of these genes is generically known as spastic paraplegia gene or SPG.

SPGs responsible for the uncomplicated form of the disease have been identified in chromosomes 2, 8, 12, 14, 15, 19, and 20; and an autosomal dominant complicated HSP gene has been found in chromosome 10. Autosomal recessive HSP may be caused by other than the abovementioned SPGs, also located either in chromosome 8 or 15, or yet in chromosome 16. One form of autosomal recessive HSP, the Troyer syndrome, is associated with a SPG located in chromosome 13. Two different genes associated with autosomal recessive HSP have also been identified on the X chromosome. Approximately 40–50% of all cases of autosomal dominant HSP are caused by SPG located on chromosome 2.

Uncomplicated autosomal dominant HSP may start at any phase of life, from infancy or early childhood to adulthood or old age. In children, uncomplicated HSP progresses until adolescence and then stabilizes, resulting in partial walking disability. However, complete paralysis of the legs is rare in uncomplicated HSP, whatever the age of onset.

Autosomal recessive HSP is the complicated form of the disease with onset between two and 16 years of age. Complicated HSP symptoms continually progress and

may be associated with other neurological conditions, such as **epilepsy**, **mental retardation**, **peripheral neuropathy** (numbness, **pain**, and sensory changes in nerves of limb extremities), ocular (eye) degenerations, such as retinopathy and/or the destruction of optic nerve tissues (ocular neuropathy). Other clinical complications are **ataxia** (motor coordination disorders), **dysarthria** (speech disorders), nystagmus (repetitive and involuntary eye movements), and ichthyosis (abnormal dryness, scaling, and thickening of the skin). However, these neurological symptoms may be caused by other disorders present at the same time. For instance, a person with uncomplicated HSP may have peripheral neuropathy due to diabetes.

Diagnosis

Family clinical history and physical and neurological examinations are the first tools in HSP diagnosis. The physician will conduct comparative examination of muscle tone and strength between arms and legs and look for signs of weakness in specific muscle groups of the thigh, presence of abnormal increase of deep tendon brisk reflexes in the lower extremities, loss of ankle flexibility, and decrease of sensation in the lower extremities. Genetic screening for SPG is the definitive test to avoid misdiagnosis.

Treatment

There is no curable or preventive treatment for HSP, except for antispasmodic drugs to reduce muscle spasms. However, symptomatic treatment for sensitive neuropathy may also be necessary in recessive HSP. Supportive care includes physical therapy and devices to assist with walking.

Resources

BOOKS

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ORGANIZATIONS

Genetic Alliance. 4301 Connecticut Avenue, N.W., Suite 404, Washington, DC 20008-2369. (202) 966-5557 or (800) 336-GENE (4363); Fax: (202) 966-8553. info@geneticalliance.org. <http://www.geneticalliance.org>.

National Ataxia Foundation (NAF). 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447-4752. (763) 553-0020; Fax: (763) 553-0167. naf@ataxia.org. <http://www.ataxia.org>.

Spastic Paraplegia Foundation. P.O. Box 1208, Forston, GA 31808. (978) 256-2673. info@sp-foundation.org. <http://www.sp-foundation.org>.

Worldwide Education & Awareness for Movement Disorders (WE MOVE). 204 West 84th Street, New York, NY 10024. (212) 875-8312 or (800) 437-MOV2 (6682); Fax: (212) 875-8389. wemove@wemove.org. <http://www.wemove.org>.

Sandra Galeotti

Heredopathia atactica polyneuritiform *see* **Refsum disease**

Herpes zoster *see* **Shingles**

Hirayama syndrome *see* **Monomelic amyotrophy**

Holoprosencephaly

Definition

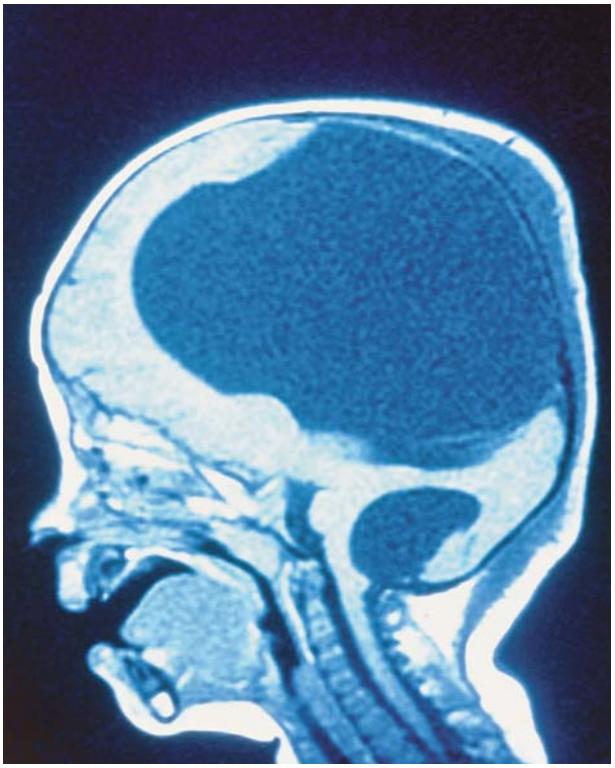
Holoprosencephaly is a birth defect caused by failure of the forebrain (prosencephalon) to grow as two separate hemispheres in the first few weeks of fetal life. The more complete the failure to divide, the worse the resulting abnormalities of brain, skull, and face. In its most severe form, holoprosencephaly entails the development of a tiny, undivided forebrain and is fatal before birth. Equivalent terms are arhinencephaly, holotelencephaly, and telencephalosynapsis. The prefix *holo* means undivided.

Description

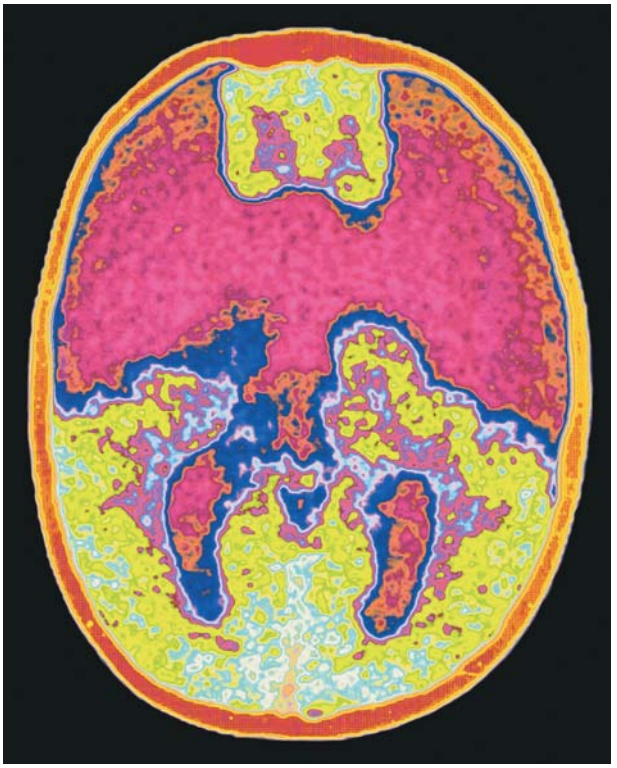
There are three degrees of severity of holoprosencephaly: (1) *alobar* holoprosencephaly, in which a tiny, single-lobed, nonfunctional forebrain brain develops, along with other severe cerebral abnormalities and severe facial deformities including cyclopism, or formation of a single, nonfunctional eye where the bridge of the nose should be; (2) *semilobar* holoprosencephaly, in which the brain is partly divided and there may be significant facial deformities such as cleft palate; and (3) *lobar* holoprosencephaly, in which the brain is partly divided, but there is some fusion of structures along the midline. Some authorities distinguish a fourth category to include various mild abnormalities of prosencephalic division, namely olfactory aplasia (absence of olfactory bulbs and tracts) and middle interhemispheric variant, in which the posterior frontal and parietal lobes of the brain are not well-separated.

Demographics

Holoprosencephaly occurs in a small number of live births, with estimates varying from one in 5,000 to one in 31,000. However, its actual incidence is much higher, since many fetuses with holoprosencephaly, approximately 97%, are either stillborn or spontaneously aborted (miscarried). The rate of holoprosencephaly among all



MRI of a 20-month-old girl with holoprosencephaly. The dark area represents the abnormally large fluid-filled ventrical typical of this disease. *(Simon Fraser / Neuroradiology Dept. / Newcastle General Hospital / Science Photo Library.)*



MRI of a brain with holoprosencephaly. The red area represents the large, fluid-filled cavity that develops where the forebrain would normally be. *(Mehau Kulyk / Photo Researchers, Inc.)*

pregnancies may therefore be as high as 1:200 or 1:250. As of 2004, the medical literature did not note a higher prevalence of holoprosencephaly in any particular racial group or geographic area.

Causes and symptoms

Holoprosencephaly has no single cause, but about half of all cases are associated with abnormal karyotype (abnormal numbers of chromosomes), especially trisomy 13 (extra copy of chromosome 13) and trisomy 15 (extra copy of chromosome 15). It can also run in families as an autosomal dominant, autosomal recessive, or X-linked recessive trait. Currently, researchers believe that holoprosencephaly might be linked to as many as 12 chromosomal regions on 11 chromosomes.

Risk is increased if the mother has diabetes or has an infection during pregnancy such as syphilis, herpes, cytomegalovirus, rubella, or toxoplasmosis. Use of certain drugs or other substances during pregnancy (e.g., alcohol, aspirin, lithium, thorazine, **anticonvulsants**, hormones, retinoic acid) has also been suggested as a risk factor. Women who have had previous miscarriages and bleeding in the first trimester are also more likely to have fetuses with holoprosencephaly.

Alobar holoprosencephaly causes death, either before or soon after birth. Cyclopia or formation of a single eye often occurs, with the nose being absent, having only a single nostril, or being replaced by a proboscis (small, tubular nose) either above or below the eye. Less severe degrees of holoprosencephaly cause **mental retardation** ranging from profound to mild. The eyes may be closely set together, the nose may be malformed, and there may be cleft lip (premaxillary agenesis). Children who survive birth generally have facial deformities, **spasticity**, **seizures**, problems with regulating body temperature, apneic attacks (spells of stopped breathing), psychomotor retardation, sleep disorders, gastroesophageal reflux, and other problems. However, holoprosencephaly occurs along a continuum, and at the mild end of the spectrum development may be essentially normal.

Diagnosis

Ultrasonic examination of the fetal brain has made early detection of holoprosencephaly common. In infants born live, a preliminary diagnosis may be based on extremely small head size (**microcephaly**) and on examination of the face, which is often deformed by the

Key Terms

Autosomal dominant disorder A genetic disorder caused by a dominant mutant gene that can be inherited by either parent.

Autosomal recessive disorder A genetic disorder that is inherited from parents that are both carriers, but do not have the disorder. Parents with an affected recessive gene have a 25% chance of passing on the disorder to their offspring with each pregnancy.

Microcephaly An abnormally small head and underdeveloped brain.

Prosencephalon The part of the brain that develops from the front portion of the neural tube.

X-linked disorder Disorders caused by genes located on the X chromosome.

underlying developmental defects of the brain and skull. In particular, midfacial hypoplasia (subnormal growth of the features along the midline of the face) is strongly correlated with holoprosencephaly. Half of all cases of agnathia (total or virtual absence of a lower jaw) are also associated with holoprosencephaly. However, about 30% of cases of severe holoprosencephaly occur with normal development of the face. Ultrasound may give early warning of holoprosencephaly during fetal development; **magnetic resonance imaging** is the definitive method for diagnosing holoprosencephaly in non-severe cases.

Treatment team

If holoprosencephaly is known to have occurred in the family, consultation with a geneticist before or during pregnancy may help a woman determine if she is at higher risk for conceiving infants with holoprosencephaly. If a woman has diabetes, she should see a doctor with expertise in diabetes care to obtain the best possible care before and during pregnancy, including help in achieving tight blood-glucose control, as this can reduce a diabetic woman's risk of having a child with birth defects to near normal.

Treatment

There is no cure for holoprosencephaly. Severe forms are fatal. For children with milder forms, treatment is directed at the symptoms rather than the disease. For example, drugs such as **diazepam** (Valium) and baclofen can be used to moderate spasticity (involuntary muscle tightening). Dorsal rhizotomy (cutting of the sensory spinal nerve roots), often done for the relief of intractable **pain**, can also be used to treat spasticity. Difficulty sleeping, common in children with holoprosencephaly, may be helped by such medications as Valium, chloral hydrate, or Melatonin. Low muscle tone in the esophageal sphincter, leading to gastroesophageal reflux ("spitting up" of the stomach contents into the esophagus and possibly out of the mouth, as occurs normally in small infants), can be treated with drugs that increase the speed with which the stomach and intestines pass material along and with antacids, which decrease the acidity of stomach contents and make gastroesophageal reflux less harmful. Emotional and intellectual care must be adjusted to the degree of retardation in each case.

Prognosis

The prognosis for an infant born with holoprosencephaly depends on the severity of the cerebral and other defects. The prognosis for an infant with severe holoprosencephaly is poor; most do not survive past six months, and those that do are likely to suffer profound mental retardation. At the mild end of the spectrum, where brain development may be nearly normal, a normal lifespan is likely.

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ORGANIZATIONS

Carter Centers for Research in Holoprosencephaly. c/o Texas Scottish Rite Hospital, P.O. Box 190567, 2222 Welborn Street, Dallas, TX 75219-9982. (214) 559-8411; Fax: (214) 559-7835. hpe@tsrh.org. <http://www.stanford.edu/group/hpe>.

Larry Gilman, Ph.D.

HTLV-1 associated myelopathy

Definition

Damage to the nerves (myelopathy) of the spinal cord caused by infection with the human T lymphotrophic virus type-1 is termed HTLV-1 associated myelopathy.

Description

HTLV-1 associated myelopathy is evident mainly as a chronic weakening of muscles, especially those in the legs. Weakening can be so severe as to produce partial paralysis. The myelin covering of spinal cord nerve cells can become damaged, as can the elongated part of the cell termed the axon.

HTLV-1 associated myelopathy is also known as **tropical spastic paraparesis** and additionally as HTLV-1 associated myelopathy/tropical spastic paraparesis.

Demographics

Myelopathy occurs in approximately 0.25 % of those infected with HTLV-1, typically in adults aged 40–60. The viral infection is associated with diseases including adult T-cell leukaemia, Acquired Immunodeficiency Syndrome (**AIDS**), various neurological disorders, inflammation of the uveal tract of the eye, and degenerative or arthritic **pain**.

HTLV-1 is common in Japan, the Caribbean, and some areas of Africa. Correspondingly, the associated myelopathy is more prominent in these regions, compared to other areas of the globe.

Causes and symptoms

HTLV-1 associated myelopathy is the result of infection with the HTLV-1 virus. The common routes of transmission are through breast milk, transfused blood (especially prior to 1989 when donated blood was not tested for HTLV-1), sexual intercourse, and drug injection.

Until the viral link was established in the mid-1980s, HTLV-1 associated myelopathy was thought to result in the inflammation of the **central nervous system** caused by infection by the bacteria *Treponema pallidum* (the cause of syphilis) or *Treponema pertenue* (the cause of yaws), or by a nutritional deficiency.

In addition to the damage to nerve myelin and axon, the white and grey matter of the spinal cord sometimes becomes infiltrated with certain white blood cells, along with nerve cell astrocytes. White lesions can develop along the length of the spinal cord. Occasionally, the entire cord can become swollen.

Along with the progressively increasing muscle weakness, patients also can display impaired sense of touch and pain receptivity, and malfunction of muscles called sphincters, which can contract to restrict the flow of some body fluids and relax to resume flow. Leakage of urine is a problem in over 90% of those with this form of myelopathy. Patients can also develop eye inflammation, arthritis, dryness of the cornea and conjunctiva, and skin inflammation.

Key Terms

Myelopathy A disorder in which the tissue of the spinal cord is diseased or damaged.

Diagnosis

Diagnosis can be made using several clinical observations. A medical history will show that the current symptoms were not present during childhood. Within two years of the first appearance of symptoms, a person will likely have experienced an increase in the frequency of urination, and weakness, numbness, pains, or cramps in both legs. In a physical examination, an increased knee-jerk reaction is seen. Difficulty using both legs is evident. Finally, eye abnormalities such as changes in the appearance of the pupil are present.

The visualization of spinal cord nerve damage can also aid in diagnosis. Lesions and swelling associated with the spinal cord can be visualized by **magnetic resonance imaging (MRI)**.

Demonstration of the presence of HTLV-1 is an important part of the diagnosis. Antibodies to several viral proteins can be detected shortly after an infection begins. But, within a few months, an infection can become undetectable using antibody detection techniques. Thus, the absence of HTLV-1 antibodies does not necessarily rule out an infection. HTLV-1 genetic material can be detected from lymphocyte cells using a sensitive technique called polymerase chain reaction.

A more reliable diagnostic finding can be an increased level of a compound called neopterin in the cerebrospinal fluid (CSF) that is obtained by a lumbar puncture. Neopterin is released by immune cells called macrophages when they are stimulated as part of an immune response to the infecting virus. As well, lymphocyte cells in the CSF can adopt a characteristic flower-like appearance.

Treatment team

Family physicians, neurologists and other specialized clinicians, physical therapists, and caregivers are all part of the treatment team.

Treatment

Currently, there is no specific treatment regimen for HTLV-1 associated myelopathy. Steroid medications help lessen symptoms and discomfort in many people. Drug therapy with lioresal or tizanidine can help relieve muscle spasms. The leakage of urine due to malfunction of the

urinary sphincter muscle can be treated using oxybutynin, or managed by use of a catheter.

The use of plasmapheresis, in which plasma is withdrawn, antibodies removed, and the antibody-free liquid put back into the person, has not shown promise for HTLV-1 myelopathy. Interestingly, this technique is useful in treating myelin damage caused in other disorders such as **Guillain-Barré syndrome**.

Recovery and rehabilitation

Physical and occupational therapy is useful in maintaining muscle function.

Clinical trials

A clinical trial sponsored by the National Institute of Neurological Disorders and Stroke has been underway since 1997 in which blood samples are collected from patients in order to evaluate the functioning of the immune system and the levels of the virus during the course of the disease.

Prognosis

While the disorder may become progressively worse, HTLV-1 associated myelopathy is seldom fatal. People with the disorder normally live for several more decades after being diagnosed. A better outcome typically results when steps are taken to lessen the chance of urinary tract infection (which can commonly occur when a catheter is used), and skin inflammation.

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ORGANIZATIONS

National Institute for Allergy and Infectious Diseases. National Institutes of Health, 31 Center Drive, Room 7A50, MSC 2520, Bethesda, MD 20892-2520. (301) 435-3848. <http://www.niaid.nih.gov>.

National Institute for Neurological Disorders and Stroke. P.O. Box 5801, Bethesda, MD 20824. (301) 496-5761 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders. P.O. Box 1968, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Brian Douglas Hoyle, PhD

Huntington chorea *see* **Huntington disease**

Huntington disease

Definition

First described by Dr. George Huntington in 1872, Huntington disease (HD) is a relatively common hereditary neurological condition that most commonly affects people in their adult years. HD is a progressive disorder that often involves thinking and learning problems, psychological disturbances, and abnormal movements. HD has been well studied and documented in family histories across the world. This ultimately led to the discovery of the HD gene, now known to be responsible for the disorder.

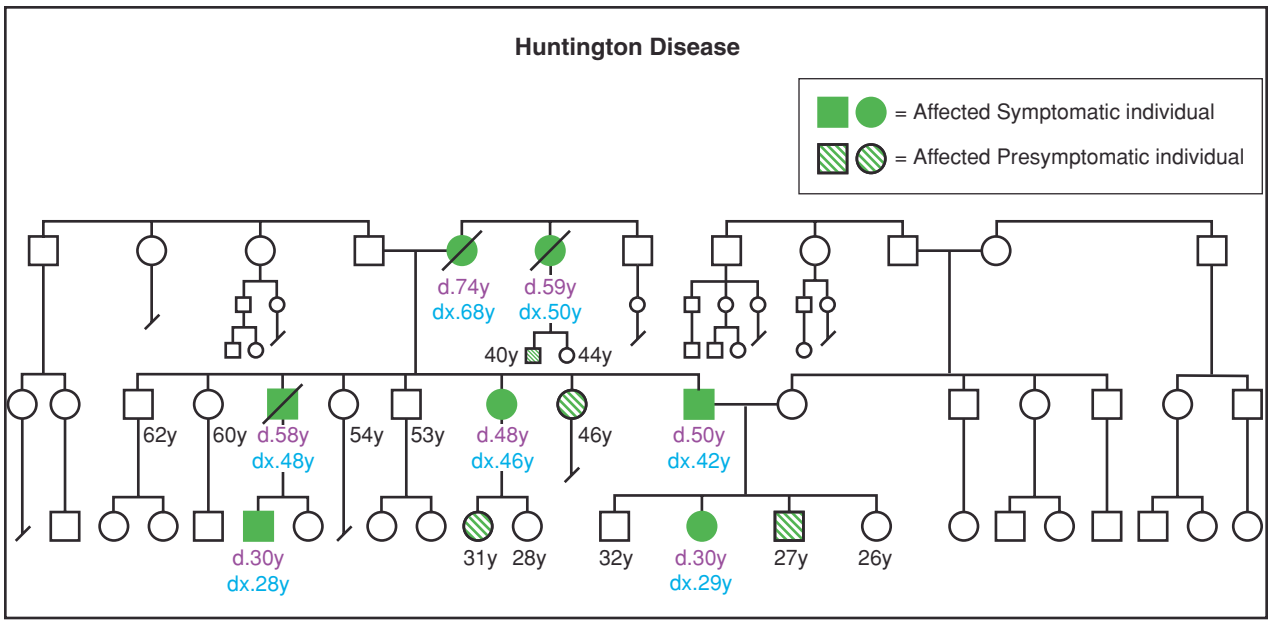
Description

Huntington disease is also known by the name Huntington (or Huntington's) **chorea**; "chorea" refers to neurological diseases that are characterized by spasmodic movements of the limbs and facial muscles. This is because about 90% of people with HD have chorea. These movements may be mild at first, but can worsen and become more involuntary with time.

About two-thirds of people with HD first present with neurological signs, while others first have psychiatric changes. Other neurological signs include various abnormal movements, changes in eye movements, difficulty speaking, difficulty swallowing, and increased reflexes.

A general decline in thinking skills occurs in essentially everyone with HD. This may begin as general forgetfulness and progress to difficulty gathering thoughts or keeping and using new knowledge. People with HD often also have psychiatric changes, including significant personality and behavior changes.

The majority of those with HD first develops symptoms between the ages of 35 and 50 years. Symptoms vary considerably between people and sometimes within families, so it is difficult to predict an individual's exact experience with HD if he or she is diagnosed with the condition. Disease progression occurs in everyone, with death usually seen 10–30 years after its onset.



See Symbol Guide for Pedigree Charts. *(Gale Group.)*

Demographics

HD is estimated to occur in the United States and most of Europe at a rate of about five cases per 100,000 people. Pockets of populations exist where the prevalence may be a bit higher, such as those with western European ancestors. Conversely, HD is estimated to have a much lower prevalence in Japan, China, Finland, and Africa. For example, the frequency of HD in Japan has been estimated at between 0.1 and 0.38 per 100,000 people.

Symptoms of HD typically begin after about age 35 years. However, in some families a juvenile form of HD has been seen with an onset of symptoms in the first or second decades of life. About a quarter of people with the condition are diagnosed past the age of 50 years. HD is a disease that affects males and females equally.

Currently, genetic testing is widely available to identify a well-documented mutation in the HD gene. Testing is available for confirmation of a clinical diagnosis, or for those at risk but who, as yet, have no symptoms. Predictive genetic testing (for those who are asymptomatic) typically involves a specialized protocol with pretest and post-test counseling, requiring coordinated care with various medical professionals.

Causes and symptoms

Some neurological changes have been seen in HD. However, the connection of many of these changes to the disease's symptoms is still not understood. Atrophy of the basal ganglia and corpus striatum are common neurological findings in HD, which may worsen over time. Cortical atrophy is often present, and this may be seen with **magnetic resonance imaging (MRI)** or computed tomography (**CT**) scans. From pathology studies after death, brain atrophy is most prominent in the caudate, putamen, and cerebral cortex in people with HD. Total brain weight may be reduced by as much as 25–30% in people who have advanced cases of HD.

A specific mutation in the HD gene called a triplet expansion causes symptoms of the condition to occur. The four different deoxyribonucleic acid (DNA) bases that make up genes are abbreviated as A, C, T, and G. Three DNA bases, CAG, are naturally repeated in the HD gene; a certain number of repeats is considered normal. People with symptoms of HD have a higher number of repeats than the usual range. Unfortunately, the number of CAG repeats can increase (or expand) from generation to generation, and this usually occurs in men. This genetic process is called anticipation; it cannot be predicted when and how the CAG repeats will expand in someone when they have children. A larger CAG repeat size is generally associated with developing symptoms at a younger age.

HD is inherited in an autosomal dominant manner, which means that an affected individual has a one in two chance to pass the disease-causing mutation to his or her children, regardless of the gender. Children who inherit a disease-causing mutation will develop signs of HD at some point in their lives. On the other side of that, children

who do not inherit the mutation should not develop the disease. Strong family histories of HD have been well documented and studied across the globe.

HD is usually first suspected with the observation or progression of abnormal movements. The initial reasons for seeking medical attention are often clumsiness, tremor, balance trouble, or jerkiness. Chorea is a frequent symptom.

The areas of the body most commonly affected by chorea are the face, limbs, and trunk. As the chorea progresses, breathing, swallowing, and the mouth and nasal muscles may become involved. Muscles may become extremely rigid and gait may show signs of **ataxia**. Chorea may also be mixed with other **movement disorders** such as **dystonia**. Visual muscles may also be affected, and this can eventually lead to difficulties with vision, speech, swallowing, and breathing.

Weight loss is a common symptom in HD, which may occur despite a proper intake of calories and nutrients. Because people with HD are frequently moving, it is thought this continual activity increases metabolic rates and may explain the weight loss. However, the exact cause for weight loss in HD is still not well understood.

Mental impairment is an eventual sign of HD. This may begin at about the same time as movement abnormalities. If a diagnosis of HD is made, cognitive decline may have actually begun earlier, but might have gone unnoticed until other symptoms of the condition began to develop.

General forgetfulness, loss of mental flexibility, difficulty with mental planning, and organization of sequential activities may be early signs of HD. Reduced attention and concentration spans are common, and this may lead to one being quite distractible. **Aphasia** and **agnosia** are less evident than in Alzheimer's disease, but overall cognitive speed and efficiency are usually affected. The ability to speak is usually maintained, but people with HD may eventually have difficulty with complex words or finding the correct words to express their thoughts. Late-stage symptoms may include difficulty with visual and spatial relations.

The last category of symptoms in HD is that involving psychological disturbances. Irritability and **depression** are common early signs of HD. People may initially be incorrectly diagnosed with psychiatric diseases like **schizophrenia** and delusional disorder, particularly if they have no other symptoms of HD. This is probably because a large percentage of people with HD have significant personality changes or affective psychosis. Behavioral issues can include intermittent explosiveness, apathy, aggression, alcohol abuse, sexual problems and deviations, paranoid delusions, and an increased appetite. Suicide occurs in 5–12% of people with HD. Late-stage disease is often quite significant and can be disabling. Weight loss, sleep problems, and incontinence are common signs of advanced HD.

Juvenile HD occurs when someone develops symptoms in the first two decades of life; this occurs in about 5–10% of all HD cases. Symptoms are distinct from those associated with adult-onset forms of HD. For example, chorea rarely occurs in people who develop HD in their first decade of life. However, dystonia and rigidity can be very significant for those individuals. Common characteristics of people with juvenile HD diagnosed before age 10 include declining performance in school, mouth muscle abnormalities, rigidity, and problems with their gait. **Seizures** are also a somewhat unique characteristic of juvenile HD.

Complications related to immobility are often the cause of death in people with HD. Abnormal muscular movements, particularly those related to swallowing and breathing, may cause someone to die from aspiration pneumonia and other infections; such a cause of death occurs years after the onset of the disease.

People with juvenile HD diagnosed between the age of 10 and 20 may have symptoms similar to adult-onset HD. Others may have more severe behavioral and psychiatric problems noticed before anything else. Common among people with juvenile HD is a father with adult-onset HD.

Diagnosis

Until the discovery of the HD gene on chromosome 4 in 1993, the diagnosis of the condition was made purely on a clinical basis. This can be somewhat challenging because of similarities with other hereditary and non-hereditary conditions involving chorea.

A careful neurological examination and documentation of abnormal movements are important to diagnose HD. **Sydenham's chorea** is a nonhereditary, infectious cause of chorea. It most often occurs in children and adolescents following a streptococcal infection, and the chorea associated is slightly different than that with HD. About 30% of people with rheumatic fever or polyarthritis develop Sydenham's chorea two to three months later. Symptoms may even come back in pregnancy, or in people taking oral contraceptives. The chorea in Sydenham's chorea is brisk and abrupt, but it is more flowing and somewhat slower in HD. Treatment for Sydenham's chorea usually involves bed rest, sedation, and antibiotic therapy with medications like penicillin.

Movements with characteristics of dystonia and athetosis, called choreoathetosis, are also common in HD.

Key Terms

Affective psychosis Abnormalities in mood, emotions, feelings, sensibility, or mental state.

Agnosia Inability to notice or process sensory stimuli.

Anticipation Genetic phenomenon in which a triple repeat DNA mutation expands in a future generation, causing symptoms to develop earlier.

Aphasia Inability to communicate by speaking, writing, or signing.

Aspiration pneumonia Infection of the lungs, caused by the presence of foreign material like food.

Ataxia Uncoordinated muscular movement; often causes difficulty with walking and other voluntary movements.

Athetosis Slow, writhing involuntary movements that involve muscle flexing and extension.

Atrophy Wasting or loss of tissue.

Basal ganglia Large masses of gray matter at the base of the brain; typically describes the corpus striatum and cell groups around it.

Bradykinesia Slowness in movement.

Caudate A region of gray matter near the lateral ventricle of the brain; also called caudate nucleus.

Cerebral cortex Grey material covering the entire surface of the brain.

Chorea Irregular, unpredictable, brief, jerky movements that randomly affect the body.

Corpus striatum Region of the brain that contains the caudate nucleus and putamen.

Cortical Related to a cortex, such as the cerebral cortex.

Dementia General decline in cognitive function.

Deoxyribonucleic acid (DNA) The chemical bases that make up genes.

Dopamine Neurotransmitter chemical, typically found in the basal ganglia of the brain.

Dystonia State of abnormal muscle tone, with either too much or too little.

Gait The way in which one walks.

Mutation A change in the order of DNA bases that make up genes, akin to a misspelling.

Neuropathy Term for any disorder affecting the nervous system or cranial nerves.

Polyarthritis Inflammation of several joints at the same time.

Putamen Structure in the brain that is connected to the caudate nucleus and a component of the corpus striatum.

Rheumatic fever Fever following a throat infection with group A Streptococcus, typically affecting children and young adults.

Tremor An involuntary trembling movement.

People with HD may be able to more easily mask their movements at first, because they are not that intrusive in the early stages. Tardive **dyskinesia** is a nonhereditary cause of chorea that may be mistaken for HD in an individual on antipsychotic medications.

Chorea occurs in 1–7% of people with **lupus**, and in a proportion of people with drug-related problems. It is important to rule out nonhereditary causes of chorea because treatments may exist for them, which may increase quality of life for the affected person.

Although very useful for many other neurological conditions, looking at the brain with techniques like **magnetic resonance imaging** (**MRI**) or computed tomography (CT) scans currently are not as helpful in diagnosing HD. These techniques may help find some typical brain changes in HD. For example, caudate atrophy is typically associated with advanced HD. Studies have shown that serial CT scans of the basal ganglia in at-risk individuals without symptoms may show signs of caudate atrophy before the disease even shows symptoms. These types of imaging studies can be useful to rule out other diagnoses that may mimic HD, because those may involve other specific brain changes.

An important step in diagnosing HD is to take a careful family history. Strong family histories with multiple generations affected, with roughly equal males and females affected, are common in HD.

Many hereditary conditions mimic HD. People who are diagnosed with HD much later in life may seem similar to people with **Parkinson's disease**, because abnormal movements may be the primary symptom. Neuroacanthocytosis is a hereditary condition with chorea, but it should be considered if muscle loss, absent lower limb tendon reflexes, neuropathy, and specific results on a blood test are present. Benign hereditary chorea is an autosomal dominant condition in which the chorea is not progressive, and

does not involve any cognitive decline. Dentatorubropallidoluysian atrophy (DRPLA) is another hereditary condition that mimics HD; it typically affects adults and involves **dementia**, ataxia, and seizures, along with chorea. As a group, the hereditary spinocerebellar ataxias (SCAs) may mimic some of the movement abnormalities seen in HD. However, the psychological and cognitive components may not be present in the SCAs.

Often, diagnosis is most clearly made with genetic testing, which is done to confirm a suspected clinical diagnosis. Genetic testing identifies the exact number of CAG repeats in each copy of a person's HD gene.

There are several CAG repeat ranges that may be found through testing. Each genetic laboratory may use slightly different ranges, so test results should be interpreted carefully. Generally, a range of 10–27 CAG repeats is considered to be normal. If someone has results in these ranges, this person does not have HD, and will not develop signs of it.

A range of 27–35 CAG repeats will not cause symptoms of HD in the person. In this range, the repeat size may rarely increase when passed on to children. In other words, the person with this test result will not develop symptoms of HD, but he or she may have a child who develops symptoms. This would particularly be the case if the person were a man, because of the anticipation phenomenon.

A range of 36–39 CAG repeats is considered a range where the person may or may not develop HD symptoms at some point in his or her life. Additionally, the repeat may or may not expand to his or her children.

People with an HD gene that has greater than 39 CAG repeats will develop symptoms of HD at some point in their lives. They would have a 50% chance of passing this gene on to future children.

People with juvenile HD usually have much larger CAG repeat sizes than those who have the typical form of HD. Despite this, it is still impossible to predict exactly when someone may develop symptoms, or to predict the exact symptoms they will experience.

Genetic testing for those who have symptoms is fairly straightforward, and often ordered with the aid of a **neurologist**. Predictive testing for HD, as it is called when the person does not have symptoms, is a bit more complicated. This is because there are many complex factors in the testing process.

Ideally, at-risk asymptomatic individuals have several appointments before genetic testing is performed. They should see a neurologist for a thorough examination to identify any subtle signs of HD. They should also see a **neuropsychologist** for an evaluation. The neuropsychologist can help assess whether a person is a good candidate for genetic testing, potentially reducing the risk for poor outcomes, like suicide, following positive results. Individuals should also see a medical geneticist and genetic counselor to receive thorough information about the risks, benefits, and limitations of genetic testing.

Much has been studied about the myriad of issues with genetic testing in HD. Risks from any outcome can be considerable, and these may include a sudden change in family dynamics, self-image, or serious emotional and psychological harms.

Health, life, or disability insurance discrimination from HD testing may be a possibility, especially related to positive results. Employment may also be an issue. In October 2003, a young teacher in Germany was refused a permanent job because members of her family have HD; she was found to be at risk for the condition during a required governmental medical examination. Currently, there is not enough documentation in the medical literature to know what the actual risks are related to these issues. Awareness and discussion of these issues are important in pretest counseling.

Limitations and benefits from genetic testing should be given equal weight as well. Results may not be easily understood, simply identifying one and one's children to be potentially at risk. These types of vague results can cause great angst to an at-risk individual. However, benefits from testing may include relief from years of worry, empowerment from medical knowledge, and the ability to make life plans or tailor medical care based upon more accurate information.

Generally, at-risk asymptomatic children under age 18 are not tested for HD. The decision to learn their genetic status should be theirs, and at a time they feel is appropriate. Along the same lines, prenatal genetic testing for HD is not done, except in cases involving special circumstances or assistive reproductive techniques.

Treatment team

Treatment for people with HD is highly dependent on their symptoms. A multidisciplinary team and approach can be very helpful. A treatment team may include a neurologist, neuropsychologist, medical geneticist, genetic counselor, physical therapist, occupational therapist, speech therapist, registered dietitian, social worker, psychotherapist, psychiatrist, ophthalmologist, and a primary care provider. Some hospitals offer day clinics devoted to people with HD, which makes things much easier in terms of coordinating appointments. Pediatric specialists in these fields may help in the care for children.

Treatment

Currently, there is no known cure for Huntington disease. No specific treatment is known to slow, stop, or reverse the progressive nature of the disease. Current

treatment for HD is mainly focused on relieving symptoms and reducing the impact of physical and mental complications related to the disease.

Medications are available to help treat chorea in HD, including therapies for blocking dopamine receptors, or those that deplete dopamine from its natural storage sites in the brain. Medications like these are tetrabenazine, pimozide, and haloperidol. They can have side effects, like drowsiness and a lessened ability to make voluntary movements. Some find the side effects to be more troublesome than the chorea, so medications should be prescribed under careful supervision.

Psychiatric problems in HD are often treated with medications as well. Some selective serotonin reuptake inhibitors (SSRIs) with trade names like Celexa, Paxil, Prozac, and others have been effective. Some tricyclic antidepressants like Nordil, Marplan, and Eldepryl have been effective. Lastly, some monoamine oxidase inhibitors (MAOIs) like Elavil, Tofranil, and Anafranil have been useful in treating depression.

Benzodiazepine and antipsychotic drugs can be used to treat anxiety, irritability, and agitation in HD. It is rare to find a medication without side effects, and drug interactions are also important to consider. As yet, no medications have been found helpful to treat the cognitive problems in HD.

Other therapies have been tested through **clinical trials** to see whether the disease progression may be slowed in any way. A combination of coenzyme Q10 and remacemide has been tested in mice, showing it to be helpful in reducing weight loss and brain loss. In a study by The Huntington Study Group in 2001, people with early-stage HD were given coenzyme Q10 or remacemide, but neither had significant effects. A 2000 study found that minocycline, an antibiotic, delayed motor decline in mice by 14%.

Riluzole is a drug currently used to treat people with **amyotrophic lateral sclerosis** (ALS, or Lou Gehrig's disease). In clinical trials with HD patients in 1999, the drug reduced chorea in about a third of people over six weeks. Behavior was improved by about 61% after 12 months.

Studies are under way to see whether transplanting fetal cells from the corpus striatum will be helpful to treat people with HD. This follows closely on the heels of similar trials with people who have Parkinson's disease. As of early 2004, preliminary results seem promising but much more time is needed to fully study and interpret them.

Recovery and rehabilitation

Supportive therapy for people with HD is very helpful, and often greatly needed as time goes on. It may begin shortly after diagnosis and continue for years, until the disease becomes advanced and supportive care is needed.

Physical therapy, speech therapy, and dietary advice can be extremely important and most effective when in tandem. Special consideration should be given to nursing and supportive care, home health care options, diet, special adaptive equipment, and eligibility for governmental benefits. A practical approach with common sense, emotional support, and careful attention to a family's needs is effective for many people with HD.

Clinical trials

As of early 2004, many clinical trials were under way to study Huntington disease:

- Family Health after Predictive Huntington Disease (HD) Testing, sponsored by National Institute of Nursing Research (NINR).
- Minocycline in Patients with Huntington's Disease, sponsored by FDA Office of Orphan Products Development.
- Prospective Huntington At-Risk Observational Study (PHAROS), sponsored by National Institute of Neurological Disorders and Stroke (NINDS) and National Human Genome Research Institute (NHGRI).
- Neurobiological Predictors of Huntington's Disease (PREDICT-HD), sponsored by NINDS.
- Brain Tissue Collection for Neuropathological Studies, sponsored by National Institute of Mental Health (NIMH).

Prognosis

Prognosis has historically been somewhat bleak for people with HD. Complications related to movement abnormalities and immobility, such as pneumonia and respiratory complications, are a common cause of death in HD. Though no cure is currently available, treatments or therapies may be available in the future to maintain a better quality of life, and these continue to offer hope.

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Huntington's Disease Society of America. 158 West 29th Street, 7th Floor, New York, NY 10001-5300. (212) 242-1968 or (800) 345-HDSA (4372); Fax: (212) 239-3430. hdsainfo@hdsa.org. <http://www.hdsa.org>.

Huntington Society of Canada. 151 Frederick Street, Suite 400, Kitchener, Ontario N2H 2M2, Canada. (519) 749-7063 or (800) 998-7398; Fax: (519) 749-8965. info@hsc-ca.org. <http://www.hsc-ca.org>.

International Huntington Association. Callunahof 8, 7217 St Harfsen, The Netherlands. + 31-573-431595. iha@huntington-assoc.com. <http://www.huntington-assoc.com>.

Deepti Babu, MS, CGC

Hydantoins

Definition

Hydantoin **anticonvulsants** are most commonly used in the treatment of **seizures** associated with **epilepsy**, a neurological dysfunction in which excessive surges of electrical energy are emitted in the brain. Some hydantoins, such as phenytoin, are also indicated for use as skeletal muscle relaxants and in the treatment of severe nerve **pain**, as in **trigeminal neuralgia**.

Purpose

While hydantoins control the seizures associated with epilepsy, there is no known cure for the disorder. The precise mechanisms by which hydantoins work are unknown, but they are thought to exert their therapeutic effect by depressing abnormal neuronal discharges in the **central nervous system** (CNS).

Description

For the treatment of seizures, hydantoins may be used alone or in combination with other anti-epileptic drugs (AEDs) or anticonvulsants. However, the use of multiple anticonvulsants and AEDs should be carefully monitored by the prescribing physician. Phenytoin, mephenytoin, ethotoin, and fosphenytoin are the individual hydantoin anticonvulsants. They are marketed under several brand names, including Cerebyx, Dilantin, Mesantoin, Peganone, and Phentek.

Recommended dosage

Hydantoins anticonvulsants are available in oral and injectable (phenytoin and fosphenytoin only) forms. Orally-administered hydantoins are available in the form of tablets, capsules, or oral suspension. Hydantoins are prescribed by physicians in varying daily dosages.

Some hydantoin anticonvulsants are taken in divided daily doses, twice daily. Others are administered in a single daily dose. A double dose of any hydantoin should not be taken. If a dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped.

It may take several weeks to realize the full benefits of hydantoins. Beginning any course of treatment including hydantoins requires a gradual dose-increasing regimen. Children and adults typically take a smaller daily dose for the first two weeks. Daily dosages of hydantoins may then be slowly increased over time. When ending a course of treatment that includes hydantoin anticonvulsants, physicians typically taper the patient's daily dose over a period of several weeks. Suddenly stopping treatment with hydantoins may cause seizures or pain to occur or return with greater frequency.

Precautions

Persons taking hydantoins should consult the prescribing physician before taking non-perscription medications. Patients should avoid alcohol and CNS depressants (medications that make one drowsy such as antihistimines, sleep medications, and some pain medications) while taking hydantoins. These medications may increase the frequency and severity of the side effects of hydantoins. Hydantoins may also potentiate the action of alcohol, and alcohol can increase the risk or frequency of seizures.

Hydantoins may not be suitable for persons with a history of thyroid, liver, or kidney disease, depressed renal function, diabetes mellitus, porphyria, **lupus**, mental illness, high blood presure, angina (chest pain), or irregular heartbeats and other heart problems. Before beginning treatment with hydantoins, patients should notify their

Key Terms

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Neurogenic pain Pain originating in the nerves or nervous tissue.

Trigeminal neuralgia A disorder affecting the trigeminal nerve (the 5th cranial nerve), causing episodes of sudden, severe pain on one side of the face.

physician if they consume a large amount of alcohol, have a history of drug use, are nursing, pregnant, or plan to become pregnant.

Physicians usually advise women of child-bearing age to use effective birth control while taking hydantoin anticonvulsants. Many anticonvulsant medications, including hydantoins, have been shown to increase the risk of birth defects. Patients who become pregnant while taking hydantoins should contact their physician.

Some hydantoin anticonvulsant medications may be prescribed for children; however, children sometimes experience increased side effects. Research indicates that some children who take high doses of hydantoins for an extended period of time may experience mild learning difficulties or not perform as well in school.

Side effects

In some patients, hydantoins may produce some mild side effects. Drowsiness and **dizziness** are the most frequently reported side effects of anticonvulsants. Other general side effects of hydantoins that usually resolve without medical attention include:

- mild coordination problems
- constipation
- muscle twitching
- unpleasant taste in mouth or dry mouth
- unusual or excessive hair growth on face or body.

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication. However, if any symptoms persist or become too uncomfortable, the perscribing physician should be consulted.

Other, uncommon side effects of hydantoins may indicate an allergic reaction or other potentially serious condition. A patient taking hydantoin who experiencs any of the following symptoms should contact their physician immediately:

- rash, excessive bruising, or bluish patches on the skin
- bleeding in the gums or mouth
- ringing or vibrations in the ears
- general loss of motor skills
- severe lack of appetite
- altered vision
- difficulty breathing
- chest pain or irregular heartbeat
- faintness or loss of consciousness
- persistent fever or pain

Interactions

Hydantoins may have negative interactions with some antacids, anticoagulants, antihistimines, antidepressants, antibiotics, pain killers and monoamine oxidase inhibitors (MAOIs). Other medications such as amiodarone, diazoxide, **felbamate**, phenybutazone, sulfonamides (sulfa drugs), corticosteroids, sucralfate, rifampin, and warfarin may also adversely react with hydantoins.

Some hydantoins should not be used with other anticonvulsants. For example, phenytoin (a hydantoin) when used with valproic acid (a non-hydantoin anticonvulsant) may increase the seizure frequency. However, some patients may use hydantoins with other seizure prevention medications if carefully monitored by a physician.

Hydantoins may decrease the effectiveness of contraceptives, including oral contraceptives (birth control pills), progesterone implants (Norplant), and progesterone injections (Depo-Provera).

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Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. <http://www.aesnet.org>.

Adrienne Wilmoth Lerner

Hydranencephaly

Definition

Hydranencephaly is a rare congenital deformity (a deformity that occurs during fetal development) that is characterized by the absence of the cerebral hemispheres of the brain. Instead, the regions of the brain known as the left and right cerebral hemispheres are replaced by sacs that are filled with cerebrospinal fluid.

Description

The absence of the cerebral hemispheres may not be apparent in the first days following birth. The normal and involuntary actions of a newborn such as sucking, swallowing, and crying all occur, as the brainstem controls these actions, and it is usually normal. Moreover, the baby with hydranencephaly appears physically normal, including the size of the head.

The normal behaviors of a growing infant reflect the functions of the left and right cerebral hemispheres. The left hemisphere is normally associated with the acquisition of language. The right hemisphere participates in the perception of space and distance. These sorts of skills are not yet developed in a newborn. Within several weeks to months of birth, the symptoms of hydranencephaly can become apparent.

Demographics

Hydranencephaly is a rare occurrence. It is estimated that one or two babies are born with hydranencephaly worldwide for every 10,000 births. There is no indication that any gender or race is any more susceptible to the disorder.

Causes and symptoms

Within a few weeks of birth, the infant typically becomes irritable and the contraction of the muscles (muscle tone) becomes more pronounced. Muscles may spasm. **Seizures** can occur. Other symptoms that can develop with time include poor vision or the total loss of vision, poor or no growth, deafness, paralysis, and impaired intellectual development (such as language difficulty).

Hydranencephaly may be caused by a genetic defect, infection associated with vessels, or a trauma that occurs after the twelfth week of pregnancy. Maternal exposure to carbon monoxide early in pregnancy has also been implicated as a possible cause, along with the possibility of early **stroke** in the developing fetus, or as a result of infection with some viruses.

Diagnosis

Diagnosis is based on the appearance of symptoms noted above. Diagnosis may not be made for weeks or months following birth, because of the initial normal appearance and behavior of the newborn. Prior to birth, ultrasound can reveal hydranencephaly, although techniques for surgical correction in the fetus have not been developed.

Treatment team

A range of medical help, from a family practitioner to pediatric surgeon, can be involved. As well, nurses and family members are part of the care-giving team. Social service workers can refer parents of children with hydranencephaly to community support organizations.

Treatment

There is no definitive treatment for hydranencephaly. Usually, symptoms are treated as they occur and support is provided to make the child as comfortable and happy as possible. Medications are given to control seizures and if excess cerebrospinal fluid collects near the brainstem, a shunt is usually surgically inserted to facilitate redirection of the excess fluid.

Recovery and rehabilitation

Rehabilitation is not stressed for the infant with hydranencephaly, as the long-term prognosis is poor. Physical and occupational therapists may assist in providing treatment to maintain muscle tone for as long as possible, and positioning aids when necessary. Medications are given to control seizures and for comfort.

Clinical trials

As of January, 2004, there were no **clinical trials** underway or planned in the United States for the study of hydranencephaly. Organizations such as the National Institute for Neurological Disorders and Stroke undertake and fund studies designed to reveal more about the normal development patterns of the brain. By understanding how development can be disrupted, scientists attempt to learn strategies for detecting defects and methods to correct them.

Prognosis

The long-term outlook for children with hydranencephaly is poor. Most children die in their first year of life, although survival past the age of 10 can rarely occur.

Key Terms

Brainstem The stalk of the brain that connects the two cerebral hemispheres with the spinal cord. It is involved in controlling vital functions, movement, sensation, and nerves supplying the head and neck.

Seizure A sudden attack, spasm, or convulsion.

Currently, the oldest known survivor was 20 years, 6 months old.

Special concerns

Providing support for parents of babies born with hydranencephaly includes genetic counseling and referrals to support groups, where parents can learn practical advice and share information with other parents of children similarly affected. Additionally, mothers who have given birth to a baby with hydranencephaly may be tested for some of the viruses suspected in playing a part in the fetal development of hydranencephaly, including toxoplasmosis, cytomegalovirus, and Herpes simplex virus.

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ORGANIZATIONS

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605. (914) 428-7100 or (888) 663-4637; Fax: (914) 428-8203. askus@marchofdimes.com. <http://www.marchofdimes.com>.

National Information Center for Children and Youth with Disabilities. P.O. Box 1492, Washington, DC 20013-1492. (202) 884-8200 or (800) 695-0285; Fax: (202) 884-8441. nichcy@ead.org. <http://www.nichcy.org>.

National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders. 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Brian Douglas Hoyle, PhD

Hydrocephalus

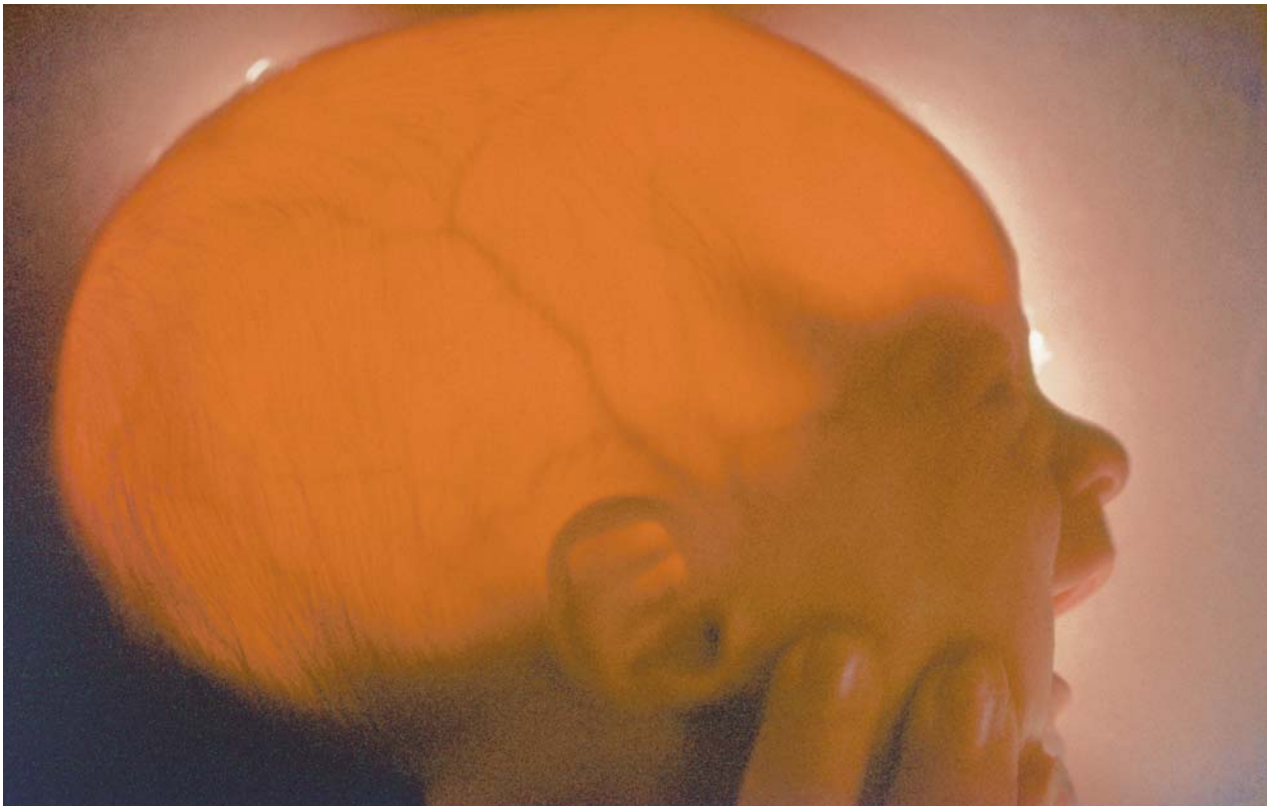
Definition

The word hydrocephalus derives from the Greek words *hydro*, meaning water, and *cephalus*, meaning head. Hydrocephalus is the result of the excessive accumulation of fluid in the brain. Traditionally, hydrocephalus has been described as a disease characterized by increased intracranial pressure (ICP), increased cerebrospinal fluid (CSF) volume, and dilatation of the CSF spaces known as cerebral ventricles.

Description

Hydrocephalus is the result of an imbalance between the formation and drainage of cerebrospinal fluid. This imbalance appears when an injury or illness alters the circulation of CSF; one or more of the ventricles of the brain become enlarged as CSF accumulates. However, hydrocephalus is not a single disease entity, as a wide number of underlying diseases are responsible for causing retention of CSF, resulting in ventricular dilatation and increased intracranial pressure (ICP). In infants and children, for example, hydrocephalus usually results from a birth defect, viral infection, head injury, hemorrhage, meningitis, or tumor.

In adults, the causes of hydrocephalus include brain damage due to **stroke** or injury, Alzheimer's disease, or obstruction of the ventricles. Often, the cause is unknown. Conditions responsible for hydrocephalus in a fetus include infantile congenital (present at birth) hydrocephalus, hydrocephalus associated with encephalocele or myelomeningocele, posthemorrhagic hydrocephalus in newborns, and postmeningitic hydrocephalus. Conditions responsible for hydrocephalus in adults include hydrocephalus following subarachnoid hemorrhage, idiopathic adult hydrocephalus, and posttraumatic hydrocephalus. Tumors can also result in hydrocephalus in both children and adults. Based on the different kind of CSF circulation in the brain, hydrocephalus can be divided into two types: communicating and non-communicating. In communicating hydrocephalus, the CSF circulation pathways are competent from the ventricles inside of the brain to the fluid spaces just below the third ventricle. Non-communicating (obstructive) hydrocephalus refers to hydrocephalus that



Sideview of the skull of infant suffering from hydrocephalus. *(© Lester V. Bergman/Corbis. Reproduced by permission.)*

develops from a blockage of the normal circulation of CSF within the brain. In most cases, it refers to a blockage between the third and fourth ventricles.

Demographics

Overall incidence of infantile hydrocephalus is approximately one to two per 1,000 live births. The overall prevalence of hydrocephalus in the United States is about 0.5%. When cases of **spina bifida** are included, congenital hydrocephalus occurs in two to five births per 1,000 births. The incidence of acquired hydrocephalus in adults is not known because it occurs as a result of injury, illness, or environmental factors. Normal pressure hydrocephalus was found to be significantly more prevalent in males, and can occur in adults of any age group. The age distribution in children and teenagers is disputed.

Causes and symptoms

Approximately 16 oz (500 ml) of CSF are formed within the brain each day, by cells located on the wall of the four ventricles in the brain. Once formed, CSF circulates among all the ventricles before it is absorbed. The normal adult volume of circulating CSF is about 2 oz (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.

Hydrocephalus can be subdivided into three forms, involving the following:

- Disorders of cerebrospinal fluid circulation. Tumors, hemorrhages, congenital malformations, and infections can cause such obstructions in the circulation of cerebrospinal fluid.
- Disorders of cerebrospinal fluid absorption, resulting from diseases such as the superior vena cava syndrome and sinus thrombosis.
- Disorders of cerebrospinal fluid production: This is the less common form of hydrocephalus resulting from tumors that secrete cerebrospinal fluid in excess of its absorption.

Congenital hydrocephalus is thought to be caused by a complex interaction of genetic and environmental factors. The origin of hydrocephalus in congenital cases is unknown. Very few cases (less than 2%) are inherited (X-linked hydrocephalus). The most common causes of

hydrocephalus in acquired cases are tumor obstruction, trauma, intracranial hemorrhage, and infection.

The two most common adult forms of hydrocephalus are hydrocephalus ex-vacuo and normal pressure hydrocephalus. Hydrocephalus ex-vacuo occurs when a stroke or injury damages the brain, yielding a brain substance. Although there is more CSF than usual, the CSF pressure may or may not be elevated. Normal pressure hydrocephalus is an abnormal increase of CSF in the brain's ventricles due to the gradual blockage of the CSF-draining pathways. This may result from a subarachnoid hemorrhage, head trauma, infection, tumor, or complications of surgery. The ventricles enlarge to handle the increased volume of the CSF, and the compression of the brain from within by the fluid-filled ventricles destroys or damages brain tissue. Fluctuation of CSF pressure from high to normal to low can also be present.

For congenital-onset hydrocephalus, early symptoms include enlargement of the head (increased head circumference), bulging fontanelles (soft spots) with or without enlargement of the head size, separation of sutures (the flexible and fibrous joints between the skull bones of an infant), and vomiting. Symptoms of continued hydrocephalus include irritability and muscle **spasticity**. Late symptoms of congenital-onset hydrocephalus seen in children up to five years of age include decreased mental function, delayed development, slow or restricted movement, difficulty feeding, lethargy, and delayed growth.

In children, symptoms depend on the amount of damage caused by ICP. Symptoms may be similar to many of those in infants or may include **headache**, vomiting, vision changes such as crossed eyes, uncontrolled eye movements, loss of coordination, poor gait (walking pattern), mental confusion, or psychosis. For adult-onset hydrocephalus, headaches and nausea are the most common symptoms. Other signs of the condition include difficulty focusing the eyes, unsteady gait, weakness of the legs, sudden falls, and a distinctive inability to walk forward. As hydrocephalus progresses, decreased mental activity appears, including lethargy, apathy, impaired memory, and speech problems. Urinary and bowel incontinence can also occur. During the final stage, **dementia** involving loss of movement, sensory functions, and cognitive abilities may result.

Diagnosis

Ultrasound can be used to diagnose prenatal hydrocephalus. Although fetal hydrocephalus may be an isolated finding, it is more frequently found along with other cerebral anomalies, including neural tube defects. Diagnosis after birth may be suggested by symptoms; however, imaging studies of the brain are the mainstay of diagnosis. Computed tomography (**CT**) and **magnetic resonance imaging (MRI)** reveal enlarged ventricles and may indicate a specific cause of hydrocephalus, such as a tumor or hemorrhage. The presence of papilledema (elevation or swelling of the optic disc) also indicates that hydrocephalus that is well developed. In rare cases, long-standing hydrocephalus causes blindness.

Small abnormalities that may not be seen with CT scanning, such as cysts and abscesses, are often seen with **MRI**. These studies can also help the neurosurgeon differentiate between communicating and non-communicating hydrocephalus. In cases of suspected normal pressure hydrocephalus, a lumbar puncture (spinal tap) may help determine CSF pressure. Also, a cisternagram can be useful to evaluate the dynamics of CSF flow in the brain and spinal chord. Cisternography can reveal CSF concentration, obstruction, leakage, and pressure. Also, certain biochemical markers in the blood have been described in the disease. They include increased neurofilament light protein (NFL) and tau protein, both markers of neuronal degeneration; increased myeline basic protein (a marker of demyelination; and albumin); and a marker of the blood-brain barrier function.

Treatment team

Treatment of hydrocephalus for children or adults will likely involve a **neurologist**, neurosurgeon, obstetrician, pediatrician, and specialty nurses and physical therapists.

Treatment

Medical treatment is first aimed at reducing intracranial pressure, while the need for a more permanent solution is determined. Reduction of fluid intake and administration of drugs such as mannitol, glycerol, urea (drugs with an osmotic effect), or furosemide (a diuretic) are able to reduce ICP and CSF production.

External drainage of the CSF is useful for urgent reduction of intracranial pressure, as well as of ventricular or subarachnoid hemorrhage. Complications include overdrainage, blocked tube, or bacterial contamination. The placement of a permanent **ventricular shunt** (internal shunting) is a common procedure. Around 33,000 shunts are placed in the United States each year; almost half of them to replace previous shunt devices. CSF from the ventricles in the brain is usually shunted to the peritoneum, pleura, ureter, bladder, or vascular spaces such as the jugular or subclavian veins. Most shunts are connected to the peritoneum. Some shunts operate according to intracranial pressure by using a valve system able to regulate the flow at a pressure close to the normal values of ICP. Others are programmable and can be adjusted to open at a given ICP. Complications include overdrainage that may cause intracranial hypotension, **subdural hematoma**,

Key Terms

Cerebrospinal fluid (CSF) The clear fluid made in the ventricular cavities of the brain that bathes the brain and spinal cord.

Gait Posture and manner of walking.

Hydrocephalus A condition characterized by the abnormal accumulation of cerebrospinal fluid within the ventricles of the brain.

Increased intracranial pressure (ICP) Increased pressure within the skull caused by extra tissue or fluid in the brain.

Papilledema Swelling of the optic disc, where the optic nerve enters the eyeball, or elevation of the optic nerve, and indication of increased intracranial pressure.

Ventricle The cavities or chambers within the brain that contain the cerebrospinal fluid.

shunt occlusion, and infection. The risk of shunt failure is greater within the first year (between 25–40% of shunts must be replaced). The subsequent failure rate is around 5% for each year.

Other surgical procedures include, in some cases, choroid plexectomy, third ventriculostomy, and ventricular reservoir. Ventricular reservoir is basically a catheter inserted into a ventricle of the brain to draw CSF. This procedure is much simpler than placing a full shunt system and is used to provide temporary control of ICP until a full shunt can be placed.

Recovery and rehabilitation

Hydrocephalus is a chronic condition, and clinical symptoms are based on the time of insurgence of the disease. With appropriate, early treatment, a normal lifespan with few limitations can be reached. After surgery, specially trained medical professionals carefully monitor the patient. Some symptoms such as headaches may disappear immediately due to the release of excess pressure. The symptoms associated with normal pressure hydrocephalus (walking difficulties, mild dementia, poor bladder control) may improve quickly, or may take weeks to months to improve. In some patients, little or no improvement is also possible.

The length of the patient's hospital stay will be determined by the rate of recovery. If neurological problems persist, rehabilitation may be required to further the patient's improvement. However, recovery may be limited by the extent of the damage already caused by the hydrocephalus. Because hydrocephalus is an ongoing condition, patients do require long-term follow up. Follow-up diagnostic tests, including CT scans, MRI, and x rays, may be performed to determine if the shunt is working correctly.

Clinical trials

Ventricular shunts are the most common surgical treatment for hydrocephalus and appear to be the safest. It is possible that choroid plexectomy and third ventriculostomy may become more feasible in the future if better procedures and equipment are developed.

As of mid-2004, several **clinical trials** to study hydrocephalus were underway, including a trial to evaluate the efficacy and safety of endoscopic choroid plexus coagulation with third ventriculostomy in the treatment of idiopathic normal pressure hydrocephalus, sponsored by the Frenchay Hydrocephalus Research Fund. The National Institute of Neurological Disorders and Stroke is sponsoring a study to establish the physiology of **syringomyelia**. Updated information on these and other ongoing clinical trials may be found at the National Institutes of Health website for clinical trials at <http://www.clinicaltrials.gov>.

Prognosis

Untreated hydrocephalus has a survival rate of 40–50%, with the survivors having varying degrees of intellectual, physical, and neurological disabilities. Prognosis for treated hydrocephalus varies, depending on the cause. If the child survives for one year, more than 80% will have a fairly normal lifespan. Approximately one-third will have normal intellectual function, but neurological difficulties may persist. Hydrocephalus not associated with infection has the best prognosis, and hydrocephalus caused by tumors has a very poor prognosis. About 50% of all children who receive appropriate treatment and follow up will develop IQs in the near-normal or normal range.

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ORGANIZATIONS

Hydrocephalus Association. 870 Market Street, Suite 705, San Francisco, CA 94102. (415) 732-7040 or (888) 598-3789; Fax: (415) 732-7044. info@hydroassoc.org. <http://www.hydroassoc.org>.

National Hydrocephalus Foundation. 12413 Centralia Road, Lakewood, CA 90715-1623. (562) 402-3523 or (888) 857-3434; Fax: (562) 924-6666. hydrobrat@earthlink.net. <http://nhfonline.org>.

Antonio Farina, MD, PhD

Hydromyelia

Definition

Hydromyelia (HM) is a condition characterized by widening of the central canal of the spinal cord. Fluid can accumulate in this space, creating increased pressure on the spinal cord. The term hydromyelia is sometimes used interchangeably with a closely related condition, **syringomyelia** (or syringohydromyelia). Syringomyelia (SM) is a condition in which fluid collects in the area of the spinal cord that is outside the central canal. The end result of hydromyelia and syringomyelia is essentially the same: an abnormal cyst (collection of fluid) in the spinal cord that is associated with a wide range of neurological complaints and signs. For simplicity, the term syringomyelia is used to refer to a fluid-filled cyst in the spinal cord that is inside or outside of the central canal.

Description

Syringomyelia is a variable condition in which the symptoms depend on the location and extent of the cavitation (hollowing out) of the cord. Over time, the expansion and elongation of the fluid-filled cavity (or cyst) can destroy the center of the spinal cord. This damage to the spinal cord results in **pain**, weakness, and loss of sensation for the affected individual. Syringomyelia may be an isolated finding or may be found in association with a syndrome that disrupts the flow of cerebral spinal fluid (CSF), such as the **Arnold-Chiari malformation** or the **Dandy-Walker** malformation.

The earliest known description of cystic dilatation (widening) of the spinal cord dates back to the sixteenth century. The terms syringomyelia and hydromyelia were first used in published reports in 1827 and 1859, respectively.

Demographics

Syringomyelia occurs across all races and ethnic groups and affects both children and adults. Although syringomyelia usually appears in midlife, it can occur at any age. Estimates of the incidence of syringomyelia vary and range from 1 in 18,000 to as high as 1 in 1,300 people in the United States.

Causes and symptoms

The causes of syringomyelia are not well understood. It is thought that syringomyelia occurs when one or more factors interfere with the normal development of the spinal canal during formation of the embryo or when factors such as trauma to the spinal cord, infection, or a mass (such as tumor) interfere with the fluid dynamics in the spinal cord. Arnold-Chiari malformation is the leading cause of syringomyelia. Syringomyelia occurs in as many as one-quarter of people who have a **spinal cord injury**. Various theories have been postulated to explain how movement of cerebrospinal fluid and pressure in the **central nervous system** (the brain and spinal cord) interact to produce this defect. In some cases, genetic factors may play a role in the development of this condition.

The symptoms of syringomyelia can be quite variable and depend upon the location and extent of the cyst. Common symptoms of syringomyelia in affected individuals include:

- extreme pain or "heavy" feeling in the neck; shoulders are usually numb
- headaches
- leg or hand weakness
- numbness or loss of sensation in the hands and feet
- problems with walking
- loss of bowel and bladder control
- spasticity and paralysis of the legs
- visual disturbances
- ataxia

Key Terms

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.

- speech problems
- scoliosis (curvature of the spine)

Diagnosis

Diagnosis of syringomyelia is based on neurological exam and results of neuroradiological imaging studies. The neurological exam of an affected individual will show loss of sensation in the hands, balance problems, decreased strength, difficulty walking or an abnormal gait, and abnormal reflexes. Some people with no symptoms or mild symptoms are diagnosed with syringomyelia incidentally in the course of evaluation for another condition. Imaging studies used to diagnose syringomyelia include **magnetic resonance imaging (MRI)**, CINE **MRI** (a type of MRI that shows the flow of cerebrospinal fluid), and **electromyography** (EMG). In some cases it may be technically difficult to distinguish hydromyelia from syringomyelia.

Treatment

Currently, there is no cure for syringomyelia. Neurosurgery is the primary method of treatment for this condition. Surgery tends to be reserved for those individuals with moderate or severe neurological problems. The goal of the various neurosurgical techniques is to restore normal flow of cerebral spinal fluid. There are four main categories of procedures:

- decompression procedures
- laminectomy and syringostomy
- terminal ventriculostomy
- percutaneous aspiration

Surgical interventions for syringomyelia have limitations and carry risks for potentially severe complications. The decision to operate is generally based on the severity of symptoms and the findings on MRI or other imaging studies. Patients are followed closely after surgery for signs of further neurological impairment. Some patients will need to undergo more than one surgery.

Treatment team

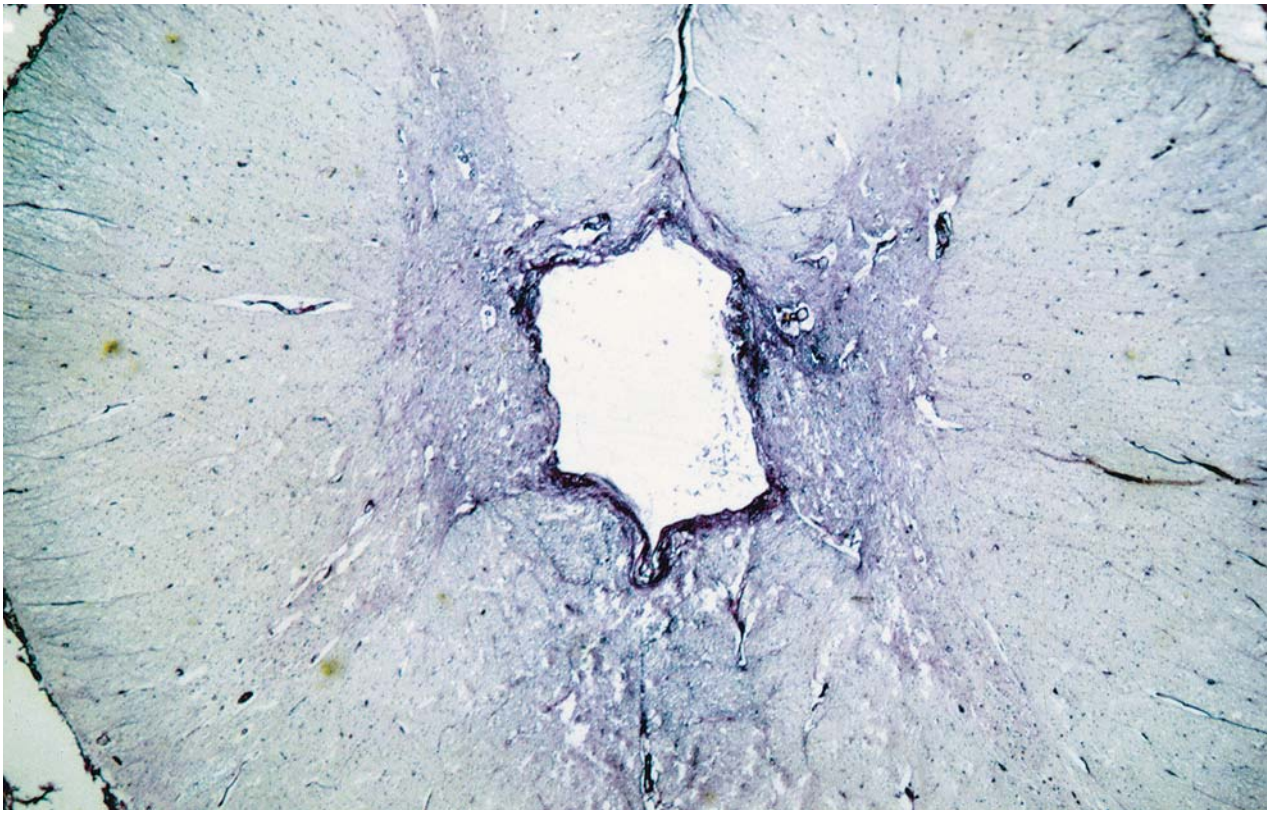
Management of syringomyelia requires a multidisciplinary approach. In addition to the patient's primary health care professionals, medical professionals involved in the care of patients with syringomyelia generally include a **neurologist** and a neurosurgeon. Additional specialists in pain management and rehabilitation may also be needed.

Recovery and rehabilitation

Patients with syringomyelia may require a wide range of rehabilitation services including physical therapy, occupational therapy, and speech therapy to help them compensate for weakness and loss of function. Chronic pain can pose a significant problem for some patients. Management of chronic pain may include prescription and non-prescription medications, physical therapy, occupational therapy, medical procedures such as nerve blocks or trigger point injections, psychological therapy, and chiropractics.

Clinical trials

As of early 2004, there were three **clinical trials** for patients with syringomyelia, all of which are sponsored by the National Institute of Neurological Disorders and **Stroke** (NINDS). There is a study (Study and Surgical Treatment of Syringomyelia) to establish the mechanism(s) of progression of primarily spinal syringomyelia (PSS). More information on this study can be obtained at http://clinicalstudies.info.nih.gov/detail/A_2001-N-0085.html or by contacting the patient recruitment and public liaison office at (800) 411-1222 or prpl@mail.cc.nih.gov. In another study (Establishing the Physiology of Syringomyelia), researchers would like to learn more about how the CSF pressure and flow contribute to the progression of syringomyelia. More information can be obtained at http://clinicalstudies.info.nih.gov/detail/A_1992-N-0226.html or by contacting the patient recruitment and public liaison office. Finally, there is a study (Genetic Analysis of the Chiari I Malformation) whose purpose is to better understand the genetic factors related to the Chiari I malformation. More information can be found at http://clinicalstudies.info.nih.gov/detail/A_2000-N-0089.html or by contacting the patient recruitment and public liaison office. There is also an ongoing genetic research study for Chiari type I malformation and syringomyelia (CMI/S) to determine whether or not there is a genetic component to CMI/S. Interested patients and families may find more information at the Center for Human Genetics at Duke University at http://wwwchg.mc.duke.edu/patients/cms.html or by contacting the center at (800) 283-4316 or syringo@dnadoc.mc.duke.edu.



The widened spinal cord canal associated with hydromyelia. *(Custom Medical Stock Photo. All Rights Reserved.)*

Prognosis

The course of syringomyelia is not well defined. Some untreated patients will experience a spontaneous remission of symptoms. Among treated patients, some will have a permanent end to their neurological deficits whereas others will only experience temporary relief of symptoms. Long-term studies of affected patients are needed to better understand the natural history and prognosis of this condition.

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American Syringomyelia Alliance Project, Inc. P. O. Box 1586, Longview, TX 75606-1586. (903) 236-7079 or (800) ASAP-282; Fax: (903) 757-7456. info@ASAP.org. <http://www.asap.org>.

American Chronic Pain Association (ACPA). P.O. Box 850, Rocklin, CA 95677-0850. (916) 632-0922 or (800) 533-3231; Fax: (916) 632-3208. ACPA@pacbell.net. <http://www.theacpa.org>.

National Spinal Cord Injury Association. 6701 Democracy Blvd. #300-9, Bethesda, MD 20817. (301) 214-4006 or (800) 962-9629; Fax: (301) 881-9817. info@spinalcord.org. <http://www.spinalcord.org>.

Dawn J. Cardeiro, MS, CGC

Hypercortisolism *see* **Cushing syndrome**

Hypersomnia

Definition

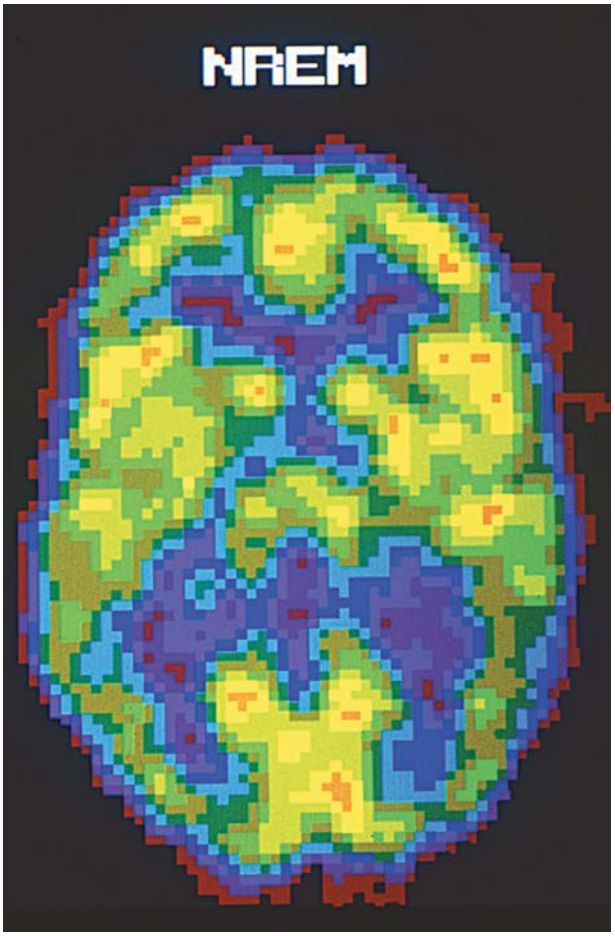
Hypersomnia refers to a set of related disorders that involve excessive daytime sleepiness.

Description

There are two main categories of hypersomnia: primary hypersomnia (sometimes called idiopathic hypersomnia) and recurrent hypersomnia (sometimes called recurrent primary hypersomnia). Both are characterized by the same signs and symptoms and differ only in the frequency and regularity with which the symptoms occur.

Primary hypersomnia is characterized by excessive daytime sleepiness over a long period of time. The symptoms are present all, or nearly all, of the time. Recurring hypersomnia involves periods of excessive daytime sleepiness that can last from one to many days, and recur over the course of a year or more. The primary difference between this and primary hypersomnia is that persons experiencing recurring hypersomnia will have prolonged periods where they do not exhibit any signs of hypersomnia, whereas persons experiencing primary hypersomnia are affected by it nearly all the time. One of the best documented forms of recurrent hypersomnia is Kleine-Levin syndrome, although there are other forms as well.

There are many different causes for daytime sleepiness that are not considered hypersomnia, and there are many diseases and disorders in which excessive daytime sleepiness is a primary or secondary symptom. Feelings of daytime sleepiness are often associated with the use of common substances such as caffeine, alcohol, and many medications. Other common factors that can lead to excessive daytime sleepiness that is not considered hypersomnia include shift work and insomnia. Shift work can disrupt the body's natural sleep rhythms. Insomnia can cause excessive daytime sleepiness because of lack of nighttime sleep, and is a separate disorder.



A colored positron emission tomography (PET) scan of the human brain during deep, non-REM sleep; the brain is active but not as active as during REM sleep. Active areas are red and yellow, inactive areas are blue. *(© Hank Morgan/ Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Demographics

Hypersomnia is an uncommon disorder. In general, 5% or fewer of adults complain of excessive sleepiness during the daytime. That does not mean all those who complain of excessive sleepiness have hypersomnia. There are many other possible causes of daytime sleepiness. Of all the people who visit sleep clinics because they feel they are too sleepy during the day, only about 5–10% are diagnosed with primary hypersomnia. Kleine-Levin syndrome is present in about three times more males than females, but it is a very rare syndrome.

Hypersomnia generally appears when the patient is between 15 and 30 years old. It does not begin suddenly, but becomes apparent slowly, sometimes over years.

Causes and symptoms

People experiencing hypersomnia do not get abnormal amounts of nighttime sleep. However, they often have problems waking up in the morning and staying awake during the day. People with hypersomnia nap frequently, and upon waking from the nap, do not feel refreshed. Hypersomnia is sometimes misdiagnosed as **narcolepsy**. In many ways the two are similar. One significant difference is that people with narcolepsy experience a sudden onset of sleepiness, while people with hypersomnia experience increasing sleepiness over time. Also, people with narcolepsy find daytime sleep refreshing, while people with hypersomnia do not.

People with Kleine-Levin syndrome have symptoms that differ from the symptoms of other forms of hypersomnia. These people may sleep for 18 or more hours a day. In addition, they are often irritable, uninhibited, and make indiscriminate sexual advances. People with Kleine-Levin syndrome often eat uncontrollably and rapidly gain weight, unlike people with other forms of hypersomnia. This form of recurrent hypersomnia is very rare.

The causes of hypersomnia remain unclear. There is some speculation that in many cases it can be attributed to problems involving the hypothalamus, but there is little evidence to support that claim.

Diagnosis

Hypersomnia is characterized by excessive daytime sleepiness, and daytime naps that do not result in a more refreshed or alert feeling. Hypersomnia does not include lack of nighttime sleep. People experiencing problems with nighttime sleep may have insomnia, a separate sleep disorder. In people with insomnia, excessive daytime sleepiness may be a side effect.

The Diagnostic and Statistical Manual of Mental Disorders which presents the guidelines used by the American Psychiatric Association for diagnosis of disorders, states that symptoms must be present for at least a month, and must interfere with a person's normal activities. Also, the symptoms cannot be attributed to failure to get enough sleep at night or to another sleep disorder. The symptoms cannot be caused by another significant psychological disorder, nor can they be a side effect of a medicinal or illicit drug or a side effect of a general medical condition. For a diagnosis of recurrent hypersomnia, the symptoms must occur for at least three days at a time, and the symptoms have to be present for at least two years.

Treatment team

A number of specialists deal with sleep problems, including internal medicine physicians, psychiatrists, neurologists, and sleep disorder specialists.

Key Terms

Hypothalamus A part of the forebrain that controls heartbeat, body temperature, thirst, hunger, blood pressure, blood sugar levels, and other functions.

Narcolepsy A disorder characterized by frequent and uncontrollable attacks of deep sleep.

Treatments

There have been some attempts at using drugs to treat hypersomnia. No substantial body of evidence supports the effectiveness of these treatments. Stimulants are not generally recommended to treat hypersomnia as they treat the symptoms but not the base problem. Some researchers believe that treatment of the hypothalamus may be a possible treatment for hypersomnia.

Prognosis

Kleine-Levin syndrome has been reported to occasionally resolve by itself around middle age. Except for that syndrome, hypersomnia is considered both a lifelong disorder and one that can be significantly disabling. There is no body of evidence that concludes there is a way to treat the majority of hypersomnia cases successfully.

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American Academy of Sleep Medicine. 6301 Bandel Road NW, Suite 101, Rochester, MN 55901. (507) 287-6006. <www.asda.org>.

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Hypertonia *see* **Spasticity**

Hypotonia

Definition

Hypotonia means "low tone," and refers to a physiological state in which a muscle has decreased tone, or tension. A muscle's tone is a measure of its ability to resist passive elongation or stretching.

Description

Hypotonia is more a description than a diagnosis. It is most often seen in newborns (congenital) and infants, but it may persist through adolescence into adulthood. Another name for infantile hypotonia is "floppy baby syndrome." This refers to the tendency of a hypotonic infant's arms, legs, and head to "flop," or dangle loosely, when they are picked up or moved. In the past, the term "benign congenital hypotonia" was used for many cases in which no obvious cause for the hypotonia could be detected. Better diagnostic techniques and increased knowledge of neuromuscular disorders, however, have resulted in much less frequent use of this term.

Demographics

Hypotonia is the most common muscular abnormality seen in neonatal (newborn) neurological disorders. It affects males and females equally, and shows no preponderance in any particular ethnic group or race. An increase in the occurrence of hypotonia in recent years is correlated with increased survival rates of infants born significantly premature, since these children are at increased risk for neurological problems.

Causes and symptoms

The causes of hypotonia are varied and numerous. Some involve trauma to, or diseases of, the brain or spinal cord (CNS), while others affect the peripheral nerves, neuromuscular junction, or the muscles themselves. A disorder of the nervous system is a neuropathy, while a muscle disease is a **myopathy**. A neuromuscular condition is one in which a neurological disorder results in associated muscular symptoms.

Key Terms

Congenital Present at birth.

Muscle tone Also termed tonus; the normal state of balanced tension in the tissues of the body, especially the muscles.

Myopathy Any abnormal condition or disease of muscle tissue, characterized by muscle weakness and wasting.

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

Neuropathy A disease or abnormality of the peripheral nerves (the nerves outside the brain and spinal cord). Major symptoms include weakness, numbness, paralysis, or pain in the affected area.

CNS trauma and infection are perhaps the most common cause of hypotonia, both in infants and in children. Insult to the brain may occur prenatally (before birth), perinatally (around the time of birth), or postnatally (after birth).

Prenatal CNS damage may be caused by certain maternal/fetal infections, maternal diseases, problems with the placenta or umbilical cord, or maternal use of harmful substances such as alcohol or certain drugs. Most congenital brain malformations, however, have no discernible cause and are likely due to chance maldevelopment of a very complex organ. Perinatal asphyxia/hypoxia (lack of oxygen to the baby's brain) occurs less frequently than is commonly believed, but does present a risk for CNS damage that can result in hypotonia. The greatest risk for asphyxia/hypoxia is from complicated and/or premature deliveries. Infants who are born healthy may sustain postnatal brain injury if they suffer from breathing difficulties, develop an infection in the lining of the brain (see Meningitis), or suffer some other type of physical trauma or abuse.

While it is less common, hypotonia may develop in an adult. This is again most often the result of CNS trauma or disease, usually affecting the **cerebellum**. The primary function of the cerebellum is control of balance and coordination, including maintaining passive tension/tone of the muscles, such as muscular control required for standing.

A number of different genetic disorders are associated with hypotonia, and may affect the nerves (and by extension the muscles), or the muscles only. Most genetic conditions are generalized (affecting multiple muscle groups) and progressive. Some genetic conditions are hereditary

A six-week-old baby girl is held horizontally by the trunk in a test for hypotonia, sometimes called "floppy infant syndrome." *(Saturn Stills / Science Photo Library.)*

(autosomal recessive or X-linked recessive) and some are sporadic (chromosomal disorders). Hereditary conditions would typically imply a 25% recurrence risk for siblings on the affected child, while the chance for another child with the same chromosomal abnormality is usually about 2–3%.

In addition to low muscle tone, infants with hypotonia may also exhibit excessive flexibility of the joints (hypermobility), decreased deep tendon reflexes (e.g., tapping the knee joint produces little or no muscle jerk), and difficulties with sucking and swallowing. Children in whom hypotonia persists often show delays in gross motor skills such as sitting up, crawling, and walking. They may also have difficulties with coordination and exhibit speech delays. In some cases, symptoms may persist into adulthood. Hypotonia itself is not associated with decreased intellectual development, but the underlying cause may pose significant risks for developmental delay and **mental retardation**.

Diagnosis

Diagnosis of the cause of hypotonia may involve a number of different medical methods, procedures, and tests. These include:

- A complete prenatal (before birth) and perinatal (around the time of birth) history. Along with this a complete family medical history should be obtained.
- A physical examination to determine the degree of hypotonia and the muscles affected
- An electromyelograph (EMG), measures muscle response to electrical stimulation
- A nerve conduction velocity (NCV), measures a nerve's ability to transmit electrical impulses to and from the muscle
- Electroencephalogram (EEG), a test that measures the electrical activity in the brain
- A muscle **biopsy** to analyze the microscopic structure of affected muscle
- Biochemical tests on muscle tissue and blood
- Genetic tests to look for possible sporadic (chance occurrence) or hereditary genetic errors affecting the brain, nerves, and/or muscles
- Imaging studies (**CT scan** or **MRI**) of the brain and spinal cord

Determining which tests to use depends on the clinician's judgment of what is most likely to be the underlying cause of the hypotonia. This in turn is based upon the history and physical findings. In some cases, different doctors will order different tests based upon their area of expertise. There is always a possibility that a diagnosis will not be determined. The term for hypotonia without a diagnosis is "idiopathic," which literally means "unknown cause."

Treatment team

Along with normal pediatric care, specialists who may be involved in the care of a child with hypotonia include developmental pediatricians (specialize in child development), neurologists, neonatologists (specialize in the care of newborns), geneticists, occupational therapists, physical therapists, speech therapists, orthopedists, pathologists (conduct and interpret biochemical tests and tissue analysis), and specialized nursing care. Depending on the cause and progression of hypotonia, treatment and evaluation may be needed throughout life.

Treatment

Unlike the wide array of potential causes of hypotonia, treatment options for low muscle tone are somewhat limited. In very severe cases, treatment may be primarily supportive, such as mechanical assistance with basic life functions like breathing and feeding, physical therapy to prevent muscle atrophy and maintain joint mobility, and measures to try and prevent opportunistic infections such as pneumonia. Treatments to improve neurological status might involve such things as medication for a seizure disorder, medicines or supplements to stabilize a metabolic disorder, or surgery to help relieve the pressure from **hydrocephalus** (increased fluid in the brain). If the neurologic condition is untreatable, physical and occupational therapy may help to improve muscle tone, strength, and coordination.

Recovery and rehabilitation

In all cases, frequent or periodic monitoring of muscle tone and performance, along with neurological status, should be done to determine if the hypotonia is worsening, static, or improving. Effective recovery and rehabilitation can only be achieved if an accurate status of the condition is known. Since muscle weakness often accompanies hypotonia, efforts to improve muscle strength may also improve low muscle tone. Some individuals with persistent symptoms may need assistance with mobility, such as a walker or wheelchair. Occupational and physical therapy can assist individuals in developing alternative methods for accomplishing some everyday tasks they may find difficult. Speech therapy is primarily directed at young children to help them develop language skills early, but can be beneficial at any age if the muscles of the face and throat are hypotonic.

Clinical trials

Prognosis

Determining a prognosis depends on determining a diagnosis for hypotonia. Some genetic conditions are fatal in infancy, while others result in permanent disability and mental retardation. For those few genetic metabolic disorders that are treatable, improvement may be dramatic, or minimal. Outcomes for hypotonia caused by CNS trauma or infection depend on the severity of neurologic damage. Mild trauma obviously has the best chance for improvement and recovery, but even significant neurologic deficits may improve over time.

Most individuals with a nongenetic form of hypotonia will improve to some degree. From a broad perspective, some individuals with hypotonia will respond very little or not at all to any treatment method attempted, while in others the condition will resolve on its own; each case is unique.

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March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605. 888-663-4637; Fax: 914-428-8203. <http://www.marchofdimes.com>.

Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718-3208. 800-572-1717; Fax: 520-529-5300. <http://www.mdausa.org/>.

National Institute of Child Health and Human Development Clearinghouse. PO Box 3006, Rockville, MD 20847. 800-370-2943. <http://www.nichd.nih.gov>.

National Organization for Rare Disorders (NORD) . P.O. Box 1968, 55 Kenosia Avenue, Danbury, CT 06813-1968. 203-744-0100; Fax: 203-798-2291. <http://www.rarediseases.org>.

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Hypoxia

Definition

Hypoxia generally refers to a lack of oxygen in any part of the body. In a neurological context, it refers to a reduction of oxygen to the brain despite adequate amounts of blood.

Key Terms

Depolarization Occurs when a neuron exchanges ions, causing an influx of sodium and calcium inside the cell and an efflux of potassium out of the cell.

Description

A decrease in oxygen supply to the brain can occur due to choking, strangling, suffocation, head trauma, carbon monoxide poisoning, cardiac arrest, and as a complication of general anesthesia. A failure to deliver oxygen and glucose to the brain causes a cascade of abnormal events. The extent of damage is directly proportional to the severity of the injury. The severity of cerebral ischemia, a low-oxygen state caused by arterial obstruction or lack of blood supply, and the duration of blood-flow loss in the brain determine the extent of brain damage. The neurons can suffer temporary dysfunction, or there may be irreversible damage to nerve cells that are sensitive to minute changes in oxygen levels. Severe damage involving extensive areas can occur (cerebral infarction). Cerebral hypoxia/ischemia can be caused by a broad spectrum of diseases that affect the cardiovascular pumping system or the respiratory system. There are four types of disorders to consider: focal cerebral ischemia, global cerebral ischemia, diffuse cerebral hypoxia, and cerebral infarction.

Focal cerebral ischemia

Focal cerebral ischemia (FCI) is often results from a blood clot in the brain. The blood flow in the affected area is reduced. The reduction could be severe or mild but usually FCI causes irreversible injury to sensitive neurons. The clinical signs and symptoms last approximately 15–30 minutes.

Global cerebral ischemia

Global cerebral ischemia (GCI) is a serious condition caused by ventricular fibrillation or cardiac asystole, which stops all blood flow to the brain. If the GCI lasts more than five to ten minutes, then it is likely the person will have suffered a loss of consciousness that makes recovery doubtful.

Diffuse cerebral hypoxia

Diffuse cerebral hypoxia (DCH) is limited to conditions that cause mild to moderate hypoxemia, or low arterial-oxygen content due to deficient blood oxygenation. Pure cerebral hypoxia causes cerebral dysfunction but not irreversible brain damage. Pure cerebral hypoxia can occur due to pulmonary disease, altitude sickness, or severe anemia.

Cerebral infarction

Cerebral infarction (CI) is a severe condition caused by a focal vascular occlusion in an area of the brain. This causes an area of destruction resulting from a lack of oxygen delivery.

Pathology of cerebral ischemia

Lack of oxygen causes neurons in the brain to die in several ways. Autolysis can occur, which results from the digestion of nerve tissues by enzymes. Cerebral infarction causes the death of neurons; transient cessation of the **cerebral circulation** for a few minutes causes selective areas of ischemic necrosis. This type of necrosis is especially evident in highly vulnerable neurons that are sensitive to abrupt oxygen deprivation. More prolonged periods of moderate-to-severe hypoxemia or carbon monoxide poisoning can cause a loss of the outer sheath of neurons.

Molecular mechanisms of cerebral hypoxia

In cases of severe ischemia to brain tissue, the tissue loses structural integrity within a few seconds or a few minutes. Soon after there is an abnormal exchange of ions in neurons through a process called depolarization; this is characterized by an influx of sodium and calcium ions inside the neuron, and a simultaneous efflux of potassium ions outside the neuron.

Cerebral edema

Cerebral edema refers to abnormal increases in water content in the brain and occurs with all types of cerebral ischemia and hemorrhagic **stroke**. Increased water retention in the brain causes an increase in intracranial pressure. This pressure causes the brain to be pushed against the skull, resulting in neurologic deterioration and death due to herniation. Cerebral edema and herniation of the brain is the cause of death for approximately 75% of all fatal stroke victims and 33% of fatalities for all ischemic events to the brain.

Symptoms

Symptoms vary depending on the severity of damage. Symptoms of mild cerebral hypoxia can include poor judgment, memory loss, inattentiveness, and a decrease in motor coordination. In more severe cases, there can be permanent neurologic deficits, coma, **seizures**, or death.

Treatment

Treatment depends on the cause and availability of equipment. Treatment is urgent and includes basic and advanced life-support measures. It is important to maintain breathing, dispense intravenous fluids and medications, and maintain stability with blood products and medications that control blood pressure and seizures. The outlook depends on the extent of cerebral ischemia.

Resources

BOOKS

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Brain Injury Association. 8201 Greensboro Drive, Suite 611, McLean, VA 22102. (703) 761-0750 or (800) 444-6443; Fax: (703) 761-0755. FamilyHelpline@biausa.org. <http://www.biausa.org>.

National Rehabilitation Information Center (NARIC). 4200 Forbes Boulevard, Suite 202, Lanham, MD 20706-4829. (301) 562-2400 or (800) 346-2742; Fax: (301) 562-2401. naricinfo@heitechservices.com. <http://www.naric.com>.

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I

Idiopathic neuropathy

Definition

Idiopathic neuropathy is a disorder that affects the peripheral nerves and has no identifiable primary cause. According to this definition, a third of all neuropathies can be classified as idiopathic neuropathies.

Description

The nervous system is divided into two parts: the **central nervous system** (CNS) and the **peripheral nervous system** (PNS). The brain and spinal cord compose the CNS, and the nerves that lead to or branch off the CNS compose the PNS.

Peripheral neuropathies encompass a wide range of disorders in which peripheral nerves are damaged. It may also be referred to as peripheral neuritis (inflammation of peripheral nerves), or if many nerves are involved, the terms polyneuropathy or polyneuritis may be used.

Some of the causes of peripheral neuropathies are common, such as diabetes, and others are extremely rare, such as acrylamide poisoning and certain inherited disorders. Sometimes peripheral neuropathies seem to happen for no particular reason. In such cases, they are called idiopathic, meaning of unknown cause. Idiopathic neuropathies can be classified as idiopathic mononeuropathies and polyneuropathies. An idiopathic mononeuropathy, or **radiculopathy**, refers to the involvement of a single nerve or nerve root, respectively. A polyneuropathy usually refers to the diffuse involvement of peripheral nerves.

Clinical manifestations depend on the type and distribution of the affected nerve population, the degree to which they are damaged, and the course of the disease. For example, if a motor nerve is damaged, the neuropathy manifests as weakness and muscle atrophy, whereas if the damage involves sensory nerves, it may cause loss of sensation, **pain**, and sensory **ataxia**.

Demographics

Idiopathic peripheral neuropathies occur typically in middle-aged and elderly individuals and affect two million people in the United States. However, epidemiological studies are scarce. Available studies suggest that 2.4–8% of all adults may have some form of neuropathy. The most common cause is diabetes, which accounts for approximately one-third of all neuropathies; the remaining two-thirds are idiopathic and of all other known causes.

Causes and symptoms

There are no known causes for idiopathic neuropathies, and therefore they are considered primary diseases. If a cause is detected, then the neuropathy is secondary to that, and not idiopathic.

Nonetheless, there are many different peripheral neuropathies, among them the idiopathic type, which demonstrates the functional diversity of PNS activities. Symptoms may involve sensory, motor, or autonomic functions. Symptoms are classified based on the affected nerve type and the duration of disease development. Acute development refers to symptoms that have appeared within days, and subacute refers to those that have evolved over a number of weeks. Early chronic symptoms are those that take months to a few years to develop, and late chronic are the ones that have been present for several years.

Most times, the first symptoms include numbness, tingling and pain, unsteadiness when standing or walking, muscle weakness (including weak ankles), or cramps and faintness. Depending on the affected group of nerves, secondary symptoms may vary from loss of vibratory sensation at the toes to loss of temperature perception to muscle atrophy.

Diagnosis

Several tests are necessary in order to eliminate all the possible primary causes of the disease, after which idiopathic neuropathy may be defined as a diagnosis; hence it

Key Terms

Electromyography A test that detects electric activity in muscle that is used to determine nerve or muscle damage.

Idiopathic A disease or condition of unknown cause or origin.

Neuropathy A disease or condition of the nervous system or a nerve.

Paresthesia Abnormal numbness or tingling sensation, whether spontaneous or evoked.

is a diagnosis of exclusion. The patient's history plays a major role in the diagnosis and has to include all symptoms, date of onset, duration, extension of affected area, and amount of discomfort and pain. Specific details about tingling, numbness, weakness, or other symptoms are also very important.

During the neurological evaluation, a physical examination will test for loss of vibratory sensation, ankle jerks, and other reflexes. Sensations in the feet and hands will be evaluated. The purpose of these tests is to assess the neurological function, including muscle strength, autonomic nerve function, and the ability to feel different sensations.

An **electromyography** may be performed to measure the electrical activity of muscles and nerves. Through this measurement, the physician is able to detect the presence of nerve damage, the possible cause of the damage, and if damaged nerves are responding to treatment. If necessary, other tests can be used, such as a nerve **biopsy**, a lumbar puncture (spinal fluid analysis), and **magnetic resonance imaging (MRI)**, which creates images of the body and its organs that may be used in the confirmation or exclusion of disorders with similar symptoms.

Blood tests are commonly employed to check for vitamin deficiencies, toxic elements, and evidences of abnormal immune responses. The quantitative sensory test (QST) is a method used to assess damage to small nerve endings (temperature changes) and large nerve endings (vibration changes). Autonomic tests measure how autonomic nerves respond to stimulation. Data collected will indicate if the autonomic nervous system is functioning adequately, or if nerve damage is present. The quantitative sudomotor axon reflex test (QSART) is used to assess small nerve fibers linked to sweat glands. QSART is used to diagnose painful, small fiber neuropathies when nerve conduction test results are normal.

Treatment

Treatment for idiopathic neuropathies is mostly symptomatic, including pain therapy for paresthesias, physical and occupational therapy to help improve mobility and function, supportive measures to maintain blood pressure, and bowel and bladder function if the autonomic system is involved.

Treatment options for reducing pain include medication, injection therapy, and physical therapy. Surgery may be needed to treat some causes of neuropathy (e.g., **carpal tunnel syndrome**, radiculopathy).

Because analgesics (aspirin, ibuprofen) are usually ineffective against pain caused by neuropathy, treatment often involves medications that target nerve cells. Antidepressants such as **gabapentin** and amitriptyline are usually the first medications prescribed. Side effects of these drugs include drowsiness, **dizziness**, low blood pressure, and **fatigue**. Other medications include **anticonvulsants** (**carbamazepine** and **lamotrigine**), local anesthetics (lidocaine), and antiarrhythmics (mexiletine). Anticonvulsants may cause low white blood cell counts, nausea, vomiting, and dizziness. Side effects of lidocaine and mexiletine include nervousness, lightheadedness, drowsiness, and double vision.

Topical treatment with capsaicin cream may be prescribed for patients with focal neuropathy. Capsaicin causes stinging upon application and is often combined with a local anesthetic to reduce this side effect.

Injection therapy involves injecting a nerve block (lidocaine) into the area surrounding affected nerves, preventing the nerve from carrying impulses to the brain and temporarily reducing symptoms. Injection therapy is often used with other treatments such as medication and physical therapy.

Discontinuing medication or exposure to toxic substances may eliminate neuropathy caused by drugs or toxins. Vitamin supplements may be used to treat nutritional neuropathy. Physical therapy, including **exercise**, massage, and heat, and **acupuncture** (insertion of fine needles into specific points on the body) may be used to treat symptoms.

Treatment for the causes of neuropathy include antibiotics or antiviral agents for infectious neuropathies, immunomodulating agents for immune-mediated neuropathies, improved glycemic control for diabetic neuropathies, and surgery for compressive neuropathies.

Over-the-counter pain relievers can help treat mild-to-moderate pain associated with **peripheral neuropathy**. There are two main types of over-the-counter pain relievers: acetaminophen and nonsteroidal anti-inflammatory

drugs (NSAIDs). Acetaminophen is used to treat mild-to-moderate pain and reduce fever, but it is not very effective at reducing inflammation. Acetaminophen provides relief from pain by increasing the pain threshold. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain, swelling, stiffness, and inflammation. Two drugs in this category, ibuprofen and naproxen, also reduce fever. When these drugs are taken regularly, they build up in the blood to levels that fight pain caused by inflammation and swelling, and also provide general pain relief.

Support groups often help patients cope with feelings of isolation and frustration and improve their quality of life.

Clinical trials

As of 2004, there were no **clinical trials** for idiopathic neuropathies; however, there are several that aim at other types of neuropathies, such as the diabetic neuropathy.

Prognosis

Prognosis and complications depend on the type and severity of the neuropathy. Idiopathic neuropathies range from a reversible problem to a potentially fatal complication. In the best-case scenario, a damaged nerve regenerates. Nerve cells cannot be replaced if they are killed, but they are capable of recovering from damage. The extent of recovery is tied to the extent of the damage, to the patient's age, and to the general health status. Recovery can take weeks to years due to the slow neuronal regrowth rate. Full recovery may not be achieved in some cases.

Special concerns

Complementary and alternative therapies can help manage pain caused by neuropathies. These are noninvasive, drug-free treatments that support natural body healing. They may be used alone or combined with other medications and treatments. Some alternative therapies are biofeedback, acupuncture, and relaxation techniques.

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The Jack Miller Center for Peripheral Neuropathy, University of Chicago. 5841 South Maryland Avenue, MC2030, Chicago, IL 60637. (773) 702-5546. maa@myositis.org. <http://millercenter.uchicago.edu/index.shtml>.

The Neuropathy Association. 60 East 42nd Street, New York, NY 10165-0999. (212) 692-0662 or (800) 247-6968; Fax: (212) 696-0668. info@neuropathy.org. <http://www.neuropathy.org>.

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Immune-mediated encephalomyelitis *see* **Acute disseminated encephalomyelitis**

Inclusion body myositis

Definition

Inclusion body myositis (IBM) is an inflammatory muscle disease characterized by progressive muscle weakness and wasting. The common feature of IBM is the abnormal finding of inclusion bodies, or granular material, in muscle fibers. The onset generally occurs gradually over months or years, and persons often experience falling and tripping as the first symptoms. Inclusion body myositis affects both proximal (closest to the center of the body) and distal (farthest from the center of the body) muscles.

Description

Sporadic inclusion body myositis is the most common muscle disease in people aged 50 years and older with an unknown cause. The disease was named in 1971, when scientists noted a case of myositis (muscle inflammation) that showed granular material in muscle fibers called inclusion bodies. The inclusion bodies are now recognized to contain abnormal deposits of amyloid proteins, similar to those found in the brain of patients with Alzheimer's disease. The deposits may represent a protein product left within the muscle fibers as they degenerate.

The onset of IBM is insidious, with symptoms often having been present for more than five years before diagnosis. The course of the disease is progressive over months

or years, leading to severe disability. IBM may appear identical to another inflammatory myositis called **polymyositis**, although differences are clear in more than half of cases.

Weakness and impairment of muscle function are the hallmarks of IBM, and weakness distribution is variable, with both proximal (closest to the center of the body) and distal (farthest from the center of the body) muscles affected. Diminished deep-tendon reflexes and wasting (atrophy) of the involved musculature occur. Thus, loss of finger dexterity and grip strength may be present, while falling and tripping appear as the first signs. Patients often suffer from **fatigue** and reduced tolerance to exertion, and consequently become out of breath easily.

Demographics

There are no data currently available for the incidence of IBM internationally, although it has been reported in Europe and Asia. IBM is thought to account for approximately 15–20% of all cases of inflammatory myositis in the United States. Mortality rate (rate of deaths) is difficult to assess, as most people with IBM are older and may die of other coexisting medical problems. There is no race prevalence, but it is uncommon among African Americans. The male/female ratio is 3:1 and most affected individuals are 50 years or older. Nevertheless, IBM does not seem to affect life expectancy.

Causes and symptoms

The causes of IBM remain unknown and it is thought to be a multifactorial disease. Aging factors may play an important role as pathogenic (disease-causing) components. Research has been made to establish whether IBM might be influenced by environmental factors. Thus, inflammation may be a secondary component occurring in response to foreign proteins called antigens, such as viral proteins or altered muscle proteins, and perhaps induces an autoimmune response (a reaction of the organism against itself).

A possibility that excessive accumulation of certain proteins within muscle fibers can induce inflammation is supported by the findings in transgenic mice studies in which mice were modified to express these human proteins. The results have shown that when synthesizing large amounts of the protein in the muscles, mice developed an age-related motor deficit with muscle inflammation. Also, aging muscle fiber was shown to promote accumulation of abnormal proteins, suggesting an aging-based degenerative process. It has been shown that muscle can secrete this protein and thus, it might cause inflammation by stimulating the immune system to react against the affected muscle.

Key Terms

Autoimmune An immune response by the body against its own tissues or cells.

Inclusion bodies Small intracellular bodies found within another intracellular body, characteristic of certain diseases.

Myositis Inflammation of a muscle.

The stimulus for excessive amyloid production is unknown, and whether this precedes inflammation, or vice-versa, remains to be determined.

Genetic causes of IBM have also been proposed, and studies focused on human leukocyte antigen genes that encode for proteins that influence immune response. They were found related to the development of IBM, but their role is not clear.

As an acquired process, weakness or impairment of muscle function in the area(s) affected is the primary symptom of IBM. The distribution of weakness is variable, but most muscles are affected, including those in the neck, hip, quadriceps, back, shoulder, wrist, and finger. Many people with IBM notice shrinking, or atrophy, in the arms and thighs as the muscles become weaker. As thighs are affected by atrophy, sudden falls may occur.

Lower leg weakness can cause difficulty lifting up the foot, which can lead to tripping. Difficult swallowing, or dysphagia, is a common problem in up to 40% of persons with IBM, and choking may become a problem when ingesting some types of food or liquids. Weakness of facial muscles is sometimes seen. Fatigue and reduced tolerance to exertion are common, and cardiac disease is also present in those with IBM, although its relation to IBM has not been demonstrated. The disease itself does not cause **pain**; however, weakened muscles can predispose to injuries affecting bones, joints and soft tissues. Elderly patients normally die of other clinical problems rather than of IBM, and most suffer some degree of disability as disease progresses.

Diagnosis

The IBM diagnosis is carried out according to clinical features and laboratory studies. The illness lasts longer than six months and the age of onset is greater than 30 years old. People with IBM have considerable quadriceps and wrist and finger flexor weakness. Blood tests show high levels of creatine kinase, a muscle enzyme released by damaged muscle. **Electromyography** (EMG) can be used to detect the electrical impulses of muscle contraction, which exhibit

a different pattern in IBM patients. Although useful, EMG cannot be taken as a definite diagnosis.

As IBM muscles are damaged, muscle **biopsy** is the definitive test. In a muscle biopsy, a small sample of the muscle is taken under local anesthesia. Laboratory analysis can identify the inclusion bodies within muscle fibers and the invasion of the damaged tissue by immune cells featuring the inflammation with muscle destruction. This appearance will allow the pathologist and clinician to confirm the diagnosis of IBM. None of the other clinical or laboratory features are mandatory if muscle biopsy features are diagnostic. Muscle biopsy is also important for the exclusion of other neuromuscular diseases.

It has been suggested that **magnetic resonance imaging (MRI)** may be useful detecting active myositis and recognizing selective patterns of muscle involvement in IBM. **MRI** is also helpful in selecting an appropriate biopsy site. The results of such studies are also useful to guide therapeutic decisions when a biopsy is not possible or the biopsy findings are inconclusive.

Because of the imprecise nature of muscle weakness in IBM, a diagnosis is sometimes delayed for years after the onset of weakness. In some patients, the initial biopsy may not disclose the diagnosis, and a second biopsy may be necessary.

Treatment team

A **neurologist** or rheumatologist is the primary consultant for IBM treatment, along with allied health care areas including but not limited to physical therapists and otolaryngologists (ear, larynx, and upper respiratory tract specialists).

Treatment

Currently, no treatment has been shown to be effective against the different forms of IBM. Some moderate success has been obtained with the drug therapy combination of corticosteroids and methotrexate or human intravenous immunoglobulins. New therapeutic protocols are currently being tested. Physical therapy, occupational therapy, and ergotherapy (treatment of disease by muscular **exercise**) are commonly prescribed.

Recovery and rehabilitation

In most cases of IBM, there is continued deterioration in spite of the treatment reduction of muscle inflammation and immune cells invasion of muscle tissue. Because of the slow progression, any treatment trial should last for at least six months (possibly 12–18 months) to evaluate benefits. Physical therapy and occupational therapy may help patients as disability increases.

Clinical trials

No treatment has shown to be effective against IBM; however, new therapies are currently being tested. The National Institute of Neurological Disorders and Stroke (NINDS) is sponsoring a study entitled "Immune Abnormalities in Sporadic Inclusion Body Myositis." This is an investigative study intended to better define the pathogenesis of IBM. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is recruiting patients to a study, "Study and Treatment of Inflammatory Muscle Diseases," which intends to obtain useful material for immunological studies and to sponsor standard therapies for patients. It is likely that in the future more therapeutic trials of drugs in IBM will be organized.

Prognosis

IBM generally worsens progressively and slowly. Some observations of stabilizations and remissions, spontaneous or under treatment, have been reported but are usually only temporary.

Special concerns

Exercise is generally helpful by getting the most out of diseased muscles. Falls and injuries, however, can cause substantial disability. Patients, therefore, have the difficult task of undertaking regular exercise within their capability, but avoiding injury through accident. Because weakened muscles cannot carry an excessive load, keeping to an ideal weight is helpful. A well-balanced diet is also helpful. Patients with severe inflammation of the muscles may need extra protein to balance their loss.

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ORGANIZATIONS
Myositis Association of America. 755 Cantrell Ave., Suite C, Harrisonburg, VA 22801. (540) 433-7686; Fax: (540) 432-0206. maa@myositis.org. <http://www.myositis.org>.

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Incontinentia pigmenti

Definition

Incontinentia pigmenti is a rare genetic disease resulting in a neurocutaneous disorder. Neurocutaneous means that the disorder affects the nervous system and that clinical abnormalities can involve the skin, hair, and teeth of affected individuals.

Description

Incontinentia pigmenti patients develop discolored, abnormally pigmented skin that is distributed randomly and asymmetrically. Occasionally, persons with incontinentia pigmenti experience cognitive delays (including **mental retardation**), but most have normal intelligence. Muscle weakness in one or both sides of the body is also characteristic of the disorder. Incontinentia pigmenti is also known as Bloch-Sulzberger syndrome, as well as incontinentia pigmenti, type 2.

Demographics

Incontinentia pigmenti is considered rare, with only about 1,000 affected individuals reported in medical literature. The gene that is defective in this disease is located on the X chromosome and is inherited as a dominant disorder, meaning that each child of an affected mother has a 50% risk of inheriting the faulty gene and the disorder. Most male fetuses affected with incontinentia pigmenti die before birth; more females are affected with the disorder.

Causes and symptoms

Incontinentia pigmenti results in defects in the skin, nails, hair, and teeth. The disorder is caused by mutations in the IKBKG gene, located on the X chromosome. This gene encodes a protein that is important during human development. Approximately 80% of affected individuals have mutations in this gene. Cases can be caused by inherited mutations or spontaneous mutation that occur randomly in families; therefore, there is an absence of a family history.

Defects in the skin usually develop at birth in four distinct stages. The first stage usually occurs before four months old when the blisters appear in the skin. The second stage involves a wart-like rash that eventually turns into the third stage, in which regions of swirling, darkened pigmentation (skin color) appear after six month of age (and into adulthood). The last stage is characterized by linear hypopigmentation, or areas of the body that are less darkly pigmented.

Neurological problems associated with incontinentia pigmenti occur in about 25% of cases and include cerebral atrophy (deterioration and loss of brain cells), leading to poor muscle control and weakness. Mental retardation and **seizures** are also similarly present.

Other symptoms include defects in the teeth, with too few or too many present. The finger and toenails can often be brittle or pitted, often resembling fungal infections. Patients often have alopecia (hair loss) that occurs on the scalp or body trunk and extremities. Hair can appear patchy and hair loss can occur in areas that blistered during the first stage of the disease. Some patients have been reported to have defects in blood flow in the retina of the eye, predisposing them to retinal detachment during childhood.

Diagnosis

Diagnosis is achieved first by a clinical diagnosis from a clinical geneticist, followed by molecular genetic testing in a CLIA-approved diagnostic laboratory. This test usually supports DNA sequencing of the IKBKG gene. A mutation in this gene can confirm the clinical diagnosis. The clinical diagnosis requires the presence of involved skin that displays any or all the following symptoms, including blisters anywhere on the body except the face, usually before four months of age, hyperpigmentation (increased areas of pigment) occurring on the trunk of the body that fades during adolescence, and/or hairless streaks or patches that occur after adolescence.

Treatment team

The treatment team consists of a **neurologist**, clinical geneticist, genetic counselor, speech pathologist, ophthalmologist, and a dermatologist. A specialist that deals with **learning disorders** or developmentally delayed children may be necessary in certain cases.

Treatment

As there is no cure for incontinentia pigmenti, treatment is based on symptoms. The risk of infection from blisters is a consideration, and topical medications can often be used to lessen the associated **pain**. Corrective dentistry might be necessary to help with eating and talking.

Key Terms

Cognitive delay Impairment or slowing of the mental processes of thinking and acquiring knowledge.

Dominant disorder A disorder resulting from an inheritance pattern where one parent has a single, faulty dominant gene, and has a 50% chance of passing on that faulty gene to offspring with each pregnancy.

Hyperpigmentation An excess of melanin, leading to abnormal areas of increased dark skin color.

Hypopigmentation A deficiency of melanin, leading to abnormal areas of lighter skin color.

Neurocutaneous Conditions involving unique manifestations of the skin, hair, teeth, and nervous system, usually with familial tendencies.

Recovery and rehabilitation

There is no cure for incontinentia pigmenti. A speech pathologist and a nutritionist can often help with rehabilitation to address problems associated with speech difficulties and difficulties eating.

Clinical trials

As of mid-2004, there were no ongoing **clinical trials** specific for the study or treatment of incontinentia pigmenti.

Prognosis

The skin abnormalities can improve with age and in some instances disappear completely. The prognosis for neurological abnormalities depends on each case, but is often permanent and significant. Life expectancy, however, is considered normal.

Special concerns

Genetic counseling is important in cases in which there is a family history of incontinentia pigmenti, or in which there is a clinical diagnosis.

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ORGANIZATIONS

Incontinentia Pigmenti International Foundation (IPIF). 30 East 72nd Street, 16th Floor, New York, NY 10021. (212) 452-1231; Fax: (212)452-1406. ipif@ipif.org. <http://www.imgen.bcm.tmc.edu/IPIF>.

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Infantile hypotonia *see* **Hypotonia**

Infantile phytanic acid storage disease *see* **Refsum disease**

Infantile Refsum disease *see* **Refsum disease**

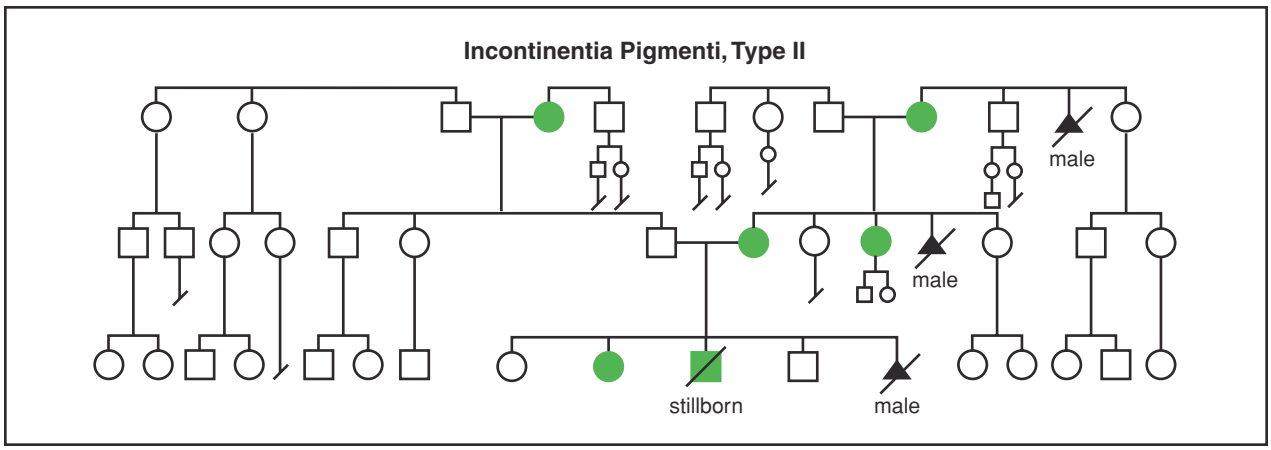
Infantile spasms

Definition

Infantile spasms (IS) are **seizures** seen in **epilepsy** of infancy and early childhood. The typical pattern of an infantile spasm occurs soon after arousal from sleep, and involves a sudden bending forward and stiffening of the body, arms, and legs. Additionally, arching of the torso can also be seen during an infantile spasm. Infantile spasms typically last for one to five seconds and occur in clusters, ranging from two to 100 spasms at a time.

Description

Infantile spasms were first described by the English physician W.J. West (1794–1848) in 1841. West's paper, published in the first volume of the medical journal *Lancet,* was a landmark in the development of pediatric neurology, and the seizure syndrome also became known as West syndrome. West observed the condition in his own infant son, giving a precise and complete description of the symptoms, along with the gradual mental deterioration, and intractability of the syndrome. Other neurological disorders, such as **cerebral palsy**, may be seen in almost half of infants with infantile spasms.



See Symbol Guide for Pedigree Charts. *(Gale Group.)*

Infantile spasms may have variable features, but have been categorized primarily into three subtypes based on manifestations of posture and patterns of muscle involvement during the seizure. Flexor spasms involve flexion of the neck, trunk, and extremities. Extensor spasms consist of extension of the neck, trunk, and extremities. Mixed flexor-extensor spasms involve combinations of the above.

In many patients, spasms exhibit characteristic patterns involving time. Fifty to eighty percent of the epileptic spasms occur in clusters of two to more than 100 seizures. Patients may have dozens of clusters and several hundred spasms per day, but individual variability in seizure frequency is often large. Although spasms rarely occur during sleep, clusters of spasms are frequently activated after awakening from sleep. Spasms are occasionally triggered by loud noises with associated arousal from drowsiness and sleep, but are generally not sensitive to stimulation by human voices.

Key Terms

Electroencephalogram (EEG) A procedure that uses electrodes on the scalp to record electrical activity of the brain. Used for detection of epilepsy, coma, and brain death.

Epilepsy Disorder associated with the disturbed electrical discharges in the central nervous system that cause seizures.

Seizure Abnormal electrical discharge of brain tissue, often resulting in abnormal body movements or behaviors.

Demographics

In the United States, infantile spasms constitute 2% of childhood epilepsies, and 25% of epilepsies with onset in the first year of life. The rate of IS is 1.6–5.0 cases per 10,000 live births. As many as 5% of infants with this condition eventually die from complications of the seizures. Although males are affected slightly more often than females, no significant gender difference is noted.

Causes and Symptoms

The number of neurological diseases that can result in infantile spasms is very large, but some of the major categories include intrauterine injury and infection, disorders caused by lack of blood flow to the fetal brain, developmental malformations of the cerebral cortex, metabolic disorders, other genetic or chromosomal defects, meningitis, and tumors. These seizures are assumed to reflect abnormal interactions between the cortex and brainstem structures. The frequent onset of the spasms in infancy suggests that an immature **central nervous system** may be important in the formation of infantile spasm syndrome. One theory states that the effect of different stressors in the immature brain produces an abnormal excessive secretion of corticotropin-releasing hormone, which causes spasms.

In 90% of children with the condition, infantile spasms occur in the first year of life, typically between three to six months of age. Often, in the beginning, the attacks are brief, infrequent and not typical, so it is quite common for the diagnosis to be delayed. Frequently, because of the pattern of attacks and the cry that a child gives during or after an attack, they are initially thought to be due to colic, or gastric distress.

The typical pattern is of a sudden flexion (bending forward) in a tonic (stiffening) fashion of the body, arms, and legs. Sometimes, however, the episodes are of the extensor type (arching). Usually, they are symmetrical, but sometimes one side is affected more than the other.

Typically, each episode lasts a few seconds, followed by a pause of a few seconds, and a further spasm. While single spasms may occur, infantile spasms usually occur in sets of several spasms in a row. It is common for babies with infantile spasms to become irritable and for their development to slow down or even regress until the spasms are controlled.

Diagnosis

Information about the child's seizures and about the pregnancy, birth, and progress since birth, will help the physician in making the diagnosis. The diagnosis of infantile spasms is made by a combination of the typical features, along with a characteristic electroencephalogram (EEG), which shows a very disorganized pattern termed hypsarrhythmia.

Most children with infantile spasms will need a number of tests, such as blood, urine, and cerebrospinal fluid (fluid which circulates around the brain and spinal cord) sampling, in an attempt to screen for any infection or metabolic abnormality. X-ray studies such as CT scans, ultrasound, or **MRI** will be performed to evaluate the structure of the brain.

Treatment Team

The treatment team usually includes pediatric neurologists, neurosurgeons, nurses specializing in epilepsy care, and dietitians. In addition to conventional therapies, the team provides the latest in diagnostic and therapeutic approaches, including such innovations as the ketogenic diet, diagnostic video telemetry, and epilepsy surgery for intractable seizures. New epilepsy studies focus in investigating promising new drugs and other novel therapies.

Treatment

Due to the poor prognosis of infantile spasms, treatment is usually initiated quickly and aggressively after diagnosis, often at the risk of serious side effects, with the hope of changing the natural history of the disease. Antiepileptic medications are the mainstay of therapy for infants with infantile spasms. Unfortunately, no one medical treatment gives satisfactory relief for all patients. In most open-label or retrospective studies, adrenocorticotrophic hormone ACTH or prednisone induces a reduction or complete cessation of spasms, as well as an improvement in the EEG, in approximately 50–75% of patients. This effect is usually achieved within a couple weeks. Patients unresponsive to ACTH may respond to prednisone and vice-versa. A large variety of ACTH doses have been used, but there is no evidence that larger doses (150 units/day) are more effective than lower doses (20–30 units/day). While relapses occur in about one-third to one-half of patients, a second course of ACTH is often effective.

Among conventional anti-seizure drugs, valproate and nitrazepam have been shown to be effective as first-line therapy. In addition to medication, there are some potential surgical options for infantile spasms, although they may only be applicable to a small percentage of patients. Although in most patients the precise source of the spasms in the brain cannot be localized, there is a small minority of patients who have secondarily generalized spasms from lesions in the brain that can be surgically removed.

Newer anti-seizure medicines such as Vigabatrin, although not yet approved in the United States, have shown promise in reducing the frequency of infantile spasms by increasing the brain's available amount of GABA, a neurotransmitter that helps transmit information as it bridges the gaps between nerve cells.

Recovery and rehabilitation

Infantile spasms usually cease spontaneously by age five, but are often replaced by seizures of other types. Therefore, emphasis is placed on lifelong seizure prevention rather than recovery. Maintaining control of seizures in infancy can sometimes reduce developmental delays and **mental retardation**, although most infants will already have significant neurological impairment before the onset of symptoms.

Clinical trials

Although as of early 2004, there were no ongoing **clinical trials** for infantile spasms, the National Institutes of Health (NIH) sponsors research related to many seizure disorders. Information on the numerous current clinical trials for the study and treatment of seizure disorders can be found at the NIH website: <http://clinicaltrials.gov/search/term=Seizure+Disorder>.

Prognosis

Infantile spasms usually resolve with or without treatment in the majority of patients, generally by mid-childhood. However, other seizure types arise in 50–70% of patients. Similarly, on long-term follow-up, chronic intractable (unable to respond to treatment) epilepsy is present in approximately 50% of patients with a history of infantile spasms.

Mental retardation occurs in 70–90% of persons with infantile spasms, usually involving severe to profound retardation. Other neurological deficits, such as cerebral palsy, may be seen in about 30–50% of patients. By far, the most important factor in predicting neurological prognosis, including developmental outcome and long-term epilepsy, is the underlying cause of the seizures.

Factors that have been associated with a good prognosis include normal neurological exam and development at onset, absence of other seizure types at onset, older age of onset, short duration of spasms, and early effective treatment of spasms (reported with ACTH).

Special concerns

Once infants begin to have infantile spasms, they often fail to meet new milestones and may even regress, losing mental or physical skills previously learned. When the seizures begin, parents may notice a loss of interest in people and objects in the child's environment. Social interaction may diminish, smiling may cease, sleep may become disrupted, and the child may seem irritable or indifferent to surroundings. A child who had learned to sit may stop sitting or even lose the ability to roll over; a child who had been babbling happily may become silent or fussy.

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Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (301) 459-3700 or (800) 332-1000. (301) 577-2684. postmaster@efa.org. <http://www.epilepsyfoundation.org>.

National Organization for Rare Disorders (NORD). 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

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Inflammatory myopathy

Definition

Inflammatory **myopathy** is a term that defines a group of muscle diseases involving inflammation and degeneration of skeletal muscle tissues. They are thought to be autoimmune disorders. In inflammatory myopathies, inflammatory cells surround, invade, and destroy normal muscle fibers as though they were defective or foreign to the body. This eventually results in discernible muscle weakness. This muscle weakness is usually symmetrical and develops slowly over weeks to months or even years.

When using the term inflammatory myopathy, one is actually considering three separate disease entities, namely **dermatomyositis** (DM), **polymyositis** (PM), and **inclusion body myositis** (IBM). Although all of these diseases result in muscle weakness, each is unique in its development and treatment.

Description

Inflammatory myopathies include a diverse group of disorders ranging from localized varieties confined to a single muscle or group of muscles, to diffuse forms in which there is widespread involvement of the skeletal muscles.

Inclusion body myositis (IBM) mainly affects individuals over the age of 50. The onset is truly insidious with symptoms often having been present for more than five years before diagnosis. Clinically and histologically, IBM may appear identical to another inflammatory myositis called polymyositis, although differences are clear in more than half the patients.

Weakness in (IBM) may be localized in the extremities, or asymmetric, and it may be accompanied by diminished deep-tendon reflexes. Disease progression is usually slow and steady in some, while it seems to plateau in others, leaving them with fixed weakness and atrophy (muscle wasting) of the involved musculature. In the muscle tissue, a characteristic change in IBM is the presence of intracellular rimmed vacuoles (pockets). The muscle fibers with pockets are now recognized to contain abnormal deposits of amyloid proteins.

Polymyositis usually occurs after the second decade of life and is a subacute myopathy (one that occurs over time) that evolves over weeks or months, and presents with weakness of the arm and leg muscles. PM mimics many other myopathies. It should be viewed as a syndrome of diverse causes that occurs separately or in association with other autoimmune disorders. In PM, muscle fibers are found to be in varying stages of necrosis (tissue death) and regeneration.

Key Terms

Amyloid A waxy, translucent, starch-like protein that is deposited in tissues during the course of certain chronic diseases such as rheumatoid arthritis and Alzheimer's disease.

Autoimmune Pertaining to an immune response by the body against its own tissues or types of cells.

Dermatomyositis (DM) is identified by a characteristic skin rash accompanying or, more commonly, preceding muscle weakness. DM affects children and adults and presents a varying degree of muscle weakness that develops slowly, over weeks to months.

Demographics

In the United States and Canada, IBM accounts for approximately 15–28% of all cases of inflammatory myopathies. IBM most frequently affects men with a male to female ratio of 3:1. No race predilection for IBM is known, but it is uncommon among African-Americans and has been reported in Europe and Asia. Assessing demographic data is difficult due to the fact that IBM patients often exhibit other medical problems.

Polymyositis (PM) is most common among black people and is most prevalent in women, with a male to female ratio of 1:2. In the United States, its incidence is one per 100,000 persons per year. Dermatomyositis (DM) affects mainly white people and is more prevalent in women, with a male to female ratio of 1:2. In the United States, the estimated incidence is 5.5 cases of DM per one million people.

Causes and symptoms

Inclusion body myositis (IBM) is thought to be a sporadic disease, meaning one that is not hereditary. The cause of IBM remains unknown, but is thought to be a form of autoimmune disease, where the immune system responds in a harmful manner to the rest of the body. Very rarely, IBM can be present within families, and it is not known whether this form is inherited or if family members have another susceptibility to whatever causes the sporadic form of the disease.

The trigger mechanism for all inflammatory myopathies remains unknown. Some scientists maintain that a viral illness causes an injury that activates a flawed immune response. Other scientists, noting that cancer sometimes occurs along side some types of inflammatory myopathy, are investigating the relationship between the two diseases. A genetic predisposition may exist for DM, and abnormal activities of certain white blood cells may be involved in the cause of both the skin and the muscle disease.

Weakness of muscle function in the area affected is usually the first symptom of inflammatory myopathy. The distribution of weakness is variable, and involvement of the knee extensor muscle and the wrist and finger flexor muscles are common. **Fatigue** is common, along with reduced tolerance to exertion, difficulty swallowing (dysphagia), and some forms of heart disease.

In polymyositis (PM), weakness and muscle **pain** on both sides of the body at rest or with use are the first signs of the disease. The weakness becomes chronic, lasting for weeks or months. If swallowing muscles are involved, dysphagia may occur. Joint pain and difficulty kneeling, climbing, or descending stairs, raising arms, and arising from a sitting or lying position are also noticeable.

People often present with skin disease as one of the initial manifestations of DM. A characteristic rash preceding or accompanying muscle weakness, or a confluent, purple-red rash with swelling in surrounding tissues appears. Other rashes seen with DM include swelling at the nail beds and a scaly purple eruption over the knuckles. Muscle involvement varies from mild to severe. The muscle wall of the heart or lung tissues may also become inflamed as a consequence of DM. Some cancers have been associated with DM, a finding much more common in adults over 60 years old.

Diagnosis

A muscle **biopsy** provides a definitive diagnosis for inflammatory myopathies. Muscle biopsy is also important for the exclusion of other neuromuscular diseases. Blood levels of creatine kinase, an enzyme present in the brain and skeletal and cardiac muscles, are usually elevated in persons with muscle damage, and are useful in the diagnosis of inflammatory myopathies.

According to The Myositis Association, the main clinical features for diagnosis of inclusion body myositis (IBM) are:

- Duration of illness greater than six months
- Age of onset greater than 30 years old
- Muscle weakness that affects the arms and legs
- At least one of the following: weakness when flexing the fingers, differing degrees of weakness when flexing and extending the wrist, and weakness in the quadriceps muscle of the thigh.

In polymyositis (PM), the presence of inflammation in muscle tissue is hallmark of the disease. The diagnosis

of PM is made when a person has continued elevated levels of serum creatine kinase and characteristic findings on muscle biopsy. Polymyositis is difficult to diagnose due to its ability to mimic other chronic diseases.

People with dermatomyositis (DM) often have characteristic rashes that accompany chronic weakness, making the tentative diagnosis easier for the physician and patient. Skin lesions can include red, raised areas on the surface of the joints of the arms and legs, face, or upper body.

Treatment team

A **neurologist** or rheumatologist is the primary consultant for both IBM and PM, with allied health care areas including but not limited to physical therapists and otolaryngology.

Treatment

Currently, no treatment has been shown to be effective against the different forms of IBM. Some moderate success has been obtained with the combination of corticosteroids and methotrexate or human intravenous immunoglobulins (IVIg). New therapeutic protocols are currently being tested.

In PM, however, high-dose corticosteroid therapy constitutes the first-line of treatment, and leads to improvement in more than 70% of persons with PM. Different therapeutic alternatives can be attempted with immunosuppressants, notably azathioprine, methotrexate and intravenous immunoglobulins (IVIg). The same approach is useful for DM.

Recovery and rehabilitation

In most cases of inflammatory myopathies, there is continued deterioration, in spite of any reduction of muscle inflammation that treatments may provide. Because of the slow progression, any medication regimes often continue for at least six months (possibly 12-18 months) to gain the most benefit. Physical therapy and occupational therapy help with walking, limb range of motion and positioning if the person's disability increases.

About 30% of persons with PM achieve complete recovery, with the majority of patients having a persistent deficit in movement and strength.

Clinical trials

The National Institute of Neurological Disorders and Stroke (NINDS) has sponsored a study entitled "Immune Abnormalities in Sporadic Inclusion Body Myositis." This is an investigative study intended to better define the pathogenesis of IBM. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is examining whether the drug infliximab (Remicade) is safe for treatment of DM and PM. Information about all current **clinical trials** can be found at the U.S government website for clinical trials: http://www.clinicaltrials.org.

Prognosis

IBM generally worsens progressively and slowly. Sometimes the condition stabilizes spontaneously or while the person is under treatment, but periods are usually transient and the inflammation reoccurs.

Before the era of corticosteroids, PM and DM were particularly severe diseases with spontaneous survival rates of less than 40%. Currently, in the absence of an underlying disease such as cancer, PM and DM in adults have a relatively favorable prognosis, with a five-year survival rate of around 90%. For children, the vascular damage of DM can be responsible for severe complications, such as perforations or hemorrhages.

Special concerns

Exercise is generally helpful to retain movement, and helps to get the most out of diseased muscles. Falls and injuries, however, can cause substantial disability for a person with an inflammatory myopathy. It is important, therefore, to maintain regular exercise within a safe capacity and avoid injury. Because weakened muscles cannot carry an excess load, keeping to an ideal weight is also helpful. A well-balanced diet is important and people with severe inflammation of the muscles may need extra protein.

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Muscular Dystrophy Association. 3300 E. Sunrise Drive, Tucson, AZ 85718,. (800) 572-1717. mda@mdausa.org. <http://www.mdausa.org/index.html>.

Myositis Association of America. 755 Cantrell Ave., Suite C, Harrisonburg, VA 22801. (540) 433-7686; Fax: (540) 432-0206. maa@myositis.org. <http://www.myositis.org>.

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Interferons

Definition

Interferons are a group of proteins called cytokines produced by white blood cells, fibroblasts, or T-cells as part of an immune response to a viral infection or other immune trigger. The name of the proteins comes from their ability to interfere with the production of new virus particles.

Purpose

Interferons affect the immune system in a number of ways. For example, interferon beta can enhance the activity of lymphocyte cells while simultaneously inhibiting other immune cells from becoming stimulated. Additionally, interferon beta regulates the production of interferon gamma. Interferons can also inhibit viruses from establishing an infection inside human cells. Interferon alfa displays anti-tumor activity.

The exact molecular details of how interferons act is still unclear. They may make surface-exposed antigens of tumors even more capable of stimulating the immune system, which in turn would elicit a greater response from the T-cells of the immune system. Tumor growth may also be slowed or retarded by interferon-mediated damage to the blood cells that supply the tumor with nourishment.

Description

There are three types of interferons: alfa, beta, and gamma. Alfa and beta interferons, which are grouped together as type I interferon, are produced by white blood cells and a type of connective tissue cell called a fibroblast. Gamma interferon (or type II interferon) is manufactured T-cells. Production occurs when the T-cells are activated such as during an infection.

The alfa and beta interferons share some biological activities, but also have activities that are distinct from one another. These similarities and differences reflect the common and different binding of the interferons to various targets (receptors) on the surfaces of human cells.

Alfa interferon is manufactured by Roche Products (trade name Pegasys) and Schering-Plough (Viraferon-Peg). Biogen (Avonex) and Serono (Rebif) both market an interferon-designated beta-1a. Both of the beta-1a interferons are produced in genetically engineered mammals. For example, Rebif is produced in Chinese hamster ovary cells that contain the gene coding for human interferon beta.

An interferon designated as beta-1b enhances the activity of T-cells, while simultaneously reducing the production cytokines that operate in the inflammatory response to infection and injury. As well, this interferon retards the exposure of antigens on the surface of cells (and so lessens the development of an immune response to the antigens), and retards the appearance of white blood cells (lymphocytes) in the **central nervous system**.

Key Terms

Demyelinating diseases A group of diseases characterized by the breakdown of myelin, the fatty sheath surrounding and insulating nerve fibers. This breakdown interferes with nerve function, and can result in paralysis. Multiple sclerosis is a demyelinating disorder.

Interferon alfa A potent immune-defense protein that is used as an anti-cancer drug.

The reduction of the immune response can lessen the damage to nerve cells in diseases such as **multiple sclerosis**. In this disease, the immune system is stimulated to react against the myelin sheath that surrounds the cells, a phenomenon called demyelination. Demyelination produces a malfunction in the transmission of impulses from nerve to nerve and from nerve to muscle.

Infection with the virus that causes hepatitis C is hindered by interferon via the binding to a site on human cells that is also used by the virus. Thus, the virus cannot enter and infect the host cell.

In the late 1980s, a large clinical trial conducted in the United States and Canada evaluated the influence of interferon beta-1b (Betaseron, marketed by Berlex) made in bacteria using genetic engineering technology. Specifically, the bacterium *Escherichia coli* contained a piece of genetic material (plasmid) that contains the gene coding for human beta interferon. The study was double-blind (neither the test participants or the researchers knew which person was receiving the real drug or a placebo). The two-year study demonstrated that those people receiving the interferon had fewer reappearances of the symptoms, and fewer nerves in the brain were damaged.

Betaseron was approved in 1993 by the U.S. Food and Drug Administration for use by people affected with multiple sclerosis. Avonex was approved in 1996 and Rebif in 2002.

Recommended dosage

Interferons are normally injected. They are not taken by mouth as the strong digestive enzymes of the stomach will degrade them.

For use in multiple sclerosis, interferon beta-1a is injected into the muscle (intramuscular injection), and beta-1b is injected just below the skin (subcutaneous injection). The injections are usually given every other day. The recommended dose for beta-1a and 1b is 0.03 mg and 0.25 mg, respectively. Initial doses of beta-1b should be far less (i.e., 0.0625 mg), with a gradual increase in dose over six weeks.

Precautions

Patients who have had **seizures** or who are at risk for a seizure should be closely monitored following the injection of interferon, as should those with heart disorders such as angina, congestive heart failure, or an irregular heartbeat.

It is not known if interferon can be expressed in breast milk. Concerned mothers may opt to cease breast-feeding while receiving interferon therapy.

Side effects

Interferon beta 1-a and 1-b commonly produce flu-like symptoms, including fever, chills, sweating, muscle aches, and tiredness. These side effects tend to diminish with time. Menstrual cycle changes have also been documented in a significant number of women.

Far less commonly, interferon beta 1-a and 1-b can produce suicidal feelings in someone who is already clinically depressed. Death of cells around an injection site (necrosis) can occur, as can swelling and bruising. Allergic reactions are possible. The massive and sometimes fatal allergic reaction termed anaphylaxis occurs rarely. Other side effects include liver and thyroid malfunction, and altered blood chemistry (fewer platelets and red and white blood cells).

Interactions

As of December 2003, drug interaction studies have not been conducted.

Resources

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National Multiple Sclerosis Society. 733 Third Avenue, New York, NY 10017. (800) 344-4867. <http://www.nationalmssociety.org>.

Brian Douglas Hoyle, PhD

Intestinal lipodystrophy *see* **Whipple's disease**

Intracranial cysts *see* **Arachnoid cysts**

J

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 hemispheres), causing irregular breathing and severe muscle weakness. Other features of the syndrome include jerky eye movements, abnormal balance and walking, and mental handicap. Additionally, 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.

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.

Causes and symptoms

Although the underlying genetic cause remains unknown, there have been numerous instances of siblings (brothers and sisters) 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 classified as an autosomal recessive disorder. Autosomal means that both males and females can have the condition. Recessive means that both parents carry 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% (one in four) 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.

The cerebellum is the second largest part of the brain. It is located just below the cerebrum, and is 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, muscles, 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 send an appropriate signal back. The effect is to either increase or decrease the function of different muscle groups, making 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

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.

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. The individuals's breathing alternates between deep rapid breathing (almost like panting) and periods of severe apnea (loss of breathing). This is usually noticeable at birth. The rate of respiration 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 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). The 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 that the in-

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.)*

fant 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 team

A pediatric **neurologist** usually sees children with Joubert syndrome. Physical, occupational, and speech and language therapists are important members of the treatment team.

Treatment

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 life span 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>.

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K

Kennedy's disease

Definition

Kennedy's disease is a rare genetic neurodegenerative disorder that affects the motor neurons (cells that are important for normal function of the brain and spinal cord). It is a progressive disorder that leads to increasing severity of motor dysfunction and subsequent deterioration of muscle strength, muscle tone, and motor coordination. It was first described by the American physician William R. Kennedy in 1966.

Description

As Kennedy's disease is a progressive neurodegenerative disorder, affected individuals have physical, mental, and emotional impacts. Physically, the neurological degenerative process results in muscle weakness and eventual muscle wasting that can affect the patient's ability to walk or move. Kennedy's disease is also called spinal bulbar muscular atrophy, or SBMA, because both the spinal and bulbar neurons are affected.

Demographics

Kennedy's Disease is inherited through the X chromosome, and since males only have one X chromosome inherited from their carrier mother, they are usually affected while females are usually carriers. Therefore, sons of carrier mothers will be affected and all her daughters have a 50% chance of being a carrier. Although affected males often have a low sperm count or are infertile, if they are capable of reproducing, all male children will be unaffected and all female children will be unaffected carriers. In some cases, women who are carriers also exhibit clinical symptoms, although they are generally less severe. Kennedy's disease is a rare disease, with only one in 50,000 males affected and no particular pattern among various races or ethnic groups.

Causes and symptoms

Symptoms do not usually develop until between the second and fourth decades of life, although an earlier (and a later) age of onset have been documented. Symptoms initially are mild and include **tremors** while stretching hands, muscle cramps after exertion, and fasciculations (visible muscle twitches). Muscle weakness often develops in the arms and legs, beginning usually in the shoulder or midsection. It is most noticeable in the legs and the arms. Breathing, swallowing, and talking are functions that require bulbar muscles controlled by motor nerves that communicate with the brain. The effects of bulbar muscle dysfunction can be manifested by slurred speech and dysphagia (swallowing difficulties). In later stages, patients often develop aspiration pneumonia (pneumonia caused by food and fluids traveling down the bronchial tubes instead of the trachea due to poor ability to swallow).

Kennedy's disease is caused by a trinucleotide repeat expansion in the androgen receptor gene. This means that three letters in the DNA alphabet (cytosine-adenine-guanine, or CAG) that are normally repeated 10–36 times expand to produce a larger repeat size of approximately a 40–62 repeated trinucleotide sequence. This sequence is unstable and can change from one generation to the next leading to further expansions. The specific mechanism explaining how this trinucleotide repeat expansion (which leads to an increased length in the protein it encodes) causes the disease is unknown.

Diagnosis

Patients with Kennedy's disease usually receive a definitive diagnosis in a clinical molecular genetics laboratory. This requires DNA extraction from blood, followed by testing the gene that causes Kennedy's disease for a mutation. Kennedy's disease can be misdiagnosed as **spinal muscular atrophy** and Lou Gehrig's disease due to similar symptoms displayed.

Key Terms

Dysphagia Difficulty swallowing.

Fasciculations Fine muscle tremors.

X-linked disorder A disorder resulting from a genetic mutation on the X chromosome. Usually, males, having only one X chromosome, are affected with X-linked disorders; females are usually carriers.

Treatment team

The treatment team caring for a patient with Kennedy's disease includes a **neurologist**, physical therapists, occupational therapists, gastroenterologists, and genetic counselors.

Treatment

Although research efforts are underway, currently there is no treatment for Kennedy's disease. Medical treatment is based on lessening the symptoms. Physical therapy is useful in reducing the side affects from the progressive muscle weakness.

Recovery and rehabilitation

In the absence of a cure, patients usually do not recover and the symptoms progress during their lifetime. Lifestyle changes may become necessary, especially late in the disease. These changes, in more severe cases, can include (but are not limited to) help eating, wheelchair access at home, and help with using the restroom and changing clothes.

Prognosis

Kennedy's disease is a neurodegenerative disorder that is slow in its progression. It is likely that individuals will become wheelchair bound during the later stages of the disease. Although individuals will have certain difficulties in motor function and may have special needs, the lifespan of affected individuals is not thought to be shortened.

Special concerns

Genetic counseling is important in this disorder since the presence of one affected offspring means that it is likely the disease gene was inherited and that there is a risk that there will be affected offspring in subsequent generations. The possibility of infertility due to low sperm count should also be discussed during the counseling, especially in cases that develop early. Also, gynecomastia (enlarged breasts) in males due to reduced virilization can also have psychosocial consideration and need to be addressed. Erectile dysfunction and/or testicular atrophy may also affect males.

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National Organization of Rare Disorders. PO Box 8923, New Fairfield, CT 06812-8925. (203) 746-6518 or (800) 999-6673; Fax: (203) 746-6481. orphan@rarediseases.org. <http://www.rarediseases.org>.

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Bryan Richard Cobb, PhD

Kinsbourne syndrome *see* **Opsoclonus myoclonus**

Klippel Feil syndrome

Definition

Klippel Feil syndrome is a rare congenital (present at birth) disorder in which there is abnormal fusion of some of the cervical (neck) vertebrae.

Description

People with Klippel Feil syndrome are often identified due to three major characteristics: a short neck, a low hairline, and restricted neck mobility due to the fused cervical vertebrae. Klippel Feil syndrome can occur as a lone defect, or in association with other abnormalities, including scoliosis (curved spine), **spina bifida** (a birth defect

involving the spinal column and cord), cleft palate, and a variety of defects involving the ribs, urinary tract, kidneys, heart, muscles, brain, and skeleton. Facial defects and problems with hearing and breathing may also occur in Klippel Feil syndrome.

Klippel Feil syndrome has been organized into three basic types. In type I, all of the cervical and upper thoracic vertebrae are fused together into one block. In type II, one or two pairs of cervical vertebrae are fused together. In type III, there is lower thoracic or lumbar fusion as well as cervical fusion.

Demographics

Although not a lot of data has been collected regarding how often Klippel Feil syndrome occurs, the information available suggests that the incidence of this condition ranges from about one in 42,400 births to about three in 700 births. Boys are slightly more likely than girls to have this condition (1.5:1).

Causes and symptoms

Klippel Feil syndrome is believed to occur during very early fetal development, when the cervical vertebrae do not segment normally. The exact mechanism that causes the defect is unkown.

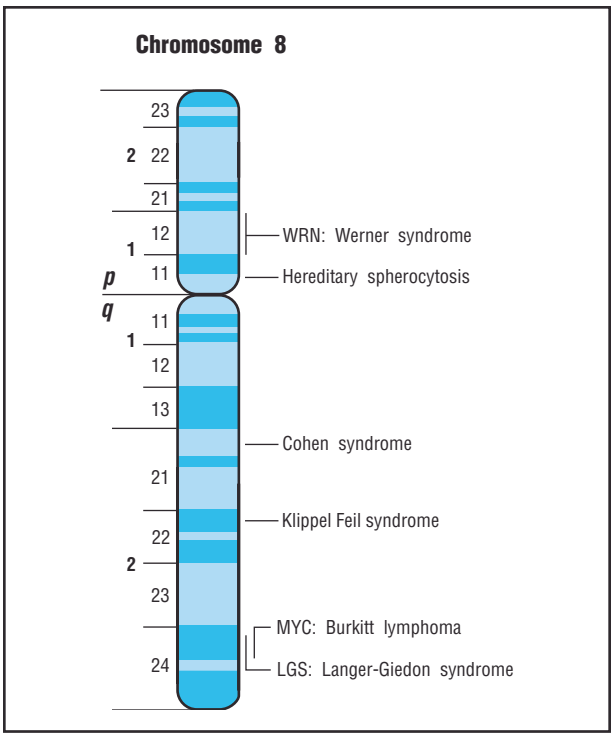
Although most cases of Klippel Feil syndrome occur spontaneously, there have been a few reports of Klippel Feil syndrome that showed a pattern of inheritance within a family. In some cases, maternal alcoholism and subsequent fetal alcohol syndrome seems to be associated with Klippel Feil syndrome.

Many individuals with Klippel Feil syndrome have no symptoms. Individuals who have more minimal degrees of fusion can live completely normally and partake in all activities. They may never become aware that they have any abnormality at all. Individuals with more severe degrees of fusion will be obviously impaired in terms of their neck mobility. Some individuals will suffer from torticollis or wry neck, a condition in which the neck muscles pull the neck to one side. If the spinal cord is constricted by the abnormal vertebrae, neurological symptoms (weakness, numbness, tingling) may result.

A full 30–40% of all individuals with Klippel Feil syndrome will have significant structural abnormalities of their urinary tract. These often lead to chronic kidney infections (pyelonephritis), and a high risk of kidney failure.

Diagnosis

Diagnosis is usually established through a variety of imaging techniques, such as plain x-ray films of the neck and spine, **CT scan**, or **MRI**. Other diagnostic studies



Klippel Feil syndrome, on chromosome 8. *(Gale Group.)*

should be done to uncover associated defects. For example, children diagnosed with Klippel Feil syndrome should have a thorough hearing screening performed, due to the high risk of associated hearing problems. The cardiovascular system and the kidneys and urinary tract may also require evaluation.

Treatment team

The treatment team will depend on the degree of disability brought on by the vertebral defects, and the presence of any associated problems. In more mildly affected individuals, a pediatrician and orthopedic surgeon may collaborate to achieve a diagnosis. In more severely affected individuals, a **neurologist** or neurosurgeon may need to be involved as well. Depending on what other body systems are involved, a cardiologist, nephrologist, urologist, and orofacial surgeon may be consulted. An audiologist can consult about hearing issues. A physical therapist and occupational therapist can be very helpful in helping with issues of mobility and ability to tend to activities of daily living.

Treatment

More mildly affected individuals will require no treatment. Other individuals may need surgery to improve cervical stability, correct scoliosis, and improve any

Key Terms

Cervical Referring to the neck. Cervical vertebrae are the first seven bones of the spine.

Cleft palate A birth defect in which the roof of the mouth (palate) has an abnormal opening (cleft).

Congenital A condition that is present at birth.

Lumbar Referring to the lower back. There are five lumbar vertebrae.

Spina bifida A birth defect in which there is an abnormal opening of the spinal column. The disability caused by this opening depends on the degree of the opening, and whether there are associated abnormalities of the development of the spinal cord and nerves.

Thoracic Referring to the area of the torso commonly called the chest. There are 12 thoracic vertebrae.

Torticollis A condition in which the muscles of the neck are abnormally contracted, pulling the neck off to one side.

Vertebrae The stacked bones of the spinal column. There are seven cervical vertebrae, twelve thoracic vertebrae, five lumbar vertebrae, five sacral vertebrae (normally fused into the sacrum in adults), and four coccygeal vertebrae (normally fused into the coccyx in adults).

constriction of the spinal cord. Depending on the degree of scoliosis, a brace may be helpful.

Physical therapy can be very helpful in order to improve strength and mobility. Occupational therapy can help more severely restricted individuals learn how to best perform activities of daily living, despite the limitations of their condition.

Prognosis

The prognosis is excellent for very mildly affected people with Klippel Feil syndrome. With careful medical attention, the prognosis can be good for more severely affected individuals as well.

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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.

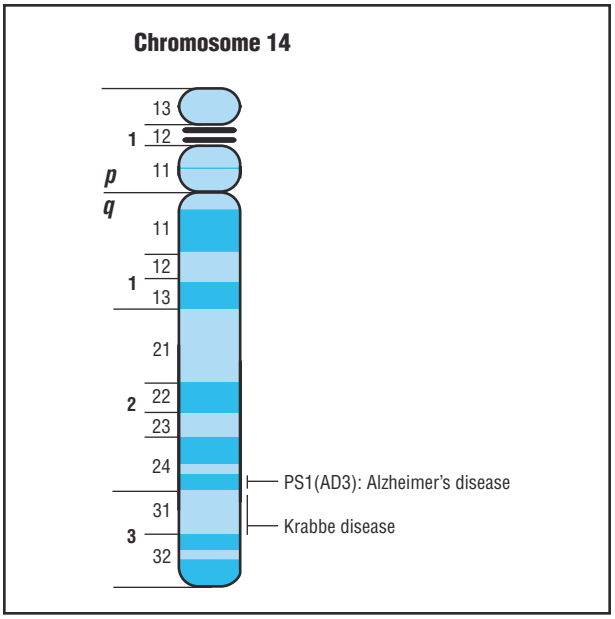
Description

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.

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



Krabbe disease, on chromosome 14. *(Gale Group.)*

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.

Causes and symptoms

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.

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.

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 juvenile 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 5% 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 computed 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.

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.

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 terminating an affected pregnancy.

Treatment team

The treatment team for a child with Krabbe disease should include a **neurologist**, general surgeon to place certain types of feeding tubes, and a hematologist if bone marrow or stem cell transplants are being considered. Physical and occupational therapists can help plan for daily care of the child and provide exercises to decrease muscle rigidity.

Treatment

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
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Kugelberg-Welander disease *see* **Spinal muscular atrophy**

Kuru

Definition

Kuru is the name of a progressively disabling and ultimately fatal brain infection caused by a unique protein particle called a prion.

Key Terms

Classic Creutzfeldt-Jakob disease A rare, progressive neurological disease that is believed to be transmitted via an abnormal protein called a prion.

Fatal familial insomnia A rare, progressive neurological disease that is believed to be transmitted via an abnormal protein called a prion.

Gerstmann-Sträussler-Scheinker syndrome A rare, progressive neurological disease that is believed to be transmitted via an abnormal protein called a prion.

New variant Creutzfeldt-Jakob disease A more newly identified type of Creutzfeldt-Jakob disease that has been traced to the ingestion of beef from cows infected with bovine spongiform encephalopathy. Known in the popular press as Mad Cow Disease.

Transmissible spongiform encephalopathy A term that refers to a group of disease, including kuru, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and new variant Creutzfeldt-Jakob disease. These diseases share a common origin as prion diseases, caused by abnormal proteins that accumulate within the brain and destroy brain tissue, leaving spongy holes.

Description

Kuru was first described in a specific tribal group in Papua, New Guinea. The word "kuru" means "to shake or tremble" in this tribal group's language. Individuals in New Guinea are believed to have acquired the infection through a cannibalistic ritual involving the blood and brains of deceased tribal members.

Because infection with kuru may occur years or decades before the advent of actual symptoms of the disease, it belongs to a group of diseases originally known as slow virus infections. Currently, slow virus infections are classed together as transmissible spongiform encephalopathies (TSE). TSEs include kuru, **Creutzfeldt-Jakob disease**, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia. The TSE new variant called Creutzfeldt-Jakob disease (also known colloquially as "Mad Cow Disease") has received a great deal of public attention. The TSEs, including kuru, involve abnormal clumps of protein that accumulate throughout the brain, destroying brain tissue and leaving spongy holes.

Demographics

Kuru reached epidemic proportions among tribal members in the 1950s. Since the practice of cannibalism was halted, the disease has essentially disappeared. Some sources suggest that as few as zero to 10 cases of kuru are diagnosed each year.

Causes and symptoms

Kuru is caused by an infectious protein particle called a prion, which stands for proteinaceous infectious particle. A prion is similar to a virus, except that it lacks any nucleic acid, which prevents it from reproducing. Prions are abnormal versions of proteins that are found in the membranes of normal cells. These abnormal proteins can be passed directly to individuals through the ingestion of prion-infected tissue or when open sores on the recipient's skin are exposed to prion-infected tissue. In addition to being transmissible (as are other infectious agents like viruses or bacteria), prions are unique because they can also be acquired through genetic inheritance.

Symptoms of kuru tend to begin in later middle age, years or decades after the prion was actually acquired. Early symptoms include lack of energy, intense **fatigue**, **headache**, weight loss, joint **pain**, difficulty walking, twitchy muscles, personality changes, mood swings, memory problems, and bizarre behavior. As the disease progresses, the individual experiences stiff muscles, involuntary movements, problems talking, hallucinations, increased confusion, blindness, and sometimes **dementia**. Death often occurs within three months to two years of the initial symptoms.

Diagnosis

Diagnosis is arrived at through characteristic abnormalities found on the electroencephalogram (EEG), a test of brain waves and electricity. Seventy-five percent of individuals with kuru will display these specific abnormalities on EEG. **MRI** studies and biopsies (tissue samples) from the brain may also show changes that are characteristic of slow virus infection.

Treatment team

Diagnosis of slow virus infection is usually made by a **neurologist**.

Treatment

There are no available treatments for kuru. It is relentlessly progressive, incurable, and fatal. Supportive care for the patient and his or her family is the only treatment.

Prognosis

Kuru is always fatal.

Resources

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Rosalyn Carson-DeWitt, MD

L

Lambert-Eaton myasthenic syndrome

Definition

Lambert-Eaton myasthenic syndrome is an autoimmune disease that causes muscle weakness and easy fatigability, particularly in the pelvic muscles and thighs.

Description

In order to understand Lambert-Eaton myasthenic syndrome, it's important to have some understanding of the basics of nerve transmission and stimulation of muscle movement. Nerve impulses in the body are electrical and chemical currents that travel down a nerve fiber. When they reach the end of that nerve fiber, they trigger the release of the neurotransmitter chemical acetylcholine. Acetycholine must cross a tiny gap called the synapse in order to stimulate the muscle to contract. The nerves leading to the synapse or synaptic junction are called the presynaptic nerves.

In the case of Lambert-Eaton myasthenic syndrome, the body's immune system accidentally treats specialized areas (called calcium channels) along the presynaptic nerve as if they were foreign. These calcium channels are vital to the presynaptic nerve's ability to release acetylcholine into the synaptic junction. The immune cells attack the calcium channels as they would attack an invader such as a virus or bacteria. When the calcium channels are damaged, the release of acetylcholine into the synapse is compromised, resulting in less acetycholine being available to stimulate the muscle.

Lambert-Eaton myasthenic syndrome has a very strong association with cancer, particularly small-cell lung cancer. The symptoms of Lambert-Eaton myasthenic syndrome often occur prior to diagnosis with lung cancer. In fact, about two-thirds of all people with Lambert-Eaton myasthenic syndrome will be diagnosed with some type of cancer, usually small-cell lung cancer, within two to three years of the onset of their initial symptoms of Lambert-Eaton myasthenic syndrome. Other types of cancer associated with Lambert-Eaton myasthenic syndrome include non-small-cell lung cancer; lymphosarcoma; malignant thymoma; and carcinoma of the breast, stomach, colon, prostate, bladder, kidney, or gallbladder.

Because of the strong connection between Lambert-Eaton myasthenic syndrome and cancer, it is sometimes considered to be a paraneoplastic syndrome (a syndrome in which substances produced by cancer cells prompt abnormalities in the body at a distance from the actual site of the malignancy). In the case of Lambert-Eaton myasthenic syndrome, it is thought that the immune system produces immune cells in response to the presence of early cancer cells. These immune cells cross-react with the calcium channels on nerve cells, resulting in the symptoms of Lambert-Eaton myasthenic syndrome.

Demographics

Lambert-Eaton myasthenic syndrome is very rare, only striking about five people per every one million annually. At any one time, there are thought to be about 400 people in the United States suffering from Lambert-Eaton myasthenic syndrome. Twice as many men than women are affected, and the average age at diagnosis is about 60 years of age. Family history of Lambert-Eaton myasthenic syndrome is a known risk factor for development of the disease, as is a personal history of smoking.

Causes and symptoms

In Lambert-Eaton myasthenic syndrome, the immune system accidentally attacks the calcium channels of the presynaptic nerve cells, preventing normal release of the neurotransmitter acetylcholine into the synaptic junction, and compromising the flow of nervous information between the presynaptic and postsynaptic nerves.

Symptoms of Lambert-Eaton myasthenic syndrome begin with weakness and some achiness and tenderness in

Key Terms

Acetylcholine A neurotransmitter that carries a signal from the nerve fiber to the muscle to direct contraction.

Autoimmune Refers to a disease in which the body's immune system is directed against parts of the body itself, causing damage.

Paraneoplastic syndrome A syndrome in which substances produced by cancer cells prompt abnormalities in the body at a distance from the actual site of the malignancy.

Plasmapheresis A procedure in which harmful cells are removed from the blood plasma.

Presynaptic Before the synapse.

Ptosis Eyelid droop.

Synapse The gap, cleft, or junction between nerve cells or between a nerve cell and the muscle fiber.

the thigh and pelvic muscles. The upper arms may also exhibit some weakness. Due to the weak thigh and upper arm muscles, the patient's walk may have a waddling appearance, and it may be difficult for the patient to lift his or her arms above the head. **Exercise** may initially improve the weakness, but the weakness may become more pronounced as exercise continues. Eyelids may droop (ptosis). Many patients notice uncomfortably dry eyes, mouth, and skin. Patients may develop difficulty chewing, swallowing, and/or speaking, as well as constipation, sudden drops in blood pressure when rising from lying down to sitting or standing, abnormalities of sweating, and erectile problems in men.

Diagnosis

Lambert-Eaton myasthenic syndrome may be diagnosed by demonstrating the presence of specific antibodies in the blood that are directed against aspects of the presynaptic nerve, such as the calcium channels. Studies of nerve conduction and muscle function will reveal a variety of abnormalities. When Lambert-Eaton myasthenic syndrome is diagnosed, a search should also be done for the presence of a previously undiagnosed cancer, especially small-cell lung cancer.

Treatment team

Patients with Lambert-Eaton myasthenic syndrome should be examined and then treated by both a **neurologist** and an appropriate cancer specialist (oncologist).

Treatment

When a cancer is identified, the first concern should be the appropriate treatment of that malignancy. Secondarily, treatment of Lambert-Eaton myasthenic syndrome may include medications to improve transmission of nerve impulses across the synaptic junction (such as pyridostigmine bromide) as well as immunosuppressant agents (such as corticosteroids, azathioprine, cyclosporine, or intravenous immungoglobulin) to decrease the immune system's ability to further damage the presynaptic nerves. A treatment called plasmapheresis may help remove damaging immune cells from the blood.

Prognosis

The prognosis of individuals with Lambert-Eaton myasthenic syndrome varies widely. In fact, the most important element of prognosis involves the prognosis associated with any existing cancer.

Special concerns

Patients who develop Lambert-Eaton myasthenic syndrome should be thoroughly screened for the presence of a previously undetected cancer. If none is found, the patient should undergo regularly scheduled surveillance to monitor for the subsequent development of a malignancy.

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Rosalyn Carson-DeWitt, MD

Laminectomy

Definition

Laminectomy is a surgical procedure that entails opening the spinal column to treat **nerve compression** in the spinal cord.

Purpose

Laminectomy may be performed when an abnormality causes spinal nerve root compression that causes leg or arm **pain** that limits activity. Numbness or weakness in hands, arms, legs, or feet, and problems controlling bowel movements or urination are indication for surgical consideration.

Precautions

Before surgery, patients should refrain from medications and activities as deemed appropriate by the anesthesiologist and surgeon. These precautions can include avoidance of blood thinners such as Advil or Motrin. After surgery, there can be serious complications. Patients should go to a hospital emergency department if they develop loss of bladder or bowel control (or if they cannot urinate); if they are unable to move their legs (indicates nerve or spinal cord compression); experience sudden shortness of breath (possible blood clot in the lungs causing a condition called pulmonary embolism); or if they develop pneumonia or some other heart/lung problem.

Description

Laminectomy can also be called back surgery, disc surgery, or discectomy. Laminectomy is a surgical procedure used in an attempt to treat **back pain**. The most common site for back pain is usually the lower back, or lumbar spine. A disc acts like a shock absorber for the spinal cord, which contains nerves that exit from foramina, or holes in a disc. A disc (or vertebral disc) is made up of a tough outer ring of cartilage with an inner sac containing a jellylike substance called the nucleus pulposis. When a disc herniates, the jellylike substance pushes through and causes the harder outer ring (annulus fibrosus) to compress a nerve root in the spinal cord. Herniation of a vertebral disc can cause varying degrees of pain. Approximately 25% of persons who have back pain have a herniated disc, causing a condition called **sciatica**, causing pain to be felt through the buttocks into one or both legs. The most serious compression disorder in the spinal cord is a condition called the cauda equine syndrome. The cauda equine is an area in the spinal cord where nerve roots of all spinal nerves are located. Cauda equine syndrome is a serious condition that may cause loss of all nerve function below the area of compression, which can cause loss of bladder and bowel control. Such a condition is a surgical emergency and immediate decompression is required without delay.

Key Terms

Annulus fibrosus A fibrous and cartilage ring that forms the circumference of a vertebrae.

Lamina Flat plates of bone that form part of a vertebrae.

Nucleus pulposus Central core of a vertebrae.

Typically, conservative medical therapy is attempted for the treatment of a herniated disc. Surgery should be considered when recurrent attacks of pain cause interference with work or daily activities. The decision for surgery is indicated for chronic cases and should be made jointly between the patient and surgeon. Severe deficit can cause patients to have loss of nerve function, causing movement deficits in affected areas. Back pain is more common in men than women and more common in Caucasians than among other racial groups. Back pain results in more lost work than any other medical condition or disability. As a disorder, back pain has been documented through the ages since the first discussions date more than 3,500 years ago in ancient Egyptian writings.

Laminectomy as a procedure is not exclusive to a herniated disc. Laminectomy is used for metastatic tumor invasion of the spinal cord (which causes compression), and for narrowing of the spinal cord (a condition called spinal stenosis.)

In the United States, approximately 450 cases of herniated disc per 100,000 require surgery. Men are two times more likely to have back surgery as women and the average age for surgery is 40–45 years. More than 95% of all laminectomies are performed on the fourth and fifth lumbar vertebrae (lumbar laminectomy). Back pain is ranked second (behind the common cold) among the leading causes of missed workdays. Approximately one in five Americans, typically 45–64 years of age, will experience back pain. Each year, an estimated 13 million people will see their primary care practitioner for chronic back pain. Approximately 2.4 million Americans are chronically disabled from back pain, and another 2.4 million are temporarily disabled.

Description of surgical procedure

Typically, the patient is placed in the kneeling position to reduce abdominal weight on the spine. The surgeon makes a straight incision over the affected vertebrae (can

be anywhere in the spinal cord) extending to the bony arches of the vertebrae (lamina.) The surgical goal is to completely expose the involved nerve root. To expose the nerve root(s), the surgeon removes the ligament joining the vertebrae along all or part of the lamina. The nerve root is pulled back toward the center of the spinal column, and all or part of the disc is removed. Muscle is placed to protect the nerve root(s) and the incision is closed.

Preparation

Weeks before surgery, the surgeon (a neurosurgeon or orthopedic spine surgeon) will make a general medical assessment and establish fitness for surgery. Days before the procedure, an assessment with the anesthesiologist is necessary to discuss anesthetic options during surgery: whether to use general or spinal anesthesia. A careful history should include information about all prescription and over-the-counter (OTC) medications. Anti-inflammatory agents such as aspirin or ibuprofen (Advil, Motrin) should be stopped several days before surgery. If the patient smokes, smoking should stop at least several days before surgery. Typically, imaging studies such as x rays or **magnetic resonance imaging (MRI)**, heart tracing studies (ECG), and routine blood work are performed before surgery. No food is permitted after midnight before surgery.

Anyone undergoing surgery that lasts more than two hours may be at risk of developing a blood clot, and administering heparin (an anticoagulant) may reduce the possibility of this complication. If heparin is administered to a patient receiving laminectomy, careful monitoring and blood tests are necessary to ensure that the blood is not excessively thinned, which can cause bleeding.

Aftercare

During recovery, patients will lie on a side or supine (back). There may be pain and patients will typically wear compression stockings to avoid blood-clot formation, a complication that can occur after surgery. There may be a catheter placed in the bladder to collect and measure urine output. Pain medications will be administered, and sometimes the surgeon will allow patient-controlled analgesia (PCA) with a pump that enables patients to self-deliver pain medications. Walking is encouraged hours after surgery and breathing exercises may be performed to avoid loss of air in a lung or pneumonia. It is advised to bend at the hip, not at the waist, and to avoid twisting at the shoulders or hips. The first few days after surgery may pose problems with sleeping, especially if therapeutic positions are different from normal sleeping positions. Different types of pillow positioning may be helpful (especially under the neck and knees.) To make getting out of bed easier, the patient should move the body as a unit, tighten the abdominal muscles, and roll to the side or edge of the bed and press down with arms on the bed to help raise the body while concurrently and carefully swinging legs to the floor. Typically, the surgeon will schedule an appointment with postoperative patients about one week after the procedure. At about seven days, the surgeon will remove any sutures (stitches) or staples that were placed during operation. Follow-up with the personal primary care practitioner occurs within the first month after operation.

In-home recovery

Recovery can be easier at home if patients have someone to drive for them for one or two weeks after surgery. Short, frequent walks each day may help speed recovery. Return to work is possible within one to two weeks for sedentary work, but may take more time (two to four months) if employment is strenuous with physical demands. Driving is usually not advised for one to two weeks after surgery, since postoperative medications for pain may cause drowsiness as a side effect, which can impair driving ability.

Risks

After laminectomy (postoperative), there is a risk of developing complications that can include blood clots, infection, excessive bleeding, worsening of back pain, nerve damage, or spinal fluid leak. It is possible to experience drainage at the incision site, redness at the incision area, fever (over 100.4° F), or increasing pain and numbness in arms, legs, back, or buttocks. Additionally, patients may experience inability to urinate, loss of bladder or bowel control, a severe **headache**, or redness, swelling, or pain in one extremity. If any of these signs or symptoms appears, patients are advised to immediately call the surgeon. If the sutures or staples come out, or if the bandage becomes soaked with blood, a call to the surgeon is necessary without delay.

Normal results

Some studies indicate that surgery provides better results than observation alone after one follow-up visit to the physician. However, other studies reveal that there is no statistical difference between conservative medical treatment or surgery 10 years after surgery.

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ORGANIZATIONS

The American Back Society. 2647 International Boulevard, Suite 401, Oakland, CA 94601. (510) 536-9929; Fax: (510) 536-1812. info@americanbacksoc.org. <http://www.americanbacksoc.org>.

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Lamotrigine

Key Terms

Bipolar disorder A psychiatric disorder marked by alternating episodes of mania and depression. Also called bipolar illness, manic-depressive illness.

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Neurotransmitter A chemical that is released during a nerve impulse that transmits information from one nerve cell to another.

Seizure A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain, resulting in abnormal body movements or behaviors.

Definition

Lamotrigine is an anticonvulsant medication used in the treatment of **epilepsy**. Epilepsy is a neurological disorder in which excessive surges of electrical energy are emitted in the brain, causing **seizures**. Lamotrigine is usually reserved for difficult-to-control seizures that have not responded to other anticonvulsant medications. In psychiatry, lamotrigine is also indicated in the treatment of bipolar disorder (manic-depression).

Purpose

While lamotrigine controls seizures associated with epilepsy, there is no known cure for the disorder. Although the precise mechanism by which lamotrigine exerts its therapeutic effect is unknown, lamotrigine is thought to act at sodium channels in the neuron (nerve cell) to reduce the amount of excitatory **neurotransmitters** that the nerve cell releases. Neurotransmitters are chemicals that aid in the transfer of nerve impulses from one nerve junction to the next. With decreased levels of these neurotransmitters, the electrical activity in the brain that triggers seizures is reduced.

In the treatment of bipolar disorders, lamotrigine's effect upon neurochemicals stabilizes mood, preventing sudden, unpredictable, and severe episodes of mania and **depression**.

Description

For the treatment of epilepsy-related seizures, lamotrigine may be used alone or in combination with other anti-epileptic drugs (AEDs) or **anticonvulsants**. In the United States, lamotrigine is sold under the brand name Lamictal.

Recommended dosage

Lamotrigine is taken orally, in either tablet or chewable form. Chewable tablets may be dispersed into a liquid solution, according to the prescribing physician's instructions. Lamotrigine is prescribed by physicians in varying daily dosages, usually ranging 200–900 mg per day divided into two doses.

Beginning any course of treatment that includes lamotrigine requires a gradual dose-increasing regimen. The safety and effectiveness of lamotrigine in children under age 18 have not been proven; therefore, the drug is seldom used in children. Adults typically take an initial dose for the first two weeks that is slowly increased over time. It may take several weeks to realize the full benefits of lamotrigine, especially in those patients taking lamotrigine for the treatment of bipolar disorders.

A double dose of lamotrigine should not be taken. If a dose is missed, it should be taken as soon as possible. However, if it is within four hours of the next dose, then the missed dose should be skipped. When ending a course of treatment that includes lamotrigine, physicians typically direct patients to gradually taper down their daily dosages over a period of several weeks. Stopping the medicine suddenly may severely alter mood or cause seizures to occur, even in patients taking lamotrigine for the treatment of bipolar disorders.

Precautions

A physician should be consulted before taking lamotrigine with certain non-prescription medications. Patients should avoid alcohol and CNS depressants (medications that make one drowsy or tired, such as antihistimines, sleep medications, and some **pain** medications), while taking lamotrigine. Lamotrigine can exacerbate the side effects of alcohol and some other medications. Alcohol may also increase the risk or frequency of seizures.

Lamotrigine may not be suitable for persons with a history of liver or kidney disease, depressed renal function,

mental illness, anemia, high blood pressure, angina (chest pain), or irregular heartbeats and other heart problems. Before beginning treatment with lamotrigine, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are nursing, pregnant, or plan to become pregnant.

Lamotrigine's safety during pregnancy has not been established. Persons taking lamotrigine (and other AEDs or anticonvulsants) should be aware that many AEDs and anticonvulsants cause birth defects. Patients who become pregnant while taking any AED or anticonvulsants should contact their physician immediately.

Side effects

Lamotrigine is generally well tolerated. However, in some patients, lamotrigine may produce some of the traditionally mild side effects associated with anticonvulsants. **Headache**, nausea, and unusual tiredness and weakness are the most frequently reported side effects of anticonvulsants. Other possible side effects that do not usually require medical attention include:

- mild coordination problems
- mild dizziness
- abdominal pain
- sinus pain
- sleepiness or sleeplessness
- diarrhea or constipation
- heartburn or indigestion
- aching joints and muscles or chills
- unpleasant taste in mouth or dry mouth

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication. However, if any symptoms persist or become too uncomfortable, the prescribing physician should be consulted.

Other, uncommon side effects of lamotrigine can be serious and may indicate an allergic reaction. Severe and potentially life-threatening rashes have occurred during treatment with lamotrigine, occurring approximately once in every 1,000 persons who take the drug. In the unusual event that this rash develops, it normally occurs within the first eight weeks of treatment. A patient taking lamotrigine who experiences any of the following symptoms should contact a physician immediately:

- rash or bluish patches on the skin
- sores in the mouth or around the eyes
- depression or suicidal thoughts
- mood or mental changes, including excessive fear, anxiety, hostility
- general loss of motor skills
- persistent lack of appetite
- altered vision
- difficulty breathing
- chest pain or irregular heartbeat
- faintness or loss of consciousness
- persistent, severe headaches
- persistent fever or pain

Interactions

Lamotrigine may have negative interactions with some antacids, antihistamines, antidepressants, antibiotics, and monoamine oxidase inhibitors (MAOIs). Other medications such as HIV protease inhibitors (indinavir), ritonavir (Norvir), ipratropium (Atrovent), isoniazid, **phenobarbital** (Luminal, Solfoton), nefazodone, metronidazole, **acetazolamide** (Diamox), propranolol (Inderal), rifampin (Rifadin, Rimactane), and warfarin may also adversely react with lamotrigine. Oral contraceptives (birth control pills) may decrease the amount of lamotrigine absorbed by the body.

Lamotrigine may be used with other seizure prevention medications, if advised by a physician.

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ORGANIZATIONS

Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. <http://www.aesnet.org>.

Adrienne Wilmoth Lerner

Lateral femoral cutaneous nerve entrapment

see **Meralgia paresthetica**

Learning disorders

Definition

Learning disorders (LD) refer to a significant deficit in learning due to a person's inability to interpret what is seen and heard, or to link information from different parts of the brain.

Description

Academic deficiency is frequently associated with neurologic and psychological disorders. Severe academic problems may occur as a primary disorder of learning. Learning disorders can be classified in three major types: disorder of written expression (DWE); reading disorder (RD); and mathematics disorder (MD). The description of learning disorders corresponds to the educational legal designation of learning disabilities. Learning disabilities are legally defined by Public Law in a law called the Individuals with Disabilities Education Act, or IDEA. The IDEA defines a learning disability as a disorder in written or spoken language that results in an imperfect ability to listen, think, read, spell, write, or do mathematics. The act excludes persons who have learning impairments that are solely due to hearing problems, visual problems, motor problems, **mental retardation**, or due to environmental deprivation. The rules and related laws of IDEA stipulate that children with LD are entitled to free education and special services. A fourth category of LD has also been established for an LD that does not fulfill all the criteria (called an LD not otherwise specified.) Age of onset of LD is closely related to clinical presentation. Most cases of LD can be detected between preschool and second grade. Typically, onset of LD before first grade, often demonstrates developmental delay in learning new concepts at home, or as a delay in performance in school (delay is observed relative to other children and is observed by school officials). If the onset of LD occurs in early grade school (first or second grade), then observations typically include slow learning and difficulty completing and mastering schoolwork which often results in poor grades.

Demographics

LD occurs in approximately 5% to 10% of the population of which about 50% are classified as reading disorder. The remaining 50% of LD falls under the categories of disorder of written expression, mathematics disorder or atypical LD. LD is more common in males than females by 2:1 or 4:1 ratio. Children with LD have an increased risk for emotional behavioral problems and comorbidity (50% of the 1.6 million children with **attention-deficit hyperactivity disorder** [ADHD] have an LD). Approximately 2% to 8% of elementary school children have reading disorder (dyslexia). Speech disorder occurs in approximately 10% of children younger than 8 years of age. ADHD is a comorbid condition that occurs in approximately four million school-aged children (20% of them are unable to focus their attention to required tasks in school and at home).

Key Terms

Algorithms A sequence of steps designed to calculate or determine a task.

Phoneme A discrete unit of a language that corresponds to a similar discrete unit of speech sound.

Phonics A system to teach reading by teaching the speech sounds associated with single letters, letter combinations, and syllables.

Rote learning Learning by means of repitition and memorization, usually without significant understanding of the concepts involved.

Causes and symptoms

Reading Disorder

The cause of reading disorder is underactivity in the left superior posterior temporal lobe (planum temporale). Research using functional and structural neuroimaging techniques, demonstrates that this underactivity is evident during reading tasks. It is believed that the planum temporale is a region that is important for phonologic processing. Genetic studies reveal that there is a higher concordance rate for RD in identical (71%) than fraternal (49%) twins. Additionally, heritability of RD may be more than 50% especially in a disorder with a focal deficit in phonologic processing (phonologic dyslexia). Some genetic investigations have identified possible genes for RD, located on chromosome six and 15. Modern research techniques have demonstrated that RD is the result of brain deficits in processing sound units and sound-symbol relationships.

Most of the persons diagnosed with reading disorder (RD) have average or higher intelligence. RD is considered synonymous with **dyslexia**, since spelling and reading are related. Persons with RD often have deficits with spelling. Affected individuals have difficulty with phonologic processing. This means that affected persons have deficits in the process of identifying and manipulating individual sounds (phonemes) within larger sound units (morphemes and words.) Symptoms usually appear before early grade school. Patients cannot translate a visual stimulus (letters) into a meaningful blend of sounds (i.e. they

have deficits in phonics). Reading is slower and more mechanical even with treatment. Typically, reading takes more effort in affected patients, often requiring intense concentration, especially on the pronunciation and identification of individual words. The increased concentration required during reading can impair the person's attention ability, causing mental fatigue, attention problems (less attention available for comprehension and memory). Sometimes, but not often, children may have visualization-comprehension or memory deficits causing RD. Persons with visualization-comprehension weakness often exhibit difficulty visualizing what is being read. The cause of visualization-comprehension weakness occurs because of deficits in visual organization (nonverbal skills.) This is a vital deficit since reading comprehension is based on some visualization (nonverbal skills.) However, in the majority of affected children with RD it is the deficits in phonologic processing (processing phonemes within morphemes and words) that are responsible for difficulty with comprehension or memory.

Mathematics Disorder

The cause of mathematics disorder (MD) is thought to be due to a nonverbal weakness. MD could take various forms and therefore the causes also change. There may be deficits visualizing and visually organizing mathematical concepts and manipulations. Some patients may have short-term or working memory deficits which can interfere with processing mathematical calculations. The cause of MD can be linked to a larger atypical LD.

The symptoms of MD can vary. Patients can exhibit dyscalculia or acalculia (deficits in mathematical calculation). Dyscalculia patients may over-rely on memory and tangible aids, because they have deficits to mentally calculate arithmetic manipulations. Symptoms in some patients can include deficits in memory (short term and working memory or deficits in visual organization or mathematical concepts).

Disorder of Written Expression

The cause of the disorder of written expression in some persons may be due to deficits in visual-motor integration and motor coordination. Most causes of DWE occur because there are deficits in the brain concerning information translation from auditory-oral modality to visual-written modality. The cause of this deficit is unknown.

Patients often exhibit spelling deficits that include problems with punctuation, grammar, and development of ideas during writing. Writing samples from persons with DWE are typically brief, simple, or may be difficult to comprehend because of grammar and punctuation errors. Patients with visual-motor deficits write with so much care that they often lose track of ideas and thoughts. If motor coordination is the only cause then symptoms may be classified more appropriately as a motor skills disorder not a DWE. Typically symptoms are not apparent until the third or fourth grade, when academic exercises demand development of ideas.

Diagnosis

The diagnosis of LD can be made if there is significant discrepancy between intelligence test scores (raw ability to learn) and achievement test score (actual learning achievement). However, the diagnosis can be a complex process since there is no universal agreement concerning the magnitude of discrepancy between test scores, nor is there a consensus concerning which test scores should be analyzed to obtain a statistical analysis of discrepancy. Tests should be administered to establish that low intelligence alone is not the cause of underachievement (i.e. children with mental retardation are not diagnosed with LDs.) There are several psychological tests that separately measure intelligence (i.e. Wechsler Intelligence Scale for Children) and achievement (Kaufman Test of Educational Achievement, K-TEA).

Treatment Team

The treatment team typically includes school counselors, education specialists, specialists in learning disorders, school psychologists or clinical psychologists (with advanced clinical training in administration and interpretation of psychological tests (psychometrics). Tests for achievement and intelligence should be administered and interpreted by a clinical psychologist or a school psychologist. Only a duly licensed or certified clinical or school psychologist can administer the recommended psychological tests. A full written report of results and interpretation of results is typically prepared and submitted to concerned persons.

Treatment

Before treatment is initiated, a very comprehensive evaluation is necessary with standardized achievement and intelligence tests.

Treatment for RD-affected persons involves a plan that provides intensive tutoring to develop phonologic processing and fluent word reading with treatment objectives that emphasize comprehension. There are several treatment approaches (Gillingham-Stillman Approach, Fernald-Keller Approach or Lindamood-Bell Reading Program) that provide intensive phonic practice and phonic associations with sensory integration or mnemonic strategies to remember letter-sound blends and relationships.

Treatment for MD can vary widely since MD can have a variety of causes and presentations. The treatment program is typically highly individualized and specific to enhance and expand upon strengths to improve weaknesses and math errors. Sometimes analogies are utilized to demonstrate abstract concepts and to build upon concepts (concrete learning) until the concept becomes understood or mastered. Flash cards and practice drills can help to memorize simple mathematical operations such as multiplication tables. MD due to visual-organization deficits can be treated with visualization techniques to improve math errors.

Treatment for DWE can involve interventions that help to improve written expression caused by a deficit in the expressive task of writing. There are several treatment plans that include writing in more "natural environments" (i.e. encourages keeping a diary or making "lists"), writing notes and outlines before attempting writing prose, and talking-to-writing progression. The talking-to-writing progression approach initially involves the affected child taking the role of dictating while another person writes for the child. As the treatments progress, the roles are gradually reversed until the child is able to dictate and write without assistance. Treatment continues with dictation until the child is independently thinking and writing. Treatment interventions for atypical LDs involve objectives to expand on the child's strengths (i.e. verbal and rote learning strengths) and to provide additional experience and practice in nonverbal weakness areas. Atypical LDs are complex disorders and treatment interventions are detailed and typically include teaching social and nonverbal material with extensive practice and concrete examples; teaching the affected person in rote in a predictable fashion; and the utilization and application of known algorithms to new situations. Additionally, treatment can include practicing organizational skills at home; practicing attention to visual and auditory (verbal information); and to encourage supervised and highly structured and interactive peer experiences.

Clinical trials

There are many **clinical trials** (http://www.nlm.nih.gov) currently in progress. The studies currently sponsored by governmental agencies focus on topics that include coping, diagnosis, symptoms specific aspects of disorders, and law and public policy.

Prognosis

It is rare for persons with LD to completely improve their academic deficiencies. However, performance in the area of weakness can significantly improve with appropriate treatment interventions.

Recovery

Recovery is slow and patients are often in specialized intervention programs (MD, DWE) or are part of programs that offer specific treatments (RD).

Other Atypical LDs

There are two common patterns of working memory deficits. Nonverbal learning disability (NVLD) is a neuropsychological syndrome characterized by deficits in comprehension, motor skills, visual-perception organization, tactile perception and novel problem solving, comprehension, visual memory, concept formation, and integration/organization of information. However, NVLD patients exhibit strengths in simple verbal skills, rote learning, memory, and knowledge of facts. In addition to weakness in mathematical achievement most persons affected by NVLD also tend to have problems with written expression, reading comprehension and social skills. Persons affected with working memory deficits tend to lose track of information as they are mentally processing that information or other information. Patients with working memory deficits often have problems with mathematical manipulations (which requires working memory), and the disorder is often accompanied by ADHD. Working memory is defined as the ability to remember information while executing another cognitive task.

Resources

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National Center for Learning Disabilities. <http://www.ld.org>.

National Institute on Deafness and Other Communication Disorders. <http://www.nidcd.nih.gov>.

ORGANIZATIONS

National Institute of Mental Health, Office of Communications. 6001 Executive Boulevard, Room

8184, MSC 9663, Bethesda, MD 20892-9663. (301) 443-4513 or 1-866-615-6464; Fax: (301) 443-4279.

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Lee Silverman voice treatment

Definition

Lee Silverman voice treatment (LSVT) is a technique for improving the voice volume of patients with **Parkinson's disease** (PD) and other neurological disorders.

Purpose

Most patients with PD experience a decreased voice volume and decreased intelligibility of their speech as their disease progresses. The purpose of LSVT is to reverse that decline by focusing the patient's attention on increasing voice volume through an intensive set of exercises. The treatment program was developed by two speech language pathologists, and is named after one of the first patients to undergo the program.

Precautions

The treatment program is entirely safe, as it consists only of vocal exercises.

Description

The LSVT program occurs in 16 one-hour sessions given four times per week and spaced over one month. The program includes at-home exercises the patient must complete for an additional hour (two hours on non-class days). The sessions are led by specially trained speech professionals who have been certified by the LSVT Foundation, a nonprofit organization devoted to improving speech among PD patients through the LSVT method.

During the sessions, patients are taught to "think loud," that is, to focus their conscious efforts on increasing voice volume. The intensive schedule of the workshops and frequent encouragement and reinforcement from the speech professionals provide an effective training system in which the patient learns to consistently increase voice volume. Exercises to increase breath support may also be used, although for many patients, focusing on increasing the volume is sufficient.

A consequence of the PD disease process is a decrease in the strength of vocal effort, due to the slowed movements and stiffness that characterize the disease, as well as a possible alteration in the sensory processing of sounds that is used to modulate the voice level. Despite the loss of volume, patients continue to believe their voice volume is adequate. Therefore, a key feature of LSVT is to make patients aware that their normal, pre-treatment voice level is too soft, and to help them find the correct level for normal speech. During the workshops, patients are taught methods to increase their vocal efforts by breathing more deeply and expelling air more fully and to "think shout." Patients are trained to reach the correct volume and to self-correct even when they feel they are speaking too loudly.

Another key feature of the program is building up the length and complexity of the vocalizations the patient is expected to deliver at the increased volume. Practice and feedback begin with single words to train the patient about the correct volume and the breath support required to produce that volume. Training moves on to simple and frequently used phrases so that the habit of loudness becomes associated with habitually used phrases. Sentences, reading aloud, and conversations follow.

Repetition and reinforcement are essential parts of the program. Through constant practice and reinforcement from the therapist, the patient learns to "recalibrate" the level of effort and to become accustomed to using a louder voice than beforehand. Reinforcement from family members and others in the community is also important in solidifying the gains made during the treatment program. Patients practice with tape recorders and sound-level meters to increase the degree of feedback.

Aftercare

No aftercare is involved, although the patient is instructed to continue practicing the exercises learned during the treatment program.

Risks

There are no risks to this treatment. Not all patients can sustain the prolonged and intense effort required in the program. Patients who have had cognitive decline may have difficulty complying with all of the instructions during training.

Normal results

Patients who engage in the program dramatically increase their voice volume to return to the correct levels. They learn to be understood much better and communication renormalizes.

Resources

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Richard Robinson

Key Terms

Brainstem The portion of the brain which lies between the cerebrum and the spinal cord that controls the functions of breathing, swallowing, seeing, and hearing.

Mitochondria A part of the cell that is responsible for energy production.

Seizure A disorder of the nervous system due to a sudden, excessive, disorderly discharge of the brain neurons.

Leigh disease

Definition

Leigh syndrome is an early onset, progressive neurological disease that involves defects in the normal function of the mitochondria. The mitochondrion is a small organelle located in most cells and is responsible for producing energy for cells and tissues throughout the body.

Description

Leigh syndrome is caused by defective cellular respiration that supplies many tissues with energy. The disorder is severe and can be particularly difficult for family members, as infants are among the severely affected. Leigh syndrome is also known as necrotizing **encephalopathy**.

Demographics

Leigh syndrome is a very rare disease that affects different peoples relatively equally. Some studies have shown that more males are affected than females.

Causes and symptoms

In Leigh syndrome, symptoms usually develop within the first year of life; rarely, symptoms can develop during later childhood. The infant usually initially develops symptoms that include **hypotonia** (decreased muscle tone), vomiting, and **ataxia** (balance or coordination abnormalities). Overall, failure to grow and thrive is usually the primary reason parents seek medical help. Eventually, the infant experiences **seizures**, lactic acidosis (an excess of lactic acid, a normal product of carbohydrate metabolism, in the body), and respiratory and kidney impairment.

Various abnormalities of the eyes are also common in Leigh syndrome. Ophthalmoplegia (paralysis of some or all of the muscles of the eye) is a typical finding, along with optic atrophy (degeneration of the optic nerve) and pigmentary retinopathy, a disorder that eventually leads to blindness.

On the cellular level, persons with Leigh syndrome have an inability to produce ATP (an energy source for the cell) in the mitochondria. Tissues that are not provided with adequate energy replenishment usually die. Irreversible damage can occur first in cells requiring much energy, such as the brain, leading to mental impairments and developmental delay. Many parts of the brain are affected by the lack of ATP in Leigh disease, including the basal ganglia, which helps regulate motor performance; the brainstem, which controls the functions of breathing, swallowing, seeing, and hearing; and the **cerebellum**, which coordinates balance and voluntary muscle movement.

Several genetic causes explain how persons develop Leigh disease, and several genes are involved. These genes include defects found in nuclear DNA as well as the smaller, less widely known mitochondrial DNA. Genes from both genomes contribute to the normal function of the mitochondria. Mutations in genes from the nuclear and the mitochondrial DNA have both been implicated in Leigh disease.

Diagnosis

In general, diagnosis of Leigh syndrome is often difficult due to the broad variability in clinical symptoms as well as the many different genetic explanations that cause this disease. Genetic testing for specific nuclear or mitochondrial DNA mutation is helpful in this regard.

Laboratory studies can assist in the diagnosis of Leigh syndrome. A muscle **biopsy** often determines if there are abnormalities associated with the mitochondria. Additionally, as the mitochondria are responsible for producing energy, a deficiency in a protein complex that has an important function in the mitochondria is often detected. In Leigh syndrome, this deficiency is found in one of five complexes that make up the mitochondrial respiratory system. One of these complexes, complex IV, or cytochrome c oxidase (COX), is commonly deficient. Although a COX deficiency is associated with Leigh syndrome, it can also indicate other mitochondrial abnormalities. Similarly,

there are mutations found in other complexes that can cause Leigh syndrome.

Treatment team

Treatment for Leigh syndrome is aimed at easing the disease-related symptoms and involves neurologists, pediatricians, clinical geneticists, nurses, and other related caretakers. Psychological counseling and support for family members caring for a child with Leigh disease is often encouraged.

Treatment

Currently, there is no treatment that is effective in slowing the progression of Leigh disease. Thiamine or vitamin B1 is usually given. Sodium bicarbonate may also be prescribed to help manage lactic acidosis.

Recovery and rehabilitation

As there is no cure for Leigh disease and the nature of the disorder is rapidly progressive, maintaining function for as long as possible is the primary focus rather than recovery. Physical therapists often assist in exercises designed to maintain strength and range of motion. As the disease progresses, occupational therapists can provide positioning devices for comfort.

Clinical trials

As of early 2004, there are no **clinical trials** to treat or cure Leigh syndrome. However, studies are underway to better understand all mitochondrial diseases in an effort to identify treatments and, eventually, a cure.

Prognosis

Soon after the onset of symptoms, the progression of Leigh disease is unrelentingly rapid. Death usually occurs from respiratory failure within two years following the initial symptoms, and usually by age six.

Resources

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ORGANIZATIONS

The National Leigh's Disease Foundation. P.O. Box 2222, Corinth, MS 38834. (601) 286-2551 or (800) 819-2551.

United Mitochondrial Disease Foundation. 8085 Saltsburg Road, Suite 201, Pittsburgh, PA 15239. (412) 793-8077; Fax: (412) 793-6477. info@umdf.org. <http://www.umdf.org/>.

Bryan Richard Cobb, PhD

Lennox-Gastaut syndrome

Definition

Lennox-Gastaut syndrome (LGS) is one of the most severe forms of **epilepsy** (a seizure disorder) that develops in children usually between one and eight years old. It is characterized by several types of **seizures**, developmental delay, and behavioral disturbances such as poor social skills and lack of impulse control.

Description

Lennox-Gastaut syndrome can be the result of any one of many neurological problems of childhood that begins with intractable, or hard to control, seizures. French physician Samuel Auguste A. D. Tissot (1728–1797) first described the syndrome in 1770. He reported an 11-year-old boy with frequent drop attacks, **myoclonus** (jerking movements), and progressive functional impairment. Seizure types vary among children with LGS. The tonic seizures of LGS include stiffening of the body, upward deviation of the eyes, dilation of the pupils, and altered respiratory patterns. Atonic seizures are also experienced by children with LGS and involve a brief loss of muscle tone and consciousness, which causes abrupt falls. Other seizures common in LGS include the atypical absence seizure type (staring spells) and myoclonic seizures (sudden muscle jerks).

Lennox-Gastaut syndrome frequently affects language development in children, ranging from little or no verbal ability to slowness in ideation and expression. Varying degrees of motor difficulties hinder age-appropriate activities such as walking, skipping, or using a writing instrument. Severe behavioral disorders such as hyperactivity, aggressiveness, and autistic tendencies and personality disorders are nearly always present. There is usually **men-**

tal retardation and sometimes a tendency for psychosis that eventually develops with LGS.

In young children, LGS usually begins with episodes of sudden falls. In the school-age group, behavioral disturbances may be the heralding signs, along with sudden falls. This is soon followed by frequent seizures, episodes of **status epilepticus** (a continuous seizure state that is associated with a change in the child's level of awareness), progressively deteriorating intellectual functions, and personality disturbances. By age six, most children with LGS have some degree of mental retardation.

When children grow older, the types of seizures often change. In most cases, the drop seizures subside. They are replaced by partial, complex partial, and secondarily generalized convulsions. Among teenagers, complex partial seizures are the most common form.

Demographics

In the United States, Lennox-Gastaut syndrome accounts for 1–4% of older children with epilepsy, but 10% of children with epilepsy beginning in the first five years of life. In Europe, studies demonstrated that the proportion of patients with LGS seems similar to that in the US.

No racial differences exist in the occurrence of LGS; however there are differences in respect to sex and age. Males are affected more often than females; the relative risk of occurrence of LGS is significantly higher in boys than in girls (one in 10,000 boys, and one in 50,000 girls). The average age for the onset of seizures is three years.

Causes and symptoms

Causes

Often no specific cause is identifiable, however, some of the known causes include:

- developmental malformations of the brain
- genetic brain diseases such as **tuberous sclerosis**, and inherited metabolic brain diseases
- brain injury due to problems associated with pregnancy and birth, including prematurity, asphyxia, and/or low birth weight
- severe brain infections, including encephalitis, meningitis, toxoplasmosis, and rubella

In many instances, LGS follows earlier **infantile spasms**, which are sudden spasms or body bending, either at the trunk or neck. These episodes usually begin between three and eight months of age, and may develop into the mixed seizure pattern that characterizes LGS at two to three years of age.

Key Terms

Seizure Abnormal electrical discharge of neurons in the brain, often resulting in abnormal body movements or behaviors.

Vagus nerve Tenth cranial nerve and an important part of the autonomic nervous system, influencing motor functions in the larynx, diaphragm, stomach, and heart, and sensory functions in the ears and tongue.

Symptoms

The main symptom of LGS is the occurrence of seizures. Several different seizure types occur, and a child may experience some or all of these:

- In drop attacks, the child falls suddenly to the ground. This may be because the legs suddenly fold up (atonic seizure) or stiffen (tonic seizures), or because of a violent jerk (myoclonic seizure) that throws the child to the floor.
- During atypical absences, the child appears to be vacant or to stare blankly. Sometimes these seizures are associated with blindness or nodding of the head. Often, children are able to continue their activity to some extent during the seizure. These episodes are usually very brief, but frequent. Sometimes these seizures occur so frequently that they merge into one another. Such a phenomenon can lead to what is called non-convulsive status epilepticus. During these episodes, children may appear to switch off, but can be partly responsive, drool, be unable to speak or eat properly, and be wobbly on their feet.
- Tonic seizures are often difficult to detect as they occur much more frequently at night. During these attacks, there is general stiffening of the arms or legs. This may be associated with the eyes rolling up or the head moving back. Sometimes, breathing is interrupted and the child may turn blue. If the attacks last for more than 10–20 seconds, the arms often start to tremble rapidly while remaining stiff.

Most children with LGS experience some degree of impaired intellectual functioning or mental retardation. In approximately 65% of children with LGS, intellectual disability is evident, either previous to or at the time of diagnosis. Behavioral disturbances are also usually present, including persistent attention-seeking behavior, impulsiveness, lack of regard for personal safety and fearlessness, and, in severe cases, autistic behaviors. These behavior disturbances may be the result of the condition

causing LGS, effects of a particular medication, uncontrolled epilepsy, difficulty interpreting information, or even a lower level of concept understanding.

Diagnosis

LGS is diagnosed by some or all of the following symptoms, including:

- presence of a mixed seizure pattern
- some degree of developmental delay or intellectual disability
- distinct, slow, spike-and-wave pattern shown during electroencephalogram (EEG)

Magnetic resonance imaging (MRI) is an important part of the search for an underlying cause in a child with LGS. Abnormalities revealed by **MRI** associated with LGS include tuberous sclerosis, brain malformations, or evidence of previous brain injury.

Treatment team

Treatment for LGS involves a multidisciplinary team that may include a **neurologist**, a **neuropsychologist**, and a neurosurgeon. A dietitian may help with specialized diet regimens.

Treatment

The drug treatment for LGS is based on the use of anti-epileptic drugs that are effective in reducing the number of seizures. However, the improvement often only lasts for a period of months or, rarely, a year or more. **Carbamazepine**, sodium valproate, vigabatrin, **lamotrigine**, and the **benzodiazepines** (clobazam, in particular) are often prescribed.

One alternative treatment involves a ketogenic diet in which 87% of calories come from fat, 6% from carbohydrates, and 7% from protein. The diet is restrictive, difficult to follow, but has shown results in reducing seizures in some affected children. Other less conventional therapies such as intravenous immunoglobulin therapy have also been attempted.

For children with repeated drop attacks, a procedure to cut the corpus collosum (the large group of nerve fibers connecting the two halves of the brain) may be very helpful. However, this procedure involves significant surgery and is not always effective, and seizures may return after several months or years.

An implanted vagus nerve stimulator is effective in reducing seizures in many children with Lennox-Gastaut syndrome. It is a device, similar in size to a heart pacemaker, that is implanted in the chest with a lead wrapped around the vagus nerve in the neck. It is able to stimulate the vagus nerve automatically at adjustable intervals. The device may take months to show maximum benefit, and requires a surgical procedure for insertion as well as for removal. The batteries require replacement approximately every eight to ten years, which entails further surgery.

Recovery and rehabilitation

A very small percentage of children with LGS experience a spontaneous improvement in seizures, usually during adolescence. In these cases, mental function also shows some improvement. In the overwhelming majority of cases, however, emphasis is placed on maximizing quality of life rather than recovery.

Protective devices such as helmets and pads may be necessary during periods of high seizure activity, but many children and parents consider them too burdensome and restrictive for continuous daily use.

Clinical trials

Although as of early 2004 there were no ongoing **clinical trials** for LGS, the National Institutes of Health (NIH) sponsors research related to many seizure disorders. Information on the numerous current clinical trials for the study and treatment of seizure disorders can be found at the NIH Web site: <http://clinicaltrials.gov/search/term=Seizure+Disorder>.

Prognosis

The prognosis for individuals with LGS is unfavorable, but variable. Long-term studies of children with LGS found that a majority of patients continue to have typical LGS characteristics (mental retardation, treatment-resistant seizures) many years after onset. Children with an early onset of seizures, prior history of West syndrome, higher frequency of seizures, or constant slow EEG background activity have a worse prognosis than those with seizures beginning later in childhood. Tonic seizures may persist and be more difficult to control over time, while myoclonic and atypical absences become easier to control.

Special concerns

It is recognized that the frequency of seizures may be associated with the child's level of alertness. The child who is overexcited or lacks sufficient stimulation may experience more seizures. Therefore, a stable but stimulating environment may be important in reducing the number of daily seizures. This may include a strict routine of regular meals, sleep, and medication.

Providing for the safety of a child with Lennox-Gastaut syndrome is a 24-hour concern for parents. Coupled

with safety concerns, children with LGS are often dependent for personal care such as toileting, management of behavioral impulses, and interpretation of attempts at communication. Often, **respite** care can provide parents with a chance to reenergize. As the child matures into adulthood, an assisted living center or group home may help provide maximum independence and social integration, along with continued medical supervision.

Resources

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ORGANIZATIONS

Lennox-Gastaut Syndrome Group. 3872 Lyceum Avenue, Los Angeles, CA 90066. (310) 391-0335; Fax: (310) 397-2687. CandaceLGS@aol.com.

Epilepsy Foundation. 4351 Garden City Drive, Suite 500, Landover, MD 20785-7223. (301) 459-3700 or (800) EFA-1000 (332-1000); Fax: (301) 577-2684. postmaster@efa.org. <http://www.epilepsyfoundation.org/>.

NIH/NINDS Brain Resources and Information Network. PO Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424; Fax: (301) 402-2186. <http://www.ninds.nih.gov/>.

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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 the complete absence of a particular 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. Males with Lesch-Nyhan syndrome develop neurological 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

Demographics

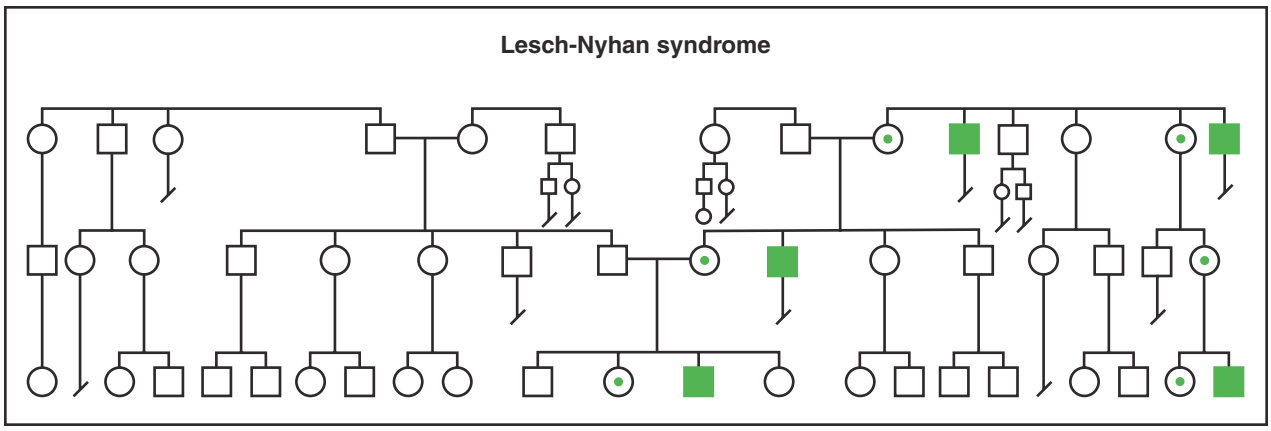
Lesch-Nyhan syndrome affects approximately one in 380,000 live births. It occurs evenly among races. Almost always, only male children are affected. Women carriers usually do not have any symptoms. Women carriers can occasionally develop inflammation of the joints (gout) as they get older.

Causes and symptoms

The syndrome is caused by a severe change (mutation) in the HPRT **gene**. Since the HPRT gene is located on the X chromosome, Lesch-Nyhan syndrome is considered an X-linked disorder and therefore only affects males.

The HPRT 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.

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



See Symbol Guide for Pedigree Charts. *(Gale Group.)*

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.

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 team

Patients with Lesch-Nyhan syndrome should be cared for by neurologists (to monitor and treat neurological symptoms); urologists and/or nephrologists (to treat kidney stones and kidney damage); orthopedic surgeons (to treat joint problems); and psychiatrists or psychologists (to create a behavioral program).

Treatment

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.

Resources

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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>.

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Leukodystrophy

Definition

Leukodystrophy refers to a group of rare genetic disorders affecting the central and peripheral nervous systems. They are neurodegenerative diseases characterized by abnormalities in myelin, the fatty substance that surrounds, insulates, and facilitates the function of nerve cells.

Description

Leukodystrophy derives from two Greek words; "leuko" means white, referring to the white matter (myelin) of the nervous system, and "dystrophy" means abnormal growth or development. Myelin insulates, or sheaths, nerve cells, helping them to transmit electrical nerve signals. It is a complex substance composed of a number of fat and protein molecules. Without myelin, nerve cells cease to function and eventually die. It also covers the spinal cord and the long nerve cell projections, known as axons, which innervate all of the peripheral tissues.

Key Terms

Ataxia A condition marked by impaired muscular coordination, most frequently resulting from disorders in the brain or spinal cord.

Hypotonia Having reduced or diminished muscle tone or strength.

Mitochondria Spherical or rod-shaped structures of the cell. Mitochondria contain genetic material (DNA and RNA) and are responsible for converting food to energy.

Myelin A fatty sheath surrounding nerves throughout the body that helps them conduct impulses more quickly.

Neuropathy A disease or abnormality of the peripheral nerves (the nerves outside the brain and spinal cord). Major symptoms include weakness, numbness, paralysis, or pain in the affected area.

Nystagmus An involuntary, rhythmic movement of the eyes.

Organelle A specialized structure within a cell, which is separated from the rest of the cell by a membrane composed of lipids and proteins, where chemical and metabolic functions take place.

Paraplegia Loss of voluntary movement and sensation of both lower extremities.

Peroxisome A cellular organelle containing different enzymes responsible for the breakdown of waste or other products.

Spasticity Increased mucle tone, or stiffness, which leads to uncontrolled, awkward movements.

More than 15 different types of leukodystrophy have been described, the most common of which will be discussed here. They are all caused by either an abnormality in one of the protein components of myelin, or by a defective or missing enzyme that assists in the production or normal degradation of myelin. As such, leukodystrophies are often referred to as demyelinating or dysmyelinating diseases, as well as leukoencepalopathies.

Based on the part of the nervous system that is most affected, leukodystrophies may be categorized as central (brain and spinal cord), peripheral, or combined. The neurologic symptoms vary widely, both within and between the different types. All types of leukodystrophy are genetic (present at conception), progressive, and never spontaneously resolve. None of the leukodystrophies can be cured, and effective treatments are limited.

Demographics

Most of the individual leukodystrophies are rare. The most common type is **Canavan disease**, with an incidence of about one in 8,000, followed by X-linked **adrenoleukodystrophy** (XL-ALD), which occurs in one in 40,000 male births. Some types of leukodystrophy are more common in certain ethnic groups, such as Canavan disease in Ashkenazi Jews, or globoid cell leukodystrophy (GLD) and **metachromatic leukodystrophy** (MLD) in Scandinavians.

As indicated, all types of leukodystrophy are genetic, with several patterns of inheritance represented. Genes reside on the chromosomes in the nucleus of each cell; a normal complement is 46 chromosomes arranged in 23 pairs. The first 22 pairs are the autosomes, and the last pair, designated X and Y, are the sex chromosomes. Males have one X and one Y, while females have two X chromosomes. One of each chromosome/gene pair is contributed by each parent at conception.

Autosomal recessive inheritance refers to a disorder that only occurs if both copies of a gene pair are defective. An affected individual is typically born to unaffected parents, who each silently carry one copy of the disease gene. Each time parents who both carry the same recessive gene conceive a pregnancy, there is a 25% chance they will both transmit the disease gene and have an affected child.

Autosomal dominant inheritance requires that only one copy of a gene pair be defective in order to develop the disorder. Each offspring of a parent with an autosomal dominant disorder has a 50% risk of inheriting the gene. In some conditions (e.g., **Alexander disease**), most cases are due to a new mutation of the gene in a sperm or egg (unaffected parent).

A male who inherits the gene for an X-linked recessive disorder develops the condition because he has no normal gene on a second X chromosome to compensate for it. Female carriers of an X-linked recessive disorder are usually unaffected, but not always. If they do develop signs/symptoms, they tend to have later onset and milder symptoms. A woman who carries an X-linked recessive gene faces one of four possible outcomes with each pregnancy: affected male, unaffected male, carrier female, and noncarrier female. If an affected male has children, all of

his daughters will be carriers, but none of his sons will be affected.

Causes and symptoms

All of the leukodystrophies are caused by either a defective protein component of myelin, or by a malfunctioning enzyme that interacts with one of the protein or lipid constituents. In some cases, defective, deficient, or absent myelin may cause neurons in the central or **peripheral nervous system** to degenerate. In other cases the neurons remain intact, but transmission of normal signals through the nerves is affected. Brief synopses of the most common leukodystrophies are provided below.

Adrenoleukodystrophy (ALD), also called Addison disease with cerebral sclerosis, or melanodermic leukodystrophy, is inherited primarily as an X-linked recessive trait, but there is also a rare autosomal recessive form (neonatal ALD). X-linked ALD is caused by defects in the ABCD1 gene, also known as the ALDP (ALD protein) gene. A defective enzyme in the peroxisomes (organelles that assist in degrading substances, including some components of myelin) fails to break down very long chain fatty acids (VLCFA), which then accumulate to harmful levels in the nervous system and adrenal glands. About 35% of affected individuals have the childhood or adolescent cerebral form of ALD, which is the most severe. Age of onset ranges from four to ten years, with initial symptoms of behavioral changes, hyperactivity, and learning problems. The skin takes on a bronzed appearance due to adrenal gland dysfunction. Within several years, significant visual and auditory deficits develop, motor coordination worsens, and nearly all boys with the condition are in a vegetative state by their mid-teens. Adult adrenomyeloneuropathy (AMN) affects 30% of men with ALD, onset of symptoms may occur anywhere from adolescence to late adulthood, and progression of the disorder may occur over several decades. Adrenal dysfunction occurs first, and subsequent neurological impairments may include spastic paraplegia, **peripheral neuropathy**, impotence, sphincter disturbances, and hypogonadism. Approximately 10% of individuals develop an adult cerebral form, which is similar to the childhood variety, but with milder symptoms and slower progression. Another 15% have adrenal insufficiency only, and 10% of males who are positive for an ALDP gene mutation are presymptomatic at the time of testing. About 15% of carrier females develop some degree of neurologic impairment.

Alexander disease is designated as an autosomal dominant condition, but most reported cases are thought to be due to new mutations in the glial fibrillary acidic protein gene (GFAP). The average age of onset in the infantile form is six months, with death by age five. Signs/symptoms include progressive macrocephaly (large head), psychomotor regression, **spasticity**, and **seizures**. The less common juvenile and adult forms have a slower clinical course, present with **ataxia** and spasticity, but usually have normal intellect. Affected adults may show relapsing-remitting symptoms, similar to **multiple sclerosis**. The presence of Rosenthal fibers and glial fibrillary acidic proteins (GFAP) around the nerves are classic histological signs.

Canavan disease, also referred to as spongy degeneration of the CNS, is autosomal recessive, secondary to mutations in the aspartoacylase gene (ASPA). Symptoms typically begin two to four months after birth, with death occurring by 10 years of age. Signs/symptoms include increased head circumference, deafness, optic atrophy, nystagmus, blindness, initial **hypotonia** followed by spasticity, and seizures.

Cerebrotendinous xanthomatosis (CTX) is autosomal recessive, and results from mutations in the CYP27A1 gene. Large deposits of cholesterol and one of its derivatives, cholestanol, are found throughout the body, particularly the Achilles tendons, brain, and lungs. Most individuals with CTX have been diagnosed as juveniles. Signs/symptoms include cataracts and tendon xanthomas (fatty tumors) in the early stages, with ataxia, spasticity, mild **mental retardation**, **dementia**, psychiatric symptoms, respiratory insufficiency, and myocardial infarction due to atherosclerosis developing over subsequent decades.

Globoid cell leukodystrophy (GLD), also known as **Krabbe disease** and galactocerebrosidase deficiency, is autosomal recessively inherited, and caused by defects in the glycosylceramidase (GALC) gene. The four clinical forms of GLD, based on age of onset, are infantile, late infantile, juvenile, and adult. About 90% are diagnosed with infantile GLD, with onset at several months of age, and severe neurologic deterioration progressing to death in early childhood. Signs/symptoms include deafness, blindness, irritability, episodic fever, mental deterioration, hypertonia in early stage, hypotonia later, seizures, motor deterioration, and peripheral neuropathy. The other forms of GLD vary widely in severity of symptoms and rate of progression, but those diagnosed later tend to have a better prognosis.

Leigh syndrome, also called subacute necrotizing **encephalopathy** (SNE), refers to at least eight distinct disorders inherited as autosomal recessive or X-linked recessive traits. Another six types exhibit an unusual hereditary pattern known as mitochondrial inheritance. Mitochondria are energy producing organelles that contain their own genes. With rare exceptions, all of the mitochondria in the first cell of the embryo come from the egg. Therefore, mitochondrial inheritance resembles X-linked

Different types of leukodystrophy may mimic each other, as well as other neurodegenerative diseases (e.g., multiple sclerosis), so multiple tests could be attempted before a diagnosis is reached. A few individuals with a neurodegenerative disorder may never receive a diagnosis. A board-certified geneticist is most likely to make the correct diagnosis, using the fewest tests in the least amount of time.

Carrier testing, as well as prenatal diagnosis, depends upon the availability of an established biochemical or genetic marker. The availability and accuracy of these tests are constantly changing for all genetic disorders, and the interpretation of results may be complicated. For rare disorders such as the leukodystrophies, it is especially critical to seek a consultation with a genetics counselor or geneticist to obtain the most complete and current information available.

Treatment team

A **neurologist** manages the basic care of an individual with a neurodegenerative disorder. Given their special training and greater familiarity with these rare diseases, a geneticist would likely be consulted to make or confirm the diagnosis. The geneticist and/or genetics counselor also provides support for the family, along with the most current information on the natural history and inheritance of the disorder, options for diagnostic and prenatal testing, availability of specialized reproductive procedures, and referrals to other specialists and support groups. A diagnosis of leukodystrophy might also require involvement of neonatal intensive care unit (NICU) staff, a developmental pediatrician, occupational and physical therapists, and health professionals associated with institutional or specialized home care.

Treatment

In the majority of cases, there is no effective treatment for an individual diagnosed with a leukodystrophy. However, several of the conditions do respond to specific treatments.

Bone marrow transplantation has been shown to be successful in treating XL-ALD (and MLD), but only in very specific situations. The use of "Lorenzo's oil," a food product consisting of oleic acid, to treat XL-ALD has not been shown in multiple studies to provide any consistent benefit. Adrenal insufficiency in ALD can be successfully managed with the use of glucocorticosteroids.

Effective treatment of Refsum disease is possible with a diet low in phytanic acid. Improvements in ataxia, neuropathy and ichthyosis are seen, but the diet cannot restore any vision or hearing loss that has occurred.

The use of chenodeoxycholic acid and cholic acid (CDCA), in combination with a cholesterol lowering drug, for the treatment of CTX has been successful in stopping the progression of the disease.

In general, all that can be offered to most individuals with a leukodystrophy is supportive care and therapy to address their neurologic symptoms.

Clinical trials

As of 2004, a primary focus for research on the treatment of leukodystrophies is on the use of stem cells from umbilical cord blood for transplantation, known as allogeneic hematopoietic stem cell transplantation. The cells are easily obtained, and are less likely than bone marrow to elicit immune system reactions in the patient. There has been some success in treating GLD, and there is hope that both XL-ALD and MLD will respond favorably as well. Both the United Leukodystrophy Foundation (ULF) and the National Institute of Neurological Disorders and Stroke (NINDS) (see below) are excellent sources of information for research being conducted on the various forms of leukodystrophy.

Prognosis

The prognosis for leukodystrophy depends on the specific diagnosis. In general, a younger age of symptom onset implies a worse prognosis. With few effective treatments, and the progressive nature of hereditary, myelin-related disorders, the overall prognosis for individuals with leukodystrophy is poor.

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Kennedy Krieger Institute. 707 North Broadway, Baltimore, MD 21205. 888-554-2080. <http://www.kennedykrieger.org>.

MLD Foundation. 21345 Miles Drive, West Linn, OR 97068-2878. 800-617-8387; Fax: 503-212-0159. <http://www.MLDfoundation.org>.

National Tay-Sachs and Allied Diseases Association, Inc. 2001 Beacon Street, Boston, MA 02135. 800-906-8723. <http://www.NTSAD.org>.

NIH/NINDS Brain Resources and Information Network. PO Box 5801, Bethesda, MD 20824. 800-352-9424. <http://www.ninds.nih.gov/>.

United Leukodystrophy Foundation. 2304 Highland Drive, Sycamore, IL 60178. 800-728-5483. <http://www.ulf.org/>.

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Levetiracetam

Definition

Levetiracetam is an anti-epileptic drug (AED). It is often used in combination with other medications in the treatment of **epilepsy**, a neurological dysfunction in which excessive surges of electrical energy are emitted in the brain.

Purpose

While levetiracetam controls the partial **seizures** (focal seizures) associated with epilepsy, there is no known cure for the disorder. In partial epileptic seizures, neural disturbances are limited to a specific region of the brain and the affected person usually remains conscious throughout the seizure. Although the precise mechanisms by which it works are unknown, levetiracetam is thought to exert its therapeutic effect by decreasing the abnormal activity and excitement within the area brain that may trigger partial seizures.

Research indicates that levetiracetam may also be effective in treating neurogenic **pain**.

Description

In the United States, levetiracetam is sold under the brand name Keppra. A newer generation medication, levetiracetam lacks many of the usual side effects commonly assoicated with other AEDs. Levetiracetam has fewer negative interactions with other AEDs or anti-convulsants, and may be used in combination with other AEDs in the treatment of epilepsy.

Key Terms

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Neurogenic pain Pain originating in the nerves or nervous tissue.

Partial seizure An episode of abnormal activity in a localized (specific) part of the brain that causes changes in attention, movement, or behavior.

Recommended dosage

Levetiracetam is taken by mouth in tablet form. It is available in 250 mg, 500 mg, and 750 mg tablets. Levetiracetam is prescribed by physicians in varying total daily dosages, usually from 1000 mg to 3000 mg. Patients typically take divided doses (equal to one half of the total daily dose) twice daily.

Like many other AEDs, beginning a course of treatment which includes levetiracetam requires a gradual dose-increasing regimen. Adults and teenagers 16 years or older typically take 1000 mg a day for the first two weeks. Daily dosages of levetiracetam may then be increased by as much as 1000 mg every two weeks until reaching the maximum therapeutic dose (usually not more than 3000 mg). It may take several weeks to realize the full benefits of levetiracetam.

It is important not to take a double dose of levetiracetam. If a dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, then the missed dose should be skipped.

When ending treatment of AEDs, including levetiracetam, physicians typically direct patients to gradually reduce their daily dosages over a period of several weeks. Stopping the medicine suddenly may cause seizures to return or occur more frequently.

Precautions

A physician should be consulted before taking levetiracetam with certain non-perscription medications. Patients should avoid alcohol and CNS depressants (medications that make one drowsy or tired, such as antihistimines, sleep medications, and some pain medications)

while taking levetiracetam. It can exacerbate the side effects of alcohol and other medications.

Levetiracetam may not be suitable for persons with a history of kidney disease, depressed renal function, or mental illness.

Before beginning treatment with levetiracetam, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant, or plan to become pregnant. Levetiracetam's safety during pregnancy has not been established. Patients taking levetiracetam with other AEDs or anti-convulsants should be aware that many AEDs and anti-convulsants have been shown to cause birth defects in animals. Patients who become pregnant while taking any AED or anti-convulsants should contact their physician immediately.

Side effects

Research indicates that levetiracetam is generally well tolerated and lacks many of the traditional side effects associated with AEDs. However, levetiracetam may case a variety of usually mild side effects in some patients. Cough, **dizziness**, and muscle weakness are the most frequently reported side effects of levetiracetam. Other possible side effects that do not usually require medical attention include:

- dryness or soreness of throat
- fever
- hoarseness or voice changes
- sleepiness or unusual drowsiness
- tender, swollen glands in neck
- numbness, prickling, "pins and needles," or tingling feelings
- loss of appetite or weight loss

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication. However, if any symptoms persist or become too uncomfortable, consult the prescribing physician.

Other, uncommon side effects of levetiracetam can indicate a potentially serious condition. A patient taking levetiracetam who experiencs any of the following symptoms should immediately contact their physician:

- clumsiness or unsteadiness
- depression, paranoia, or other significant mood changes
- double vision
- problems with memory
- lower back or side pain
- painful or difficult urination
- shortness of breath, wheezing, or troubled breathing.

Interactions

Levetiracetam is often used with other other seizure prevention medications, as prescribed by a physician. Unlike many other AEDs and anti-convulsants, levetiracetam does not decrease the effectiveness of oral contraceptives (birth control pills).

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American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507, USA. <http://www.aesnet.org>.

Adrienne Wilmoth Lerner

Levodopa *see* **Antiparkinson drugs**

Lewy body dementia

Definition

Lewy body **dementia** (LBD) is a neurodegenerative disorder that can occur in persons older than 65 years of age, which typically causes symptoms of cognitive (thinking) impairment and abnormal behavioral changes.

Description

The condition was first described by Frederick Lewy in 1941 when he described Lewy bodies, which are abnormal inclusions in the cytoplasm (components of a cell outside the nucleus) of cells found in patients who had

Parkinson's disease (PD). There is some controversy concerning the relationship between Lewy body dementia and Parkinson's disease. When cognitive impairment and behavioral disturbance are early and prominent symptoms, then LBD is the likely diagnosis. When motor symptoms are the predominant and early symptoms, then Parkinson's disease is likely to be the diagnosis. Typically, on autopsy examination of the brain, both PD and LBD would probably demonstrate Lewy bodies. Autopsy examination is the only method to available for a definitive diagnosis.

The signs and symptoms of LBD stem from a multifactorial cause of disrupted bidirectional (two-way) information flow in neurons, especially those located in the frontal lobe; that is, there are abnormalities in the chemicals that regulate and pass on message signals between neurons in the brain. Alterations in neurotransmitter chemicals can also impair nerve cell circuitry, causing abnormalities in bidirectional information flow.

Most patients with LBD also have brain evidence of Alzheimer's disease pathology. Additionally, most patients with LBD possess amyloid plaques in their cerebral cortex. Lewy bodies can also occur in a genetically transmitted form of Alzheimer's disease, Pick's disease, and Down syndrome.

Demographics

Dementia (used as a general term) has been an increasingly common disorder that is especially more frequent in the elderly. Dementia affects 7% of the general population older than 65 years and that incidence increases with age to 30% of those age 80 years and older. Autopsy results in the United States estimate that LBD accounts for 10–20% of dementia cases. Approximately 40% of patients with Alzheimer's disease also have LBD. Data from autopsy results in Europe and Japan reveal similar frequencies as reported in studies from the United States. No data is available concerning age, gender, or potential risk factors.

Causes and symptoms

The formation of Lewy bodies is thought to occur because of an abnormal increase in the production of a normally occurring protein in nerve cells called alpha-synuclein. Called upregulation, this overproduction can cause substances to accumulate or multiply in increased numbers. Other theories propose that alpha-synuclein may become insoluble (unable to mix in a watery environment), which could make the molecule more prone to accumulate abnormally in the brain.

Symptoms can include cognitive impairment, neurological signs, sleep disorder, and autonomic failure. Cognitive impairment is the presenting feature of LBD in most cases. Patients have recurrent episodes of confusion that progressively worsen. The fluctuation in cognitive ability is often associated with shifting degrees of attention and alertness. Cognitive impairment and fluctuations of thinking may vary over minutes, hours, or days.

Psychological manifestations

Psychological manifestations of LBD predominantly include:

- delusions, false beliefs, or wrong judgments held to be true despite incontrovertible evidence to the contrary
- visual hallucinations, strong subjective perception of an imaginary event or object
- apathy, an indifference or absence of interest in the environment
- anxiety, apprehension, or dread that causes symptoms of rapid heart rate, restlessness, tension, and shortness of breath

Neurological symptoms in patients affected with LBD include extrapyramidal features early in the disease. The extrapyramidal symptoms in LBD can be differentiated from other dementias such as Parkinson's disease. Patients affected with LBD tend to show axial involvement with greater postural instability and facial impassivity, and less tremor. Disorders of sleep in patients with LBD typically can include impairment of rapid-eye-movement (REM) sleep; REM sleep behavior disorder causes vivid and frightening dreams. Patients may also exhibit loss of muscle tone or cataplexy, hypersomnolence (an increased inclination to sleep), hallucinations, and **narcolepsy**. Patients with LBD also have deficits in the autonomic nervous system, part of which regulates specific body functions such as blood pressure and bladder control. Autonomic abnormalities can cause **orthostatic hypotension** and urinary incontinence.

Diagnosis

Clinically, patients have features of fluctuating cognitive impairment such as from alert to confused state, recurrent visual **hallucination**, **depression**, and REM sleep disorder. Patients may have impairment of memory retrieval and they often do poorly on tests that measure visuospatial skills such as copying figures or drawing a clock. Patients may have mild gait (walking) impairment. An accurate diagnosis can include identification of target symptoms, including cognitive impairment, psychological disorders (hallucinations, depression, sleep disorder, and behavioral disturbances), extrapyramidal motor features or **autonomic dysfunction** (orthostatic hypotension), or urinary incontinence. Standard blood tests are ordered and additional tests are typically required, including thyroid studies, vitamin B-12 levels, and, if appropriate, tests for **Lyme disease**, syphilis, or HIV since these infections can affect the brain. Currently, there are no specific tests used

Key Terms

Alzheimer's disease A neurodegenerative disorder that causes nerve-cell death and symptoms that typically include loss of thinking and language ability, and memory impairment.

Autonomic failure Refers to failure in the autonomic nervous system, which comprises two divisions called the parasympathetic nervous system, which slows heart rate, increases intestinal and gland activity, and relaxes sphincter muscles; and the sympathetic nervous system, which accelerates heart rate, raises blood pressure, and constricts blood vessels.

Cataplexy A sudden loss of muscle tone.

Dementia A progressive loss of intellectual functions without impairment of consciousness or perception. The condition is often associated with brain disease and persons exhibit symptoms such as disorientation and impaired memory, judgment, and intellect.

Down syndrome A genetic disorder, also called trisomy 21, characterized by mental retardation, heart defects, slanting eyes, short fingers, broad short skull, and broad hands.

Hallucinations False perceptions that can occur without a true sensory stimulus.

Narcolepsy A genetically determined disorder characterized by recurrent episodes of daytime sleep, disrupted nighttime sleep, cataplexy, hallucinations, and sleep paralysis.

Orthostatic hypotension A fall in blood pressure due to a change in body position, usually from the sitting position to an erect or standing position.

Parkinson's disease A neurodegenerative disorder that results in changes to neurons in the brain stem, causing affected persons to have symptoms that include a resting tremor, speech impairments, movement disorders, shuffling walk, stooped posture, and dementia.

Pick's disease A neurological degenerative disorder that causes deterioration of social skills and personality, and causes impairment of memory, language, and intellect.

Urinary incontinence Unable to control urinary excretion.

to diagnose LBD. A **magnetic resonance imaging (MRI)** scan is indicated to distinguish LBD from another disorder called vascular dementia, which can present with similar clinical signs and symptoms. It is important to exclude diseases or drugs that can cause **delirium**.

Treatment team

The treatment team can be broad, including general practitioners, geriatric psychotherapists, emergency services, or movement disorder specialists. Additionally, the team can include family members, primary care practitioners, caregivers, and neurologists. Special consultations from a **neurologist** with special expertise in dementias may be appropriate for caregiver education.

Treatment

The management of LBD can be approached in four stages: accurate diagnosis, identification of target symptoms, nonpharmacological treatment, and pharmacological treatment. Nonpharmacological interventions include management of environment and other necessities associated with LBD patient care. Caregiving skills should be specifically tailored to the patient. Pharmacological treatment can include several different medications, most notably a class of drugs called **cholinesterase inhibitors**. These medications tend to increase a brain neurochemical called acetylcholine, which is an excitatory brain chemical that is decreased in persons with LBD. With a typical dose of a cholinesterase inhibitor (Donepezil or Aricept), the symptoms of visual hallucinations, apathy, anxiety, sleep disorder, and cognitive impairments can be improved. Generally, medications can be utilized to slow the rate of cognitive decline, treat agitation and hallucinations, treat depression, and improve cognition and/or alertness.

Recovery and rehabilitation

Generally, there are no dietary restrictions for persons affected with LBD, except for those who have swallowing impairment. Physical therapy and an **exercise** program can be useful to maintain mobility. There are potential problems for patients who drive a motor vehicle, and family members and caregivers should be advised.

Clinical trials

Currently, the National Institute of Neurological Disorders and Stroke (NINDS) supports research concerning diagnosis, prevention, and treatment. Research efforts studying the biological consequences of Lewy body formation and mechanisms of disease progression are funded by NINDS.

Prognosis

LBD is a slowly progressive chronic disorder. However, the rate of progression may be faster than in Alzheimer's disease. The disease is fatal from complications of poor nutrition, swallowing difficulties, and immobility.

Special concerns

Primary caregivers and family members require information concerning management of symptoms such as hallucinations, agitation, and cognitive changes. Children of patients with LBD may require genetic counseling. Family members should be aware that LBD affects job performance and medical leave of absence or early retirement may be advisable. Driving may become problematic and should be addressed with the medical treatment team, patient, and family.

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Lidocaine patch

Definition

Lidocaine belongs to a class of local and topical anesthetic medications. As lidocaine causes a temporary numbness or loss of sensation when injected in the tissues, it is used as a local anesthetic and in the treatment of **pain**. When given intravenously, lidocaine is also an antiarrythmic agent, capable of correcting some ventricular arrythmias of the heart. The lidocaine patch is a topical treatment that is especially helpful in the treatment of pain associated with postherpetic neuralgia, a condition that can occur after infection with the herpes varicella zoster (**shingles**) virus. Additionally, the lidocaine patch is sometimes used in the treatment of some chronic forms of nerve pain such as the pain associated with fibromyalgia.

Purpose

The lidocaine patch relieves pain and discomfort by blocking signals sent to nerve endings in the skin. Almost 20% of the one million Americans who develop shingles yearly experience long-term pain after the infection has resolved. People over age 60 are especially prone to postherpetic neuralgia.

Description

The lidocaine patch is composed of an adhesive material containing 5% lidocaine that is applied to a polyester felt backing. When it is applied to the skin, lidocaine is released into the epidermal and dermal layers of the skin, reducing pain at the site of the dysfunctional nerves damaged by the prior herpes zoster infection. The lidocaine patch provides pain reduction without numbness of the affected skin.

In the United States, the lidocaine patch is sold under the name of Lidoderm.

Recommended dosage

The lidocaine patch is available in varying doses. Patches are applied directly to healthy, non-broken skin close to the source of pain or discomfort. Patients may typically apply up to three patches at one time. However, patches should not be worn longer than 12 hours in a 24-hour period. Patches can be cut into smaller pieces before removing the release liner and applying to the skin. Clothing may be worn over the applied patch.

If a dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, then the missed dose should be skipped. More patches than are instructed by the prescribing physician should never be applied.

Precautions

Lidocaine may not be suitable for persons who have had a past reaction to any local anesthetic. Patients should discuss past adverse reactions to anesthetics with their physician before using the lidocaine patch. The lidocaine

Key Terms

Herpes varicella zoster virus The virus that typically causes chicken pox in children; then may reactivate later in life to cause shingles.

Topical For application to the surface of the skin.

patch may also not be suitable for persons with a history of severe liver disease. Additionally, the lidocaine patch should be used with caution in persons receiving antiarryhthmic drugs.

Hand-washing is important after handling or applying the lidocaine patch. Contact with eyes should be avoided. The zipper pouch containing the lidocaine patches should be completely closed after opening, as the patches will lose potency if allowed to dry. Patches can be cut with scissors to the size and shape necessary to fit facial areas, but care should be used not to allow the material in the lidocaine patch to enter the eye. The lidocaine patch should never be chewed or ingested, or used to relieve pain inside the mouth.

Side effects

As only minute amounts of lidocaine enter the bloodstream from the patch, side effects are few. Most patients tolerate normal use of the lidocaine patch well, but some patients may experience usually mild side effects. Localized tingling may occur. If a rash or burning sensation occurs after application, the patch should be removed and not reapplied until the irritation subsides. If any symptom becomes uncomfortable, patients should consult the prescribing physician.

Some patients may be allergic to topical lidocaine and the lidocaine patch. Medical treatment should be sought immediately if any of the following symptoms occur:

- cough
- difficulty breathing or swelling of the tongue
- dizziness, **fainting**, or loss of consciousness
- hives or swelling of the face
- trouble breathing

Other less common side effects of the lidocaine patch may be serious, potentially indicating that too much medication is being absorbed into the body. A patient should seek medical treatment if experiencing:

- excessive, all-over numbness
- blurred or double vision
- ringing or buzzing in the ears
- uncontrollable nervousness, shaking
- slow heartbeat

Interactions

As the lidocaine patch is topical treatment and only minute amounts of the drug are absorbed into the bloodstream, interactions with other drugs are few. The lidocaine patch may have rare negative interactions with digoxin (Lanoxin) or any medications for irregular heartbeats. Some antibiotics, antidepressants, and monoamine oxidase inhibitors (MAOIs) may adversely react with the lidocaine patch or lessen its effectiveness.

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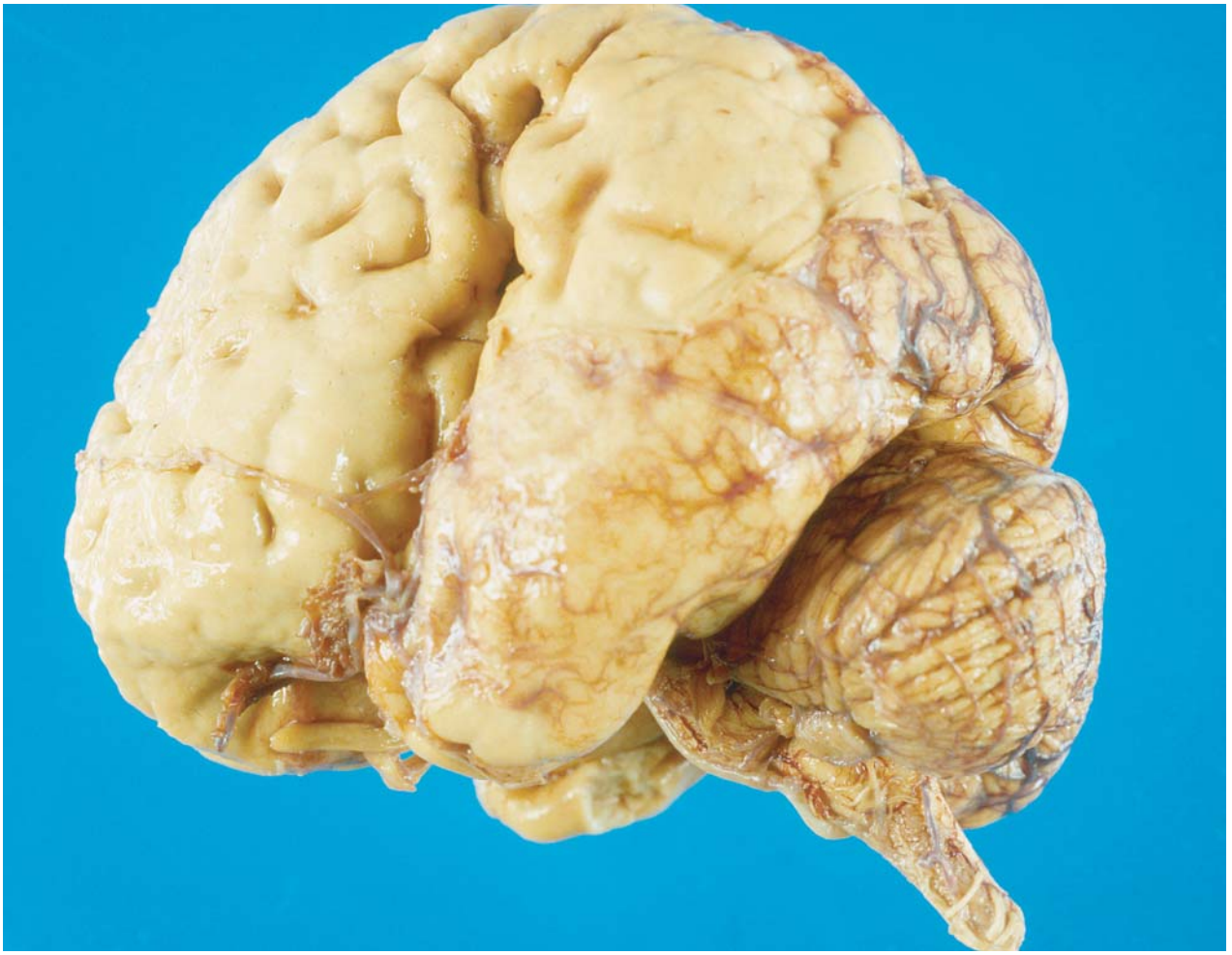
Adrienne Wilmoth Lerner

Lissencephaly

Definition

Lissencephaly is a neurological disorder of early brain development that leads to the gross appearance of a smooth brain. The malformed brain lacks the characteristic convolutions of the normal cerebral cortex and is abnormally thick. Lissencephaly is part of a spectrum of brain malformations, which are referred to as the agyria-pachygyria-band spectrum and are caused by abnormalities in neuronal migration, a critical process in brain development. These disorders range from complete absence of folds (agyria) to milder forms such as subcortical band heterotopia or double cortex syndrome, a neurological disorder where the malformed brain has two distinct



The disconnected hemispheres of a brain affected with agenesis of the corpus callosum. *(Custom Medical Stock Photo. All Rights Reserved.)*

layers of cerebral cortex. In pachygyria, there are localized areas of abnormally large folds and, in general, it is less severe than agyria. Scientific research on mice and humans has revealed several important genes responsible for causing lissencephaly.

Description

Lissencephaly was first described by Owen in 1868 and means "smooth brain," which describes the gross appearance of the brain. Microscopically, the brain appears abnormally thick and disorganized. The layering of the cerebral cortex is grossly abnormal, with four layers instead of the normal six layers.

Lissencephaly can be divided into two main subtypes. Type I, also known as classical lissencephaly, is distinguished by the smooth surface of the cerebral cortex and an abnormal four-layered cortex. Classical lissencephaly can be associated with abnormalities of the rest of the brain, including malformation of the corpus callosum or **cerebellum**. Lissencephaly can also be associated with other developmental abnormalities such as facial deformities in a syndrome known as the Miller-Dieker syndrome. Type II, or "cobblestone" lissencephaly, is characterized by a bumpy appearance of the abnormal surface of the brain. The cortex in Type II lissencephaly is completely abnormal and there are no distinguishable layers. This subtype tends to be associated with genetic syndromes affecting muscles, as in the Walker-Warburg syndrome. Different genes and distinct processes are thought to be responsible for causing the two types of lissencephaly.

Demographics

Type I lissencephaly is more common and comprises 43% of lissencephaly syndromes in some studies. Type II lissencephaly accounted for 14% of lissencephalies. The remainder in these studies were comprised of various disorders such as pachygyria.

Key Terms

Cerebral cortex The layer of gray matter that makes up the surface of cerebral hemispheres of the brain. It is responsible for controlling sensation, movement, and higher cognitive functions.

Causes and symptoms

Lissencephaly is due to a defect in neuronal migration, a sequence of events in early brain development in which nerve cells travel to their final destinations to populate and form the six layers of the cerebral cortex. This process occurs between 12 and 16 weeks gestation. When the brain first forms, neurons are generated in a region of the brain known as the ventricular zone. From there, they travel by crawling outward along other cells, known as radial glia, to reach the cortical surface. The traveling neurons need instructions on when to start, continue, and stop moving, and these processes are controlled by a complicated molecular machinery.

Several genes have been implicated in causing lissencephaly, and their roles in neuronal migration are currently being characterized. The first gene causing lissencephaly, LIS1, was identified in patients with Miller-Dieker syndrome, a genetic syndrome caused by deletions of chromosome 17 that is a combination of lissencephaly and other facial deformities. So far, five genes have been identified that cause type I lissencephaly in humans. Among them, LIS1, DCX, and RELN have been implicated as important at various steps during neuronal migration. DCX, a gene on the X-chromosome, is responsible for the double cortex syndrome, a milder subtype of lissencephaly, which has the unusual appearance of a brain with two layers of cerebral cortex, one normal and one abnormally situated in the white matter. This abnormal layer, called a band heterotopia, represents the neurons that have started and failed to migrate completely to their destination. For type II lissencephaly, only one gene, fukutin, has been identified. Presumably, the disorder in type II lissencephaly is an abnormal overmigration of neurons, which causes nerve cells to accumulate beyond the cortical surface, leading to the cobblestone appearance. Other nongenetic causes of lissencephaly include cytomegalovirus infection.

Babies with lissencephaly may appear normal at birth, but then progress to severe developmental delay, **seizures**, and failure to thrive at several months of age. There may be abnormally small head size, known as **microcephaly**. Seizures are usually difficult to treat and start out in the first few months of life. Patients may also develop **cerebral palsy** and decreased muscle tone. Patients with milder forms such as double cortex syndrome may not develop symptoms until later in early childhood. They may have only mild developmental delay and seizures without microcephaly.

Diagnosis

Diagnosis is usually made by neuroimaging. A computer tomography (**CT**) or **magnetic resonance imaging (MRI)** scan shows a smooth brain with the lack of characteristic folds. MRI may delineate the band of abnormal nerve cells in the double cortex syndrome. MRI may also show abnormalities in other areas of the brain in certain forms of lissencephaly. Genetic testing can be performed in patients with lissencephaly to identify abnormalities in the LIS1 or DCX gene.

Treatment team

Management of lissencephaly usually involves a pediatrician, pediatric **neurologist**, and physical therapists. A geneticist may be involved to provide counseling and advice about family planning. Depending on the age of onset of symptoms, an adult neurologist may be involved in treating symptoms of seizures. A case manager may be involved in coordinating the different care needs of the patient and families.

Treatment

Currently, there is no cure for lissencephaly. Treatment of individuals with lissencephaly depends on the manifesting symptoms. Patients may need anticonvulsant drug therapy for treatment of seizures. Muscle relaxants may be used for symptoms of increased tone.

Recovery and rehabilitation

Due to the congenital nature of lissencephaly, patients show little recovery from their symptoms. Physical therapists may help treat symptoms of weakness or increased tone associated with lissencephaly.

Clinical trials

A clinical trial is currently ongoing and is funded by the National Institutes of Health to identify genes responsible for **neuronal migration disorders** such as lissencephaly and **schizencephaly**.

Prognosis

There is no known cure for lissencephaly. Most individuals will die at an early age due to failure to thrive or infections such as pneumonia. Patients with milder forms such as double cortex syndrome may have mild retardation

and seizures only. The response to treatment varies from individual to individual.

Special concerns

Due to developmental disability, children with lissencephaly who survive beyond the age of two may benefit from special education programs. Various state and federal programs are available to help individuals and their families with meeting these needs.

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ORGANIZATIONS

Lissencephaly Network. 10408 Bitterroot Court, Ft. Wayne, IN 46804. (260) 432-4310. LissencephalyOne@aol.com. <http://www.lissencephaly.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605. (914) 428-7100 or (888) MODIMES; Fax: (914) 428-8203. askus@marchofdimes.com. <http://www.marchofdimes.com>.

National Information Center for Children and Youth with Disabilities. P.O. Box 1492, Washington, DC 20013-1492. (202) 884-8200 or (800) 695-0285; Fax: (202) 884-8441. nichcy@aed.org. <http://www.nichcy.org>.

National Institute of Child Health and Human Development (NICHD). Bldg. 31, Rm. 2A32, Bethesda, MD 20892-2425. (301) 496-5133 or (800) 370-2943. NICHDClearinghouse@mail.nih.gov. <http://www.nichd.nih.gov>.

Walsh Lab Web Site. 4 Blackfan Circle, Boston, MA 02115. (617) 667-0813; Fax: (617) 667-0815. cwalsh@bidmc.harvard.edu. <http://walshlab.bidmc.harvard.edu/>.

Peter T. Lin, MD

Locked-in syndrome

Definition

Locked-in syndrome is a condition in which an individual is fully conscious, but all the voluntary muscles of the body are completely paralyzed, with the exception of the muscles controlling eye movement.

Description

Locked-in syndrome is a catastrophic condition that prevents an individual from voluntarily moving any muscles of the body, other than those that control eye movement. As a result, the individual cannot move or speak, although some communication is possible through blinking or eye movements. Despite the devastating loss of function, an individual with locked-in syndrome is completely conscious and aware, able to think and reason normally. Luckily, locked-in syndrome is exceedingly rare.

About 40–70% of people suffering from locked-in syndrome die within a short time of suffering the causative injury.

Causes and symptoms

Locked-in syndrome can occur after severe, catastrophic brain injuries due to massive **stroke**, traumatic head injury, or ruptured aneurysm. Diseases that destroy the myelin sheath around nerves and the toxic effects of medication overdose can also cause locked-in syndrome. The most common cause involves any condition that affects an area of the brain called the ventral pons; all of the nerve tracts responsible for voluntary movement pass through the ventral pons. Areas of the brain responsible for cognition and consciousness are above the level of the ventral pons, and are therefore preserved.

Symptoms include complete inability to control any voluntary muscles in the body, other than those for eye movements and blinking. Reasoning, thinking, consciousness, and awareness are preserved. Normal sleep and wake cycles persist throughout the locked-in state.

Diagnosis

Diagnosis is evident in a conscious individual with no muscle functioning, save for the ability to respond to questions by blinking a certain number of times per the

interviewer's directions. Further diagnostic tests will be required to determine the underlying cause of the condition; **CT** or **MRI** scans can reveal the presence of an aneurysm or stroke.

Treatment team

Patients with locked-in syndrome are cared for by critical care specialists, neurologists, and physiatrists. A variety of therapists may also work with such patients, including physical therapists, occupational therapists, speech and language therapists, and psychotherapists.

Treatment

There is no cure for locked-in syndrome. Treatment is supportive.

Recovery and rehabilitation

One of the most important goals of rehabilitation involves finding assistive devices that can help with communication. A technique of stimulating muscle groups with electrodes (called functional neuromuscular stimulation) sometimes can help restore some small degree of functioning; however, even being able to move one finger can greatly improve an individual's ability to communicate or operate assistive devices that could improve that person's level of functioning.

Prognosis

Locked-in syndrome has a very poor prognosis, although some individuals have lived as long as 18 years with the condition.

Special concerns

Ethical dilemmas regarding the treatment and wishes of patients with locked-in syndrome are complicated.

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Rosalyn Carson-DeWitt, MD

Lou Gehrig disease *see* **Amyotrophic lateral sclerosis**

Lumbar radiculopathy *see* **Radiculopathy**

Lupus

Definition

Lupus, also known as lupus erythematosus, is an autoimmune inflammatory disorder that occurs mostly in women.

Description

Lupus produces widely varying symptoms, although joint **pain** is reported by most patients and skin lesions are common. Lupus can cause short periods of symptoms alternating with healthy periods, or can progress into a life-threatening disorder affecting the heart, kidneys, and other organs.

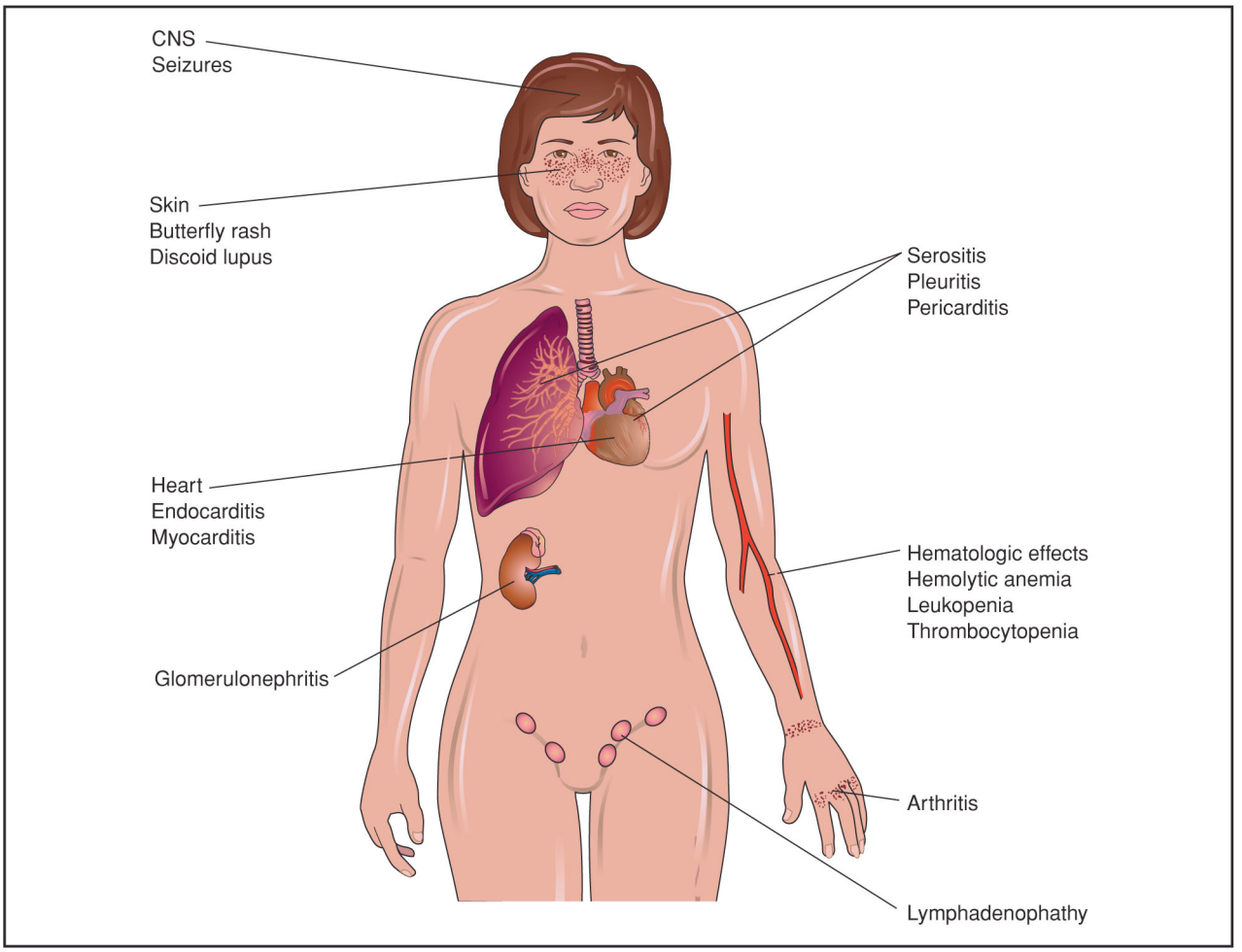
Why the disease is termed lupus is unknown, but it has been known as a distinct disorder and called lupus by European physicians since at least the tenth century A.D. The term erythematosus was first attached to the disease in the 1850s, and it refers to the patchy congestion of skin capillaries with blood (erythema) that often accompanies the disease.

Demographics

Between one million and 1.5 million Americans have some form of lupus. The incidence among women is 10–15 times greater than among men, and it is two to three times more common among African Americans, Hispanics, Asians, and Native Americans than among whites. Lupus most often appears for the first time in women between the ages of 15 and 44. Twenty thousand people die of lupus-related causes in the United States annually.

Causes and symptoms

Lupus is an autoimmune disorder, a disease in which the body's immune system turns against the body itself. In a healthy person, the immune system defends against invading organisms but does not, in general, attack the body's own tissues. The cause of lupus is unknown. However, it is known that lupus has a genetic component, which means a predisposition to lupus can be inherited. Approximately 10% of lupus patients have one or more direct relatives with lupus. (Note that this means that 90% of lupus patients have no such relatives; however, it shows a



Systemic lupus erythematosus (SLE) is an autoimmune disease in which the individual's immune system attacks, injures, and destroys the body's own organs and tissues. Nearly every system of the body can be affected by SLE, as depicted in the illustration above. *(Illustration by Electronic Illustrators Group.)*

Key Terms

Autoimmune disorder A disorder characterized by abnormal functioning of the immune system that causes the body to produce antibodies against its own tissues.

Cutaneous Relating to the skin.

Erythema Redness of the skin due to congestion of the capillaries, usually due to injury, infection, or inflammation.

genetic connection because 10% is a much higher figure for familial lupus than can be attributed to chance alone.) Lupus has been definitely linked to genes on chromosome 1 and less certainly to genes on chromosomes 4 and 6.

Given genetic susceptibility, the disease may either develop spontaneously or be triggered by some environmental factor. Environmental factors known to trigger lupus include infections (e.g., Epstein-Barr virus, which infects 99% of children with lupus, but only 70% of healthy children), antibiotics, ultraviolet light (the rays in sunlight or sunlamp-light that causes sunburn), stress, smoking, certain medications, and hormones (especially estrogen, the female sex hormone).

Lupus manifests as a continuum or spectrum of disorders. However, it is common to divide lupus cases into four categories or groups:

- Systemic lupus erythematosus. This is the most serious form of lupus and affects about 70% of all persons with lupus. It is termed systemic because, in this variety of lupus, the body's immune system attacks one or more essential body systems. Targets may include the brain, kidneys, heart, pancreas, or other organs.

- Discoid or cutaneous lupus erythematosus. This variety of lupus is less severe, in that it attacks the skin only. However, it can be disfiguring, often attacking the skin of the face. The term discoid is derived from the round (disc-shaped) lesions that appear on the skin. About 10–15% of lupus patients have cutaneous lupus.
- Drug-induced or drug-related lupus erythematosus. This term refers to lupus that develops after a patient has taken a medication. Medications that can trigger drug-induced lupus include procainamide or hydralazine. Many of the substances that can potentially trigger lupus fall into the class of aromatic amines, or hydrazines. For example, the aromatic amine paraphenylenediamine is present in certain hair dyes and has been associated with lupus or lupus-like syndrome. Tartrazine (a food coloring, FD&C yellow No. 5), which is present in thousands of foods and medications, has also been associated with lupus. Cocaine abuse can induce lupus and several other connective-tissue diseases, as can exposure to certain metals (e.g., mercury). Between 10,000 and 15,000 people are diagnosed with drug-induced lupus annually in the United States.
- Mixed connective tissue disease. Approximately 10% of patients with lupus also have symptoms of one or more additional connective-tissue diseases.

The symptoms of lupus are quite varied. In discoid lupus, red patches (erythema) appear symmetrically on the cheeks, possibly extending to the face, neck, scalp, and other parts of the body. No organ other than the skin is affected (or the disease is classified as systemic, rather than discoid). Systemic lupus may begin suddenly, signaled by fever, or develop slowly over months or years. Chronic **fatigue** is a common symptom. Symptoms related to impairment of any organ may occur. The lupus disease process in a given organ is named after that organ; for example, inflammation of the kidneys is termed lupus nephritis, and inflammation of the brain is termed lupus cerebritis. Kidney involvement may be fatal. Over 50% of all systemic lupus patients in the United States presently have some degree of lupus cerebritis; 25–75% have neuropsychiatric symptoms at some time in their illness. Symptoms of lupus cerebritis may include headaches, **seizures**, **stroke**, psychosis, **dementia**, **peripheral neuropathy**, cerebellar **ataxia** (failure of muscular coordination, usually on one side of the body), **chorea** (jerky, involuntary movements), and others. Duration of **central nervous system** involvement may be transient (as with a migraine **headache**) or long lasting (as with dementia). Stroke incidence is 3–20% in systemic lupus patients, and is highest in the first five years of the disease. Peripheral neuropathy (**carpal tunnel syndrome**, for example) occurs in more than 20% of systemic lupus patients and cranial nerve palsies occur in 10–15%.

Exposure to the ultraviolet rays in sunlight can trigger lupus or, in a person who already has the disease, cause it to flare up. Worsening flare-ups of the disease can be life threatening because they can include inflammation and failure of the kidneys. Also, declining memory and mental sharpness with long-term lupus is common.

Diagnosis

Lupus is notoriously difficult to diagnose. Many cases are not diagnosed until the patient has suffered irreversible kidney damage; for patients who do not have organ-threatening disease, diagnosis takes an average of two years of searching among physicians and conditions. The telltale erythematous skin lumps or rashes that give lupus erythematosus the latter half of its name eventually appear in 90% of systemic lupus patients and all discoid lupus patients, but may not appear early enough in the course of the disease to guarantee timely diagnosis. Additionally, no single lab test can confirm lupus, although certain antibody tests can help to distinguish lupus from other diseases.

Diagnosis of systemic lupus is based on a list of 11 criteria listed by the American College of Rheumatology. If four or more of the 11 criteria are met, a patient is deemed to have systemic lupus. The criteria include discoid or macular rash (often in a classic facial butterfly pattern across the nose and cheeks), photosensitivity, ulcers in the mouth, kidney dysfunction, and the presence of various blood factors such as anti-DNA antibody or anti-nuclear antibody (antibody that targets cell nuclei).

Approximately 15% of diagnoses of lupus may be misdiagnoses of other disorders, including fibromyalgia, seronegative spondyloarthropathies such as ankylosing spondylitis or Reiter's syndrome, autoimmune thyroiditis, and **multiple sclerosis**.

Although diagnosis of lupus cerebritis is particularly difficult, even if a patient has lupus, this does not necessarily mean that the neurological symptoms are due to lupus. Imaging studies cannot necessarily distinguish lupus cerebritis, although **magnetic resonance imaging (MRI)** studies are considered helpful. **Positron emission tomography (PET)** imaging has a high sensitivity to changes in the brain resulting from lupus cerebritis.

Treatment team

As with other neurological diseases in which the spectrum of symptoms varies widely, the treatment team must be designed for each individual case of lupus. A dermatologist will be involved if skin lesions are present; a **neurologist**, if cognitive loss is a possibility; a nephrologist will monitor kidney function; and a rheumatologist is often involved because of the frequency of joint pain. Other specialists will be needed depending on what organ systems are affected.

Treatment

There is no known cure for lupus. However, there are numerous interventions designed to lessen the severity of the disease. These interventions can be classed as pharmacologic (drug-based) or nonpharmacologic.

Pharmacologic interventions (drug therapies)

Five categories of medication are used to treat systemic lupus patients: sunscreens and steroid lotions, nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., acetaminophen or ibuprofen), corticosteroids (e.g., prednisone to suppress the autoimmune response and control inflammation), anti-malarial drugs, and cytotoxic agents (i.e., chemotherapy drugs that are used for cancer, such as methotrexate, azathioprine, and cyclophosphamide).

Cytotoxic agents are used in order to decrease steroid dosage. Anticoagulants (blood thinners) may also be prescribed. For patients with non-organ-threatening disease, the antimalarial drug hydroxychloroquine is often prescribed; prednisone is often prescribed in cases of organ-threatening disease. New lupus drugs are under investigation; with recent increases in knowledge about the genetic and molecular basis of autoimmune disorders, including lupus, pharmacological treatment breakthroughs are possible at any time.

Nonpharmacologic (non-drug) interventions

All persons with lupus should guard against exposure to the sun and use protective clothing, sunscreen, and common sense when going outdoors. Adequate **exercise** can protect against fatigue, obesity, osteoporosis (weakening of the bones), and hyperlipidemia (excessive fats in the blood plasma). In some cases, dietary restrictions may be helpful, including especially the avoidance of food allergens and foods that may trigger lupus symptoms (such as alfalfa seeds). Vitamins, minerals, and dietary fatty acids have been shown to moderate lupus symptoms in some cases. On the other hand, some dietary supplements such as melatonin and Echinacea can worsen symptoms of some autoimmune diseases.

For lupus cerebritis, therapy choices include all the above options for alleviating the disorder throughout the rest of the body. Drug therapy can also include psychotropic medications such as antipsychotics, antidepressants, and **benzodiazepines** to stabilize mood, if this is affected. Unfortunately, long-term use of corticosteroids, one of the mainstays of pharmacological lupus treatment, may itself cause psychiatric symptoms. Experimental investigation of pheresis of cerebrospinal fluid for treatment of lupus cerebritis (cerebrospinal fluid is withdrawn from, filtered, and returned to the patient) was begun in the early 1990s.

Clinical trials

As of mid-2004, approximately 25 lupus-related **clinical trials** were in progress, including investigations of monoclonal antibody therapy, the genetics of lupus, quality-of-life improvement, ultraviolet light therapy, stem-cell transplantation therapy, the mechanisms of kidney and brain damage, and many other aspects of lupus. Updated information on these trials can be found at the National Institutes of Health clinical trials website at <http://www.clinicaltrials.gov> for up-to-date information.

Prognosis

Prognosis for the individual patient depends on the severity of the disease process. Lupus can be fully compatible with a normal lifespan, or can result in fatal organ failure, depending upon the progression of the disorder in each individual.

Before corticosteroids became available, half of all patients with systemic lupus died within two years. Today, half of systemic lupus patients with organ-threatening complications survive for 20 years or longer. However, most systemic lupus patients eventually die from infections or from heart disease complicated by long-term use of corticosteroids.

There is some evidence that lupus may spontaneously resolve in part or whole, or resolve in response to treatment, in some lupus patients who have had the disease long term (i.e., 10 years or more).

Special concerns

Psychological counseling may be helpful, given that a diagnosis of lupus is life altering, and stress and frustration can enhance symptoms while searching for a diagnosis. Genetic counseling may be appropriate, as children of women with lupus have a 10% chance of developing lupus if female and 2% if male, while 20% of offspring overall will develop an autoimmune disorder of some type.

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ORGANIZATIONS

Lupus Foundation of America. 2000 L Street, N.W., Suite 710, Washington, DC 20036. (202) 349-1155; Fax: (202) 349-1156. <http://www.lupus.org/>.

Larry Gilman

Lyme disease

Definition

Lyme disease, which is also known as Lyme borreliosis, is an infection transmitted by the bite of deer ticks carrying the spirochete (spiral-shaped bacterium) *Borrelia burgdorferi*. The disease was named for Lyme, Connecticut, the town where it was first diagnosed in 1975 after a puzzling outbreak of juvenile arthritis. The organism that causes the disease was identified in 1982 and named for its discoverer, Willy Burgdorfer.

Description

Lyme disease is classified as a zoonosis, which means that it is a disease of animals that can be transmitted to humans under natural conditions; it cannot be transmitted person-to-person. *B. burgdorferi* is carried by infected deer ticks (more precisely known as black-legged ticks) and passed to humans or household pets when they are bitten by the ticks. In the United States, the white-footed mouse is the usual host of immature (nymphal and larval) ticks, while deer are the most common hosts of the adult ticks. In Europe, sheep are the usual hosts of adult infected ticks. Adult black-legged ticks are hard to detect because of their small size; an adult male tick, for example, is about 0.039 in (1 mm) long. An adult female is slightly larger, about 0.051 in (1.3 mm) long.

Ticks feed on their hosts by piercing the skin and slowly sucking blood through the broken tissue. The spirochete enters the host as the tick fills itself with blood. After the spirochete has been introduced into the person's skin, it may be destroyed by the body's defense mechanisms. If it is not eliminated, it may either remain in the skin or spread throughout the body through the lymphatic system or the bloodstream. *B. burgdorferi* can spread to the heart, joints, or **central nervous system** once it has gained access to the person's circulation. Studies show that *B. burgdorferi* can penetrate the central nervous system relatively early in the course of the infection without causing any neurologic symptoms. It can also remain in the person's skin for years without causing symptoms.

Lyme disease is a systemic illness, which means that it affects all parts of the body. The most commonly affected areas and organs, however, are the skin, nervous system, heart, joints, and eye. The symptoms of Lyme disease typically emerge in three stages.

It is possible for a person to contract Lyme disease more than once; having the disease does not lead to immunity.

Demographics

The risk of getting Lyme disease depends more on geographical location and the amount of time spent outdoors in tick-infested areas than on age, sex, or race per se, although about 25% of cases in the United States are reported in children younger than 14. Cases of Lyme disease have been reported in 49 of the 50 states; however, 92% of the 17,730 cases reported to the Centers for Disease Control and Prevention (CDC) in 2000 were from only nine states (Connecticut, Rhode Island, New York, Pennsylvania, Delaware, New Jersey, Maryland, Massachusetts, and Wisconsin). The disease is also found in Scandinavia, continental Europe, the countries of the former Soviet Union, Japan, and China; in addition, it is possible that it has spread to Australia.

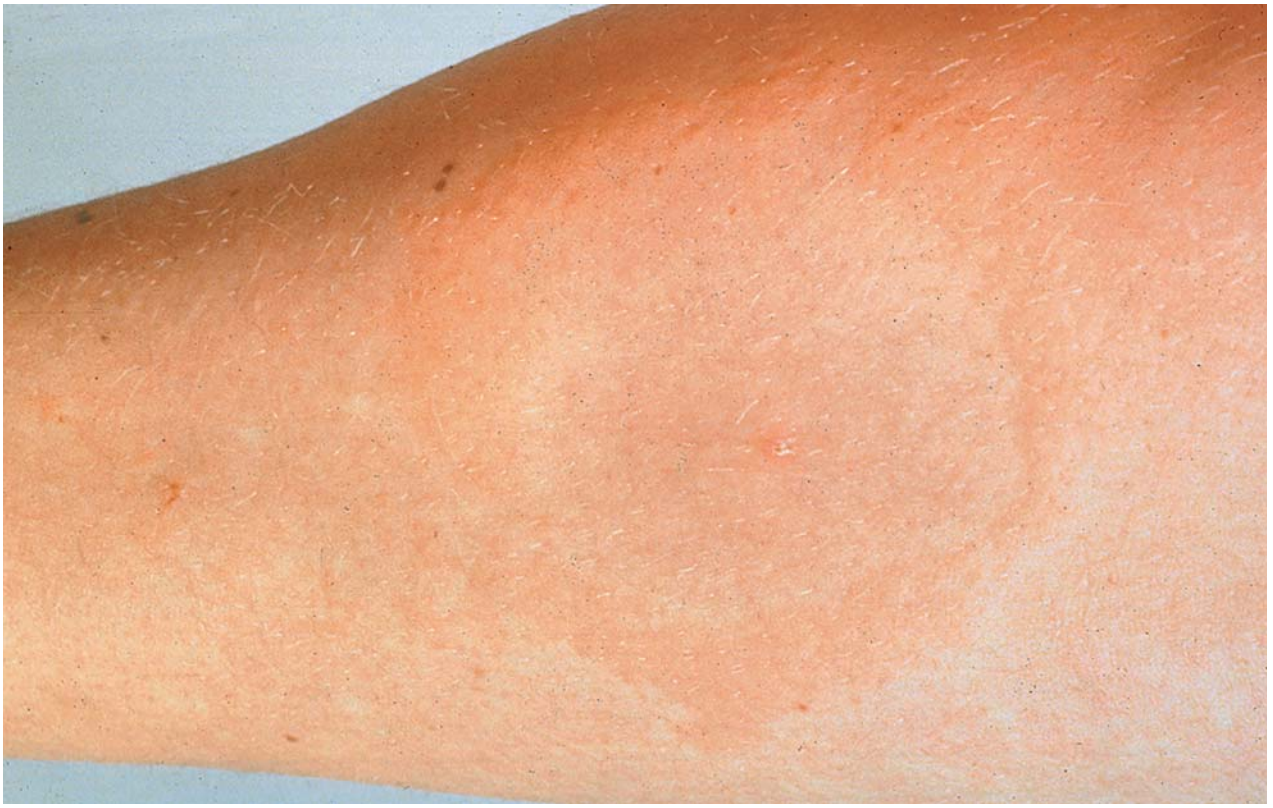
Lyme disease is seasonal in occurrence. In the United States, humans are most likely to be infected from May through August, when the ticks are most active and people are spending more time outdoors.

The number of cases reported in the United States continues to increase each year; the CDC attributes this increase to the growing size of the deer herd and the geographical spread of infected ticks rather than to improved diagnosis. In addition, some epidemiologists believe that the actual incidence of Lyme disease in the United States may be five to ten times greater than that reported by the CDC. The reasons for this difference include the narrowness of the CDC's case definition as well as frequent misdiagnoses of the disease.

Causes and symptoms

Lyme disease itself is caused by a bacterium known as *Borrelia burgdorferi*, which enters the skin through the bite of an infected tick belonging to the genus *Ixodes*. In Europe, the disease is caused by related species known as *B. afzinii* and *B. garinii*.

Currently, scientists do not completely understand exactly how *B. burgdorferi* produces the variety of symptoms that characterize Lyme disease. Some symptoms are



Lyme disease. The image shows the side of a leg at the calf with an insect bite enclosed by a distinctive, slightly raised red ring. The rash is called erythema chronicum migrans. *(© 1993 Science Photo Library. Custom Medical Stock Photo. Reproduced by permission.)*

directly caused by the spirochete, but others may result from the body's immune response to the organism.

The symptoms of Lyme disease are typically divided into three stages: early localized, early disseminated, and late. Neurologic complications are most common in disseminated and late-stage Lyme disease.

EARLY LOCALIZED DISEASE Early symptoms of Lyme disease include low-grade fever and erythema migrans, or EM, a red spot or patch on the skin that is found in about 75% of patients with Lyme disease. The initial spot is usually found on the arms, legs, armpits, or trunk within 3–32 days after the tick bite. Erythema migrans often has a ring-like or "bull's-eye" appearance, with the bite itself in the center of the affected area, surrounded by a ring of reddened and inflamed skin. The ring grows outward around the central lesion, sometimes growing as large as 27 in (70 cm) in diameter. Secondary EM lesions appear in about 20% of patients. The rash does not usually itch or burn, and typically fades in a few weeks even if untreated.

Other symptoms of early-stage Lyme disease include flu-like muscular aches and pains, **headache**, a stiff neck, and **fatigue**. Nausea and vomiting or sore throat occur in some patients, but are less common symptoms.

EARLY DISSEMINATED DISEASE Early disseminated Lyme disease is characterized by ongoing fatigue; arthritis-like pains in the joints; a headache that comes and goes; inflammation of the tendons and their protective sheaths (synovitis); and red or itchy eyes (conjunctivitis). It is common for the aches and pains in muscles and joints to move from one part of the person's body to another. About 8% of people with Lyme disease develop cardiac complications, which may include heart block and inflammation of the walls of the heart (myocarditis).

Neurologic symptoms in early disseminated Lyme disease affect about 15% of people, usually within a few weeks to months after the onset of EM. The following may be the first symptoms in people who did not develop EM, however:

- **Bell's palsy**. This refers to weakness or paralysis of the facial muscles caused by inflammation or swelling of the seventh cranial nerve. People with facial palsy caused by Lyme disease may be affected on both sides of the face.

Key Terms

Babesiosis A disease caused by protozoa of the genus *Babesia* characterized by a malaria-like fever, anemia, vomiting, muscle pain, and enlargement of the spleen. Babesiosis, like Lyme disease, is carried by a tick.

Bell's palsy Facial paralysis or weakness with a sudden onset, caused by swelling or inflammation of the seventh cranial nerve, which controls the facial muscles. Disseminated Lyme disease sometimes causes Bell's palsy.

Cerebrospinal fluid A clear fluid found around the brain and spinal cord and in the ventricles of the brain.

Disseminated Scattered or distributed throughout the body. Lyme disease that has progressed beyond the stage of localized EM is said to be disseminated.

Erythema migrans (EM) A red skin rash that is one of the first signs of Lyme disease in about 75% of patients.

Lyme borreliosis Another name for Lyme disease.

Prophylactic Treatment given to protect against or ward off disease. Many doctors give antibiotics to patients who have been bitten by ticks as a prophylactic measure against Lyme disease.

Radiculoneuropathy Disease of the nerve roots and nerves.

Spirochete A bacterium shaped like a loosely coiled spiral. The organism that causes Lyme disease is a spirochete.

Vector An animal carrier that transfers an infectious organism from one host to another. The vector that transmits Lyme disease from wildlife to humans is the deer tick or black-legged tick.

Zoonosis (plural, zoonoses) Any disease of animals that can be transmitted to humans under natural conditions. Lyme disease and babesiosis are examples of zoonoses.

This symptom may be important in diagnosis, as Bell's palsy caused by other disorders typically affects only one side of the face.

- Radiculoneuropathy. This is the medical term for disease affecting nerves and nerve roots. In Lyme disease, neuropathy often takes the form of abnormal sensations (paresthesias) in the hands or feet.
- Meningoencephalitis. This refers to inflammation of the brain tissue and the protective membranes that cover it (the **meninges**). This complication of Lyme disease often causes sleep disturbances, memory problems, difficulty concentrating, mood swings, headache, **ataxia** (loss of muscular coordination), paresis (mild paralysis), and disturbances in the person's deep tendon reflexes. To test these reflexes, or involuntary responses of certain muscles to a stimulus, the physician gently taps with a small hammer below the person's kneecap, behind the elbow, over the Achilles tendon at the back of the heel, and over the biceps and triceps muscles in the upper arm. The deep tendon reflexes are often weakened or asymmetrical in people with meningoencephalitis related to Lyme disease.

LATE DISEASE The most common symptom of late disseminated Lyme disease is swelling and **pain** in a few large weight-bearing joints, most often the knee. The affected joints are typically much more swollen than painful, but the arthritis may be accompanied by low-grade fever and fatigue. Lyme-related arthritis develops within weeks to months after the initial eruption of erythema migrans. About 10% of people diagnosed with Lyme disease develop chronic arthritis of the knee.

A late-stage complication of Lyme disease that affects the skin is acrodermatitis chronica atrophicans, a disorder in which the skin on the person's lower legs or hands becomes inflamed and paper-thin. This disorder is seen more frequently in Europe than in the United States.

People with late-stage Lyme disease may develop a neurologic disorder characterized by personality changes and problems with thinking or memory that persist in spite of antibiotic treatment. This syndrome has been called persistent Lyme disease, or PLD. One study of 33 patients diagnosed with PLD found that the most common symptoms were headache (36.4% of patients); memory problems (27.3%); insomnia (33.3%); problems with gait and coordination (36.4%); and impaired deep tendon reflexes (9%). Children with PLD have difficulty getting along with classmates in school as well as making academic progress, and are at increased risk of developing long-term psychiatric disturbances.

Diagnosis

Early diagnosis and prompt treatment are critical to preventing the neurologic complications of Lyme disease.

Patient history and symptoms

The diagnosis of Lyme disease is complicated by the fact that about 25% of patients do not develop the characteristic rash. It is important for the doctor to determine the likelihood of Lyme disease by taking a careful history of exposure to ticks, as only about 25% of patients recall being bitten. In addition to the history, the doctor will examine the patient for the following symptoms:

- Erythema migrans. When present, EM has a characteristic "bull's-eye" pattern. In addition, the bite location is often significant; tick bites are more frequently found in such body folds as the armpits or on areas on the trunk near elastic bands in bra straps or underwear.
- Fever. The fever that accompanies early Lyme disease is usually low; a high fever indicates either concurrent infection with babesiosis or a different diagnosis altogether.
- Absence of digestive or respiratory symptoms.
- Presence of fatigue, headache, and muscle or joint pains.

Laboratory tests

Blood testing is not considered necessary if the patient has EM, a history of exposure to ticks, and other indications of a high likelihood of Lyme disease. Moreover, it is difficult to culture *B. burgdorferi* from human tissues and body fluids. Timing is another important factor in interpreting blood tests for Lyme disease; patients in the early stages of the disease may continue to test negative for several weeks after being infected. Blood testing is, however, recommended for patients with Bell's palsy or myocarditis. The CDC advises doctors to perform a two-step blood test: a screening ELISA test, followed by a Western blot test for confirmation.

Polymerase chain reaction (PCR) testing may not be available in all hospitals, but can be used to detect the DNA of *B. burgdorferi* in fluid drawn from the joints of untreated patients with late-stage symptoms.

Imaging studies

Imaging studies are rarely used to diagnose Lyme disease with the exception of late-stage arthritis. X rays of patients with Lyme-related arthritis usually show considerable swelling of soft tissue; erosion of bone or cartilage also appears in a small minority of these patients.

Treatment team

Patients are usually treated initially by an emergency physician (if they have gone to an emergency room to have the tick removed) or by a primary care physician (PCP).

The PCP may consult a **neurologist**, dermatologist, or infectious disease specialist to confirm the diagnosis or advise about medications, particularly in cases of chronic or late-stage disease.

Treatment

Initial treatment

Immediate removal of an attached tick is the first step in treatment for people who know they have been bitten. Because black-legged ticks are slow feeders, it takes about 36 hours for *B. burgdorferi* to make its way into the body; infection is unlikely if the tick is removed within 24 hours of attachment. People who find ticks on themselves should *not* use a hot match, petroleum jelly, nail polish, or similar items to remove the tick. They should use fine-tipped tweezers, grasp the tick as close to the skin as possible, and pull the tick away from the skin with a steady motion. The area should then be cleansed with an antiseptic.

If the person has been bitten in an area with a high percentage of infected ticks, the doctor will usually prescribe a prophylactic (disease-preventing) course of antibiotics. The usual dosage is 10 days of oral amoxicillin, doxycycline, or cefuroxime, although a study published in 2001 reported that a single 200-mg dose of doxycycline is also effective.

Aspirin or NSAIDs may be given to relieve fever, aching muscles, and other flu-like symptoms of early Lyme disease.

Treatment of disseminated disease and neurologic complications

Patients who have developed heart block as a complication of disseminated Lyme disease may require a temporary pacemaker. Those with swollen knee joints may need to have excess fluid removed by aspiration, a procedure in which the doctor withdraws the fluid through a fine needle.

Patients with Bell's palsy may be given oral antibiotics for 21–30 days. Patients who have neurologic symptoms together with Lyme-related arthritis are usually treated with intravenous ceftriaxone.

Recovery and rehabilitation

Most patients with neurologic complications of Lyme disease recover completely following treatment with antibiotics. Those who do not respond are usually given an additional course of antibiotics. As of 2003, however, treatment recommendations for central nervous system (CNS) complications of Lyme disease are still evolving, and there is ongoing disagreement among specialists regarding the effectiveness of various treatments for PLD.

Clinical trials

As of October 2003, the National Institute of Neurological Disorders and Stroke (NINDS) is recruiting patients for a 24-week treatment study of persistent Lyme disease (PLD). The investigators will be using brain imaging (**MRI** and **PET** scans) to study the effects of intravenous antibiotic treatment on the neurologic symptoms of PLD. Two other trials are recruiting patients with Lyme disease in order to study the immune system's response to the disorder and to evaluate various treatment regimens.

Prognosis

Patients who are treated early with antibiotics and take their medications on schedule should recover completely from Lyme disease. Most long-term effects of the infection result from misdiagnosis or delayed treatment. Co-infection with such other tick-borne diseases as babesiosis and ehrlichiosis may lead to treatment failures or more severe symptoms. The few fatalities reported with Lyme disease occurred in patients who had also contracted babesiosis.

Neurologic symptoms of early disseminated Lyme disease may last for several months but usually resolve completely. Late neurologic complications of Lyme disease, however, may not respond to antibiotic therapy, particularly if diagnosis and treatment were delayed.

Special concerns

A vaccine for Lyme disease known as LYMErix was available from 1998 to 2002, when it was removed from the United States market. The decision was influenced by reports that LYMErix may be responsible for neurologic complications in vaccinated patients. Researchers from Cornell-New York Hospital presented a paper at the annual meeting of the American Neurological Association in October 2002 that identified nine patients with neuropathies linked to vaccination with LYMErix. In April 2003, the National Institute of Allergy and Infectious Diseases (NIAID) awarded a federal grant to researchers at Yale University School of Medicine to develop a new vaccine against Lyme disease.

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NINDS Information Page. *Neurological Complications of Lyme Disease.* Bethesda, MD: NINDS, 2003.

WEBSITES

Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases. *CDC Lyme Disease Home Page.* (February 20, 2004.) <http://www.cdc.gov/ncidod/dvbid/lyme/>.

ORGANIZATIONS

Centers for Disease Control and Prevention (CDC). 1600 Clifton Road, NE, Atlanta, GA 30333. (800) 311-3435. inquiry@cdc.gov. <http://www.cdc.gov>.

Lyme Disease Foundation. One Financial Plaza, Hartford, CT 06103. (860) 525-2000 or (860) 525-TICK or (800) 886-LYME. lymefnd@aol.com. <http://www.lyme.org>.

National Institute of Allergy and Infectious Diseases (NIAID). 31 Center Drive, Room 7A50 MSC 2520, Bethesda, MD 20892. (301) 496-5717. <http://www.niaid.nih.gov>.

NIH Neurological Institute. P. O. Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

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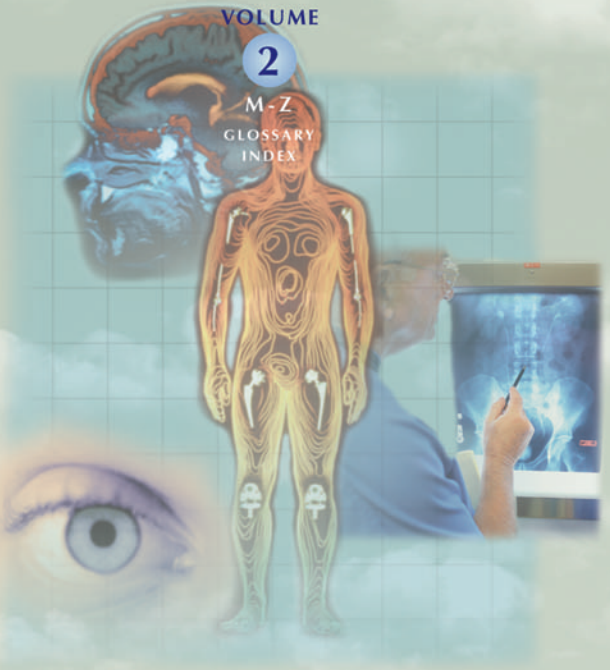

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PLEASE READ—IMPORTANT INFORMATION

The Gale Encyclopedia of Neurological Disorders is a medical reference product designed to inform and educate readers about a wide variety of diseases, syndromes, drugs, treatments, therapies, and diagnostic equipment. Thomson Gale believes the product to be comprehensive, but not necessarily definitive. It is intended to supplement, not replace, consultation with a physician or other healthcare practitioner. While Thomson Gale has made substantial efforts to provide information that is accurate, comprehensive, and up-to-date, Thomson Gale 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 are advised to seek professional diagnosis and treatment for any medical condition, and to discuss information obtained from this book with their healthcare providers.

INTRODUCTION

The Gale Encyclopedia of Neurological Disorders (GEND) is a one-stop source for medical information that covers diseases, syndromes, drugs, treatments, therapies, and diagnostic equipment. It keeps medical jargon to a minimum, making it easier for the layperson to use. *The Gale Encyclopedia of Neurological Disorders* presents authoritative and balanced information and is more comprehensive than single-volume family medical guides.

SCOPE

Almost 400 full-length articles are included in *The Gale Encyclopedia of Neurological Disorders.* Articles follow a standardized format that provides information at a glance. Rubrics include:

Diseases

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- Demographics
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INCLUSION CRITERIA

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

ABOUT THE CONTRIBUTORS

The essays were compiled by experienced medical writers, physicians, nurses, and pharmacists. GEND medical advisors reviewed most of the completed essays to insure that they are appropriate, up-to-date, and medically accurate.

HOW TO USE THIS BOOK

The *Gale Encyclopedia of Neurological Disorders* has been designed with ready reference in mind:

- Straight **alphabetical arrangement** allows users to locate information quickly.
- Bold faced terms function as print hyperlinks that point the reader to full-length entries in the encyclopedia.
- A list of **key terms** is provided where appropriate to define unfamiliar words or concepts used within the context of the essay.
- **Cross-references** placed throughout the encyclopedia direct readers to where information on subjects without their own entries can be found. Cross-references are also used to assist readers looking for information on diseases that are now known by other names; for example, there is a cross-reference for the rare childhood disease commonly known as Hallervorden-Spatz disease that points to the entry entitled Pantothenate kinase-associated neurodegeneration.
- A **Resources** section directs users to sources of further information, which include books, periodicals, websites, and organizations.
- A **glossary** is included to help readers understand unfamiliar terms.
- A comprehensive **general index** allows users to easily target detailed aspects of any topic.

GRAPHICS

The Gale Encyclopedia of Neurological Disorders is enhanced with over 100 images, including photos, tables, and customized line drawings.

ADVISORY BOARD

An advisory board made up of prominent individuals from the medical and healthcare communities provided invaluable assistance in the formulation of this encyclopedia. They defined the scope of coverage and reviewed individual entries for accuracy and accessibility; in some cases they contributed entries themselves. We would therefore like to express our great appreciation to them:

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M

Machado-Joseph disease

Definition

Machado-Joseph disease (MJD), also known as **spinocerebellar ataxia** Type 3 (SCA 3), is a rare hereditary disorder affecting the **central nervous system**, especially the areas responsible for movement coordination of limbs, facial muscles, and eyes. The disease involves the slow and progressive degeneration of brain areas involved in motor coordination, such as the cerebellar, extrapyramidal, pyramidal, and motor areas. Ultimately, MJD leads to paralysis or a crippling condition, although intellectual functions usually remain normal. Other names of MJD are Portuguese-Azorean disease, Joseph disease, Azorean disease.

Description

Machado-Joseph disease was first described in 1972 among the descendants of Portuguese-Azorean immigrants to the United States, including the family of William Machado. In spite of differences in symptoms and degrees of neurological degeneration and movement impairment among the affected individuals, it was suggested by investigators that in at least four studied families the same gene mutation was present. In early 1976, investigators went to the Azores Archipelago to study an existing neurodegenerative disease in the islands of Flores and São Miguel. In a group of 15 families, they found 40 people with neurological disorders with a variety of different symptoms among the affected individuals.

Another research team in 1976 reported an inherited neurological disorder of the motor system in Portuguese families, which they named Joseph disease. During the same year, the two groups of scientists both published independent evidence suggesting that the same disease was the primary cause for the variety of symptoms observed. When additional reports from other countries and ethnic groups were associated with the same inherited disorder, it was initially thought that Portuguese-Azorean sailors had been the probable disseminators of MJD to other populations around the world during the sixteenth century period of Portuguese colonial explorations and commerce. Presently, MJD is found in Brazil, United States, Portugal, Macau, Finland, Canada, Mexico, Israel, Syria, Turkey, Angola, India, United Kingdom, Australia, Japan, and China. Because MJD continues to be diagnosed in a variety of countries and ethnic groups, there are current doubts about its exclusive Portuguese-Azorean origin.

Causes and symptoms

The gene responsible for MJD appears at chromosome 14, and the first symptoms usually appear in early adolescence. **Dystonia** (**spasticity** or involuntary and repetitive movements) or gait **ataxia** is usually the initial symptoms in children. Gait ataxia is characterized by unstable walk and standing, which slowly progresses with the appearance of some of the other symptoms, such as hand dysmetria, involuntary eye movements, loss of hand and superior limbs coordination, and facial dystonia (abnormal muscle tone). Another characteristic of MJD is clinical anticipation, which means that in most families the onset of the disease occurs progressively earlier from one generation to the next. Among members of the same family, some patients may show a predominance of muscle tone disorders, others may present loss of coordination, some may have bulging eyes, and yet another sibling may be free of symptoms during his/her entire life. In the late stages of MJD, some people may experience **delirium** or **dementia**.

According to the affected brain area, MJD is classified as Type I, with extrapyramidal insufficiency; Type II, with cerebellar, pyramidal, and extrapyramidal insufficiency; and Type III, with cerebellar insufficiency. Extrapyramidal tracts are networks of uncrossed motor nerve fibers that function as relays between the motor areas and corresponding areas of the brain. The pyramidal tract consists of groups of crossed nerves located in the white matter of the spinal cord that conduct motor impulses originated in

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.

Cerebellar Involving the part of the brain (cerebellum) that controls walking, balance, and coordination.

Dysarthria Slurred speech.

Dystonia Painful involuntary muscle cramps or spasms.

Extrapyramidal Refers to brain structures located outside the pyramidal tracts of the central nervous system.

Genotype The genetic makeup of an organism or a set of organisms.

Mutation A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease. This change can be transmitted to offspring.

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.

Spasticity Increased mucle tone, or stiffness, which leads to uncontrolled, awkward movements.

Trinucleotide A sequence of three nucleotides.

the opposite area of the brain to the arms and legs. Pyramidal tract nerves regulate both voluntary and reflex muscle movements. However, as the disease progresses, both motor systems tracks will eventually suffer degeneration.

Diagnosis

Diagnosis depends mainly on the clinical history of the family. Genetic screening for the specific mutation that causes MJD can be useful in cases of persons at risk or when the family history is not known or a person has symptoms that raise suspicion of MJD. Initial diagnosis may be difficult, as people present symptoms easily mistaken for other neurological disorders such as **Parkinson** and **Huntington diseases**, or even **multiple sclerosis**.

Treatment

Although there is no cure for Machado-Joseph disease, some symptoms can be relieved, The medication Levodopa or L-dopa often succeeds in lessening muscle rigidity and **tremors**, and is often given in conjunction with the drug Carbidopa. However, as the disease progresses and the number of neurons decreases, this palliative (given for comfort) treatment becomes less effective. Antispasmodic drugs such as baclofen are also prescribed to reduce spasticity. **Dysarthria**, or difficulty to speak, and dysphagia, difficulty to swallow, can be treated with proper medication and speech therapy. Physical therapy can help patients with unsteady gait, and walkers and wheelchairs may be needed as the disease progresses. Other symptoms also require palliative treatment, such as muscle cramps, urinary disorders, and sleep problems.

Clinical Trials

Further basic research is needed before **clinical trials** become a possibility for MJD. Ongoing genetic and molecular research on the mechanisms involved in the genetic mutations responsible for the disease will eventually yield enough data to provide for future development and design of experimental gene therapies and drugs specific to treat those with MJD.

Prognosis

The frequency with which such genetic mutations trigger the clinical onset of disease is known as penetrance. Machado-Joseph disease presents a 94.5% penetrance, which means that 94.5% of the mutation carriers will develop the symptoms during their lives, and less than 5% will remain free of symptoms. Because the intensity and range of symptoms are highly variable among the affected individuals, it is difficult to determine the prognosis for a given individual. As MJD progresses slowly, most patients survive until middle age or older.

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Dystonia Medical Research Foundation. 1 East Wacker Drive, Suite 2430, Chicago, IL 60601-1905. (312) 755-0198; Fax: (312) 803-0138. dystonia@dystonia-foundation.org. <http://www.dystonia-foundation.org>.

International Machado-Joseph Disease Foundation, Inc. P.O. Box 994268, Redding, CA 96099-4268. (530) 246-4722. MJD@ijdf.net. <http://www.ijdf.net>.

National Ataxia Foundation (NAF). 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447-4752. (763) 553-0020; Fax: (763) 553-0167. naf@ataxia.org. <http://www.ataxia.org>.

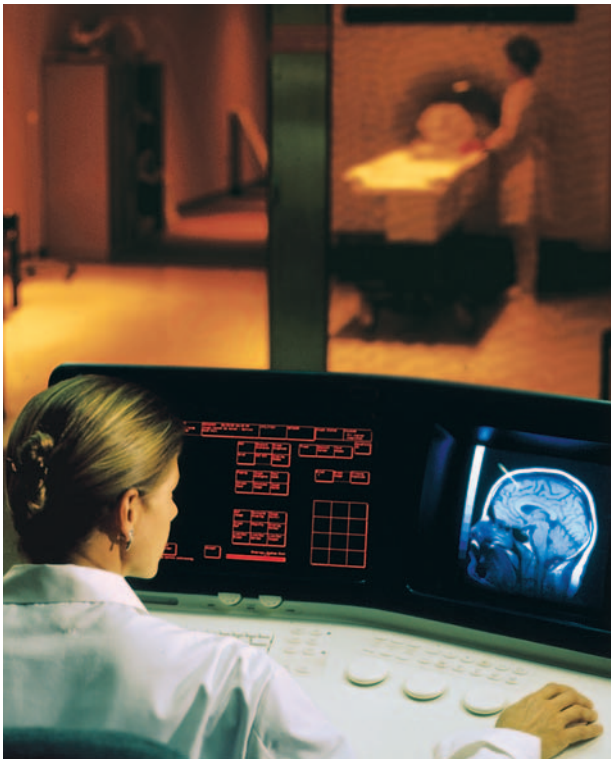
National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD (6673); Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Worldwide Education & Awareness for Movement Disorders (WE MOVE). 204 West 84th Street, New York, NY 10024. (212) 875-8312 or (800) 437-MOV2 (6682); Fax: (212) 875-8389. wemove@wemove.org. <http://www.wemove.org>.

Sandra Galeotti

Macrencephaly *see* **Megalencephaly**

Mad cow disease *see* **Creutzfeldt-Jakob disease**



Technician conducting an MRI. (*Will & Deni McIntyre/Photo Researchers, Inc. Reproduced by permission.)*

Magnetic resonance imaging (MRI)

Definition

Magnetic resonance imaging (MRI) scanners rely on the principles of atomic nuclear-spin resonance. Using strong magnetic fields and radio waves, MRI collects and correlates deflections caused by atoms into images. MRIs (magnetic resonance imaging tests) offer relatively sharp pictures and allow physicians to see internal bodily structures with great detail. Using MRI technology, physicians are increasingly able to make diagnosis of serious pathology (e.g., tumors) earlier, and earlier diagnosis often translates to a more favorable outcome for the patient.

Description

A varying (gradient) magnetic field exists in tissues in the body that can be used to produce an image of the tissue. The development of MRI was one of several powerful diagnostic imaging techniques that revolutionized medicine by allowing physicians to explore bodily structures and functions with a minimum of invasion to the patient.

In the last half of the twentieth century, dramatic advances in computer technologies, especially the development of mathematical algorithms powerful enough to allow difficult equations to be solved quickly, allowed MRI to develop into an important diagnostic clinical tool. In particular, the ability of computer programs to eliminate "noise" (unwanted data) from sensitive measurements enhanced the development of accurate, accessible and relatively inexpensive noninvasive technologies.

Nuclear medicine is based upon the physics of excited atomic nuclei. Nuclear magnetic resonance (NMR) was one such early form of nuclear spectroscopy that eventually found widespread use in clinical laboratory and medical imaging. Because a proton in a magnetic field has two quantized spin states, NMR allowed the determination of the complex structure of organic molecules and, ultimately, the generation of pictures representing the larger structures of molecules and compounds (such as neural tissue, muscles, organs, bones, etc.). These pictures were obtained as a result of measuring differences between the expected and actual numbers of photons absorbed by a target tissue.

Groups of nuclei brought into resonance, that is, nuclei-absorbing and -emitting photons of similar electromagnetic **radiation** (e.g., radio waves), make subtle yet distinguishable changes when the resonance is forced to change by altering the energy of impacting photons. The speed and extent of the resonance changes permit a nondestructive (because of the use of low energy photons) determination of anatomical structures. This form of NMR

became the physical and chemical basis of the powerful diagnostic technique of MRI.

The resolution of MRI scanning is so high that they can be used to observe the individual plaques in **multiple sclerosis**. In a clinical setting, a patient is exposed to short bursts of powerful magnetic fields and radio waves from electromagnets. MRI images do not utilize potentially harmful ionizing radiation generated by three-dimensional x-ray computed tomography (CT) scans, and there are no known harmful side effects. The magnetic and radio wave bursts stimulate signals from hydrogen atoms in the patient's tissues that, when subjected to computer analysis, create a cross-sectional image of internal structures and organs.

Healthy and diseased tissues produce different signal patterns and thus allow physicians to identify diseases and disorders.

American chemist and physicist Paul Lauterbur and British physicist Sir Peter Mansfield shared the 2003 Nobel Prize in Physiology or Medicine for their discoveries concerning the use of magnetic resonance to visualize different structures.

MRI tests, brain scans, and potential security issues

Studies of the potential of new brain wave scanners explore the possibility that MRI tests could be part of a more accurate form of polygraph (lie detector). Current polygraphs are of debatable accuracy (usually they are not admissible in court as evidence) and measure observable fluctuations in heart rate, breathing, perspiration, etc.

In a 2001 University of Pennsylvania experiment using MRI, 18 subjects were given objects to hide in their pockets, then shown a series of pictures and asked to deny that the object depicted was in their pockets. Included was a picture of the object they had pocketed and so subjects were "lying" (making a deliberate false statement) if they claimed that the object was not in their pocket. An MRI recorded an increase of activity in the anterior cinglate, a portion of the brain associated with inhibition of responses and monitoring of errors, as well as the right superior frontal gyrus, which is involved in the process of paying attention to particular stimuli.

After the September 11, 2001, terrorist attacks, a number of government agencies in the United States began to take a new look at brain scanning technology as a potential means of security screening. Such activity, along with an increase of interest in potential brain-wave scanning by the Federal Bureau of Investigation (FBI), has raised concerns among civil-liberties groups, which view brain-wave scanning as a particularly objectionable invasion of privacy.

Key Terms

Magnetic resonance imaging MRI An imaging technique used in evaluation and diagnoses of the brain and other parts of the body.

Resonance A condition in which the applied force (e.g., forced vibrations, forced magnetic field, etc.) becomes the same as the natural frequency of the target (e.g., tissue, cell structure, etc.).

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Paul Arthur

Megalencephaly

Definition

Megalencephaly (also called macrencephaly) describes an enlarged brain whose weight exceeds the mean (the average weight for that age and sex) by at least 2.5 standard deviations (a statistical measure of variation). Megalencephaly may also be defined in terms of volume rather than weight. Hemimegalencephaly (or unilateral megalencephaly) is a related condition in which brain enlargement occurs in one hemisphere (half) of the brain.

Description

A person with megalencephaly has a large, heavy brain. In general, a brain that weighs more than 1600 grams (about 3.5 pounds) is considered megalencephalic. The heaviest brain on record weighed 2850 grams (about 6.3 pounds). Macrocephaly, a related condition, refers to an abnormally large head. Macrocephaly may be due to megalencephaly or other causes such as **hydrocephalus** (an excess accumulation of fluid in the brain), and brain edema. Megalencephaly may be an isolated finding in an otherwise normal individual or it can occur in association with neurological problems (such as **seizures** or **mental retardation**) and/or somatic abnormalities (physical

Key Terms

Autosomal dominant A pattern of inheritance in which only one of the two copies of an autosomal gene must be abnormal for a genetic condition or disease to occur. An autosomal gene is a gene that is located on one of the autosomes or non-sex chromosomes. A person with an autosomal dominant disorder has a 50% chance of passing it to each of their offspring.

Autosomal recessive A pattern of inheritance in which both copies of an autosomal gene must be abnormal for a genetic condition or disease to occur. An autosomal gene is a gene that is located on one of the autosomes or non-sex chromosomes. When both parents have one abnormal copy of the same gene, they have a 25% chance with each pregnancy that their offspring will have the disorder.

Chromosome A microscopic thread-like structure found within each cell of the human body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Chromosomes contain the genetic information necessary to direct the development and functioning of all cells and systems in the body. They pass on hereditary traits from parents to child (like eye color) and determine whether the child will be male or female.

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.

Inborn error of metabolism One of a group of rare conditions characterized by an inherited defect in an enzyme or other protein. Inborn errors of metabolism can cause brain damage and mental retardation if left untreated. Phenylketonuria, Tay-Sachs disease, and galactosemia are inborn errors of metabolism.

problems or birth defects of the body). Dysmorphic facial features (abnormal shape, position or size of facial features) may also be observed in an affected individual.

According to the National Institute of Neurological Disorders and Stroke (NINDS), megalencephaly is one of the cephalic disorders, congenital conditions due to damage to or abnormal development of the nervous system. There have been various attempts to classify megalencephaly into subcategories based on etiology (cause) and/or pathology (the condition of the brain tissue and cells). Dekaban and Sakurgawa (1977) proposed three main categories: primary megalencephaly, secondary megalencephaly, and hemimegalencephaly. DeMyer (1986) proposed two main categories: anatomic and metabolic. Gooskens and others (1988) modified these classifications and added a third category: dynamic megalencephaly. The existence of different classification systems highlights the inherent difficulty in categorizing a condition that has a wide range of causes and associated pathology.

Demographics

The incidence of megalencephaly is estimated at between 2% and 6%. There is a preponderance of affected males; megalencephaly affects males three to four times more often than it does females. Among individuals with macrocephaly, estimates of megalencephaly are between 10 and 30%. Hemimegalencephaly is a rare condition and occurs less frequently than megalencephaly.

Causes and symptoms

Both genetic and non-genetic factors may produce megalencephaly. Most often, megalencephaly is a familial trait that occurs without extraneural (outside the brain) findings. Familial megalencephaly may occur as an autosomal dominant (more common) or autosomal recessive condition. The autosomal recessive form is more likely than the autosomal dominant form to result in mental retardation. Other genetic causes for megalencephaly include single gene disorders such as **Sotos syndrome** (an overgrowth syndrome), **neurofibromatosis** (a neurocutaneous syndrome), and **Alexander disease** (a **leukodystrophy**); or a chromosome abnormality such as Klinefelter syndrome. Non-genetic factors such as a transient disorder of cerebral spinal fluid may also contribute to the development of megalencephaly. Finally, megalencephaly can be idiopathic (due to unknown causes).

The cells that make up the brain (neurons and other supporting cells) form during the second to fourth months of pregnancy. Though the precise mechanisms behind megalencephaly at the cellular level are not fully understood, it is thought that the condition results from an increased number of cells, an increased size of cells, or accumulation of a metabolic byproduct or abnormal substance due to an inborn error of metabolism. It is possible that more than one of these processes may explain megalencephaly in a given individual.

There is variability in age of onset, symptoms present, rate of progression, and severity of megalencephaly. The

disorder typically presents as a large head circumference (distance around the head) either prenatally (before birth), at birth, or within the first few years of life. The head circumference may increase rapidly in the span of a few months or may progress slowly over a longer period of time. Head shape may be abnormal and skull abnormalities such as widened or split sutures (fibrous joints between the bones of the head) may occur. There may also be increased cranial pressure and bulging fontanels (the membrane covered spaces at the juncture of an infant's cranial bones which later harden).

From a neurological standpoint, the clinical picture of megalencephaly varies widely. Manifestations may range from normal intellect, as with case of benign familial megalencephaly, to severe mental retardation and seizures, as with Alexander disease, an inherited leukodystrophy (disease of the brain's white matter). Neurological symptoms that may be present or develop in a person with megalencephaly include:

- delay of motor milestones such as holding up head, rolling over, or sitting
- mental retardation
- speech delay
- poor muscle tone
- body asymmetry
- paralysis of one or both sides of the body
- poor coordination
- involuntary movements
- visual disturbances

Brain abnormalities that may be seen in individuals with megalencephaly include:

- gyral abnormalities
- neuronal heterotopias
- corpus callosum dysgenesis
- myelum dysplasia
- abnormal or an excess amount of neurons
- abnormal or an excess amount of glia cells

Diagnosis

A diagnosis of megalencephaly is based on clinical findings and results of brain imaging studies. Since megalencephaly can be a benign condition, there may well be many individuals who never come to medical attention. Though no longer used as a primary means of diagnosing megalencephaly, an autopsy may provide additional evidence to support this diagnosis. The evaluation of a patient with suspected megalencephaly will usually consist of questions about medical history and family history, a physical exam that includes head measurements, and a developmental and/or neurological exam. It may be necessary to obtain head circumference measurements for first-degree relatives (parents, siblings, children). Depending upon the history and clinical findings, a physician may recommend imaging studies such as CT (computed tomography) scan or **MRI** (**magnetic resonance imaging**). Findings on **CT scan** or MRI consistent with a diagnosis of megalencephaly are an enlarged brain with normal-sized ventricles and subarachnoid spaces. The volume (size) of the brain may be calculated or estimated using measurements from the CT or MRI. A patient with megalencephaly may be referred to specialists in neurology or genetics for further evaluation. Laboratory testing for a genetic condition or chromosome abnormality may also be performed.

Treatment

There is no specific cure for megalencephaly. Management of this condition largely depends upon the presence and severity of associated neurological and physical problems. In cases of benign familial megalencephaly, additional management beyond routine health care maintenance may consist of periodic head measurements and patient education about the inheritance and benign nature of the condition. For patients with neurological and/or physical problems, management may include anti-epileptic drugs for seizures, treatment of medical complications related to the underlying syndrome, and rehabilitation for neurological problems such as speech delay, poor muscle tone, and poor coordination. Placement in a residential care facility may be necessary for those cases in which megalencephaly is accompanied by severe mental retardation or uncontrollable seizures.

Treatment team

The types of professionals involved in the care of patients is highly individualized because the severity of symptoms varies widely from patient to patient. For patients with associated neurological and/or physical problems, the treatment team may include specialists in neonatology, neurology, radiology, orthopedics, rehabilitation, and genetics. Genetic counseling may be helpful to the patient and family, especially at the time of diagnosis. Participation in a support group may also be beneficial to those families adversely affected by megalencephaly.

Recovery and rehabilitation

The optimal remedial strategies for individuals with megalencephaly depend upon the presence and severity of associated neurological and physical problems. Interventions such as speech, physical, and occupational therapy

may be indicated for individuals with megalencephaly. Early intervention services for young children and special education or other means of educational support for school-aged children may be recommended if developmental delays, learning disabilities, or other barriers to learning are present. The goal of these therapies is to maximize the patient's success in school, work, and life in general. A child with megalencephaly may be eligible to have an Individual Education Plan (IEP). An IEP provides a framework from which administrators, teachers, and parents can meet the educational needs of a child with learning disabilities. Depending upon severity of symptoms and the degree of learning difficulties, some children with megalencephaly may be best served by special education classes or a private educational setting.

Clinical trials

As of 2004, there were no active **clinical trials** specifically designed to study megalencephaly. Patients with underlying syndromes that produce megalencephaly may be candidates for clinical trials that relate to that particular syndrome. For more information, interested individuals may search for that specific condition (for example, neurofibromatosis) at www.clinicaltrails.gov.

Prognosis

The prognosis for megalencephaly varies according to the presence and severity of associated problems such as intractable seizures, paralysis, and mental retardation. Hemimegalencephaly is often associated with severe seizures, hemiparesis (paralysis of one side of the body), and mental retardation and as such, it carries a poor prognosis. In the case of a fetus diagnosed with megalencephaly, prediction of outcome remains imprecise.

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National Institute of Child Health and Human Development (NICHD) Information Resource Center. P. O. Box 3006, Rockville, MD 20847. (301) 496-7101 or (800) 370-2943. NICHDInformationResourceCenter@mail.nih.gov. <http://www.nichd.nih.gov>.

National Institute of Neurological Disorders and Stroke (NINDS, Brain Resources and Information Network (BRAIN). P. O. Box 5801, Bethesda, MD. (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 1968, 55 Kensonia Avenue, Danbury, CT 06813. (203) 744-0100 or 800-999-NORD (6673); Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Dawn J. Cardeiro, MS, CGC

Meige syndrome *see* **Hemifacial spasm**

Melodic intonation therapy

Definition

Melodic intonation therapy (MIT) uses melodic and rhythmic components to assist in speech recovery for patients with **aphasia**.

Purpose

Although MIT was first described in the 1970s, it is considered a relatively new and experimental therapy. Few research studies have been performed to analyze the effectiveness of treatment with large numbers of patients. Despite this, some speech therapists use the method for children and adults with aphasia as well as for children with developmental **apraxia** of speech.

The effectiveness of MIT derives from its use of the musical components melody and rhythm in the production of speech. A group of researchers from the University of Texas have discovered that music stimulates several different areas in the brain, rather than just one isolated area. They also found a strong correlation between the right side of the brain that comprehends music components and the left side of the brain that comprehends language components. Because music and language structures are similar, it is suspected that by stimulating the right side of the brain, the left side will begin to make connections as well. For this reason, patients are encouraged to sing words rather than speak them in conversational tones in the early phases of MIT. Studies using **positron emission tomography** (**PET**) scans have shown Broca's area (a region in the left frontal brain controlling speech and language comprehension) to be reactivated through repetition of sung words.

Precautions

Patients and caregivers should be aware that there is little research to support consistent success with MIT. Theoretically, this form of therapy has the potential to improve speech communication to a limited extent.

Description

Melodic intonation therapy was originally developed as a treatment method for speech improvements in adults with aphasia. The initial method has had several modifications, mostly adaptations for use by children with apraxia. The primary structure of this therapy remains relatively consistent however.

There are four steps, or levels, generally outlining the path of therapy.

- Level I: The speech therapist hums short phrases in a rhythmic, singsong tone. The patient attempts to follow the rhythm and stress patterns of phrases by tapping it out. With children, the therapist uses signing while humming and the child is not initially expected to participate. After a series of steps, the child gradually increases participation until they sign and hum with the therapist.
- Level II: The patient begins to repeat the hummed phrases with the assistance of the speech therapist. Children at this level are gradually weaned from therapist participation.
- Level III: For adults, this is the point where therapist participation is minimized and the patient begins to respond to questions still using rhythmic speech patterns. In children, this is the final level and the transition to normal speech begins. *Sprechgesang* is the technique used to transition the constant melodic pitch used up to this point with the variable pitch in normal conversational speech.
- Level IV: The adult method incorporates *sprechgesang* at this level. More complex phrases and longer sentences are attempted.

Preparation

Preparation for MIT involves some additional research into the therapy and discussions with a **neurologist** and a speech pathologist. It is important to have an understanding of the affected brain areas. MIT is most likely to be successful for patients who meet certain criteria such as non-bilateral brain damage, good auditory aptitude, non-fluent verbal communication, and poor word repetition. The speech pathologist should be familiar with the different MIT methodologies as they relate to either adults or children.

Aftercare

There is no required aftercare for MIT.

Risks

There are no physical risks associated with the use of melodic intonation therapy.

Normal results

The expected outcome after completion of the MIT sequence is increased communication through production of intelligible word groups. Patients are typically able to form short sentences of 3–5 words, but more complex communication may also be possible depending on the initial cause of speech impairment.

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Key Terms

Aphasia Loss of the ability to use or understand language, usually as a result of brain injury or disease.

Apraxia Loss of the ability to carry out a voluntary movement despite being able to demonstrate normal muscle function.

Pitch The property of sound that is determined by the frequency of sound wave vibrations reaching the ear.

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American Speech-Language-Hearing Association. 10801 Rockville Pike, Rockville, MD 20852. (301) 897-5700 or (800) 638-8255; Fax: (301) 571-0457. action center@asha.org. <http://www.nsastutter.org>.

Music Therapy Association of British Columbia. 2055 Purcell Way, North Vancouver, British Columbia V7J 3H5, Canada. (604) 924-0046; Fax: (604) 983-7559. info@mtabc.com. <http://www.mtabc.com>.

The Center For Music Therapy. 404-A Baylor Street, Austin, TX 78703. (512) 472-5016; Fax: (512) 472-5017. info@centerformusictherapy.com. <http://www.centerformusictherapy.com>.

Stacey L. Chamberlin

Ménière's disease

Definition

Ménière's disease is a disorder characterized by recurrent vertigo, sensory hearing loss, tinnitus, and a feeling of fullness in the ear. It is named for the French physician, Prosper Ménière, who first described the illness in 1861. Ménière's disease is also known as idiopathic endolymphatic hydrops; "idiopathic" refers to the unknown or spontaneous origin of the disorder, while "endolymphatic hydrops" refers to the increased fluid pressure in the inner ear that causes the symptoms of Ménière's disease.

Description

Patients with Ménière's disease have periodic attacks characterized by four major symptoms:

- Vertigo. This is a spinning or whirling sensation that affects the patient's sense of balance; it is sometimes violent. The vertigo is often accompanied by nausea and vomiting.
- Fluctuating loss of hearing.
- Tinnitus. This is a sensation of ringing, buzzing, or roaring noises in the ear. The most common type of tinnitus associated with Ménière's is a low-pitched roaring.
- A sensation of fullness, pressure, or discomfort in the ear.

Some patients also experience **headaches**, diarrhea, and **pain** in the abdomen during an attack.

Attacks usually come on suddenly and last from two or three to 24 hours, although some patients experience an aching sensation in the affected ear just before an attack. The attacks typically subside gradually. In most cases, only one ear is affected; however, 10–15% of patients with Ménière's disease are affected in both ears. After a severe attack, the patient often feels exhausted and sleeps for several hours.

The spacing and intensity of Ménière's attacks vary from patient to patient. Some people have several acute episodes relatively close together, while others may have one or two milder attacks per year or even several years apart. In some patients, attacks occur at regular intervals, while in others, the attacks are completely random. In some patients, acute attacks are triggered by psychological stress, menstrual cycles, or certain foods. Patients usually feel normal between episodes; however, they may find that their hearing and sense of balance get slightly worse after each attack.

Demographics

The National Institute on Deafness and Other Communication Disorders (NIDCD) estimates that, as of 2003, there are about 620,000 persons in the United States diagnosed with Ménière's disease. Another expert gives a figure of 1,000 cases per 100,000 people. About 46,000 new cases are diagnosed each year; some neurologists, however, think that the disorder is underdiagnosed.

Ménière's disease has been diagnosed in patients of all ages, although the average age at onset is 35–40 years of age. The age of patients in several controlled studies of the disorder ranged from 49 to 67 years.

Although Ménière's disease has not been linked to a specific gene or genes, it does appear to run in families. About 55% of patients diagnosed with Ménière's have significant family histories of the disorder. Women are slightly

more likely than men to develop Ménière's; various studies report female-to-male ratios between 1.1:1 and 3:2.

There is no evidence as of 2003 that Ménière's disease occurs more frequently in some racial or ethnic groups than in others.

Causes and symptoms

The underlying causes of Ménière's disease are poorly understood as of late 2003. Some geneticists proposed in 2002 that Ménière's disease might be caused by a mutation in the COCH gene, which is the only human gene known to be associated with inherited hearing loss related to inner ear dysfunction. In 2003, however, two groups of researchers in Japan and the United Kingdom reported that mutations in the COCH gene are not responsible for Ménière's. Other theories about the underlying causes of Ménière's disease that are being investigated include virus infections and environmental noise pollution.

One area of research that shows promise is the possible relationship between Ménière's disease and migraine headache. Dr. Ménière himself suggested the possibility of a link, but early studies yielded conflicting results. A rigorous German study published in late 2002 reported that the lifetime prevalence of migraine was 56% in patients diagnosed with Ménière's disease as compared to 25% for controls. The researchers noted that further work is necessary to determine the exact nature of the relationship between the two disorders.

The immediate cause of acute attacks is fluctuating pressure in a fluid inside the inner ear known as endolymph. The endolymph is separated from another fluid called perilymph by thin membranes containing nerves that govern hearing and balance. When the endolymph pressure increases, there is a sudden change in the rate of nerve cells firing, which leads to vertigo and a sense of fullness or discomfort inside the ear. In addition, increased endolymph pressure irritates another structure in the inner ear known as the organ of Corti, which lies inside a shell-shaped structure called the cochlea. The organ of Corti detects pressure impulses, which it converts to electrical impulses that travel along the auditory nerve to the brain. The organ of Corti contains four rows of hair cells that govern a person's perception of the pitch and loudness of a sound. Increased pressure from the endolymph affects the hair cells, causing loss of hearing (particularly the ability to hear low-pitched sounds) and tinnitus.

Diagnosis

Diagnosis of Ménière's disease is a complex process requiring a number of different procedures:

- Patient history, including family history. A primary care physician will ask the patient to describe the symptoms experienced during the attacks, their severity, the dates of recent attacks, and possible triggers.
- Physical examination. Patients often come to the doctor's office with signs of recent vomiting; they may be pale and sweaty, with a fast pulse and higher than normal blood pressure. There may be no unusual findings during the physical examination, however, if the patient is between episodes. If the doctor suspects Ménière's disease on the basis of the patient's personal or family history, he or she will examine the patient's eyes for nystagmus, or rapid and involuntary movements of the eyeball. At this point, a primary care physician may refer the patient to an audiologist or other specialist for further testing.
- Hearing tests. There are several different types of hearing tests used to diagnose Ménière's. The Rinne and Weber tests use a tuning fork to detect hearing loss. In Rinne's test, the examiner holds the stem of a vibrating tuning fork first against the mastoid bone and then outside the ear canal. A person with normal hearing or Ménière's disease will hear the sound as louder when it is held near the outer ear; a person with conductive hearing loss will hear the tone as louder when the fork is touching the bone. In Weber's test, the vibrating tuning fork is held on the midline of the forehead and the patient is asked to indicate the ear in which the sound seems louder. A person with conductive hearing loss on one side will hear the sound louder in the affected ear, while a person with Ménière's disease will hear the sound louder in the unaffected ear. Other hearing tests measure the person's ability to hear sounds of different pitches and volumes. These may be repeated in order to detect periodic variations in the patient's hearing.
- Balance tests. The most common balance tests used to diagnose Ménière's disease are the Romberg test, in which the patient is asked to stand upright and steady with eyes closed; the Fukuda test, in which the patient is asked to march in place with eyes closed; and the Dix-Hallpike test, in which the doctor moves the patient from a sitting position to lying down while holding the patient's head tilted at a 45-degree angle. Patients with Ménière's disease tend to lose their balance or move from side to side during the first two tests. The Dix-Hallpike test is done to rule out benign paroxysmal positional vertigo (BPPV), a condition caused by small crystals of calcium carbonate that have collected within a part of the inner ear called the utricle. Some patients with Ménière's disease may have a positive score on the Dix-Hallpike test, indicating that they also have BPPV.
- Blood tests. These are ordered to rule out metabolic disorders, autoimmune disorders, anemia, leukemia, or infectious diseases (**Lyme disease** and neurosyphilis).
- Transtympanic electrocochleography (ECoG). This test involves the placement of a recording electrode close to

Key Terms

Audiologist A healthcare professional who specializes in diagnostic testing of hearing impairments and rehabilitation of patients with hearing problems.

Cochlea A spiral-shaped tubular structure resembling a snail's shell that forms part of the inner ear.

Conductive hearing loss A type of medically treatable hearing loss in which the inner ear is usually normal, but there are specific problems in the middle or outer ears that prevent sound from getting to the inner ear in a normal way.

Endolymph The fluid contained inside the membranous labyrinth of the inner ear.

Endolymphatic hydrops Another term for Ménière's disease. It defines the disorder in terms of increased fluid pressure in the inner ear.

Idiopathic Of unknown cause or spontaneous origin. Ménière's disease is considered an idiopathic disorder.

Labyrinth The inner ear. It consists of the membranous labyrinth, which is a system of sacs and ducts made of soft tissue; and the osseous or bony labyrinth, which surrounds and contains the membranous labyrinth.

Labyrinthectomy Surgical removal of the labyrinth of the ear. It is done to treat Ménière's disease only when the patient has already suffered severe hearing loss.

Mastoid bone The bony area behind and below the ear.

Nystagmus Rapid and involuntary movements of the eyeball. Measuring and recording episodes of nystagmus is part of the differential diagnosis of Ménière's disease.

Otolaryngology The branch of medicine that treats disorders of the ear, nose, and throat.

Otology The branch of medicine that specializes in medical or surgical treatment of ear disorders.

Perilymph The fluid that lies between the membranous labyrinth of the inner ear and the bony labyrinth.

Prophylaxis A measure taken to prevent disease or an acute attack of a chronic disorder.

Tinnitus A sensation of ringing, buzzing, roaring, or clicking noises in the ear.

Vertigo An illusory feeling that either one's self or the environment is revolving. It is usually caused either by diseases of the inner ear or disturbances of the central nervous system.

the cochlea of the patient's ear; it is done to detect distortion of the membranes in the inner ear. ECoG is most accurate when performed during an attack of Ménière's.

- Electronystagmography (ENG). This test is done to evaluate the functioning of the patient's vestibular and oculomotor (eye movement) systems. It takes about 60–90 minutes to complete and includes stimulating the inner ear with air or water of different temperatures as well as measuring and recording the patient's eye movements in response to lights and similar stimuli. ENG can cause **dizziness** and nausea; patients are told to discontinue all medications for two weeks before the test and to take the test on an empty stomach.
- Imaging studies. **MRIs** and **CT scans** are done to detect abnormalities in the shape or structure of the cochlea and other parts of the inner ear, to rule out tumors, and to detect signs of multiple sclerosis.

Treatment team

A family care practitioner may suspect the diagnosis of Ménière's disease on the basis of the patient's history and physical examination, but the tests required to rule out other diseases or disorders may require specialists in endocrinology, neurology, cardiology, otolaryngology, and internal medicine. Diagnostic hearing tests may be administered by an audiologist. Surgical treatment of Ménière's is usually performed by an otolaryngologist or otologist. A nutritionist or dietitian should be consulted to plan a low-salt diet for the patient.

Patients whose attacks are triggered by emotional stress may be helped by therapists who teach biofeedback, meditation, or other techniques of stress reduction.

Treatment

Medical treatment

Medical management of Ménière's disease involves prophylaxis (prevention of acute attacks) as well as direct treatment of symptoms. Prophylactic treatment begins with **diet and nutrition**. A low-salt diet is recommended for almost all patients with Ménière's, as reducing salt intake helps to lower the body's overall fluid volume. Lowered fluid volume in turn reduces the amount of fluid in the inner ear. Patients should avoid foods with high

sodium content, including pizza, smoked or pickled fish, and other preserved foods. Other foods that commonly trigger acute attacks include chocolate; beverages containing caffeine or alcohol, particularly beer and red wine; and foods with high carbohydrate or high cholesterol content. Since nicotine also triggers Ménière's attacks, patients are advised to stop smoking. The doctor may also prescribe a diuretic, usually Dyazide or Diamox, to lower the fluid pressure in the inner ear. Diuretic medications help to prevent acute attacks but will not stop an attack once it has begun.

Medications that are given to treat the symptoms of an attack include drugs that help to control vertigo by numbing the brain's response to nerve impulses from the inner ear. These include such benzodiazepine tranquilizers as **diazepam** (Valium) or alprazolam (Xanax), and such antinausea drugs as prochlorperazine (Compazine). The doctor may also prescribe steroid medications to reduce inflammation in the inner ear.

Surgical treatment

Surgery is usually considered if the patient has not responded to 3–6 months of medical treatment and is healthy enough to undergo general anesthesia. There are four surgical procedures that are commonly done to treat Ménière's disease:

- Endolymphatic sac decompression or shunt. In this procedure, the surgeon inserts a small tube or valve to drain excess endolymph fluid into a space near the mastoid bone and/or removes some of the bone surrounding the endolymphatic sac in order to reduce pressure on it. The success rate is about 60–90% for controlling vertigo, but the procedure often improves the patient's hearing.
- Vestibular nerve sectioning. This procedure is typically done in patients who still have fairly good hearing in the affected ear. The surgeon enters the internal canal of the ear and separates the nerve bundles governing hearing from the nerve bundles that govern the sense of balance, in order to control the patient's vertigo without sacrificing hearing.
- Labyrinthectomy. Labyrinthectomies are performed only in patients whose hearing has already been damaged or destroyed by the disease. The surgeon removes the entire labyrinth of the inner ear. Both vestibular nerve sectioning and labyrinthectomy have a 95–98% success rate in controlling vertigo, but the patient's hearing may be impaired.
- Transtympanic medication perfusion. This procedure involves delivering medications into the middle ear through an incision in the eardrum. Once in the middle ear, the drugs are absorbed into the inner ear. Two types of drugs are used—steroids and aminoglycoside antibiotics (most commonly gentamicin). Medication perfusion is reported to have a 90% success rate.

Complementary and alternative (CAM) treatments

Acupuncture is an alternative treatment that has been shown to help patients with Ménière's disease. The World Health Organization (WHO) lists Ménière's disease as one of 104 conditions that can be treated effectively with acupuncture. In addition, such stress management techniques as autogenic training, visualization, deep breathing, and muscle stretching are helpful to many patients in lowering the frequency of acute attacks.

Recovery and rehabilitation

Patients with Ménière's are referred to rehabilitation therapy if they have not benefited from dietary changes or medication. In vestibular rehabilitation therapy, the therapist first assesses the patient's general muscular strength and coordination, gait and balance, and the triggers as well as the severity and frequency of the vertigo. Rehabilitation itself involves both balance retraining exercises and habituation exercises, which are designed to weaken the brain's response to specific positions or movements that trigger vertigo.

Clinical trials

As of 2003, no **clinical trials** for Ménière's disease were listed in the National Institutes of Health (NIH) database.

Prognosis

Ménière's disease is not fatal; however, there is no cure for it. Medical treatment between attacks and/or surgery are intended to lower the patient's risk of further hearing loss. Although patients with milder forms of the disorder may be able to control their symptoms through dietary changes alone, the long-term results of Ménière's disease typically include progressive loss of hearing, increasing vertigo, or permanent tinnitus.

Special concerns

Although Ménière's disease is not fatal by itself, it can lead to injuries caused by falls or motor vehicle accidents (if the patient has a severe attack while driving). Although moderate **exercise** is beneficial, patients diagnosed with Ménière's should avoid occupations or sports that require a good sense of balance (e.g., house painting, construction work, or other jobs that require working on ladders; bicycle or horseback riding; mountain climbing; some forms of yoga, etc.) In addition, patients should

check their house or apartment for loose rugs, inadequate lighting, unsafe stairs, or other features that could lead to slipping and falling in the event of a sudden attack. A small minority of patients are prevented by severe vertigo from working at any form of regular employment and must file disability claims.

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American Academy of Otolaryngology—Head and Neck Surgery. One Prince Street, Alexandria, VA 22314. (703) 836-4444; TTY: (703) 519-1585. webmaster@entnet.org. <http://www.entnet.org>.

Ear Foundation. 1817 Patterson Street, Nashville, TN 37203. (615) 284-7807 or (800) 545-HEAR; Fax: (615) 284-7935. earfound@earfoundation.org. <http://www.theearfound.org>.

National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health, 31 Center Drive, MSC 2320, Bethesda, MD 20892-2320. nidcdinfo@nidcd.nih.gov. <http://www.nidcd.nih.gov>.

Vestibular Disorders Association (VEDA). P. O. Box 4467, Portland, OR 97208-4467. (503) 229-7706. (800) 837-8428. veda@vestibular.org. <http://www.vestibular.org>.

Rebecca J. Frey, PhD

Meninges

Definition

Meninges (singular is meninx) is the collective term for the three membranes covering the brain and spinal cord. The meninges are composed of the dura mater (outer), the arachnoid (middle), and the pia mater (inner). In common usage, the membranes are often referred to as simply the dura, pia, and arachnoid.

Description

Dura is the Latin word for hard, while pia in Latin means soft. The dura mater was so-named because of its tough, fibrous consistency. The pia mater is thinner and more delicate than the dura mater, and is in direct contact with the neural tissue of the brain and spinal cord. Along with the arachnoid layer and the cerebrospinal fluid (CSF), the dura and pia membranes help cushion, protect, and nourish the brain and spinal cord.

Mater is Latin for mother, and thus refers to the membranes' protective and nourishing functions. Each of the meninges can also be classified as to the portion that covers the brain (e.g., dura mater cerebri or dura mater encephali), or that portion lining the spinal cord (e.g., pia mater spinalis). Arachnoid means "spidery," referring to the membrane's webbed appearance and consistency. The space between the arachnoid membrane and pia mater contains many fibrous filaments and blood vessels that attach the two layers.

Anatomy

The outer surface of the dura adheres to the skull, while the inner surface is loosely connected to the arachnoid layer. The exception is the spinal canal, where there is normally a thin layer of fat and a network of blood vessels between the dura and the bony portion of the vertebrae. There is normally no space between the dura and skull on one side, and the dura and arachnoid on the other. However, these are sometimes called "potential" spaces because abnormal conditions may create "actual" spaces there. Anything in the space between the dura and skull is called epidural (above the dura), while the space between the dura and arachnoid is considered subdural (below the dura).

There is normally an actual space between the arachnoid layer and the pia mater known as the subarachnoid space. As noted, it contains many fibrous filaments, known as trabeculae (little beams), joining and stabilizing the two layers. The importance of the subarachnoid space is that it contains the circulating CSF. It is this layer of fluid that helps to cushion the brain and protect it from sudden movements and impacts to the skull.

The pia mater has the appearance of a thin mesh, with a network of tiny blood vessels interlacing it. It is always in contact with the neural tissue of the brain and spinal cord, much like a skin. It follows all of the grooves, folds, and fissures of the brain's various lobes and prominences.

All of the meninges are composed of connective tissue, which is made up of relatively few cells, with an abundance of structural and supportive proteins.

Function

Given the singular importance of the **central nervous system** (CNS) to both basic and higher-level functions of the body, it is not surprising that a system evolved to help protect it. Thicker skull bones would certainly afford more protection against skull fracture and open head injury, but would come at the cost of greater weight for the spine to bear. If the head is struck, or strikes some other object, even unbreakable skull bones would not protect the brain from the injury that results as brain tissue impacts the inside of the skull (concussion). The layer of CSF that circulates in the subarachnoid space helps to lower this risk, although it cannot eliminate it. Wearing a sports helmet composed of a hard, plastic outer shell with firm padding inside simply mimics and augments the safety mechanism already present in the skull and outer lining of the brain.

The dura mater is the tough, but flexible, second line of defense for the brain after the skull. The flexibility of the dura is important in that most skull fractures, other than those involving severe penetrating injuries, will not result in loss of CSF through the injury site which, before the days of antibiotics and emergency medicine, would pose a serious risk for infection and death.

The arachnoid membrane provides a stable substrate and space through which the CSF can circulate, and also provides specialized tissue necessary for absorption of the CSF back into the bloodstream. The arachnoid trabeculae help to anchor the surrounding membranes and keep the subarachnoid space at a constant depth.

While the CSF is normally sterile and mostly inert—containing glucose, proteins, electrolytes (necessary minerals), and very few cells—the brain and spinal neurons nonetheless need some protection from direct contact with the fluid, which is provided by the pia mater. As blood vessels pass through the dura mater and then the subarachnoid space, they pierce the pia mater as they enter the CNS. The membrane follows the blood vessel down and becomes the external portion of the blood vessel wall.

CSF Production and Circulation

In a sense, the CSF can be thought of as a fourth layer of the meninges. The fluid is produced in, circulates through, and is reabsorbed by the meningeal layers, thus creating a self-contained system. The volume of fluid in adults is normally 100–150 ml. About 500 ml of new fluid is produced and reabsorbed each day, which means the CSF is "turned over" three times in 24 hours. It is important for the body to maintain CSF volume within the normal range, since there is limited space within the skull and spinal column. It is also important for the fluid to remain at a constant pressure. Increased fluid pressure typically leads to compression of the surrounding neural tissue, which then leads to increased fluid volume. Since the bones of the skull are not fused in a developing fetus or newborn infant, increased fluid pressure in the brain may cause the head to grow to an abnormally large size (see **Hydrocephalus**), called macrocephaly. The skull bones are fused after about 2 years of age, so increased fluid pressure and volume after that point will most likely result in compression of, and damage to, neural tissue.

The CSF is produced by a layer of densely packed capillaries and supporting cells known as the choroid plexus. It lines the upper portion of the lateral (cerebral), third, and fourth ventricles. Once produced, the CSF flows down through the fourth ventricle, and then through openings at the base of the brain and around the brain stem. Some of the fluid circulates down through the subarachnoid space encircling the length of the spinal cord, while the remainder flows up to the subarachnoid space around the brain.

Most of the fluid is absorbed back into the bloodstream through vessels lining branched projections from

Key Terms

Arachnoid membrane One of the three membranes that sheath the spinal cord and brain; the arachnoid is the middle membrane. Also called the arachnoid mater.

Cerebrospinal fluid The clear, normally colorless fluid that fills the brain cavities (ventricles), the subarachnoid space around the brain, and the spinal cord and acts as a shock absorber.

Choroid plexus Specialized cells located in the ventricles of the brain that produce cerebrospinal fluid.

Dura mater The strongest and outermost of three membranes that protect the brain, spinal cord, and nerves of the cauda equina.

Hydrocephalus An abnormal accumulation of cerebrospinal fluid within the brain. This accumulation can be harmful by pressing on brain structures, and damaging them.

Meningitis An infection or inflammation of the membranes that cover the brain and spinal cord. It is usually caused by bacteria or a virus.

Pia mater The innermost of the three meninges covering the brain.

Ventricles The four fluid-filled chambers, or cavities, found in the two cerebral hemispheres of the brain, at the center of the brain, and between the brain stem and cerebellum. They are linked by channels, or ducts, allowing cerebral fluid to circulate through them.

the arachnoid membrane called arachnoid villi, or granulations. These arachnoid granulations extend into the dura, primarily at points where large blood veins lie within the dural membrane itself. These veins traveling through the dura that drain blood and absorbed CSF from the brain are collectively known as the venous sinuses of the dura mater. The remainder of the CSF is absorbed through small lymph sacs scattered around the CNS known as perineural lymphatics.

Causes and symptoms

Infection/inflammation of the meninges is covered elsewhere (see Meningitis). Other abnormalities of the meninges typically involve situations in which a fluid occupies and expands the epidural, subdural, or subarachnoid spaces. For instance, blood accumulation that separates the dura from the inner side of the skull is known as an **epidural hematoma** (blood swelling). The same process occurrence between the dura and arachnoid layers is a **subdural hematoma**. Both of these conditions are most frequently caused by head trauma, but may also result from a bleeding disorder or defect in a cranial blood vessel (aneurysm).

A hemorrhage between the arachnoid membrane and the pia mater is called a subarachnoid bleed, and is usually caused by the rupture of a congenital aneurysm, hypertension, or trauma. Unlike conditions affecting the epidural and subdural spaces, a bleed into the subarachnoid space is less likely to affect its volume and increase pressure. A subarachnoid CSF infection (abscess), however, may cause increased pressure.

Meningitis may also cause bleeding into the subdural or epidural spaces, but more often results in the accumulation of fluid and pus, which are consequences of the body's response to the infection.

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Meningitis *see* **Encephalitis and meningitis**

Mental retardation

Definition

Mental retardation (MR) is a developmental disability that first appears in children under the age of 18. It is defined as a level of intellectual functioning (as measured by standard intelligence tests) that is well below average and results in significant limitations in the person's daily living skills (adaptive functioning).

Description

Mental retardation begins in childhood or adolescence before the age of 18. In most cases, it persists throughout adult life. A diagnosis of mental retardation is made if an individual has an intellectual functioning level well below average, as well as significant limitations in two or more adaptive skill areas. Intellectual functioning level is defined by standardized tests that measure the ability to reason in terms of mental age (intelligence quotient or IQ). Mental retardation is defined as an IQ score below 70–75; a normal score is 100. Adaptive skills refer to skills needed for daily life. Such skills include the ability to produce and understand language (communication); home-living skills; use of community resources; health, safety, leisure, self-care, and social skills; self-direction; functional academic skills (reading, writing, and arithmetic); and job-related skills.

In general, mentally retarded children reach such developmental milestones as walking and talking much later than children in the general population. Symptoms of mental retardation may appear at birth or later in childhood. The child's age at onset depends on the suspected cause of the disability. Some cases of mild mental retardation are not diagnosed before the child enters preschool or kindergarten. These children typically have difficulties with social, communication, and functional academic skills. Children who have a neurological disorder or illness such as encephalitis or meningitis may suddenly show signs of cognitive impairment and adaptive difficulties.

Mental retardation varies in severity. The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR), which is the diagnostic standard for mental healthcare professionals in the United States, classifies four degrees of mental retardation: mild, moderate, severe, and profound. These categories are based on the person's level of functioning.

Mild mental retardation

Approximately 85% of the mentally retarded population is in the mildly retarded category. Their IQ score ranges from 50–70, and they can often acquire academic skills up to about the sixth-grade level. They can become fairly self-sufficient and, in some cases, live independently, with community and social support.

Moderate mental retardation

About 10% of the mentally retarded population is considered moderately retarded. These people have IQ scores ranging from 35–55. They can carry out work and self-care tasks with moderate supervision. They typically acquire communication skills in childhood and are able to live and function successfully within the community in such supervised environments as group homes.

Severe mental retardation

About 3–4% of the mentally retarded population is severely retarded. They have IQ scores of 20–40. They may master very basic self-care skills and some communication skills. Many severely retarded individuals are able to live in a group home.

Profound mental retardation

Only 1–2% of the mentally retarded population is classified as profoundly retarded. These individuals have IQ scores under 20–25. They may be able to develop basic self-care and communication skills with appropriate support and training. Their retardation is often caused by an accompanying neurological disorder. Profoundly retarded people need a high level of structure and supervision.

AAMR classifications

The American Association on Mental Retardation (AAMR) has developed another widely accepted diagnostic classification system for mental retardation. The AAMR classification system focuses on the capabilities of retarded individuals rather than on their limitations. The categories describe the level of support required, including intermittent support, limited support, extensive support, and pervasive support. To some extent, the AAMR classification mirrors the DSM-IV-TR classification. Intermittent support, for example, is support that is needed only occasionally, perhaps during times of stress or crisis for the retarded person. It is the type of support typically required for most mildly retarded people. At the other end of the spectrum, pervasive support, which is life-long, daily support for most adaptive areas, would be required for profoundly retarded persons. The AAMR classification system refers to the "below-average intellectual function" as an IQ of 70–75 or below.

Demographics

The prevalence of mental retardation in North America is a subject of heated debate. It is thought to be 1–3% of the population, depending on the methods of assessment and criteria of assessment that are used. Many people believe that the actual prevalence is probably closer to 1%, and that the 3% figure is based on misleading mortality rates, cases that are diagnosed in early infancy, and the instability of the diagnosis across the age span. If the 1% figure is accepted, however, that means that 2.5 million mentally retarded people reside in the United States. Males are more likely than females to be mentally retarded at a 1.5:1 ratio.

Causes and symptoms

Causes

A variety of problems can lead to mental retardation. The three most common causes of mental retardation, accounting for about 30% of cases, are Down syndrome, fragile X, and fetal alcohol syndrome. In about 40% of cases, the cause of mental retardation cannot be found. The causes of mental retardation can be divided into broad classifications, including genetic factors, prenatal illnesses and exposures, childhood illnesses and injuries, and environmental factors.

GENETIC FACTORS About 30% of cases of mental retardation are caused by hereditary factors. Mental retardation may be caused by an inherited genetic abnormality such as fragile X syndrome. Fragile X, a defect in the chromosome that determines sex, is the most common inherited cause of mental retardation. Single-gene defects such as phenylketonuria (PKU) and other inborn errors of metabolism may also cause mental retardation if they are not discovered and treated early. An accident or mutation in genetic development may also cause retardation. Examples of such accidents are development of an extra chromosome 18 (trisomy 18) and Down syndrome. Down syndrome, also called mongolism or trisomy 21, is caused by an abnormality in the development of chromosome 21. It is the most common genetic cause of mental retardation.

PRENATAL ILLNESSES AND EXPOSURES Fetal alcohol syndrome (FAS) affects one in 3,000 children in Western countries. Fetal alcohol syndrome results from the mother's heavy drinking during the first 12 weeks (trimester) of pregnancy. Some studies have shown that even moderate alcohol use during pregnancy may cause learning disabilities in children. Drug abuse and cigarette smoking during pregnancy have also been linked to mental retardation. It is generally accepted that pregnant women should avoid all alcohol, tobacco, and recreational drugs.

Maternal infections and such illnesses as glandular disorders, rubella, toxoplasmosis, and cytomegalovirus (CMV) infection may cause mental retardation. When the mother has high blood pressure (hypertension) or blood poisoning (toxemia), the flow of oxygen to the fetus may be reduced, causing brain damage and mental retardation.

Birth defects that cause physical deformities of the head, brain, and **central nervous system** frequently cause mental retardation. Neural tube defect, for example, is a birth defect in which the neural tube that forms the spinal cord does not close completely. This defect may cause children to develop an accumulation of cerebrospinal fluid inside the skull (**hydrocephalus**). Hydrocephalus can cause learning impairment by putting pressure on the brain.

CHILDHOOD ILLNESSES AND INJURIES Hyperthyroidism, whooping cough, chicken pox, measles, and Hib disease (a bacterial infection) may cause mental retardation if they are not treated adequately. An infection of the membrane covering the brain (meningitis) or an inflammation of the brain itself (encephalitis) can cause swelling that in turn may cause brain damage and mental retardation. **Traumatic brain injury** caused by a blow to the head or by violent shaking of the upper body may also cause brain damage and mental retardation in children.

ENVIRONMENTAL FACTORS Ignored or neglected infants who are not provided with the mental and physical stimulation required for normal development may suffer irreversible learning impairment. Children who live in poverty and suffer from malnutrition, unhealthy living conditions, abuse, and improper or inadequate medical care are at a higher risk. Exposure to lead or mercury can also cause mental retardation. Many children have developed lead poisoning from eating the flaking lead-based paint often found in older buildings.

Symptoms

Low IQ scores and limitations in adaptive skills are the hallmarks of mental retardation. Aggression, self-injury, and mood disorders are sometimes associated with the disability. The severity of the symptoms and the age at which they first appear depend on the cause. Children who are mentally retarded reach developmental milestones significantly later than expected, if at all. If retardation is caused by chromosomal or other genetic disorders, it is often apparent from infancy. If retardation is caused by childhood illnesses or injuries, learning and adaptive skills that were once easy may suddenly become difficult or impossible to master.

Diagnosis

If mental retardation is suspected, a comprehensive physical examination and medical history should be done immediately to discover any organic cause of symptoms. Such conditions as hyperthyroidism and PKU are treatable. The progression of retardation can be stopped and, in some cases, partially reversed if these conditions are discovered early. If a neurological cause such as brain injury is suspected, the child may be referred to a **neurologist** or **neuropsychologist** for testing.

A complete medical, family, social, and educational history is compiled from existing medical and school records (if applicable) and from interviews with parents. Children are given intelligence tests to measure their learning abilities and intellectual functioning. Such tests include the Stanford-Binet Intelligence Scale, the Wechsler

Key Terms

Amniocentesis A test usually done between 16 and 20 weeks of pregnancy to detect any abnormalities in the development of the fetus. A small amount of the fluid surrounding the fetus (amniotic fluid) is drawn out through a needle inserted into the mother's womb. Laboratory analysis of this fluid can detect various genetic defects such as Down syndrome or neural tube defects.

Developmental delay The failure to meet certain developmental milestones such as sitting, walking, and talking at the average age. Developmental delay may indicate a problem in development of the central nervous system.

Down syndrome A genetic disorder characterized by an extra chromosome 21 (trisomy 21), mental retardation, and susceptibility to early-onset Alzheimer's disease.

Extensive support Ongoing daily support required to assist an individual in a specific adaptive area, such as daily help with preparing meals.

Hib disease An infection caused by *Haemophilus influenza*, type b (Hib). This disease mainly affects children under the age of five. In that age group, it is the leading cause of bacterial meningitis, pneumonia, joint and bone infections, and throat inflammations.

Inborn error of metabolism A rare enzyme deficiency; children with inborn errors of metabolism do not have certain enzymes that the body requires to maintain organ functions. Inborn errors of metabolism can cause brain damage and mental retardation if left untreated. Phenylketonuria is an inborn error of metabolism.

Limited support A predetermined period of assistance required to deal with a specific event, such as training for a new job.

Phenylketonuria (PKU) An inherited disease in which the body cannot metabolize the amino acid phenylalanine properly. If untreated, phenylketonuria can cause mental retardation.

Trisomy An abnormality in chromosomal development. In a trisomy syndrome, an extra chromosome is present so that the individual has three of a particular chromosome instead of the normal pair. An extra chromosome 18 (trisomy 18) causes mental retardation.

Ultrasonography A process that uses the reflection of high-frequency sound waves to make an image of structures deep within the body. Ultrasonography is routinely used to detect fetal abnormalities.

Intelligence Scales, the Wechsler Preschool and Primary Scale of Intelligence, and the Kaufman Assessment Battery for Children. For infants, the Bayley Scales of Infant Development may be used to assess motor, language, and problem-solving skills. Interviews with parents or other caregivers are used to assess the child's daily living, muscle control, communication, and social skills. The Woodcock-Johnson Scales of Independent Behavior and the Vineland Adaptive Behavior Scale are frequently used to evaluate these skills.

Treatment team

The treatment team will depend on the underlying cause of mental retardation. A neurologist, neuropsychologist, child psychiatrist, and/or development pediatrician may be helpful for nearly all cases of mental retardation, both to assess underlying cause and to plan for appropriate and helpful interventions. Other members of the treatment team will depend on the underlying cause of mental retardation, accompanying medical problems, and the severity of the deficits.

Treatment

Federal legislation entitles mentally retarded children to free testing and appropriate, individualized education and skills training within the school system from ages three to 21. For children under the age of three, many states have established early intervention programs that assess children, make recommendations, and begin treatment programs. Many day schools are available to help train retarded children in such basic skills as bathing and feeding themselves. Extracurricular activities and social programs are also important in helping retarded children and adolescents gain self-esteem.

Training in independent living and job skills is often begun in early adulthood. The level of training depends on the degree of retardation. Mildly retarded people can often acquire the skills needed to live independently and hold an outside job. Moderate to profoundly retarded persons usually require supervised community living in a group home or other residential setting.

Family therapy can help relatives of the mentally retarded develop coping skills. It can also help parents deal

with feelings of guilt or anger. A supportive, warm home environment is essential to help the mentally retarded reach their full potential.

Prognosis

People with mild to moderate mental retardation are frequently able to achieve some self-sufficiency and to lead happy and fulfilling lives. To reach these goals, they need appropriate and consistent educational, community, social, family, and vocational supports. The outlook is less promising for those with severe to profound retardation. Studies have shown that these persons have a shortened life expectancy. The diseases that are usually associated with severe retardation may cause the shorter lifespan. People with Down syndrome will develop the brain changes that characterize **Alzheimer's disease** in later life and may develop the clinical symptoms of this disease as well.

Special concerns

Prevention

Immunization against diseases such as measles and Hib prevents many of the illnesses that can cause mental retardation. In addition, all children should undergo routine developmental screening as part of their pediatric care. Screening is particularly critical for those children who may be neglected or undernourished or may live in disease-producing conditions. Newborn screening and immediate treatment for PKU and hyperthyroidism can usually catch these disorders early enough to prevent retardation.

Good prenatal care can also help prevent retardation. Pregnant women should be educated about the risks of alcohol consumption and the need to maintain good nutrition during pregnancy. Such tests as amniocentesis and **ultrasonography** can determine whether a fetus is developing normally in the womb.

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The Arc of the United States (formerly Association of Retarded Citizens of the United States). 1010 Wayne Avenue, Silver Spring, M.D. 20910. (301) 565-3842. <http://thearc.org>.

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Paula Anne Ford-Martin
Rosalyn Carson-DeWitt, MD

Meralgia paresthetica

Definition

Meralgia paresthetica is a condition characterized by numbness, tingling, or **pain** along the outer thigh.

Description

Meralgia paresthetica occurs when the lateral femoral cutaneous nerve, which supplies sensation to the outer part of the thigh, is compressed or entrapped at the point where it exits the pelvis. Usually, only one thigh is affected. Obese, diabetic, or pregnant people are more susceptible to this disorder. Tight clothing may exacerbate or cause the condition.

Demographics

Overweight individuals are more likely to develop meralgia paresthetica; men are more commonly affected than women. The disorder tends to occur in middle-aged individuals.

Causes and symptoms

Meralgia paresthetica is the result of pressure on the lateral femoral cutaneous nerve, and subsequent inflammation of the nerve. The point of pressure or entrapment is usually where the nerve exits the pelvis, running through the inguinal ligament. Being overweight, having diabetes or other risk factors for nerve disorders, wearing tight clothing or belts, previous surgery in the area of the lateral

femoral cutaneous nerve, or injury (such as pelvic fracture) predispose individuals to meralgia paresthetica.

Symptoms of meralgia paresthetica include numbness, tingling, stinging, or burning pain along the outer thigh. The skin of the outer thigh may be particularly sensitive to touch, resulting in increased pain. Many people note that their symptoms are initiated or worsened by walking or standing.

Diagnosis

The diagnosis is usually evident based on the patient's description of symptoms and the physical examination. Neurological testing will usually reveal normal thigh-muscle strength and normal reflexes, but there will be numbness or extreme sensitivity of the skin along the outer aspect of the thigh.

Treatment team

Depending on its severity, meralgia paresthetica may be treated by a family medicine doctor, internal medicine specialist, **neurologist**, or orthopedic surgeon.

Treatment

Patients with meralgia paresthetica are usually advised to lose weight and to wear loose, light clothing. Sometimes medications (amitriptyline, **carbamazepine**, or **gabapentin**, for example) can ameliorate some of the symptoms. In patients with severe pain, temporary relief can be obtained by injecting lidocaine (a local anesthetic) and steroids (an anti-inflammatory agent) into the lateral femoral cutaneous nerve. In very refractory cases, surgery to free the entrapped lateral femoral cutaneous nerve may be required in order to improve symptoms.

Prognosis

Many cases of meralgia paresthetica resolve spontaneously, usually within two years of onset.

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Rosalyn Carson-DeWitt, MD

Metachromatic leukodystrophy

Definition

Metachromatic **leukodystrophy** (MLD) is a rare degenerative neurological disease, and is the most common form of the leukodystrophies, a group of disorders affecting the fatty covering that acts as an insulator around nerve fibers known as the myelin sheath. With destruction of the myelin sheath, progressive deterioration of muscle control and intellectual ability occurs. Metachromatic leukodystrophy is inherited as an autosomal recessive trait, meaning that that the disease is inherited from parents that are both carriers, but do not have the disorder. There are three forms of MLD, distinguished by the age of onset and by the molecular defect in the gene underlying the disease.

Description

The late infantile form of metachromatic leukodystrophy, which is the most common form, usually begins in the second year of life (ranges 1–3 years). After normal early development, the infant displays irritability and an unstable walk. As the disease progresses, physical and mental deterioration occur. Developmental milestones, such as language development, are not met, and muscle wasting eventually gives way to spastic movements, then profound weakness. **Seizures** usually occur, followed by paralysis.

The juvenile form of MLD usually begins between the ages of 4 and 10 (ranges 3–20 years), and presents with disturbances in the ability to walk (gait disturbances), urinary incontinence, mental deterioration, and emotional difficulties. Some scientists distinguish between early and late juvenile MLD. Late juvenile MLD is similar to the adult form of the disease. Adult MLD begins after the age of 20 (ranges 16–30 years) and presents mainly with emotional disturbances and psychiatric symptoms, leading to a diagnosis of psychosis. Disorders of movement and posture appear later. **Dementia** (loss of mental capacity), seizures, and decreased visual function also occur.

Key Terms

Autosomal recessive disorder A genetic disorder that is inherited from parents who are both carriers, but do not have the disorder. Parents with an affected recessive gene have a 25% chance of passing on the disorder to their offspring with each pregnancy.

Demyelination Loss of the myelin covering of some nerve fibers resulting in their impaired function.

Enzyme A protein produced by living cells that regulates the speed of the chemical reactions that are involved in the metabolism of living organisms, without itself being altered in the process.

Demographics

The frequency of MLD is estimated to be 1 in 40,000 persons in the United States. No differences have been identified on the basis of race, sex, or ethnic origin.

Causes and symptoms

MLD is caused by a deficiency of the enzyme arylsulfatase A (ARSA). Without properly functioning ARSA, a fatty substance known as sulfatide accumulates in the brain and other areas of the body such as the liver, gall bladder, kidneys, and/or spleen. The buildup of sulfatide in the **central nervous system** causes demyelination, the destruction of the myelin protective covering on nerve fibers. With progressive demyelination, motor skills and mental function diminish.

MLD is an autosomal recessive inherited disease and can be caused by mutations in two different genes, the ARSA and the prosaposin gene. Mutations in the ARSA gene are far more frequent. So far, about 50 mutations have been identified in ARSA gene.

Diagnosis

Diagnosis of MLD is suspected in a person displaying its symptoms. **Magnetic resonance imaging** may be used to identify lesions and atrophy (wasting) in the white matter of the brain that are characteristic of MLD. Urine tests usually show elevated sulfatide levels. Some psychiatric disorders coupled with difficulty walking or muscle wasting suggest the possibility of MLD. Blood testing can show a reduced activity of the ARSA enzyme.

Deficiency of the ARSA enzyme alone is not proof of MLD, because a substantial ARSA deficiency without any symptoms or clinical consequences is frequent in the general population. During diagnosis and genetic counseling, these harmless ARSA enzyme deficiencies must be distinguished from those causing MLD. The only diagnostic test that solves this problem and is definitive for MLD diagnosis is analysis of the genetic mutation.

Treatment team

The treatment team usually involves a **neurologist**, a pediatrician, an ophthalmologist, an orthopedist, a genetic counselor, a neurodevelopmental psychologist, a bone marrow transplant physician, a genetic and/or metabolic disease specialist, and also a physical and an occupational therapist.

Treatment

No effective treatment is available to reverse the course of MLD. Drug therapy is part of supportive care for symptoms such as behavioral disturbances, feeding difficulties, seizures, and constipation. Bone marrow transplantation has been tried and there is evidence that this treatment might slow the progression of the disease. In infants, during a symptom-free phase of the late infantile form, neurocognitive function may be stabilized, but the symptoms of motor function loss progress. Persons with the juvenile and adult forms of MLD and with mild or no symptoms are more likely to be stabilized with bone marrow transplantation. **Gene therapy** experimentation on animal models as a possible therapy is still under consideration, and there are not yet any gene therapy-related **clinical trials** for MLD.

Recovery and rehabilitation

MLD patients require follow-up evaluation and treatment. Physical therapists, occupational therapists, orthopedists, ophthalmologists, and neuropsychologists are often involved in helping maintain optimal function for as long as possible.

Clinical trials

As of early 2004, there is one open clinical trial for MLD sponsored by Fairview University and the National Institutes of Health: "Phase II Study of Allogeneic Bone Marrow or Umbilical Cord Blood Transplantation in Patients With Lysosomal or Peroxisomal Inborn Errors of Metabolism." Further information about the trial can be found at the National Institutes of Health clinical trials website <http://www.clinicaltrials.gov/ct/show/NCT00005894?order=1>.

Prognosis

In young children with the late infantile form of MLD, progressive loss of motor and cognitive functions is rapid. Death usually results within five years after the

onset of clinical symptoms. In the early juvenile form of MLD, although progression is less rapid, death usually occurs within 10–15 years of diagnosis, and most young people with the disease die before the age of 20. Persons with the late juvenile form often survive into early adulthood, and patients with the adult form may have an even slower progression.

Special concerns

Genetic counseling is important to inform the family about the risk of occurrence of MLD in future offspring. Prenatal testing may be available on an experimental basis in some centers.

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United Leukodystrophy Foundation. 2304 Highland Drive, Sycamore, IL 60178. (815) 895-3211 or (800) 728-5483; Fax: (815) 895-2432. ulf@tbcnet.com. <http://www.ulf.org>.

Igor Medica, MD, PhD

Methylphenidate *see* **Central nervous system stimulants**

Methylprednisolone *see* **Glucocorticoids**

Microcephaly

Definition

Microcephaly is a neurological disorder where the distance around the largest portion of the head (the circumference) is less than should normally be the case in an infant or a child. The condition can be evident at birth, or can develop within the first few years following birth. The smaller than normal head restricts the normal growth and development of the brain.

Description

The word microcephaly comes from the Greek *micros* meaning small, and *kephale* meaning head. The small head circumference that is a hallmark of microcephaly has been defined as that which is either two or three standard deviations (a statistical measure of variability) below the normal average head circumference for the age, gender, and race of the child. Put another way, the head size is markedly smaller than the expected size for about 97–99% of other children.

The condition can be present at birth or may develop during the first few years of life. In the latter situation, the growth of the head fails to keep to a normal pace. This produces a small head, relatively large face (since the face keeps growing at a normal rate), and a forehead that slopes backward. The smallness of the head becomes even more pronounced with age. An older child with microcephaly also has a body that is smaller and lighter than normal. This may be a consequence of the restricted brain development.

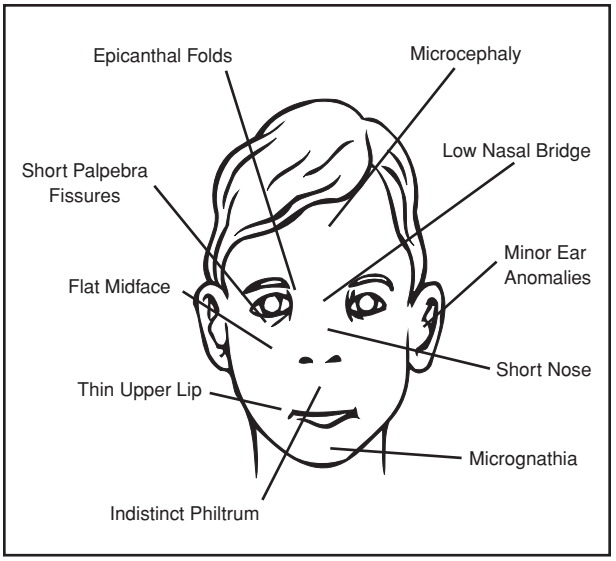
Demographics

Microcephaly is a rare neurological condition and occurs worldwide. Little detailed information on the prevalence of the disorder is available. Microcephaly does not appear to be more prevalent among any race or one gender.

Causes and symptoms

Microcephaly may have a genetic basis. If the gene defect(s) are expressed during fetal development, the condition is present at birth. This is the congenital form of the disorder. The microcephaly that develops after birth may still reflect genetically based developmental defects. As well, the delayed microcephaly can be caused if the normal openings in the skull close too soon after birth, preventing normal head growth. This condition is also referred to as **craniosynostosis**.

Other possible causes of microcephaly include infections during pregnancy (rubella, cytomegalovirus, toxoplasmosis), adverse effects of medication, and the



Microcephaly and other abnormalities produced by fetal alcohol syndrome. (*EPD Photos.)*

excessive use of alcohol by the mother during pregnancy (fetal alcohol syndrome).

The damage from microcephaly comes because of the cramped interior of the skull. This lack of space exerts pressure on the growing brain. This causes impairment and delayed development of functions such as speech and control of muscles. The impaired muscle control can produce effects ranging from a relatively minor clumsiness in body movement to the more serious and complete loss of control of the arms and legs. A child can also be hyperactive and mentally retarded, although the latter is not always present. As a child grows older, **seizures** may occur.

It should be noted that at times it is diminished growth of the brain that results in microcephaly. Without proper brain growth, the surrounding skull does not expand and microcephaly results.

Diagnosis

Diagnosis of craniosynostosis and microcephaly is made by a physician, typically during examination after birth. A physician may also be alerted to the presence of microcephaly based on the appearance of the head at birth. Other clues in the few years after birth can be the failure to achieve certain developmental milestones, and the appearance of the distinctive facial appearance.

Treatment team

The medical treatment team can consist of family and more specialized physicians and nurses. Parents and caregivers play an important role in supportive care. As various developmental challenges present themselves, physical therapists and special education providers may become part of the treatment team.

Key Terms

Craniosynostosis A birth defect of the brain characterized by the premature closure of one or more of the cranial sutures, the fibrous joints between the bones of the skull.

Microcephaly A rare neurological disorder in which the circumference of the head is smaller than the average for the age and gender of the infant or child.

Treatment

In the case of craniosynostosis, surgery can be accomplished to reopen the prematurely closed regions of the skull. This allows the brain to grow normally. There is no such treatment for the congenital form of microcephaly. Treatment then consists of providing for the person's comfort and strategies to compensate for physical and mental delays.

Recovery and rehabilitation

Recovery from craniosynostosis can be complete if surgery is done at an early enough age. For a child with other forms of microcephaly, few treatment options are available. Emphasis, therefore, is placed upon maximizing mobility and mental development, rather than recovery. Speech therapists and audiologists can help with hearing and language development. Physical and occupational therapists provide aid in walking and adaptive equipment such as wheelchairs. Special education teachers coordinate educational goals and strategies based upon the child's abilities.

Clinical trials

Although as of April 2004, there are no ongoing **clinical trials** underway for the study or treatment of microcephaly, research is being done to explore and understand the mechanisms, particularly genetic, of brain and skull development. By understanding the nature of the developmental malfunctions, it is hoped that corrective or preventative strategies might be developed.

Prognosis

With surgery, the prognosis for children with craniosynostosis can be good. However the outlook for children with other forms of microcephaly is poor, and the likelihood of having normal brain function is likewise poor.

Special concerns

As microcephaly is often associated with chromosomal abnormalities, the specific genetic cause for a person's microcephaly should be determined, if possible. Genetic counseling is available to help parents with information about their child with microcephaly and to plan for future pregnancies.

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National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Institute for Child Health and Human Development (NICHD). 31 Center Drive, Rm. 2A32 MSC 2425, Bethesda, MD 20892-2425. (301) 496-5133; Fax: (301) 496-7101. <http://www.nichd.nih.gov>.

National Organization for Rare Disorders. 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605. (914) 428-7100 or (888) 663-4637; Fax: (914) 428-8203. askus@marchofdimes.com. <http://www.marchofdimes.com>.

Brian Douglas Hoyle, PhD

Migraine headache *see* **Headache**

Miller-Fisher syndrome *see* **Fisher syndrome**

Mini-strokes *see* **Transient ischemic attack**

Mitochondrial myopathies

Definition

Mitochondrial myopathies are a group of neuromuscular disorders that result from defects in the function of the mitochondrion, a small organelle located inside many cells that are responsible for fulfilling energy requirements of the tissue. These structures serve as "power plants" and are particularly important for providing energy for both muscle and brain function due to the large requirement for energy in these tissues.

People affected with one of these disorders usually have muscle symptoms such as weakness, breathlessness, **exercise** intolerance, heart failure, **dementia**, stroke-like symptoms, deafness, blindness, **seizures**, heavy eyelids or eye problems, and/or vomiting. Originally, mitochondrial myopathies were recognized based solely on clinical findings. Currently, there are genetic explanations that provide additional information that is usually consistent with the clinical diagnosis and can, in some cases, help determine the long-term prognosis. Mitochondrial myopathies can also result as secondary effects from other diseases.

Description

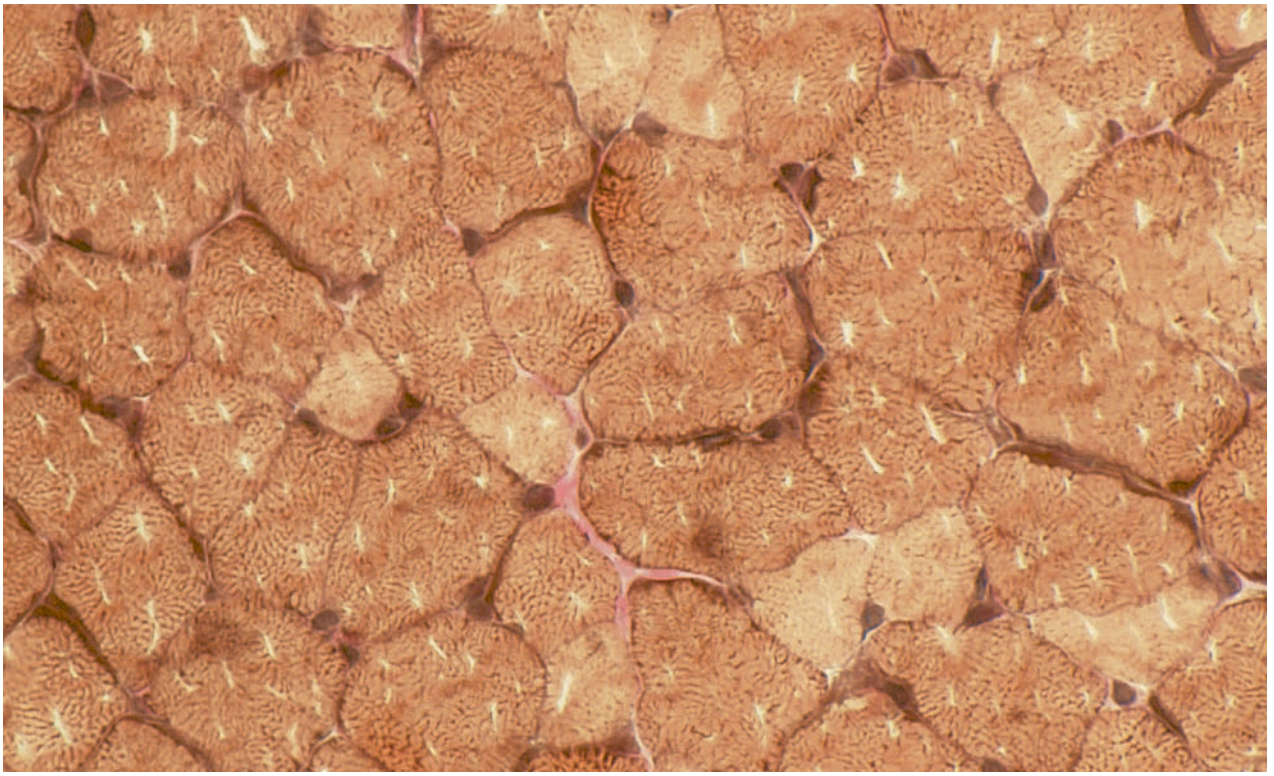
Myopathy means a disorder of the muscle tissue or muscle. Mitochondrial myopathies are, therefore, disorders of the muscle tissue caused by abnormalities of the mitochondria.

The following disorders are the most common mitochondrial myopathies, including:

- NARP: neuropathy, **ataxia** and retinitis pigmentosa
- KS: Kearns-Sayre syndrome
- Leigh's syndrome
- PEO: progressive external ophthalmoplegia
- MILS: maternally inherited Leigh's syndrome
- MELAS: mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes
- MERFF: **myoclonus epilepsy** with ragged-red fibers
- Pearson syndrome
- MNGIE: mitochondrial neurogastrointestinal **encephalopathy**
- LHON: Leber hereditary optic neuropathy

Demographics

The initial disease-causing or disease-related (pathogenic) alterations in mitochondrial DNA (mtDNA) were first identified in the early 1990s. Currently, more than 50 different single-base pathogenic mutations in the mtDNA sequence and more than 100 different pathogenic rearrangements within the genome have been identified. These include large deletions or duplications in the mtDNA sequence of bases. With the high mutation rate, it would seem that the prevalence of mitochondrial myopathies would be high; however, mitochondrial myopathies are relatively rare, having an incidence of



Fat accumulation in muscle. The focal ragged red fibers are consistent with mitochondrial myopathy.

approximately six out of every 100,000 individuals to as high as 16 out of 100,000 individuals. But there is evidence that, as part of the normal aging process, the accumulation of mtDNA mutations leads to neurological changes and abnormalities such as hearing loss or diabetes, which are normally considered to be associated with aging.

Causes and symptoms

In most cases, the primary defect in mitochondrial myopathies results from mutations in important genes that determine (encode) the structure of proteins that function in the mitochondria. Mutations can be found in DNA from the nucleus of the cell. This DNA is known as nuclear DNA, which is the DNA that most people consider with respect to human genetic diseases, but DNA is also found in the mitochondrial genome. Mitochondrial myopathies can be caused by defects in nuclear and mitochondrial DNA.

Mitochondrial DNA (mtDNA) is much smaller than nuclear DNA (nDNA). Nuclear DNA has approximately 3.9 billion base pairs in its entire sequence; mtDNA has only 16,500 pairs. Although mtDNA is much smaller in size, each cell contains anywhere from 2–100 mitochondria, and each mitochondria has 5–10 copies of its genome.

Unlike nDNA that is twisted into a double helix, mtDNA has a circular structure. Mitochondrial DNA also has a high mutation rate, almost 20 times that of the nDNA. All of these factors are important in understanding the role of mtDNA mutations in the development of inherited or other mitochondrial myopathies.

A unique feature of mtDNA is that out of the more than 1,000 mtDNA genomes within the cell, a new mutation in one of the mtDNA genomes can be replicated each time the cell divides, thus increasing the number of defective mtDNA genomes. Because the distribution of the newly replicated mtDNA into the two daughter cells is random, one of the daughter cells may contain mtDNA that is not mutated (a condition referred to as homoplasmy), while the other daughter cell inherits both mutation genomes (known as heteroplasmy, or a mixture of mutated and normal genomes). Knowing the percentage of heteroplasmy for different mutations is often helpful in determining whether the disorder will manifest symptoms, as well as how severe they might be. As a result of the heteroplasmic nature of mitochondrial myopathies, the range of symptoms and severity of symptoms is often highly variable.

Mitochondrial myopathies are caused by mutations in either the nDNA or the mtDNA. These mutations generally affect tissues that have a high demand for metabolic energy production. Some disorders only affect a single organ, but many involve multiple organ systems. Generally, nDNA

mutations result in clinical symptoms that develop during early childhood, while mtDNA mutations (either directly or as secondary effects from a nDNA mutation) lead to clinical manifestations that develop in late childhood or early adulthood. The genes that comprise the mtDNA genome encode proteins that function inside the mitochondria. For example, sugar broken down from food is used for fuel to manufacture a specific molecule, adenosine triphosphate (ATP), which is used by the cell to accomplish a variety of essential functions. ATP is produced by charged particles called electrons that come from digested food products to harness the energy. This is accomplished through five highly organized protein complexes. The first four complexes (complex I, II, III, and IV) are part of the electron transport chain and function to move the electrons towards the fifth complex (complex V), which produces the ATP molecule. A defect in any one of these complexes can lead to mitochondrial myopathies. Both DNA from the nucleus and the mitochondria are required to assemble the many subunits that make up these complexes.

The process of producing ATP requires oxygen. This is essentially why humans cannot live without it. In the absence of a properly functioning electron transport chain, precursor molecules as well as unused oxygen begin to accumulate. One molecule in particular, called lactic acid, accumulates normally during strenuous exercise when tissue demands for energy cannot be met, resulting in muscle **fatigue**. This occurs essentially by accumulation of lactic acid, or lactic acidosis. Persons with a deficiency in the electron transport chain, therefore, have symptoms similar to an athlete's muscle fatigue, but without the factor of strenuous exercise. Both muscle contraction and nerve cell stimulation requires ATP; thus, these cells are particularly sensitive to defects in mitochondrial function. Furthermore, oxygen that is not metabolized can be converted into toxic compounds called reactive oxygen species (ROS). ROS can lead to many symptoms that an individual with a mitochondrial myopathy will experience.

Inheritance and medical significance

Mitochondrial DNA is inherited almost entirely from the maternal sex cell (the egg). Therefore, mutations or alterations in the mtDNA can be transmitted from a maternal sex cell to all the mother's children, regardless of gender.

Heteroplasmy, or the condition of having both normal and mutated mtDNA genomes, has several clinically important implications. If mtDNA molecules are deleted, they are generally not transmitted from the mother to her offspring for reasons that are currently unclear. If the mtDNA is duplicated (or various sequences are repeated with the same sequences such that the total size of the genome increases by exactly the number of repeated bases) or there is a mutation that only affects one base in the sequence, there usually is some of the mutant mtDNA molecules that get transmitted. Additionally, a phenomenon called the mitochondrial genetic bottleneck occurs during the production of the mother's sex cells (eggs). This term refers to a reduction in the number of mtDNA molecules followed by an amplification of this reduced mtDNA that occurs during maturation of the mother's eggs. The result is considerable variability in the amount of mutated mtDNA molecules that each of the offspring inherits. However, in general, mothers that have a higher amount of mutated molecules are more likely to have offspring that are more severely affected compared to mothers that have a lower mutant load.

Inheritance and the nuclear genome

Not all mitochondrial proteins are produced by the mitochondrial genome. In fact, the majority is produced by the nuclear genome. Therefore, mitochondrial myopathies can be caused by mutations in both the nDNA and the mtDNA. This has important implications for genetic counselors that assess the recurrence risks in families with affected offspring. If the defect is of nuclear origin, it is typically recessive. In this case, there is a 25% chance of having an affected baby if both parents are carriers. There are also dominant disorders leading to mitochondrial myopathies that are characterized by a carrier parent passing on the mutant nuclear gene to 50% of the offspring. There are many mitochondrial myopathies that do not have a mtDNA mutation, and there are no nDNA mutations known.

Scientists are increasing their understanding of the intercommunication between the nucleus and the mitochondria. The identification of nDNA mutations that cause mitochondrial myopathies was first made when a nuclear gene involved in mtDNA replication was found to be defective in a disorder involving a patient with a mitochondrial myopathy.

Symptoms of mitochondrial myopathies are largely variable from person to person, even within the same family, and are dependent on the amount and type of genetic mutations present. These disorders can occur in infancy, childhood, or adulthood. In general, individuals with mitochondria dysfunction have abnormalities in the **central nervous system**. Defects can involve seizures, **movement disorders**, **headaches**, and cognitive (thought) disorders such as developmental delay or dementia (forgetfulness, senility). People with mitochondrial myopathies can also have hearing loss.

It is common that symptoms become apparent in a specific cluster of abnormalities and are thus considered a syndrome. For example, Kearns-Sayre syndrome can be recognized clinically due to similar symptoms that patients have. These symptoms include ocular abnormalities

Key Terms

Mitochondria A part of the cell that is responsible for energy production.

Mitochondrial DNA (mtDNA) The genetic material found in mitochondria, the organelles that generate energy for the cell. Because reproduction is by cloning, mtDNA is usually passed along female lines, as part of the egg's cytoplasm.

Myopathy A disorder of the muscle or muscle tissue.

Nucleic DNA (nDNA) The genetic material found in the nucleus of the cell.

(degeneration of the retina and external opthamaloplegia, or droopy eyelids), dysphagia (swallowing problems), progressive myopathy, and various central nervous system abnormalities such as hearing loss. Confirmation of this disorder can be performed by genetic analysis that looks for large deletions in mtDNA.

Due to the nature of the genetic and biophysical defects, mitochondrial myopathies have symptoms related to muscle weakness and atrophy. Droopy eyelids and loss of the ability to control eye movements indicate muscle wasting, which leads to paralysis, and compensatory attempts at correcting eye movements by tilting the head. Visual loss often occurs.

Muscle wasting, or myopathy, is not restricted to the eyes. The face and neck can also be affected, leading to incomprehensible speech and swallowing difficulties. Overall musculature wasting pervades many affected individuals, requiring wheelchairs and, in severe cases, assisted living requirements. Exercise-induced **pain** can also result.

Diagnosis

The diagnosis of mitochondrial myopathies is initially clinical, which means that it is based on the observable clinical manifestations that the patient shows versus results obtained from genetic analysis or laboratory tests. The physician will make careful observations of the affected child and interview the parents, in particular the mother, as it is common that she has the same mtDNA mutation, though usually at a lower percent load. Persons with mitochondrial myopathies are referred to a clinical geneticist for management and further evaluation, particularly in the absence of a confident clinical diagnosis. If there is a positive test after a genetic evaluation, genetic counseling is critical for understanding the nature of the disease and the implications for future offspring.

Diagnostic criteria

Any multi-system progressive disorder should lead a physician to suspect a mitochondrial disorder. A diagnosis can be particularly difficult if there is only one symptom. The diagnostic criteria for mitochondrial myopathies involve phenotypic evaluation (or evaluation of observable traits), followed by laboratory evaluation. A clinical diagnosis can be confirmed by laboratory studies, muscle **biopsy**, and molecular genetic evaluation, in which a geneticist analyzes the mtDNA. If a mtDNA mutation is detected, diagnosis is much more straightforward. In the absence of a mtDNA mutation, diagnosis becomes difficult.

There are several classical clinical manifestations that warrant DNA studies, such as in the case of MELAS, MERRF or LHON. Other disorders such as MNGIE require nDNA studies. In the absence of specific clinical criteria characteristic of a mitochondrial myopathy, blood plasma or cerebral spinal fluid is measured for lactic acid concentration, ketone bodies, plasma acylcarnitines, and organic acids in the urine. These are metabolites that are typically abnormal in an individual with a mitochondrial myopathy. If they are abnormal, a muscle biopsy is performed. Molecular genetic testing can often confirm a clinical diagnosis with or without positive laboratory results.

Treatment team

Treatment for patients with mitochondrial myopathies is best performed by a **neurologist** and a clinical geneticist or specialist that has experience diagnosing, treating, and managing patients with mitochondrial myopathies.

Treatment

There is no cure for mitochondrial myopathies. Therefore, treatment is solely for the purposes of minimizing pain and symptoms, and increasing mobility. Due to the wide variability in the disorders, treatment is usually individualized. Although the diseases are rare, many of their clinical symptoms are common and treatable. There are medications and lifestyle modifications that can help treat conditions such as headaches, diabetes, stroke-like symptoms, and seizures that are often associated with mitochondrial myopathies.

Medications are tailored to reduce the specific symptoms that the patient is experiencing (anticonvulsant medication may be required, for example, for an individual suffering from seizures). Dietary supplements are often used, although they have not been investigated in long-term studies. Creatine, coenzyme Q 10, and carnitine are

naturally occurring supplements that are thought to enhance ATP production.

Recovery and rehabilitation

Because there is no cure for mitochondrial myopathies, the focus is on maintaining optimum function for as long as possible, rather than recovery. Physical therapy helps extend the range of muscle movement. Occupational therapy helps with positioning and mobility devices, and trains the affected individual in strategies designed to accomplish self-care and activities of daily living. Speech therapy can help children and adults that have difficulty in speaking, as well as how to safely eat and swallow food. Hearing and visual aids (glasses) are often necessary and helpful.

Clinical trials

As of early 2004, there were few **clinical trials** to develop therapies to treat mitochondrial myopathies. There was one study to investigate the role of dichloroacetate to lower lactate levels in patients diagnosed with MELAS at the National Institutes of Health (NIH). Lactic acidosis has been shown to be associated with nerve cell and muscle cell impairment in patients that have MELAS. Decreasing the levels of lactate might help prevent severe lactic acidosis.

Prognosis

Mitochondrial myopathies are extremely variable in the symptoms produced, and so the prognosis for those affected with mitochondrial myopathies also varies. The adverse affects on muscle function are often progressive, and persons often show physical deterioration over time. Occasionally, affected persons are mentally delayed. It is difficult to determine the exact course that each individual will endure, and in many cases the symptoms are relatively mild. Life expectancy for a person with a mitochondrial myopathy depends on many different circumstances, including the percentage of mtDNA that is mutated, the type of mutation, and the tissue in which it is mutated. If it is a nDNA defect, the physical and developmental effects depend on the gene that is mutated, the location of the mutation in the gene, the importance this gene has on the function of the mitochondria, and whether there are compensatory mechanisms. Overall, the prognosis is dependent on the involvement of vital organs.

Special concerns

Perhaps one of the most problematic issues that patients with mitochondrial myopathies experience is the absence of a causative explanation for why the symptoms developed. This is especially challenging for determining recurrence risks for parents considering future pregnancies. Mitochondrial myopathic disorders can pose challenges for the entire family, especially since many affected children and adults are not born with the disorder, but the condition progressively worsens with time. Support groups are available through various national disease foundations and local community organizations.

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National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD (6673); Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

United Mitochondrial Disease Foundation. 8085 Saltsburg Road Suite 201, Pittsburgh, PA 15239. (412) 793-8077; Fax: (412) 793-6477. info@umdf.org. <http://www.umdf.org>.

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Modafinil

Definition

Modafinil is a **central nervous system** (CNS) stimulant. It is primarily used to promote wakefulness and alertness in persons with **narcolepsy**, a condition that causes excessive sleepiness and cataplexy (episodes of sudden loss of muscle control).

Purpose

Modafinil is an improvement over amphetamines in the treatment of narcolepsy. It promotes wakefulness, but has less pronounced side effects than amphetamines. Modafinil acts to combat excessive daytime sleepiness (EDS) and cataplexy, the leading symptoms of narcolepsy, by stimulating sleep-suppressing peptides (orexins) in the brain.

Description

Although primarily indicated for the treatment of narcolepsy, modafinil is also used to treat some forms of **sleep apnea**. Experimentally, modafinil is being evaluated in the treatment of **Alzheimer's disease**, **depression**, **attention-deficit hyperactivity disorder** (**ADHD**), and **fatigue** associated with **multiple sclerosis**.

Recommended dosage

Modafinil is taken by mouth in tablet form. It is prescribed by physicians in varying dosages, and is usually taken once a day, in the morning.

Precautions

In some patients, modafinil may be habit forming. When taking the medication, it is important to follow physician instructions precisely. Modafinil may cause clumsiness and impair clarity of thinking. Persons taking this medication should not drive a car or operate machinery until they know how the stimulant will affect them. Patients should avoid alcohol while taking modafinil. It can exacerbate the side effects of alcohol and other medications.

Modafinil may not be suitable for persons with a history of liver or kidney disease, mental illness, high blood pressure, angina (chest **pain**), irregular heartbeats, or other heart problems. Before beginning treatment with modafinil, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant, or plan to become pregnant. Patients who become pregnant while taking modafinil should inform their physician.

Side effects

Research indicates that modafinil is generally well tolerated. However, modafinil may case a variety of usually mild side effects. **Headache**, nausea, and upset stomach are the most frequently reported side effects of modafinil. Other possible side effects include excessive difficulty sleeping, nervousness, depression, diarrhea, dry mouth, runny nose, neck pain or stiffness, **back pain**, loss of appetite, and confusion.

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.

Narcolepsy A life-long sleep disorder marked by four symptoms: sudden brief sleep attacks, cataplexy (a sudden loss of muscle tone usually lasting up to 30 minutes), temporary paralysis, and hallucinations. The hallucinations are associated with falling asleep or the transition from sleeping to waking.

Orexin Another name for hypocretin, a chemical secreted in the hypothalmus that regulates the sleep/wake cycle. Narcolepsy is sometimes described as an orexin deficiency syndrome.

Other, uncommon side effects of modafinil can be potentially serious. Persons taking modafinil who experiences any of the following symptoms should immediately contact their physician: irregular heartbeat, unusually rapid heartbeat, shortness of breath, hives or rashes, chest pain, persistent or severe headache, and persistent fever, pain, or other sign of infection.

Interactions

Modafinil may have negative interactions with some anticoagulants (blood thinners), antidepressants, antifungals, antibiotics, and monoamine oxidase inhibitors (MAOIs). Seizure prevention medication, **diazepam** (Valium), **phenobarbital** (Luminal, Solfoton), phenytoin (Dilantin), propranolol (Inderal), and rifampin (Rifadin, Rimactane) may also adversely react with Modafinil.

Furthermore, modafinil may decrease the effectiveness of oral contraceptives (birth control pills). Patients should consult their physicians about using alternative methods of birth control while taking modafinil, and for at least one month after ending treatment.

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Adrienne Wilmoth Lerner

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.

Moebius syndrome

Definition

Moebius 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

Moebius 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.

Individuals with Moebius syndrome may also have abnormalities of their limbs, chest muscles, and tongue. The chance of **mental retardation** appears to be increased in people with Moebius syndrome, but most people with the disorder have normal intelligence.

Demographics

Moebius 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.

Causes and symptoms

Most cases of Moebius 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. The underlying problem is a defect in or absence of the sixth and seventh cranial nerves. The seventh or facial nerve normally controls facial expression. The abducens or sixth cranial nerve controls blinking and back-and-forth eye movement and is the second most commonly affected cranial nerve in Moebius syndrome. Additional cranial nerves affected in some patients control other eye movements and other functions such as hearing, balance, speech, and feeding.

The first sign of Moebius 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-Moebius or Möebius-Poland syndrome. Common limb abnormalities are missing or webbed fingers and clubfoot.

The prevalence of mental retardation in Moebius 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 Moebius syndrome. In one study of familial cases of Moebius syndrome, 3% were reported to be mentally retarded.

Diagnosis

Diagnosis of Moebius syndrome is made on the basis of clinical symptoms, especially the lack of facial expression. Because the exact genes involved in Moebius syndrome have not yet been identified, molecular genetic testing is not available.

Treatment team

Neurologists, neurosurgeons, and plastic surgeons may play a role in the treatment of a child with Moebius syndrome. Physical and speech therapists may help improve control over coordination, speech, and eating.

Treatment

The ability to smile has been restored in some cases of Moebius 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.

Prognosis

Moebius syndrome does not appear to affect life span, and individuals who are treated for their symptoms can lead normal lives.

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Moebius Syndrome Foundation (MSF). PO Box 993, Larchmont, NY 10538. (914) 834-6008. <http://www.ciaccess.com/moebius>.

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Monomelic amyotrophy

Definition

Monomelic amyotrophy (MMA) is a rare disease of the nerves that control voluntary movements of the limbs.

Description

One of the **motor neuron diseases** (MND), degenerative conditions that involve the nerves of the upper or lower parts of the body, MMA is generally a benign disease associated with minimal disability. Onset of MMA primarily occurs between the ages of 15 and 25. The main features of the disease are wasting and weakness of a single upper or lower limb. Generally, MMA progresses slowly over a period of 2–4 years, and then reaches a stationary phase during which the disease remains stable for years.

Monomelic amyotrophy may also be known as benign focal amyotrophy, single limb atrophy, Hirayama syndrome or Sobue disease. Descriptive terms such as brachial monomelic amyotrophy (MMA confined to an arm) or monomelic amyotrophy of the lower limb (MMMA of a leg) may be used to specify the type of limb affected. O'Sullivan-McLeod syndrome, a variant of MMA, is a slowly progressive form of the disease that causes weakness and wasting of the small muscles of the hand and forearm.

Demographics

Monomelic amyotrophy occurs worldwide and is most prevalent in Asia, and especially in Japan and India. According to a report in 1984, MMA of the lower limb occurs in about four in a million people in India. There is a preponderance of males with MMA; estimates of the male to female ratio range from 5:1 to 13:1.

Causes and symptoms

As of 2004, the underlying cause or causes for MMA remain unresolved. Most cases are sporadic and occur in an individual without a family history of MMA. Numerous factors—such as viral infection, vascular insufficiency (inadequate blood supply) of the spinal cord, heavy physical activity, **radiation** injury, traumatic injury, and atrophy of the spinal cord—have been suggested as possible causes of MMA. There are a few reports of familial cases of MMA.

Symptoms of MMA appear slowly and steadily over a period of time. The main features of MMA are muscle weakness and atrophy (wasting) in a portion of one limb. The weakness and wasting progresses slowly and may spread to the corresponding limb on the opposite side of the body. Symptoms can develop elsewhere in the affected limb or another limb at the same time or later in the course of the disease. Patients may notice worsening of symptoms on exposure to the cold. Other symptoms of MMA include tremor, fasciculations, cramps, mild loss of sensation, excessive sweating, and an abnormal sympathetic skin response. It is rare that individuals with MMA experience significant functional impairment.

Diagnosis

Diagnosis of MMA is based on physical exam and medical history. Physical findings include reduced muscle girth (width around the arm or leg) and decreased strength in the affected limb. Tendon reflexes tend to be normal or sluggish. Cranial nerves, pyramidal tracts, sensory, cerebellar or extrapyramidal systems are not affected. Patients may report or display symptoms described above. They may also indicate difficulty carrying out activities of daily living such as writing, lifting, getting dressed, or walking.

Tests that may aid in diagnosis of MMA include **electromyography** (EMG), imaging studies such as **magnetic resonance imaging (MRI)** and computed tomography (**CT**) scans, and muscle **biopsy**. EMG shows chronic loss of nerve cells confined to specific areas of the affected limb. **MRI** has been reported to be a useful means of determining which muscles are affected in a given patient. Muscle biopsy shows evidence of atrophy of the neurons. EMG, muscle biopsy, or isometric strength testing may also reveal significant findings in seemingly normal muscles of the affected and the contralateral limb.

Treatment

There is no cure for MMA. The goal of treatment, which is largely supportive, is to help patients optimize function and manage any disability associated with the

disorder. Treatment primarily consists of rehabilitation measures such as physical therapy and occupational therapy. Severe muscle weakness (present in a minority of cases) may require orthopedic intervention such as splinting.

Treatment team

In addition to routine health care through their primary care practitioners, individuals with MMA generally see specialists in neurology and rehabilitation. Some patients with MMA may receive comprehensive services through a **muscular dystrophy** association (MDA) clinic or another type of neuromuscular clinic. Given the rarity of MMA, the potential for rehabilitation in this disorder is unknown.

Recovery and rehabilitation

Rehabilitation for MMA consists of physical and occupational therapy. The goal of these therapies is to make full use of the patient's existing functions. Physical therapy can help a patient with MMA to strengthen muscles in a weak arm or leg. Occupational therapy can teach patients to use adaptive techniques and devices that may help compensate for difficulty with everyday tasks such as writing, buttoning, or tying shoes. Depending upon the degree of weakness in the affected limb, a person with MMA may need to use the unaffected limb for activities previously performed by the now atrophied limb.

Clinical trials

As of 2004, there were no **clinical trials** for patients with MMA. As more is learned about how MMA or related motor neuron diseases develop, it is hoped that novel therapies may be developed in the future.

Prognosis

MMA is generally a benign condition. Disability associated with MMA is typically mild. In the majority of cases, the disorder usually ceases to progress within five years of onset. People with MMA can expect to have a normal life span.

Special concerns

Initially, symptoms of MMA can be similar to early signs of other, more serious neurological disorders such as **amyotrophic lateral sclerosis** (ALS or Lou Gehrig's disease) and **spinal muscular atrophy**. For this reason, periodic neurological evaluation may be recommended to be sure that no symptoms of these or other motor neuron diseases develop.

Key Terms

Electromyography A diagnostic test that records the electrical activity of muscles. In the test, small electrodes are placed on or in the skin; the patterns of electrical activity are projected on a screen or over a loudspeaker. This procedure is used to test for muscle disorders, including muscular dystrophy.

Fasciculations Small involuntary muscle contractions visible under the skin.

Sympathetic skin response Minute change of palmar and plantar electrical potential.

Resources

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ORGANIZATIONS

Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717; Fax: (520) 529-5300. mda@mdausa.org. <http://www.mdausa.org>.

National Organization for Rare Disorders. P.O. Box 1968, 55 Kensonia Avenue, Danbury, CT 06813. (203) 744-0100 or (800) 999-NORD; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

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Motor neuron diseases

Definition

Motor neuron diseases are a group of progressive disorders involving the nerve cells responsible for carrying impulses that instruct the muscles in the upper and lower body to move. Motor neuron diseases are varied and destructive in their effect. They commonly have distinctive differences in their origin and causation, but a similar result in their outcome for the patient: severe muscle weakness. **Amyotrophic lateral sclerosis** (ALS), **spinal muscular atrophy**, **poliomyelitis**, and **primary lateral sclerosis** are all examples of motor neuron diseases.

Description

A motor neuron is one of the largest cells in the body. It has a large cell body with many extensions reaching out in 360° from the cell body (soma). These extensions are called dendrites and are chemically able to receive instructions from adjacent neurons. These instructions are received in the form of an impulse stimulation of a particular protein channel on the dendrite by a neurotransmitter termed acetycholine (ACh). Extending from the soma of the motor neuron is a long portion of the cell called the axon. When conditions are favorable, an electrical signal passes down the axon to a region of the cell identified as the axon terminals. These terminals also branch in many directions and have, at their tips, a region called the synaptic end bulb. This region releases ACh that crosses a small gap until it reaches a protein on another dendrite.

When motor neurons line up in a tract, they allow an electrical signal to spread from the brain to the intended muscle. There are a tremendous number of nerve tracts that extend to all the muscles of the body that are responsible for contraction and relaxation of all types of muscles, including smooth and cardiac, as well as skeletal muscle. When the motor neuron is affected or damaged and it cannot perform at peak performance, the muscles of the body are affected. Often, a disorder of the motor neurons results in progressive muscle atrophy (shrinking and wasting) of some, if not all, the muscles of the body. Muscle twitching (fasciculation) is common among these disorders. Motor neuron diseases are difficult to treat, debilitating to movement and, in some cases, fatal.

Amyotrophic lateral sclerosis (ALS) is a disorder that generally involves either the lower or upper motor systems of the body. In advanced stages, both regions of the body are affected. This disease is commonly known as Lou Gehrig's disease after the famous baseball player who died from the condition. It is caused by sclerosis (a hardening of the surrounding fibrous tissues) in the corticospinal tracts. Associated with the sclerosis is a loss of the tissue of the anterior horns (gray matter) in the spinal cord, including the brainstem. Lou Gehrig's disease is characterized by a wasting of the muscles that, in turn, produces weakness. The bulbar, or facial/mouth muscles can initially become involved, which may lead to slurring of speech and drooling. The significance of this involvement is that, with rapid progression, the patient may not be able to swallow properly. This may lead to the risk of choking and other difficulties with obtaining nutrition and proper respiration. Death from complications of ALS is common within five years.

Spinal muscular atrophies (SMAs) are a wide group of genetic disorders characterized by primary degeneration of the anterior horn cells of the spinal cord, resulting in progressive muscle weakness. Spinal muscular atrophies affect only lower motor neurons. In babies and children, many SMAs are rapidly progressive with paralysis of the legs, trunk, and eventually, the respiratory muscles. In teenagers and adults, SMAs are usually slowly progressive. **Kennedy's disease**, an X-linked (carried by women and passed on to male offspring) SMA, features similar wasting of facial muscles as seen in ALS, with characteristic difficulty speaking and swallowing.

Primary lateral sclerosis (PLS) is a rare motor neuron disease that resembles ALS. Primary lateral sclerosis often begins after age 50, and results in slowly progressive weakness and stiffness in the leg muscles, clumsiness, and difficulty maintaining balance. Symptoms worsen over a period of years. Muscle spasms in the legs may also occur, but in PLS, there is no evidence of the degeneration of spinal motor neurons or muscle wasting (amyotrophy) that occurs in ALS.

Unlike most motor neuron diseases, poliomyelitis results from infection with a virus. Contamination occurs through fecal or oral exposure. Once inside the body, the virus uses the cells of the gastrointestinal tract to enter the bloodstream and move throughout the body. Eventually, the poliovirus invades the nerve cells of the spinal cord and

Key Terms

Atrophy Shrinking or wasting of muscles or tissues.

Amyotrophy A type of neuropathy resulting in pain, weakness, and/or wasting in the muscles.

Contractures Abnormal, usually permanent contraction of a muscle due to atrophy of muscle fibers, extensive scar tissue over a joint, or other factors.

Dysarthria Imperfect articulation of speech due to muscular weakness resulting from damage to the central or peripheral nervous system.

Dysphagia Difficulty swallowing.

Fasciculations Fine muscle tremors or twitches.

Gait Posture and manner of walking.

Motor neuron A neuron conducting impulses outwards from the brain or spinal cord with the specific job of controlling a muscle movement.

kills the motor neurons. When the motor neurons are destroyed, the muscles they connect to become damaged and weaken. The result is varying degrees of paralysis, including difficulty swallowing, walking, breathing, and control of speech.

Demographics

Motor neuron diseases are uncommon, as about one person in 50,000 is diagnosed with a motor neuron disease in the United States each year. In total, about 5,500 people in the United States each year receive a diagnosis of a motor neuron disease.

About 20,000 Americans are living with ALS and nearly 4,500 new cases are reported annually. The peak age for onset is around 55 years of age, but younger patients have been observed. Spinal muscular atrophies and primary lateral sclerosis are rare diseases.

The occurrence of poliomyelitis is seen in records of epidemics that were intricately documented in the last 100 years. A description of an epidemic in recent times in the United States discussed a low of 4,197 cases in the early 1940s to a high of 42,033 in 1949. By 1952, the number of case had reached over 58,000. In 1955, a vaccine was developed that used weakened forms of the virus. This vaccine and the subsequent Sabin vaccine nearly wiped out polio in the world. The Americas were declared free of polio in the 1990s. In 2002, there were less than 500 cases worldwide, and in 2003, that number decreased to less than 100 cases. It is expected that by the end of the year 2005, the disease will be eradicated. Although new cases have begun to appear in regions of Africa and India, the World Health Organization (WHO) is keeping track of the outbreaks, and scientists are hopeful that poliomyelitis will soon disappear from the list of motor neuron diseases.

Causes and symptoms

Causes of many motor neuron diseases are unknown, and others have varying causes according to the specific motor neuron disease. Most cases of ALS occur sporadically for an unknown reason, however, up to 10% of ALS cases are inherited. Most spinal muscular atrophies are inherited. A virus causes poliomyelitis. Additionally, environmental factors and toxins are under study as causes or triggers for motor neuron diseases.

Muscle weakness is the symptom common to all motor neuron diseases. Muscles of the legs are most often affected, leading to clumsiness, unstable gait, or lower limb paralysis. Muscle cramps and fasciculations (twitching) occur with most motor neuron diseases. Facial muscles may also be affected, leading to difficulty with speech (**dysarthria**). Later in the course of some motor neuron diseases, the muscles involved with swallowing and breathing may be impaired (dysphagia).

Diagnosis

Diagnosis of motor neuron disease is often based upon symptoms and exclusion of other neurological diseases. Nerve conduction studies can help distinguish some forms of **peripheral neuropathy** from motor neuron disease. Electromyelogram (EMG), a test measuring the electrical activity in muscles, can support the diagnosis of ALS and some other motor neuron diseases. Although computed tomography (**CT) scans** and **magnetic resonance imaging (MRI)** scans are often normal in persons with motor neuron disease, they may help exclude spinal malformations or tumors that could be responsible for similar symptoms. A muscle **biopsy** can exclude myopathies. Diagnosis of primary lateral sclerosis is especially difficult and often delayed, as it is frequently misdiagnosed as ALS. Polio may be diagnosed by recovering the virus from a stool or throat culture, examining antibodies in the blood or, rarely, by spinal fluid analysis. Finally, molecular genetic studies can aid in the diagnosis of spinal muscular trophies and the small percentage of inherited ALS cases.

Treatment team

Caring for a person with a motor neuron disease requires a network of health professionals, community resources, and friends or family members. A **neurologist**

usually makes the diagnosis, and the neurologist and primary physician coordinate ongoing treatment and symptom relief. Physical, occupational, and respiratory therapists provide specialized care, as do nurses. Social service and mental health consultants organize support services.

Treatment

There are few specific treatments for motor neuron diseases, and efforts focus on reducing the symptoms of muscle spasm and **pain** while maintaining the highest practical level of overall health. Riluzole, the first drug approved by the U.S. Food and Drug Administration for the treatment of ALS, has extended the life of ALS patients by several months and also extended the time a person with ALS can effectively use his or her own muscles to breathe.

Other medications used to treat persons with motor neuron disease are designed to relieve symptoms and improve the quality of life for patients. These include medicines to help with **depression**, excess saliva production, sleep disturbances, and constipation.

Recovery and rehabilitation

Recovery from motor neuron diseases depends on the type of disease and the amount of muscle degeneration present. In diseases such as ALS, the emphasis is placed upon maintaining mobility and function for as long as possible, rather than recovery. With all motor neuron diseases, physical therapy can teach exercises to help with range of motion and prevent contractures (stiff muscles at the joints). Occupational therapy provides assistive devices for mobility such as wheelchairs, positioning devices, braces, and other orthotics for performing daily activities such as reaching and dressing. Respiratory therapists and speech therapists help prevent pneumonia by maintaining lung function and promoting safe eating strategies. Speech therapists also help with alternate forms of communication if facial muscles are involved.

Recovery from polio may be complete or only partial, depending on the degree of lower motor neuron damage. Years or decades after recovering from polio, persons may again experience muscle weakness and pain. This is known as postpolio syndrome. Vigorous **exercise** has been shown to cause additional weakness in postpolio syndrome, and physicians recommend energy conservation and lifestyle changes for these patients.

Clinical trials

The National Institutes of Health (NIH) has more than 20 **clinical trials** scheduled for 2004–05 for the study of motor neuron diseases, including one trial designed to evaluate a new drug, Minocycline, in the treatment of ALS. Details and up-to-date information about patient recruiting can be found at the NIH Website for clinical trails at <http://www.clinicaltrials.gov>.

Prognosis

The prognosis of persons with motor neuron diseases depends on the type of the disease and the amount and progression of muscle degeneration. Most persons with ALS die from complications of respiratory failure within five years of developing symptoms. About one out of 10 persons with ALS live a decade or longer with the disease. The prognosis for a person with spinal muscular atrophy varies greatly, according to the severity of the disease. Some forms result in immobility and death within a few years, while others impede movement, but do not affect a normal lifespan.

Special concerns

It is important to remember that even in the most severe motor neuron diseases, a person's personality, intelligence, reasoning ability, or memory are not impaired. The person with motor neuron disease also retains the senses of sight, smell, hearing, taste, and in the unaffected areas, touch.

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ALS Association (ALSA). 27001 Agoura Road, Suite 150, Calabasas Hills, CA 91301-5104. (818) 880-9007 or (800) 782-4747; Fax: (818) 880-9006. info@alsa-national.org. <http://www.alsa.org>.

Families of SMA. PO Box 196, Libertyville, IL 60048-0196. (800) 886-1762; Fax: (847) 367-7623. sma@fsma.org. <http://www.fsma.org>.

Primary Lateral Sclerosis Newsletter. 101 Pinta Court, Los Gatos, CA 95032. (408) 356-8227; Fax: (408) 356-8227. 73112.611@compuserve.com.

Brook Ellen Hall, PhD

Movement disorders

Definition

Movement disorders are a group of diseases and syndromes affecting the ability to produce and control movement.

Description

Though it seems simple and effortless, normal movement in fact requires an astonishingly complex system of control. Disruption of any portion of this system can cause a person to produce movements that are too weak, too forceful, too uncoordinated, or too poorly controlled for the task at hand. Unwanted movements may occur at rest. Intentional movement may become impossible. Such conditions are called movement disorders.

Abnormal movements themselves are symptoms of underlying disorders. In some cases, the abnormal movements are the only symptoms. Disorders causing abnormal movements include:

- **Parkinson's disease**
- Parkinsonism caused by drugs or poisons
- Parkinson-plus syndromes (**progressive supranuclear palsy**, **multiple system atrophy**, and cortical-basal ganglionic degeneration)
- Huntington's disease
- Wilson's disease
- inherited ataxias (**Friedreich's ataxia**), **Machado-Joseph disease**, and spinocerebellar ataxias)
- **Tourette syndrome** and other tic disorders
- essential tremor
- **restless legs syndrome**
- **dystonia**
- **stroke**
- **cerebral palsy**
- encephalopathies
- intoxication
- poisoning by carbon monoxide, cyanide, methanol, or manganese.

Causes and symptoms

Causes

Movement is produced and coordinated by several interacting brain centers, including the motor cortex, the **cerebellum**, and a group of structures in the inner portions of the brain called the basal ganglia. Sensory information provides critical input on the current position and velocity of body parts, and spinal nerve cells (neurons) help prevent opposing muscle groups from contracting at the same time.

To understand how movement disorders occur, it is helpful to consider a normal voluntary movement, such as reaching to touch a nearby object with the right index finger. To accomplish the desired movement, the arm must be lifted and extended. The hand must be held out to align with the forearm, and the forefinger must be extended while the other fingers remain flexed.

THE MOTOR CORTEX Voluntary motor commands begin in the motor cortex located on the outer, wrinkled surface of the brain. Movement of the right arm is begun by the left motor cortex, which generates a large volley of signals to the involved muscles. These electrical signals pass along upper motor neurons through the midbrain to the spinal cord. Within the spinal cord, they connect to lower motor neurons, which convey the signals out of the spinal cord to the surface of the muscles involved. Electrical stimulation of the muscles causes contraction, and the force of contraction pulling on the skeleton causes movement of the arm, hand, and fingers.

Damage to or death of any of the neurons along this path causes weakness or paralysis of the affected muscles.

ANTAGONISTIC MUSCLE PAIRS This picture of movement is too simple, however. One important refinement to it comes from considering the role of opposing, or antagonistic, muscle pairs. Contraction of the biceps muscle, located on the top of the upper arm, pulls on the forearm to flex the elbow and bend the arm. Contraction of the triceps, located on the opposite side, extends the elbow and straightens the arm. Within the spine, these muscles are normally wired so that willed (voluntary) contraction of one is automatically accompanied by blocking of the other. In other words, the command to contract the biceps provokes another command within the spine to prevent contraction of the triceps. In this way, these antagonist muscles are kept from resisting one another. Spinal cord or brain injury can damage this control system and cause involuntary simultaneous contraction and **spasticity**, an increase in resistance to movement during motion.

THE CEREBELLUM Once the movement of the arm is initiated, sensory information is needed to guide the finger to its precise destination. In addition to sight, the most important source of information comes from the "position sense" provided by the many sensory neurons located within the limbs (proprioception). Proprioception is what allows you to touch your nose with your finger even with your eyes closed. The balance organs in the ears provide important information about posture. Both postural and proprioceptive information are processed by a structure at the rear of the brain called the cerebellum. The cerebellum sends out electrical signals to modify movements as they

Key Terms

Botulinum toxin Any of a group of potent bacterial toxins or poisons produced by different strains of the bacterium *Clostridium botulinum*. The toxins cause muscle paralysis, and thus force the relaxation of a muscle in spasm.

Cerebral palsy A movement disorder caused by a permanent brain defect or injury present at birth or shortly after. It is frequently associated with premature birth. Cerebral palsy is not progressive.

Computed tomography (CT) An imaging technique in which cross-sectional x rays of the body are compiled to create a three-dimensional image of the body's internal structures.

Encephalopathy An abnormality in the structure or function of tissues of the brain.

Essential tremor An uncontrollable (involuntary) shaking of the hands, head, and face. Also called familial tremor because it is sometimes inherited, it can begin in the teens or in middle age. The exact cause is not known.

Fetal tissue transplantation A method of treating Parkinson's and other neurological diseases by grafting brain cells from human fetuses onto the basal ganglia. Human adults cannot grow new brain cells but developing fetuses can. Grafting fetal tissue stimulates the growth of new brain cells in affected adult brains.

Hereditary ataxia One of a group of hereditary degenerative diseases of the spinal cord or cerebellum. These diseases cause tremor, spasm, and wasting of muscle.

Huntington's disease A rare hereditary condition that causes progressive chorea (jerky muscle movements) and mental deterioration that ends in dementia. Huntington's symptoms usually appear in patients in their 40s. There is no effective treatment.

Levodopa (L-dopa) A substance used in the treatment of Parkinson's disease. Levodopa can cross the blood-brain barrier that protects the brain. Once in the brain, it is converted to dopamine and thus can replace the dopamine lost in Parkinson's disease.

Magnetic resonance imaging (MRI) An imaging technique that uses a large circular magnet and radio waves to generate signals from atoms in the body. These signals are used to construct images of internal structures.

Parkinson's disease A slowly progressive disease that destroys nerve cells in the basal ganglia and thus causes loss of dopamine, a chemical that aids in transmission of nerve signals (neurotransmitter). Parkinson's is characterized by shaking in resting muscles, a stooping posture, slurred speech, muscular stiffness, and weakness.

Positron emission tomography (PET) A diagnostic technique in which computer-assisted x rays are used to track a radioactive substance inside a patient's body. PET can be used to study the biochemical activity of the brain.

Progressive supranuclear palsy A rare disease that gradually destroys nerve cells in the parts of the brain that control eye movements, breathing, and muscle coordination. The loss of nerve cells causes palsy, or paralysis, that slowly gets worse as the disease progresses. The palsy affects ability to move the eyes, relax the muscles, and control balance.

Restless legs syndrome A condition that causes an annoying feeling of tiredness, uneasiness, and itching deep within the muscle of the leg. It is accompanied by twitching and sometimes pain. The only relief is in walking or moving the legs.

Tourette syndrome An abnormal condition that causes uncontrollable facial grimaces and tics and arm and shoulder movements. Tourette syndrome is perhaps best known for uncontrollable vocal tics that include grunts, shouts, and use of obscene language (coprolalia).

Wilson's disease An inborn defect of copper metabolism in which free copper may be deposited in a variety of areas of the body. Deposits in the brain can cause tremor and other symptoms of Parkinson's disease.

progress, "sculpting" the barrage of voluntary commands into a tightly controlled, constantly evolving pattern. Cerebellar disorders cause inability to control the force, fine positioning, and speed of movements (**ataxia**). Disorders of the cerebellum may also impair the ability to judge distance so that a person under- or overreaches the target (dysmetria). Tremor during voluntary movements can also result from cerebellar damage.

THE BASAL GANGLIA Both the cerebellum and the motor cortex send information to a set of structures deep within the brain that help control involuntary components of movement (basal ganglia). The basal ganglia send output messages to the motor cortex, helping to initiate movements, regulate repetitive or patterned movements, and control muscle tone.

Circuits within the basal ganglia are complex. Within this structure, some groups of cells begin the action of other basal ganglia components and some groups of cells block the action. These complicated feedback circuits are not entirely understood. Disruptions of these circuits are known to cause several distinct movement disorders. A portion of the basal ganglia called the substantia nigra sends electrical signals that block output from another structure called the subthalamic nucleus. The subthalamic nucleus sends signals to the globus pallidus, which in turn blocks the thalamic nuclei. Finally, the thalamic nuclei send signals to the motor cortex. The substantia nigra, then, begins movement and the globus pallidus blocks it.

This complicated circuit can be disrupted at several points. For instance, loss of substantia nigra cells, as in Parkinson's disease, increases blocking of the thalamic nuclei, preventing them from sending signals to the motor cortex. The result is a loss of movement (motor activity), a characteristic of Parkinson's.

In contrast, cell loss in early Huntington's disease decreases blocking of signals from the thalamic nuclei, causing more cortex stimulation and stronger but uncontrolled movements.

Disruptions in other portions of the basal ganglia are thought to cause tics, **tremors**, dystonia, and a variety of other movement disorders, although the exact mechanisms are not well understood.

Some movement disorders, including Huntington's disease and inherited ataxias, are caused by inherited genetic defects. Some diseases that cause sustained muscle contraction limited to a particular muscle group (focal dystonia) are inherited, but others are caused by trauma. The cause of most cases of Parkinson's disease is unknown, although genes have been found for some familial forms.

Symptoms

Abnormal movements are broadly classified as either hyperkinetic—too much movement—and hypokinetic—too little movement. Hyperkinetic movements include:

- Dystonia: sustained muscle contractions, often causing twisting or repetitive movements and abnormal postures. Dystonia may be limited to one area (focal) or may affect the whole body (general). Focal dystonias may affect the neck (cervical dystonia or torticollis), the face (one-sided or **hemifacial spasm**, contraction of the eyelid or **blepharospasm**, contraction of the mouth and jaw or oromandibular dystonia, simultaneous spasm of the chin and eyelid or Meige syndrome), the vocal cords (laryngeal dystonia), or the arms and legs (writer's cramp, occupational cramps). Dystonia may be painful as well as incapacitating.
- Tremor: uncontrollable (involuntary) shaking of a body part. Tremor may occur only when muscles are relaxed or it may occur only during an action or holding an active posture.
- Tics: involuntary, rapid, nonrhythmic movement or sound. Tics can be controlled briefly.
- **Myoclonus**: a sudden, shock-like muscle contraction. Myoclonic jerks may occur singly or repetitively. Unlike tics, myoclonus cannot be controlled even briefly.
- **Chorea**: rapid, nonrhythmic, usually jerky movements, most often in the arms and legs.
- Ballism: like chorea, but the movements are much larger, more explosive and involve more of the arm or leg. This condition, also called ballismus, can occur on both sides of the body or on one side only (hemiballismus).
- Akathisia: restlessness and a desire to move to relieve uncomfortable sensations. Sensations may include a feeling of crawling, itching, stretching, or creeping, usually in the legs.
- Athetosis. slow, writhing, continuous, uncontrollable movement of the arms and legs.

Hypokinetic movements include:

- Bradykinesia: slowness of movement.
- Freezing: inability to begin a movement or involuntary stopping of a movement before it is completed.
- Rigidity: an increase in muscle tension when an arm or leg is moved by an outside force.
- Postural instability: loss of ability to maintain upright posture caused by slow or absent righting reflexes.

Diagnosis

Diagnosis of movement disorders requires a careful medical history and a thorough physical and neurological examination. Brain imaging studies are usually performed. Imaging techniques include computed tomography scan (**CT scan**), **positron emission tomography (PET)**, or **magnetic resonance imaging (MRI)** scans. Routine blood and urine analyses are performed. A lumbar puncture (spinal tap) may be necessary. Video recording of the abnormal movement is often used to analyze movement patterns and to track progress of the disorder and its treatment. Genetic testing is available for some forms of movement disorders.

Treatment

Treatment of a movement disorder begins with determining its cause. Physical and occupational therapy may help make up for lost control and strength. Drug therapy can help compensate for some imbalances of the basal ganglionic circuit. For instance, levodopa (L-dopa) or related compounds can substitute for lost dopamine-producing cells in Parkinson's disease. Conversely, blocking normal dopamine action is a possible treatment in some hyperkinetic disorders, including tics. Oral medications can also help reduce overall muscle tone. Local injections of **botulinum toxin** can selectively weaken overactive muscles in dystonia and spasticity. Destruction of peripheral nerves through injection of phenol can reduce spasticity. All of these treatments may have some side effects.

Surgical destruction or inactivation of basal ganglionic circuits has proven effective for Parkinson's disease and is being tested for other movement disorders. Transplantation of fetal cells into the basal ganglia has produced mixed results in Parkinson's disease.

There are several alternative therapies that can be useful when treating movement disorders. The progress made will depend on the individual and his/her condition. Among the therapies that may be helpful are **acupuncture**, homeopathy, touch therapies, postural alignment therapies, and biofeedback.

Prognosis

The prognosis for a patient with a movement disorder depends on the specific disorder.

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Worldwide Education and Awareness for Movement Disorders. One Gustave L. Levy Place, Box 1052, New York, NY 10029. (800) 437-6683. <http://www.wemove.org>.

Richard Robinson

Moyamoya disease

Definition

Moyamoya disease is a rare disorder of blood vessels in the brain known as internal carotid arteries (ICA). The condition is characterized by stenosis (narrowing) or occlusion (blockage) of one or both ICA with subsequent formation of an abnormal network of blood vessels adjacent to the ICA.

Description

Moyamoya disease was first described in Japan in 1955. The term *moyamoya*, a Japanese word that means "puff of smoke," describes the appearance of the abnormal vessels that form adjacent to the internal carotid arteries. Alternate names for the disorder include spontaneous occlusion of the circle of Willis, and basal occlusive disease with telangiectasia.

Moyamoya disease can occur in children (juvenile type) or in adults (adult type). Children tend to be less than age 10 and adults are usually between ages 30 and 49. Affected individuals typically present with signs of **stroke** or other types of cerebral ischemia (decreased blood flow to an area of the brain due to obstruction in an artery), cerebral hemorrhage (bleeding), or **seizures** (mainly in children). Symptoms in an affected child or adult may include disturbed consciousness, speech deficits, sensory and cognitive impairment, involuntary movements, or vision problems. Options for treatment for people with moyamoya disease consist of medications and brain surgery. Without treatment, repeated strokes, transient ischemic attacks, brain hemorrhages, or seizures can lead to serious cognitive impairment, physical disability, or death.

Demographics

Moyamoya disease occurs worldwide and is most prevalent in Asia, and especially in Japan. According to a report in 1998, more than 6000 cases had been described. The disease occurs in about one in a million people per year. Estimates of disease incidence in Japan are as much as ten times greater. Slightly more females than males are affected. The male-to-female ratio has been reported to be around 2:3. Approximately 10% of cases of moyamoya disease are familial.

Causes and symptoms

The cause of moyamoya disease is unknown. Possible explanations for the disorder include injuries to the brain, infection, multifactorial inheritance, genetic factors, or other causes. For example, moyamoya disease has been associated with meningitis, **radiation** therapy to the skull in children, and genetic conditions such as Down syndrome, **neurofibromatosis**, and sickle cell anemia. Also, there have been reports linking a region on chromosome 3 (named MYM1) and a region on chromosome 17 (named MYM2) to moyamoya disease in some families.

The initial symptoms of moyamoya disease are somewhat different in children and adults. In children, there is ischemia due to stenosis and occlusion of the circle of

Key Terms

Stroke Interruption of blood flow to a part of the brain with consequent brain damage. A stroke may be caused by a blood clot or by hemorrhage due to a burst blood vessel. Also known as a cerebrovascular accident.

Transient ischemic attacks A brief interruption of the blood supply to part of the brain that causes a temporary impairment of vision, speech, or movement. Usually, the episode lasts for just a few moments, but it may be a warning sign for a full-scale stroke.

Willis, a ring of arteries at the base of the brain. In children, the disease tends to cause repeated "mini-strokes" known as transient ischemic attacks (TIAs) or, less often, seizures. The TIAs usually manifest as weakness of one side of the body (hemiparesis), speech disturbances, and sensory deficits. TIAs may be made worse by hyperventilation, such as with intense crying. Involuntary movements may occur. **Mental retardation** may be present.

Adults with moyamoya disease typically present with bleeding in the brain (cerebral hemorrhage) or strokes. Cerebral hemorrhage occurs as a result of breakdown of the coexisting blood vessels that formed earlier in life due to stenosis or occlusion of the ICA. The cerebral hemorrhages are commonly located in the thalamus, basal ganglia, or deep white matter of the brain. Symptoms can include disturbance of consciousness and/or hemiparesis. Adult patients with moyamoya disease may go on to have further hemorrhages and strokes which can result in significant and irreversible brain damage.

Diagnosis

A diagnosis of moyamoya disease is based on findings from neuroradiologic studies and on clinical signs consistent with this diagnosis. Neuroradiologic studies used to establish the diagnosis of moyamoya disease include cerebral **angiography**, **magnetic resonance imaging (MRI)**, magnetic resonance angiography (MRA), and computed tomography (**CT**) **scan**. Cerebral angiography is the most common means of confirming a diagnosis of moyamoya disease. There are reports indicating that MRI and MRA, which are less invasive procedures, may be used instead of cerebral angiography. CT scan findings tend to be non-specific and not as useful as CA, MRI, and MRA in making the diagnosis.

Characteristic brain findings in moyamoya disease include narrowing or occlusion of the end portion of one or both internal carotid arteries, an abnormal network or blood vessels at the base of the brain, and presence of these findings on both sides of the brain. In about 10% of cases, cerebral **aneurysms** may also be found. Nuclear medicine studies such as Xenon-enhanced CT, **positron emission tomography (PET)**, or single photon emission computed tomography (SPECT) may be performed in order to evaluate cerebral blood flow (CBF) patterns. The information obtained from CBF studies helps the **neurologist** and/or neurosurgeon to devise a treatment plan.

Treatment

There is no cure for moyamoya disease. Early treatment is important to avoid mental and physical impairment. Treatment options include medications and surgical revascularization.

Medications. Individuals having TIAs and stroke may be given antiplatelet drugs, vasodilators, or anticoagulants to help prevent future attacks. Steroid therapy may be prescribed for a person who has involuntary movements. For a patient with a cerebral hemorrhage, treatment may include management of hypertension, if present.

Surgery. The purpose of revascularization surgery in moyamoya disease is to augment or redirect blood flow in the brain. Surgical revascularization has been reported to improve cerebral blood flow, to reduce ischemic attacks, and, in children, to increase IQ. The optimal method of surgery depends on the patient's history and clinical status. There are various direct and indirect methods of restoring blood supply in the brain. Examples of direct bypass surgery include techniques known as superficial temporal artery to middle cerebral artery bypass, and extracranial-intracranial bypass to anterior or posterior cerebral artery. Examples of indirect bypass surgery include techniques known as encephaloduroarteriosynangiosis, encephalomyosynangiosis, and encephaloarteriosynangiosis.

Treatment team

Management of moyamoya disease requires a multidisciplinary approach. In addition to the patient's primary health care professionals, medical professionals involved in the care of patients with moyamoya disease generally include specialists in neurology, neurosurgery, neuroradiology, and anesthesiology. Specialists in orthopedic surgery, ophthalmology, rehabilitation, physical therapy, occupational therapy, speech therapy, and mental health may also be involved in the care of affected individuals. Psychological counseling and contact with other affected

patients may assist families in coping with this condition, especially given it's rarity.

Recovery and rehabilitation

The potential for rehabilitation in moyamoya disease depends in part on the degree of impairment caused by complications such as strokes, cerebral hemorrhages, and seizures. Interventions such as physical, occupational, and speech therapy may be recommended for management of problems such as hemiparesis, speech problems, and sensory deficits. Some patients may require assistance with daily living. In cases in which there is significant disability, consideration may be given to in-home nursing care or placement in a residential care facility that can provide 24-hour care and support services.

Clinical trials

As of 2004, there were no **clinical trials** specifically for patients with moyamoya disease. As more is learned about the causes of moyamoya disease, it is hoped that novel therapies may be developed in the future. As of 2004, one laboratory listed on the GeneTests web site (www.genetests.org) was conducting genetic research on moyamoya disease. Interested patients may discuss the feasibility of participating in this research with their physician.

Prognosis

As of 2004, the prognosis for moyamoya disease was not well defined. The prognosis depends in part on the extent of brain injury present at the time of diagnosis and the success of treatment. For example, a person who had a major stroke or cerebral hemorrhage may already be permanently impaired, both physically and mentally. Reports of clinical outcome after treatment are mixed. Some individuals experience improvement of symptoms while others continue to show progressive decline. Moyamoya disease tends to be more progressive in children than in adults. In those patients who don't stabilize clinically, significant disability or death may occur.

Special concerns

Children with moyamoya disease may have learning disabilities or mental retardation. They may also experience physical disabilities that impact academic performance. Such children may be eligible to have an Individual Education Plan (IEP). An IEP provides a framework from which administrators, teachers, and parents can meet the educational needs of a child with special learning needs. Depending upon severity of symptoms and the degree of learning difficulties, some children with moyamoya disease may be best served by special education classes or a private educational setting.

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ORGANIZATIONS

Children's Hemiplegia and Stroke Association (CHASA). 4101 West Green Oaks Blvd., PMB #149, Arlington, TX 76016. (817) 492-4325. info5@chasa.org. <http://www.hemikids.org>.

Families with Moyamoya Support Network. 4900 McGowan Street SE, Cedar Rapids, IA 52403.

National Stroke Association. 9707 East Easter Lane, Englewood, CO 80112-3747. (303) 649-9299 or 800-STROKES (787-6537); Fax: (303) 649-1328. info@stroke.org. <http://www.stroke.org>.

Dawn J. Cardeiro, MS, CGC

Mucopolysaccharidoses

Definition

The mucopolysaccharidoses (MPS) are a number of metabolic disorders that follow a chronic and progressive course and involve many body systems.

Description

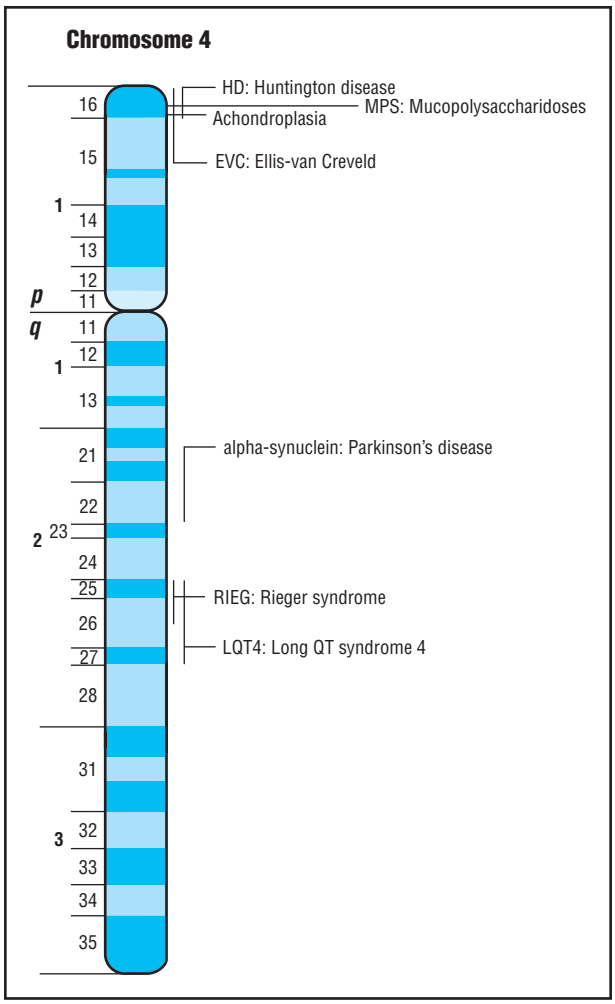
Though the symptoms and severity vary for each MPS disorder, common features include enlarged organs (organomegaly), dysostosis multiplex (abnormal bone formation), and a characteristic facial appearance. Hearing, vision, breathing, heart function, joint mobility, and mental capacity may also be affected. As of 2003, seven types of MPS have been classified. The MPS disorders are caused by absent or insufficient production of proteins known as lysosomal enzymes The specific enzyme that is deficient or absent distinguishes one type of MPS from another. However, before these enzymes were identified, the signs and symptoms expressed by an affected individual led to the diagnosis. 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 and may also referred to by their original names, which are Hurler (MPS I H), Hurler-Scheie (MPS I H/S), Scheie (MPS I S), Hunter (MPS II), Sanfilippo (MPS III), Morquio (MPS IV), Maroteaux-Lamy (MPS VI), Sly (MPS VII), and Hyaluronidase deficiency (MPS IX).

Demographics

The MPS syndromes are considered to be rare. Sanfilippo syndrome appears to be the most common MPS with a reported incidence of one in 70,000. The incidence of Hyaluronidase deficiency is not yet known. The incidence of the remaining six classes of MPS are estimated to be: one in 100,000 for Hurler syndrome; one in 500,000 for Scheie syndrome; one in 115,000 for Hurler/Scheie disease; one in 100,000 (male live births) for Hunter syndrome (mild and severe combined); one in 100,000 to one in 300,000 for Morquio syndrome (types A and B included); one in 215,000 for Maroteaux-Lamy syndrome; and less than one in 250,000 for Sly syndrome. These figures are general; more exact figures have been reported for individual MPS disorders in certain countries.

Causes and symptoms

All of the MPS are genetic conditions. MPS I, MPS III, MPS IV, MPS VI, MPS VII, and MPS IX are inherited in an autosomal recessive manner which means that affected individuals have two altered or non-functioning genes, one from each parent, for a specific enzyme that is needed to break down mucopolysaccharides. MPS II (Hunter syndrome) is inherited in an X-linked manner which means that the gene for MPS II is located on the X chromosome, one of the two sex chromosomes. Hunter syndrome primarily affects males because they have only one X chromosome and therefore lack a second, normal copy of the gene responsible for the condition. Carriers for



Mucopolysaccharidoses, on chromosome 4. *(Gale Group.)*

the autosomal recessive forms of MPS have one normal copy and one non-working copy of the MPS gene in question. Female carriers of the X-linked MPS (MPS II) have one X chromosome with a normal gene for the condition (the IDS gene) and one X chromosome with a non-working IDS gene.

The enzymes that are deficient in the MPS disorders normally break down a type of mucopolysaccharide (a long chain of sugar molecules) in the body known as glycosaminoglycans (GAGs). Glycosaminoglycans are essential for building the bones, cartilage, skin, tendons, and other tissues in the body. Normally, the human body continuously breaks down and builds GAGs. There are several enzymes involved in breaking down each GAG and a deficiency or absence of any of the essential enzymes can cause one or more GAGs to accumulate in the tissues and organs in the body. When too much GAG is stored, organs and tissues can be damaged or not function properly. The

accumulating material is stored in cellular structures called lysosomes, and these disorders are also known as lysosomal storage diseases.

MPS I

Mutations in the alpha-L-iduronidase (IDUA) gene located on chromosome 4 cause the MPS I disorders (Hurler, Hurler-Scheie, and Scheie syndromes). Initially, these three disorders 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 recognized that all three were variants of the same disorder.

MPS I H (HURLER SYNDROME) Individuals with Hurler syndrome tend to have the most severe form of MPS I. Hurler syndrome may also be referred to as severe MPS I. Infants with Hurler syndrome appear normal at birth and typically begin to develop normally. Symptoms of Hurler syndrome are often evident within the first year or two after birth. 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; affected children 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. Affected children with Hurler syndrome lose previously attained skills (milestones) and eventually suffer from profound **mental retardation**. Progressive abnormal development of all bones of the body (dysostosis multiplex) occurs in all children with Hurler syndrome. Children usually develop 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, cardiomyopathy (weakness of the heart muscle), hepatosplenomegaly (enlarged spleen and liver), clouding of the cornea, hearing loss, and **carpal tunnel syndrome**. Children with Hurler syndrome typically die within the first ten years of life.

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 Hurler syndrome but not as mild as those with Scheie syndrome. Hurler-Scheie syndrome may also be referred to as intermediate MPS I. Individuals with Hurler-Scheie syndrome tend to be shorter than expected and may develop some of the physical features seen in Hurler syndrome, but usually they are not as severe. Intellectual ability varies; individuals have normal or near normal intelligence. The prognosis for children with Hurler-Scheie syndrome is variable with some individuals dying during childhood and others living to adulthood.

MPS I S (SCHEIE SYNDROME) Scheie syndrome is considered the mild form of MPS I. Individuals with Scheie syndrome usually have normal intelligence, but there have been some reports of affected individuals developing psychiatric problems. Common physical problems include corneal clouding, heart abnormalities, and orthopedic difficulties involving the hands and back. Individuals with Scheie syndrome do not develop the facial features seen with severe MPS I. Usually life span is normal.

MPS II (Hunter syndrome)

Mutations in the iduronate-2-sulphatase (IDS) gene cause both forms of MPS II (mild and severe). Nearly all individuals with Hunter syndrome are male, because the gene that causes the condition is located on the X chromosome. The severe form is associated with progressive mental retardation and physical disability, with most individuals dying before age 15. Males with the mild form of Hunter syndrome usually have have normal or near normal intelligence. They tend to develop physical differences similar to males with the severe form, but not as quickly. 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. Men with mild Hunter syndrome can have a normal life span and some have had children.

MPS III (Sanfilippo syndrome)

MPS III is a variable condition with symptoms beginning to appear between ages two and six years of age. The condition is characterized by developmental delay, behavioral problems, and mild physical problems (as compared to other types of MPS). Specific problems include: **seizures**, sleeplessness, thick skin, joint contractures, enlarged tongues, cardiomyopathy, hyperactivity, and mental retardation. The life expectancy in MPS III is also variable. On average, individuals with MPS III live until adolescence. Initially, the diagnosis of MPS III, like the other MPS conditions, was clinical; the diagnosis was made by observation of certain physical characteristics. It was later discovered that a deficiency in one of four enzymes could lead to the developmental delay and physical symptoms associated with MPS III. Each type of MPS III is now subdivided into four groups, labeled A-D, according to the specific enzyme deficiency. All four of these enzymes help to break down the same GAG, heparan sulfate.

MPS IIIA (SANFILIPPO SYNDROME TYPE A) MPS IIIA is caused by a deficiency of the enzyme heparan sulfate sulfamidase, due to mutations in the SGSH gene on chromosome 17. Type IIIA is felt to be the most severe of the four types, in which symptoms appear and death occurs at an earlier age.

Key Terms

Carpal tunnel syndrome A condition caused by compression of the median nerve in the carpal tunnel of the hand, characterized by pain.

Cornea The clear, dome-shaped outer covering of the eye that lies in front of the iris and pupil. The cornea lets light into the eye.

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.

Hydrops fetalis A condition in which a fetus or newborn baby accumulates fluids, causing swollen arms and legs and impaired breathing.

Metabolic Refers to the chemical reactions in living organisms.

Mucopolysaccharide A complex molecule made of smaller sugar molecules strung together to form a chain. It is found in mucous secretions and intercellular spaces.

Mutation A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease. This change can be transmitted to offspring.

MPS IIIB (SANFILIPPO SYNDROME TYPE B) MPS IIIB is due to a deficiency in N-acetyl-alpha-D-glucosaminidase due to mutations in the NAGLU gene, also located on chromosome 17. 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 types of MPS III in southeastern Europe.

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, due to mutations in the GNS gene located on chromosome 12. This form of MPS III is also rare.

MPS IV (Morquio syndrome)

Morquio syndrome is characterized by severe skeletal deformities and their secondary effects on the nervous system. Intelligence is usually normal. One of the earliest symptoms seen in this condition is a difference in the way the child walks. Skeletal abnormalities can be extreme and include dwarfism, kyphosis (outward-curved spine), prominent breastbone, flat feet, and genu-valgum (knock-knees). A bone deformity known as odontoid hypoplasia (improper formation of the bones that stabilize the head and neck) can result in compression of the spinal cord, a potentially serious and life-threatening complication. As with several of the MPS disorders, Morquio syndrome was originally diagnosed by the presence of particular signs and symptoms. However, it is now known that the deficiency of two different enzymes can result in MPS IV. These two types of MPS IV are called MPS IV A and MPS IV B. MPS IV is variable in its severity. MPS IV A is the classic (typical) 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 (GALNS) is located on chromosome 16. MPS IV B is considered the milder form of the condition. The enzyme, beta-galactosidase, is deficient in MPS IV B. The gene involved with MPS IV B (GLB1) is located on chromosome 3.

MPS VI (Maroteaux-Lamy syndrome)

MPS VI is caused by deficiency of the enzyme N-acetylglucosamine-4-sulphatase (arylsulfatase B), due to mutations in the ARSD gene located on chromosome 5. Affected individuals may have a mild or severe form of the condition. Typically, the nervous system and intelligence are not affected. Individuals with a more severe form of MPS VI can develop airway obstruction, **hydrocephalus** (extra fluid accumulating in the brain), and abnormal growth and formation of the bones. 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.

MPS VII (Sly syndrome)

MPS VII, an extremely rare form of MPS, results from a deficiency of the enzyme beta-glucuronidase due to mutations in the GUSB gene on chromosome 7. MPS VII is also highly variable, but symptoms are generally similar to those seen in individuals with Hurler syndrome. In severe cases, infants may be born with *hydrops fetalis*.

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 due to mutations in the HYAL1 gene on chromosome 3. 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.

Diagnosis

Identification of symptoms is usually the first step in making an MPS diagnosis. Doctors will then use laboratory tests to establish an accurate diagnosis. They may first use a screening test that looks for glycosaminoglycans in the urine. The definitive diagnosis of an MPS is made using a biochemical test that measures the specific enzyme (known to be reduced or absent) in the individual's tissues or bodily fluids. Genetic testing may also be used to confirm a suspected diagnosis and, in some cases, to provide limited information about potential disease severity. Genetic testing is accomplished by looking for specific changes known as mutations in the gene responsible for the MPS disorder. Genetic testing is available for all of the MPS disorders except MPS IIIC, MPS IVB, and MPS IX. If the gene mutation(s) have been found in an affected individual, the same genetic test may be used for carrier screening in unaffected family members, such as adult siblings, and for prenatal diagnosis. If the DNA mutations are not found or if genetic testing is not available, carrier screening and prenatal diagnosis may be accomplished using biochemical methods. Preimplantation genetic diagnosis (PGD) is available on a research basis for MPS I and MPS II. More information on PGD for these types of MPS can be found by contacting the Reproductive Genetics Institute at (773) 472-4900 or at rgi@flash.net.

Treatment team

Treatment of MPS disorders requires a multidisciplinary approach. In addition to the patient's primary health care professionals, medical professionals involved in the care of patients with an MPS usually includes specialists in neurology, neurosurgery, ophthalmology (eyes), otolaryngology (ear-nose-throat), audiology (hearing), cardiology, pulmonology (lungs), anesthesiology, gastroenterology, nutrition, orthopedic surgery, rehabilitation (physical, occupational, and speech therapy) and genetics. Some patients with MPS may receive comprehensive services through a specialty clinic such as metabolic or neurogenetics clinic. A genetic specialist, such as a clinical geneticist or a genetic counselor, may be helpful to the patient and family, especially at the time of diagnosis or prior to genetic testing. Psychological counseling and MPS support groups may also assist families in coping with this condition.

Treatment

Treatment of the MPS disorders primarily consists of supportive care and management of complications. Bone marrow transplant (BMT) and enzyme replacement are two promising therapies that offer the possibility of altering the course of these conditions. Due to the progressive nature of the MPS disorders, regular evaluations by primary care providers and specialists is required to detect problems early. Treatment for the most common problems found in the MPS disorders is listed below.

Symmtomatic care and treatment

HYDROCEPHALUS Hydrocephalus (increased fluid in the ventricles of the brain) commonly occurs in MPS I, MPS II, MPS VI, and MPS VII due to a blocked circulation of cerebral spinal fluid in the brain. If the hydrocephalus is detected early, a surgical procedure known as ventriculoperitoneal shunting or a VP shunt may afford the affected individual with a better outcome. Periodic **CT** or **MRI** scans may be recommended to monitor for hydrocephalus in a child with MPS. In MPS III, enlarged ventricles (spaces in the brain) may occur but here the enlargement is thought to be due to cortical atrophy (loss of brain cells). It has been reported that shunting may decrease behavior problems associated with this form of MPS.

SEIZURES Seizures are a problem found in severe forms of MPS and especially in MPS III (Sanfilippo syndrome). Patients with seizures are given a type of prescription medication known as an anticonvulsant.

VISION AND HEARING Regular evaluation by an ophthalmologist is recommended to look for common eye problems including changes in the retina, glaucoma, and corneal clouding. Retinal degeneration, an eye problem that leads to night blindness and loss of peripheral vision, is common in MPS I, MPS II, and MPS III. Adding a night light to a hall or bedroom may help with this. Glaucoma is especially common in MPS I and is usually treated with medications. Corneal clouding is found in MPS I, MPS IV, MPS VI and MPS VII. People with corneal clouding have photophobia (the inability to tolerate bright light). Caps with a visor or sunglasses may be recommended to help reduce this problem. Corneal transplantation is possible for people with significantly reduced vision yet transplants may not always result in improved vision in the long term.

Hearing problems are common in the MPS disorders. Regular hearing evaluations are important so that children with hearing loss can be treated early. Hearing aids may provide some degree of improvement. Recurrent otitis media (middle ear infections) significantly contribute to hearing loss in individuals with MPS. Prescription medications are used to treat otitis media. Ventilating tubes in the ears may be used to minimize the long term effects of these infections.

CARDIOVASCULAR Many individuals with MPS show some signs of heart disease. Common problems include abnormal heart valves, narrowing of the blood vessels in the heart, and weak heart muscles (cardiomyopathy). Patients with MPS I H and the severe form of MPS II usually

have damage to the mitral valve. In MPS I H/S, MPS IS, MPS IV, and MPS VI, aortic valvular disease is more common. Medications may be prescribed for congestive heart failure and hypertension associated with underlying heart disease. Valve replacement surgery is possible and has been reported in the MPS disorders.

AIRWAY DISEASE Obstruction of the airway is a common and significant problem for individuals with MPS. This problem can be due to a narrowed trachea (wind pipe), thickened vocal cords, large adenoids or tonsils, decreased rib movement with breathing, and a large tongue. A condition known as obstructive **sleep apnea** (temporary cessation of breathing while asleep) is the most common airway problem in MPS. Treatment for sleep apnea may include: removal of adenoids and tonsils, CPAP or BiPAP treatment, or a tracheostomy. CPAP (continuous positive airway pressure) and BiPAP (bilevel positive airway pressure) are treatments that help to keep the airway open at nighttime. A tracheostomy, an permanent opening through the neck into the trachea, may be needed in severe cases of sleep apnea.

FEEDING PROBLEMS For many individuals with MPS, neurological problems eventually lead to significant problems with chewing and swallowing. Surgical placement of gastrostomy tube (G-tube) or a jejunostomy tube (J-tube) may be recommended when feeding problems cause weight loss, choking, gagging, or episodes of pneumonia.

SKELETAL DEFORMITIES Bony problems, especially of the neck, spine, and hips may require orthopedic intervention. Problems of the cervical spine due to odontoid hypoplasia (improper formation bones that stabilize the head and neck) can be quite serious. Odontoid hypoplasia can lead to slippage of the bones in the neck and compression of the spine in the cervical (neck) region. In severe cases, this spinal cord compression may result in nerve damage, paralysis or death. Odontoid hypoplasia is common in MPS IV (Morquio syndrome). Treatment includes regular monitoring with MRI or X-rays and cervical fusion surgery for severe cases. Other bony problems seen in the MPS disorders include progressive scoliosis or kyphosis (curvatures of the spine) and hip dysplasia (abnormal hip joint). Bracing and sometimes surgery may be used to treat spine curvature. A surgical procedure known as spinal fusion may be considered in patients with significant curvature. Patients with hip dysplasia may be given non-steroidal anti-inflammatory medications.

CARPAL TUNNEL SYNDROME Carpal tunnel syndrome is a common problem in MPS. Although many individuals with MPS may not have typical symptoms (numbness, tingling, **pain**), the carpal tunnel syndrome can and may be severe. Treatment options include splinting, anti-inflammatory medications and surgery.

Bone marrow transplantation (BMT)

Bone marrow transplants have been used to treat children with MPS I, MPS II, MPS III, and MPS VI. Some success has been achieved with BMT in MPS I and in MPS VI; however, this treatment is not a cure and is considered experimental due to the associated risks, including death. Some children who have undergone BMT have shown reduced progression of some disease symptoms. It remains uncertain whether BMT can prevent brain damage. BMT is not recommended as a treatment for MPS II or MPS III.

Enzyme replacement therapy

Enzyme replacement therapy is available for MPS I. A pharmaceutical form of alpha-L-iduronidase known as laronidase is available in the United States. More information may be obtained at<http://www.aldurazyme.com>. Enzyme therapy may be an option in the future for individuals with MPS IV.

Recovery and rehabilitation

Rehabilitation for the MPS disorders consists of physical, occupational, and possibly speech therapy. For example, physical therapy may help preserve joint function for individuals with joint stiffness. Joint stiffness is present in all of the MPS disorders except MPS IV and MPS IX. In physical therapy, patients may undergo range-of-motion exercises (passive bending and stretching of the arms and legs). Also, physical therapy after neck, spine or knee surgery can help patients (who could walk prior to surgery) to walk again. Occupational therapy can teach patients to use adaptive techniques and devices that may help compensate for loss of mobility and/or for loss of speech. Speech therapy may be indicated for individuals with MPS; however, this intervention may not be useful in cases in which the mental condition is rapidly deteriorating.

Hyperactivity can be a severe problem in individuals with MPS, especially in MPS III and MPS II. Medications may or may not be successful in treating this problem. Behavior modification programs may be helpful for some hyperactive MPS children. It may also be necessary to adapt the house and yard to the child.

Clinical trials

As of December 2003, there were four **clinical trials** related to the MPS disorders that were recruiting patients. A phase II/II trial to determine whether the administration of iduronate-2-sulfatase enzyme is safe and efficacious in patients with MPS II will be conducted in the United States, Brazil, Germany and England. Information on this trial can be found at <http://www.clinicaltrials.gov> or by contacting Transkaryotic Therapies at 617-613-4499. A

phase III trial to evaluate the ability of recombinant human arylsulfatase B enzyme to enhance endurance in patients with Mucopolysaccharidosis VI (MPS VI) will be conducted in the United States. Information on this trial can be found at <http://www.clinicaltrials.gov> or by contacting BioMarin Pharmaceuticals at 415-884-6700. A phase II study of allogeneic bone marrow or umbilical cord blood transplantation in patients with mucopolysaccharidosis I will be conducted in the United States. Information on this trial can be found at <http://www.clinicaltrials.gov> or by contacting the Study Chair at the Fairview University Medical Center in Minneapolis, Minnesota, at 612-624-5407. A phase II study of bone marrow or umbilical cord blood transplantation in patients with lysosomal or peroxisomal inborn errors of metabolism. Information on this trial can be found at <http://www.clinicaltrials.gov> or by contacting the Study Chair at the Fairview University Medical Center in Minneapolis, Minnesota at 612-624-5407.

Prognosis

Life expectancy for individuals with an MPS is extremely varied. In severe forms of MPS, affected individuals may die in infancy such as in the severe cases of Sly syndrome, or they may die in in childhood or adolescence such as in Hurler syndrome and severe Hunter syndrome. In milder forms of MPS such as Scheie syndrome, mild Hunter syndrome individuals can live well into adulthood. Life spans for individuals with Sanfillipo syndrome, Maroteaux-Lamy syndrome, Morquio syndrome and mild Sly syndrome are quite variable. As more MPS I patients utilize enzyme replacement therapy, new information about prognosis and life span for this disorder will be learned.

Special concerns

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. If general anesthesia is needed, it should be administered by an anesthesiologist experienced in the MPS disorders.

Children and families affected by an MPS may benefit from social services. A social worker may be able to help families obtain Social Security, Medicaid, or other assistance available from agencies that specialize in the care of persons with disabilities. A child with MPS may benefit from an Individual Education Plan (IEP). An IEP provides a framework from which administrators, teachers, and parents can meet the educational needs of a child with MPS.

Resources

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The National Institute of Neurological Disorders and Stroke (NINDS). *Mucopolysaccharidoses Information Page.* <http://www.ninds.nih.gov/health_and_medical/disorders/mucopolysaccharidoses.htm>.

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The National MPS Society. *MPS Disorder booklets.* 45 Packard Drive, Bangor, ME: The National MPS Society, 2001-2003. <http://www.mpssociety.org/lib-health.html>.

ORGANIZATIONS

Canadian Society for Mucopolysaccharide and Related Diseases. PO Box 64714, Unionville, Ontario L3R-OM9, CA. (904) 479-8701 or (800) 667-1846. rldillio@interlog.com. <http://www.mpssociety.ca>.

National MPS Society, Inc. 45 Packard Drive, Bangor, ME 04401. (207) 947-1445; Fax: (207) 990-3074. info@mpssociety.org. <http://www.mpssociety.org>.

Society for Mucopolysaccharide Diseases. 46 Woodside Road, Amersham, Buckinghamshire HP6-6AJ, UK. (149) 443-4252; Fax: (149) 443-4252. mps@mpssociety.co.uk. <http://www.mpssociety.co.uk>.

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Multi-infarct dementia

Definition

Multi-infarct **dementia** is one form of dementia that occurs when small blood vessels in the brain are blocked by blood clots or fatty deposits. The blockage interrupts the flow of blood to regions of the brain (a **stroke**), which, if sustained, causes the death of cells in numerous areas of the brain. Another form of multi-infarct dementia is inherited.

Description

Blockage or narrowing of small blood vessels by blood clots or by deposits of fat can impede the flow of blood through the vessel. Deprivation of the essential blood is catastrophic for the regions that are supplied by the vessels. In the brain, such vessel blockage can cause the death of brain cells. This event is also called a stroke. The stroke-related cell death affects the functioning of the brain.

Multi-infarct dementia is the most common form of dementia (the loss of cognitive brain due to disease or injury) due to changes in blood vessels. **Alzheimer's disease** is the most common of these so-called vascular dementias. The term multi-infarct is used because there are many areas in the brain where cell damage or death occurs. Besides dementia, multi-infarct dementia can cause stroke, headaches of migraine-like intensity, and behavioral disturbances.

An inherited form of multi-infarct dementia is designated as CADASIL, which is an acronym for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Demographics

Multi-infarct dementia usually begins between the ages of 60–75 years. For as-yet-undetermined reasons, it affects men more than women. Multi-infarct dementia is the second most common cause of dementia in older people after Alzheimer's disease, accounting for up to 20% of all progressively worsening dementias.

CADASIL occurs in young male and female adults. It has been diagnosed in Americans, Africans, and Asians, and may occur in other racial groups.

Causes and symptoms

The root cause of multi-infarct dementia is usually small blood clots that lodge in blood vessels in the brain, which results in the death of brain cells. Over time, the series of small strokes (also known as mini-strokes, transient ischemic attacks, or TIAs) magnifies the brain cell damage. Blood clots can result from an elevated blood pressure. Indeed, it is uncommon for someone affected with multi-infarct dementia not to have a history of high blood pressure.

There are a variety of symptoms caused by the brain cell loss. These include mental confusion, problems retaining information even for a short time, loss of recognition of surroundings that are familiar (which can lead to getting lost in previously familiar territory), loss of control of urination and defecation, moving with a rapid shuffling motion, difficulty in following instructions, rapid swings in emotion, and difficulty performing tasks that were previously routine. These symptoms appear in a stepwise manner, from less to more severe. As well, the initial symptoms can be so slight as to be unrecognized, disregarded, or rationalized as being due to other causes such as a temporarily stressful period. These early problems include a mild weakness in an arm or a leg, slurred speech, or **dizziness** that only lasts for a few days. As more blood vessels become blocked with the occurrence of more strokes, the more severe symptoms associated with mental decline become apparent.

CADASIL is characterized by a series of strokes, which is thought to be triggered by genetically determined deficiencies of small cerebral arteries. The defects affect blood flow to the brain in a similar fashion as occurs in multi-infarct dementia. The symptoms associated with CADASIL range from migraines to a slowly progressing series of symptoms that is similar to the symptoms that develop in multi-infarct dementia.

Diagnosis

Multi-infarct dementia is diagnosed based on the history of symptoms, especially of high blood pressure and strokes. A physician will look for several features during the examination, which include arm or leg weakness, speech difficulties, or dizziness. Tests that can be performed in the doctor's office include taking a blood pressure reading, recording the heartbeat (an electroencephalogram, or EEG), and obtaining blood for laboratory analysis. Ultrasound studies of the carotid artery may also be performed.

Diagnosis most often involves the non-destructive imaging of the brain by means of computed tomography (**CT**) or **magnetic resonance imaging (MRI)** to reveal blood clots or the characteristic damaged regions of the brain.

Key Terms

Dementia A chronic loss of mental capacity due to an organic cause.

Infarct Tissue death due to lack of oxygen resulting from a blood clot, plaque, or inflammation that blocks an artery.

Transient ischemic attack (TIA) A temporary, stroke-like event that lasts for only a short time and is caused by a blood vessel that is temporarily blocked.

Diagnosis can also be aided by an examination by a psychologist or a psychiatrist to test a person's degree of mental reasoning, ability to learn and retain new information, and attention span. Symptoms can be similar to those of Alzheimer's disease, which can complicate and delay the diagnosis of both disorders. Indeed, a person can have both disorders at the same time, as their causes are different.

Treatment team

A person with multi-infarct dementia can benefit from a support network that includes a family physician, **neurologist**, pharmacist, nurses, and supportive family members and other care givers. Community resources are also important, such as assisted living facilities, adult day or **respite** care centers, and local agencies on aging.

Treatment

There is no specific treatment for multi-infarct dementia, as the damage to the brain cells cannot be reversed. Treatment typically involves trying to limit further deterioration. This focuses on establishing and/or maintaining a lower blood pressure, which lessens the tendency of blood clot formation. Those people who are diabetic will be treated for this condition, as diabetes can contribute to stroke. Other factors that can be involved in lessening blood pressure include maintaining a target cholesterol level, **exercise**, avoiding smoking, and moderation in alcohol consumption.

Aspirin is known to reduce the tendency of the blood to clot. Some physicians will prescribe aspirin or similarly acting drugs for this purpose. As well, those with high cholesterol may benefit from a diet change and/or the use of cholesterol-lowering drugs such as statins. In some people, surgery that removes blockages in the main blood vessel to the brain (the carotid artery) can be done. Other surgical treatments that increase blood flow through vessels include angioplasty and stenting to increase arterial flow to the brain.

Recovery and rehabilitation

As damage to the brain cannot be reversed, the focus for a person with multi-infarct dementia is placed upon prevention of further brain tissue injury, and maintaining optimum independent functioning.

Clinical trials

As of May 2004, there were no **clinical trials** underway or in the process of recruiting patients for either multi-infarct dementia or CADASIL. However, research is being funded by agencies such as the National Institute of Neurological Disorders and Stroke and is aimed at understanding the development of dementia. The hope is that the diagnosis of dementias will be improved. Ultimately, the goal is to reverse or prevent the disorder.

Prognosis

The outlook for people with multi-infarct dementia is poor. While some improvement in mental faculty may occur, this is typically of short-term duration. Over longer time, mental decline is inevitable and marked.

Special concerns

A person with multi-infarct dementia is often reliant on family and friends for daily care and support. Family and caregivers can help by stimulating a person's mental activity and prompting the individual to recall past experiences. Eventually, around-the-clock care may become necessary to provide a safe and stimulating environment.

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National Institute for Neurological Diseases and Stroke (NINDS). P.O. Box 5801, Bethesda, MD 20824. (301) 496-5751. (800) 352-9424. <http://www.ninds/nih.gov>.

National Institute on Aging (NIA). 31 Center Drive, Rm. 5C27 MSC 2292, Bethesda, MD 20892-2292. (301) 496-1752 or (800) 222-2225. niainfo@nih.gov. <http://www.nia.nih.gov>.

National Institute of Mental Health (NIMH). 6001 Executive Blvd. Rm. 8184, MSC 9663, Bethesda, MD 20892-9663. (301) 443-4513 or (866) 615-6464; Fax: (301) 443-4279. nimhinfo@nih.gov. <http://www.nimh.nih.gov>.

Brian Douglas Hoyle, PhD

Multifocal motor neuropathy

Definition

Multifocal motor neuropathy is a rare condition in which the muscles in the body become progressively weaker over months to years.

Description

Multifocal motor neuropathy is often mistaken for the more catastrophic, inevitably fatal condition called **amyotrophic lateral sclerosis** (ALS). Unlike ALS, however, multifocal motor neuropathy can be treated; therefore, distinguishing between these two conditions is crucial.

Demographics

Multifocal motor neuropathy is a very rare condition, affecting only about 1 per 100,000 people in the population. Men are about three times as likely to be affected as women. Most patients are between the ages of thirty and fifty when symptoms are noted, with the average age of onset being 40 years.

Causes and symptoms

Multifocal motor neuropathy is thought to result from an autoimmune disorder; that is, the body's immune system accidentally misidentifies markers on the body's own nerve cells as foreign. The immune system then begins to produce cells that attack and injure or destroy either the nerve cells or the myelin sheath wrapped around the nerve cells. Because the myelin sheath allows messages to be conducted down a nerve quickly, injury to the sheath or to the nerve itself results in slowed or faulty nerve conduction.

Symptoms of multifocal motor neuropathy usually begin with gradually progressive weakness of the hands. Leg and foot weakness may follow, as well as decreased muscle volume (called muscle wasting), muscle cramps, and involuntary twitching and cramping of muscles. The weakness is asymmetric; that is, a muscle group on only one side of the body may be affected. Over time, numbness or tingling of affected areas may occur, although sensation is not lost.

Diagnosis

Diagnosis of multifocal motor neuropathy usually requires both a careful physical examination, as well as electromyographic (EMG) testing. Physical examination will reveal weakness and decreased muscle size, abnormal reflexes, muscle twitches, and totally normal sensation. EMG involves inserting a needle electrode into a muscle, and measuring the electrical activity within the muscle at rest and during use. A characteristic pattern of abnormal nerve conduction and muscle contraction will be noted on EMG.

Blood tests will usually reveal the presence of antibodies (immune cells) directed against ganglioside, a component of nerve cells.

Treatment team

Patients with multifocal motor neuropathy are usually cared for by neurologists.

Treatment

Treatment for multifocal motor neuropathy involves using intravenous immunoglobulin (IVIg) to dampen down the immune system's overactivity. If IVIg is not successful, then the immunosuppressant drug cyclophosphamide may be administered.

In very mild, early cases, treatment may not be necessary. If the condition progresses or prompts serious disability, treatment may be necessary. Treatment may then be required intermittently, if the condition progresses again.

Prognosis

Muscle strength usually begins to improve within three to six weeks of the initiation of treatment. Early treatment of multifocal motor neuropathy usually results in sufficient symptom resolution to prevent any permanent disability. Over many years, however, many patients will note a continued, slow progression of muscle weakness.

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Rosalyn Carson-DeWitt, MD

Multiple sclerosis

Definition

Multiple sclerosis is an inflammatory demyelinating disease of the **central nervous system**. The disease results in injury to the myelin sheath (the fatty matter that covers the axons of the nerve cells), the oligodendrocytes (the cells that produce myelin) and, to a lesser extent, the axons and nerve cells themselves. The symptoms of multiple sclerosis vary, depending in part on the location of plaques (areas of thick scar tissue) within the central nervous system. Common symptoms include weakness and **fatigue**, sensory disturbances in the limbs, bladder or bowel dysfunction, problems with sexual function, and **ataxia** (loss of coordination). Although the disease may not be cured or prevented at this time, treatments are available to reduce severity and delay progression.

Description

Multiple, or disseminated, sclerosis (MS) is a slowly progressive disease of the central nervous system (CNS), that comprises the brain and spinal cord. In 1868, French physician Jean-Martin Charcot (1825–1893) produced his lectures on "Sclerose en plaques," providing the first detailed clinical description of the disease. The cause of multiple sclerosis is unknown, and it cannot be prevented or cured. Great progress, however, is being made in treating and identifying underlying mechanisms that trigger the disease. The primary characteristic of MS is the destruction of myelin, a fatty insulation covering the nerve fibers. The end results of this process, called demyelination, are multiple patches of hard, scarred tissue called plaques. Another important feature in the disease is destruction of axons, the long filaments that carry electric impulses away from a nerve cell, which is now considered to be a major factor in the permanent disability that occurs with MS.

Multiple sclerosis is usually characterized by a relapsing remitting course in the early stages, with full or nearly full recovery initially. In the early stages, there may be little damage to axons. Over time, the disease enters an irreversible progressive phase of neurological deficit. Each relapse causes further loss of nervous tissue and progressive dysfunction. In some cases there may be chronic progression without remission or acute disease rapidly leading to death.

MS is a diverse disease. No two affected persons are the same and each will experience different combinations of symptoms with differing severity. The most common form is relapsing-remitting multiple sclerosis (RRMS), which affects 80–85% of people with MS. These patients develop disease relapses, often without a specific trigger, but possibly associated with infections. Disease relapses can last between 24 hours and several months, and the person may, or may not, completely recover. The disease is stable between relapses, although affected persons can have residual symptoms and disability.

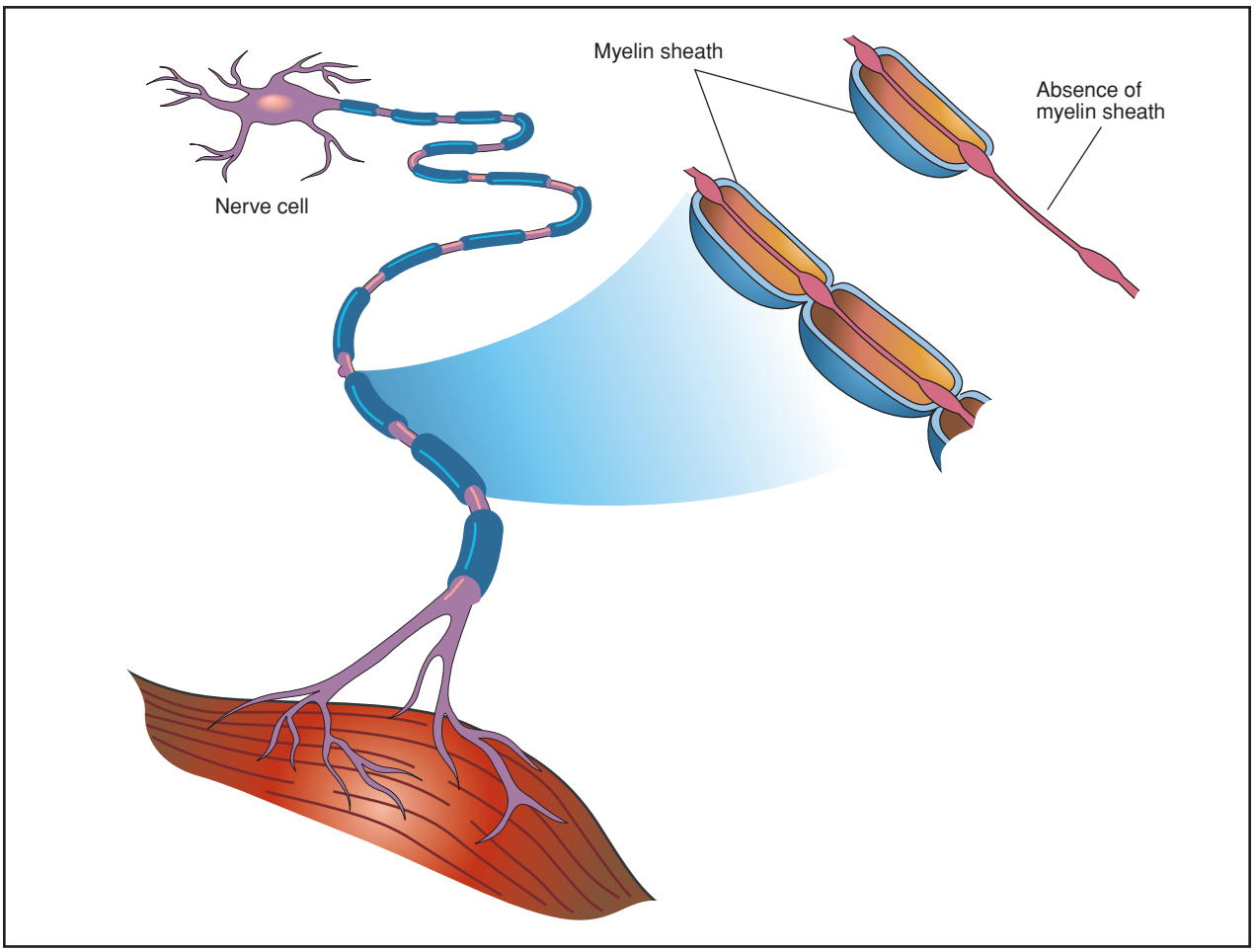
After several years, the majority (70%) of persons with MS will develop secondary progressive multiple sclerosis (SPMS), whereby they experience a progressive neurological deterioration. They may still suffer from superimposed relapses. A subcategory of RRMS patients (around 20%) has benign MS. These patients have rare and mild relapses and a long course of disease with minimal or no disability. If patients have a steady neurological decline from the onset, without relapses, they are described as having primary-progressive multiple sclerosis (PPMS). This comprises approximately 15–20% of people with the disease

A fourth, rare type of MS is progressive-relapsing multiple sclerosis (PRMS), which is considered a variant of PPMS with similar prognosis. In patients with PRMS, there is a gradual neurological decline from the beginning. It is similar to PPMS, but has superimposed, acute relapses.

Demographics

According to the National Multiple Sclerosis Society, approximately 400,000 Americans acknowledge having MS, and every week about 200 people are diagnosed. Worldwide, MS may affect 2.5 million individuals. The usual age of onset is within the third and fourth decades, although the disease can begin in childhood and also above the age of 60 years. Overall, MS occurs more frequently in women than in men, and the female-to-male ratio is approximately of 2:1. This female predominance is less defined in patients with PPMS, which typically develops at a later age.

There is a variation in the worldwide distribution of MS, with the highest prevalence in the northern and central Europe, northern North America and southeastern



MS results in injury to the myelin sheath that covers the axons of the nerve cells, the cells that produce myelin (oligodendrocytes), and, to a lesser extent, the axons and nerve cells themselves. (*Illustration by Electronic Illustrators Group.)*

Australia. Clusters, or areas with more than the expected amount, occur. There are also racial differences, with a low prevalence in Asians and Africans or people of African descent, and a higher frequency in Caucasians, especially of northern European descendent. MS is rare between the equator and latitudes 30°–35° north and south. The prevalence of MS increases proportionally with increased distance from the equator. There is no satisfactory explanation of this phenomenon, although certain variables have been researched. These include environmental factors, such as climate, humidity, hours of daily sunshine, resistance to certain viruses, and even consumption of cow's milk.

Causes and symptoms

The causes of multiple sclerosis remain unknown, but it is widely accepted that susceptibility to MS is determined by a complex interaction between susceptibility genes and environment. The most popular current theory is that the disease occurs in people with a genetic susceptibility, who are exposed to some environmental assault (a virus or a toxin) that disrupts the blood-brain barrier, a protective membrane that controls the passage of substances from the blood into the central nervous system. Most researchers consider MS to be an autoimmune disease-one in which the body, through its immune system, launches a defensive attack against its own tissues. Immune factors converge in the nerve cells and trigger inflammation and an autoimmune attack on myelin and axons. Still, a number of disease patterns have been observed in MS patients, and some experts believe that MS may prove to be not a single disorder, but may represent several diseases with different causes.

Components of myelin such as myelin basic protein have been the focus of much research because, when injected into laboratory animals, they can precipitate experimental allergic encephalomyelitis (EAE), a chronic

relapsing brain and spinal cord disease that resembles MS. The injected myelin probably stimulates the immune system to produce anti-myelin T-cells that attack the animal's own myelin.

Increasing scientific evidence suggests that genetics may play a role in determining a person's susceptibility to MS. No specific gene has been identified and it seems to have a mode of inheritance that involves multiple genes. Twin studies have shown an increased risk of 30% in identical twins, and around 5% in fraternal twins. First-degree relatives of a person with MS have a two or three percent increased risk, which, although small, is higher than in the general population. Further indications that more than one gene is involved in MS susceptibility comes from studies of families in which more than one member has MS.

Several research teams found that people with MS inherit certain regions on individual genes more frequently than people without MS. Of particular interest is the human leukocyte antigen (HLA) or major histocompatibility complex region on chromosome 6. HLAs are genetically determined proteins that influence the immune system. Another interesting candidate is CD24, which has shown to be essential for the induction of EAE in mice. CD24 is a cell surface protein with expression in a variety of cell types that can participate in the rise of MS, including activated T-cells.

An infectious cause of MS has been indicated by some studies as well as by similarities to infectious demyelinating diseases. However, infectious agents more likely shape the immune response that may induce the disease under special circumstances. Evidence is mounting that infection with the Epstein-Barr virus (EBV), which can cause mononucleosis, may also increase the risk of developing multiple sclerosis later in life. Researchers have shown that people with multiple sclerosis tend to carry higher levels of antibodies to the Epstein-Barr virus and that they seem to be at higher risk for the disease. Some of the immune cells that become programmed to attack the Epstein-Barr virus may begin to attack myelin as well.

Environmental factors, other than infectious agents, for which there is some evidence of an association with MS, include toxins, low sunlight exposure, diet factors, and trauma.

Almost any neurological deficit can occur in MS, but there are several signs and symptoms that are characteristic and their presence should suggest MS as a possible diagnosis, particularly in a young adult.

Vision disorders such as optic neuritis can occur. Optic neuritis (ON) is an inflammation of the optic nerve characterized by acute or subacute loss of vision usually in one, but occasionally in both eyes. The visual loss evolves over a period of hours or days. Vision returns to normal within two months, but may deteriorate in later years. Previous history of optic neuritis in a person who develops a neurological illness will strongly support the diagnosis of MS.

Cognitive (thought) impairment is thought to affect 40–70% of MS patients and can be present even in the early stages of MS. Approximately one-third of people with MS have some degree of memory loss. Other areas of cognitive function particularly affected in the MS patient include sustained attention, verbal fluency, and spatial perception. **Dementia** (loss of intellectual function) is often common in the latter stages of MS.

Many MS patients are temperature sensitive. In hotter weather or during a period of raised body temperature, their MS symptoms worsen. Most frequently, vision is affected and muscle weakness occurs.

About two-thirds of MS patients experience **pain** at some point during the course of the disease and 40% are never pain free. MS causes many pain syndromes; some are acute, while others are chronic. Some worsen with age and disease progression. Pain syndromes associated with MS are trigeminal (facial) pain, powerful spasms and cramps, optic neuritis pain, pressure pain, stiffened joints, and a variety of sensations including feelings of itching, burning, and shooting pain.

The Lhermitte's sign can occur, which is actually more of a symptom than a sign. A tingling or electric-like sensation down the back and legs is felt upon flexing the neck. The symptom is non-specific, but occurs more frequently in MS than in any other condition and provides an important clue to the correct diagnosis.

Urinary incontinence affects up to 90% of people with multiple sclerosis and usually occurs before major physical disability is apparent. Bladder problems are due to plaques in the spinal cord. If demyelination occurs in both controlling pathways, the bladder will neither store urine nor empty it properly. Constipation affects about 40% of people with MS. Bowel incontinence and urgency of defecation can also occur in about half of people with MS.

Fatigue is a common complaint in MS. Characteristics of fatigue include muscle weakness, coordination problems, ataxia, transient deafness, changes in taste or smell and numbness of the extremities. **Spasticity** occurs in up to 90% of MS patients and it can be painful and distressing. Spasticity is characterized by weakness, loss of dexterity, and the inability to control specific movements. It is usually more severe in the legs and torso.

Sexual dysfunction is common among people with multiple sclerosis. If MS damages the nerve pathways from the brain to the sexual organs via the spinal cord, sexual response can be directly affected. Physicians and people with MS often neglect to deal with this aspect of the

Key Terms

Autoimmune disease One of a group of diseases, like rheumatoid arthritis and systemic lupus erythematosus, in which the immune system is overactive and has lost the ability to distinguish between self and non-self. The body's immune cells turn on the body, attacking various tissues and organs.

Axon A long, threadlike projection that is part of a neuron (nerve cell).

Myelin A fatty sheath surrounding nerves throughout the body that helps them conduct impulses more quickly.

disease, and both treatments and strategies for success are available.

Depression is common in MS; some studies show that over 50% of people with MS have depression at some point in their lifetime. There is also an increased risk of suicide. If depression is present, it should be treated prior to initiating MS therapy. Depression in those with MS is treated in the same way as the general population.

Diagnosis

MS diagnosis is based upon an individual's history of clinical symptoms and neurological examination. A qualified physician, often a **neurologist**, must thoroughly review all symptoms experienced by an individual to suspect MS. Other conditions with similar symptoms must be ruled out, often requiring various tests.

The diagnosis of MS is usually made in a young adult with relapsing and remitting symptoms referable to different areas of CNS white matter. Diagnosis is more difficult in a patient with the recent onset of neurological complaints or with a primary progressive clinical course.

Laboratory studies include blood work to exclude collagen vascular disease, infections (ie, **Lyme disease**, syphilis), endocrine abnormalities, vitamin B-12 deficiency, sarcoidosis, and **vasculitis**. The examination of cerebrospinal fluid (CSF) has been used to support the diagnosis of MS. The presence of myelin basic protein in the CSF of an MS patient may be highly suggestive of activity of the MS process, but its absence does not rule out active disease.

A newer neuroimaging technique, magnetic resonance spectroscopy (MRS), has been useful in following NAA (N-acetyl-aspartate) levels in patients with multiple sclerosis. NAA is an amino acid found in neurons and axons of the mature brain. In patients with relapsing-remitting MS, NAA levels are reduced, suggesting axonal loss; however, in patients with secondary progressive MS with more disability, the NAA levels are reduced more significantly. In fact, patients with MS had lower levels of NAA even in areas of the brain previously thought to be unaffected, when compared with levels in normal persons.

Magnetic resonance imaging (MRI) remains the imaging procedure of choice for diagnosing and monitoring disease progression in the brain and spinal cord. This test can show brain abnormalities in 90–95% of patients and spinal cord lesions in up to 75% of cases, especially in elderly patients. However, MRI alone cannot be used to diagnose MS. Evoked potential tests that measure how quickly and accurately a person's nervous system responds to certain stimulation have been the most useful neurophysiological studies for evaluation of MS.

At the onset, MS may be mistaken for other inflammatory diseases of the central nervous system, such as Behçet disease, antiphospholipid syndrome or **acute disseminated encephalomyelitis** (ADEM). Pseudotumoral MS may be reminiscent of lymphoma, other tumors (glial tumors), or infectious diseases (like Lyme disease, HTLV1 infection or abcess). Recurrent relapses of neurological impairment may also be mistaken for cavernomatosis. In most cases, MRI findings, cerebrospinal fluid analysis, evoked potentials, the association with systemic signs and the relapsing remitting nature of the disease allow physicians to exclude other diseases, and to arrive at a diagnosis of MS.

Treatment team

The multidisciplinary team usually includes specialists in neurology, urology, ophthalmology, neuropsychology, and social work.

Treatment

The three goals of drug therapy in the treatment of MS are management of acute episodes, prevention of disease progression, and treatment of chronic symptoms. Specific symptoms that may be treated include muscle spasticity, lack of co-ordination, tremor, fatigue, pain, bladder and bowel dysfunctions, sexual dysfunction and depression.

Exacerbations (episodes of worsening symptoms) can be defined as temporary flare-ups, sometimes referred to as attacks or relapses. Most relapses show a degree of spontaneous recovery, but treatment is offered for those relapses that have a severe impact on function. Steroids are the treatment of choice for relapses, usually methyl-prednisolone given orally or by intravenous infusion. Before starting steroids, infection should be excluded because

steroids have immunosuppressant action and can exacerbate the infection.

Disease modifying treatments are aimed at slowing disease progression. The two current types of immunomodulatory agents used as a first line treatment are interferon beta and glatiramer acetate. Interferon beta has proved effective with RRMS and SPMS. There is currently no evidence for improvement with PPMS. Discontinuation of the treatment may be necessary because of intolerance to side effects, when a pregnancy is planned, or when it is no longer effective. Glatiramer is the appropriate treatment to reduce relapse frequency in patients with RRMS and it should not be used for both PPMS and SPMS. Stopping criteria for glatiramer are the same of interferon beta.

A number of treatments are available for managing MS chronic symptoms and complications, each one with specific drugs. Indeed, symptomatic treatment, along with supportive measures and rehabilitation, are a major part of the MS treatment.

Recovery and rehabilitation

When recovering from a symptom flare-up or learning to cope with a change in mobility, rehabilitation through physical therapy can be of great value training patients to improve mobility and to decrease spasticity and strengthen muscles. Some of those who have a physically demanding or highly stressful job may choose to make a career change, in which case vocational training is helpful.

Occupational therapy helps in assessing the patient's functional abilities in completing activities of daily living, assessing fine motor skills, and evaluating for adaptive equipment and assistive technology needs. Speech therapists assess the patient's speech, language, and swallowing and may work with the patient on compensatory techniques to manage cognitive problems.

Clinical trials

The National Institute of Neurological Disorders and Stroke (NINDS) is recruiting patients to evaluate the safety, tolerability, and effect of the drug Rolipram on MS. The NINDS is also recruiting patients with relapsing-remitting or secondary progressive multiple sclerosis to examine the safety and effectiveness of Zenapax (a laboratory-manufactured antibody) in treatment of MS. More information is available at the website: <http://www.clinicaltrials.gov>, a clinical trial service sponsored by the United States government.

Prognosis

It is generally very difficult to predict the course of MS. The disorder varies greatly in each individual, but most people with MS can expect to live 95% of the normal life expectancy. Some studies have shown that people who have few attacks in the first several years after diagnosis, long intervals between attacks, complete recovery from attacks, and attacks that are sensory in nature (i.e., numbness or tingling) tend to fare better. People who have early symptoms of tremor, difficulty in walking, or who have frequent attacks with incomplete recoveries, or more lesions visible on MRI scans early on, tend to have a more progressive disease course.

Special concerns

People with should avoid caffeine-containing beverage, which can actually be dehydrating. The diet should also be rich in fiber, particularly from whole grains, fruits and vegetables to increase digestive motility and reduce constipation. Maintenance of weight in the normal range is also desirable in order to diminishes stress on the joints and skeletal muscles.

Gait difficulty (difficulty with walking) may worsen during pregnancy, and assistive devices for walking or a wheelchair are useful at this time. During pregnancy, bladder and bowel problems may also be aggravated in women with MS who already have these dysfunctions.

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ORGANIZATIONS

The National Multiple Sclerosis Society. 733 Third Avenue, 6th floor, New York, NY 10017. (212) 986-3240 or (800) 344-4867; Fax: (212) 986-7981. nat@nmss.org. <http://www.nationalmssociety.org>.

Marcos do Carmo Oyama
Iuri Drumond Louro

Multiple system atrophy

Definition

Multiple system atrophy (MSA) is a neurodegenerative disease characterized by parkinsonism, cerebellar dysfunction, and autonomic disturbances.

Description

MSA causes a wide range of symptoms, in keeping with its name of "multiple system" atrophy. Parkinsonian symptoms include tremor, rigidity and slowed movements; cerebellar symptoms include incoordination and unsteady gait; and autonomic symptoms include **orthostatic hypotension** (drop in blood pressure upon standing) and urinary incontinence. Because of this wide variety of symptoms, it was originally thought of as three distinct diseases: **striatonigral degeneration** (parkinsonian symptoms), **olivopontocerebellar atrophy** (cerebellar symptoms) and Shy-Drager syndrome (autonomic symptoms). Further study showed the overlap among these conditions was best explained by considering them as a single disease with symptoms clustered into three groups. Historically, confusion about the disease was made even worse because olivopontocerebellar atrophy is also the name of an unrelated genetically inherited disease. It is hoped that widespread use of the name MSA will clear up some of this confusion.

Demographics

Because MSA is often misdiagnosed, figures on its prevalence are not known with certainty. It is estimated there are between 25,000 and 100,000 people in the United States with MSA. Onset is usually in the early fifties, and men are slightly more likely to be affected than women.

Causes and symptoms

The cause or causes of MSA are unknown. No genes have been found for MSA. Some evidence indicates that toxins may be responsible, but no specific agents have been identified. The brains of MSA patients reveal that cells called glia undergo characteristic changes. Glia are supportive cells for neurons, brain cells that conduct electrical signals. In MSA, glia develop tangles of proteins within them, called glial cytoplasmic inclusions. It is not known whether these actually cause MSA, or are caused by some other problem that is the real culprit.

The symptoms of MSA fall into three separate areas-parkinsonism, cerebellar symptoms, and autonomic disturbances. The distribution and severity of individual symptoms varies among patients. MSA is a progressive disease, and symptoms worsen over time.

Key Terms

Atrophy The progressive wasting and loss of function of any part of the body.

Cerebellum The part of the brain involved in the coordination of movement, walking, and balance.

Neurodegeneration The deterioration of nerve tissues.

Parkinsonism is the initial symptom in almost half of all patients. The classic symptoms of **Parkinson's disease** (**PD**)—tremor, stiffness or rigidity, and slowed movements—are seen in MSA, although tremor is not as common, and is jerkier than the tremor of PD.

Cerebellar symptoms are the initial feature in very few MSA patients, but occur in about half of patients at some point during the disease. The **cerebellum** is an important center for coordination, and degeneration of the cerebellum in MSA leads to loss of balance, incoordination in the limbs, and loss of smooth eye movements. A person with cerebellar dysfunction in MSA typically walks with a wide stance to improve stability, and may lose the hand-eye coordination that makes so many simple activities possible.

Autonomic symptoms refer to those involving the autonomic nervous system. The autonomic nervous system controls a variety of "automatic" body functions, including blood pressure, heart rate, sweating, and bladder function. Autonomic symptoms are the initial complaint in half or more of all MSA patients. The most common initial problem is urinary dysfunction in women, and erectile dysfunction in men. Urinary dysfunction may be incontinence, or inability to void the bladder. Other autonomic symptoms include lack of sweating, constipation, and fecal incontinence.

Orthostatic hypotension is a common autonomic symptom. It refers to a significant drop in blood pressure shortly after standing. It can cause **dizziness**, lightheadedness, **fainting**, weakness, **fatigue**, yawning, slurred speech, **headache**, neck ache, cognitive impairment, and blurred vision.

Other symptoms may also occur in MSA. These may include:

- vocal cord paralysis, leading to hoarseness
- swallowing difficulty
- **sleep apnea**
- spasticity

• myoclonus
• Raynaud's phenomenon (cold extremities)

Diagnosis

The diagnosis of MSA is difficult, because it is easily mistaken in its earlier stages for Parkinson's disease, which is much more common. Autonomic disturbance also occurs in PD, but is much more pronounced in MSA. MSA is the more likely diagnostic choice when disease progression is rapid, and when the patient responds mildly or poorly to levodopa, the mainstay of PD treatment. Some centers use **electromyography** of the anal sphincter (the muscles surrounding the anus) in order to confirm the diagnosis of MSA. Abnormal results indicate MSA rather than PD, although this method is not universally recognized as valid.

Neuroimaging may be used to rule out other causes of similar symptoms, such as lesions in the brain or normal pressure **hydrocephalus**.

Treatment team

The treatment team includes the **neurologist**, possibly a **movement disorders** specialist, a urologist, and a speech/language pathologist.

Treatment

There are no treatments that halt or slow the degeneration of brain cells that causes MSA. Treatment is aimed at relieving symptoms.

Treatment of parkinsonian symptoms is attempted with standard PD drugs, namely levodopa and the dopamine agonists. Unfortunately, these are rarely as effective in MSA as they are in PD, although about one-third of patients have at least a moderate response. In the best case, treatment relieves stiffness, tremor and slowed movements, allowing increased activities of daily living.

Orthostatic hypotension is treated with medications to increase retention of fluids (fludrocortisone), compressive stockings to keep blood from pooling in the legs, increasing fluids, and increasing salt intake. Midodrine, a drug that helps maintain blood pressure is often prescribed.

A urologist may be needed to define the type of urinary dysfunction the patient has, and to manage treatment. A bedside commode or condom catheter may be helpful for urge incontinence, or inability to hold urine once the urge to urinate occurs. If incomplete voiding is the problem, intermittent catheterization may be needed. Detrusor hyperreflexia, in which the bladder muscle undergoes spasms, may be treated with drugs to reduce these spasms.

Male erectile dysfunction may be treated with sildenafil or other medications.

Anhidrosis, or lack of sweating, can be dangerous in an active patient, because of the risk of overheating. Awareness of the problem and avoidance of prolonged **exercise** are helpful.

Gait **ataxia** may require a mobility aid, such as a cane, walker, or eventually a wheelchair.

Speech and swallowing problems are dealt with by a speech/language pathologist, who may work with the patient to develop swallowing strategies, and instruct in the use of assistive communication devices. Sleep apnea may be treated with continuous positive airway pressure ventilation.

Clinical trials

Clinical trials for MSA are usually directed toward better diagnosis, or symptomatic treatment. Until researchers develop a better understanding of the causes of the disease, little progress can be expected in development of treatments to slow its progression.

Prognosis

The average survival after diagnosis is 9-10 years. Death usually occurs from pneumonia or suddenly from insufficient respiration, due to degeneration of the respiratory centers in the brain.

Special concerns

Resources

PERIODICALS

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WEBSITES

Shy-Drager Syndrome/Multiple System Atrophy Support Group. <www.shy-drager-syndrome.org>.
WE MOVE. <www.wemove.org>.

Richard Robinson

Muscle-nerve biopsy *see* **Biopsy**

Muscular dystrophy

Definition

Muscular dystrophies (MD) are inherited disorders characterized by progressive weakness and degeneration of the skeletal or voluntary muscles which control movement, without a central or peripheral nerve abnormality. The muscles of the heart and other involuntary muscles are

also affected in some forms of MD, and a few forms involve other organs as well. The major forms of muscular dystrophy include myotonic, Duchenne, Becker, limb-girdle, facioscapulohumeral, congenital, oculopharyngeal, distal, Emery-Dreifuss and Fukuyama muscular dystrophy.

Description

The commonest form of these inherited disorders is the Duchenne muscular dystrophy (DMD). The disorder was originally described in the mid-nineteenth century by the English physician Edward Meryon. At a meeting of the Royal Medical and Chirurgical Society in 1851, and later published in the transactions of the society, he described in detail the clinical presentation of Duchenne muscular dystrophy, beginning in early childhood with progressive muscle wasting and weakness and leading to death in late adolescence. Furthermore, his detailed histological studies led him to conclude that the muscle membrane or sarcolemma was broken down and destroyed.

Duchenne muscular dystrophy will usually produce symptoms between the ages of three and seven in young boys. It begins with a weakness in the pelvic area first and then progresses to the shoulder muscles. As the disorder escalates, the muscles enlarge although the muscle tissue is weak. The heart muscle will also enlarge, creating problems with the heartbeat that can be detected on an electrocardiogram. In most cases, the affected child has a waddling walk, often falls, has difficulty rising from a sitting position, has a difficult time climbing stairs, is unable to fully extend the arms and legs, and may develop scoliosis (an abnormally curved spine). In most cases, children with DMD are confined to a wheel chair between the ages of ten and twelve.

Most people with Becker muscular dystrophy (BMD) first experience difficulties between the ages of five and fifteen years, although onset in the third or fourth decade or even later can occur. By definition, patients with BMD are able to walk beyond age fifteen, while patients with DMD are typically in a wheelchair by the age of twelve. Patients with BMD have a reduced life expectancy, but most survive into the fourth or fifth decade. **Mental retardation** may occur in BMD, but it is not as common as in DMD. Cardiac (heart muscle) involvement occurs in BMD and may result in heart failure.

Myotonic muscular dystrophy (MMD) affects the muscles in the hands and feet. Limb-girdle muscular dystrophy (LGMD) begins late in childhood affecting mainly the muscles of the shoulders and hips. Facioscapulohumeral muscular dystrophy (FSHD) affects only the muscles of the upper arms, face and shoulder girdle. Landouzy-Dejerine muscular dystrophy (LDMD), which is transmitted by an autosomal dominant gene, affects the face, shoulder and lower leg muscles.

Other disorders related to muscular dystrophy include Steinert's disease, Thomsen's disease, and Pompe's disease. Steinert's disease affects both males and females, causing the muscles to be unable to relax after contracting, while Thomsen's disease causes a stiffness of the legs, hands and eyelids. Pompe's disease, which is a glycogen storage disease, affects the liver, heart, nerves and muscles.

Demographics

United States

The incidence of muscular dystrophy varies, depending on the specific type. Duchenne muscular dystrophy is the most common condition. It is inherited on the X chromosome, primarily affects boys, and is the most severe type of the disease. Although women with the defective gene are carriers, they usually show no symptoms. DMD has an inheritance pattern of 1 case per 3,500 live male births, and one-third of cases are due to spontaneous new mutations.

Becker muscular dystrophy is the second most common form, with an incidence of 1 case per 30,000 live male births. Like DMD, BMD is linked to the X chromosome. Other types of MD are rare. Limb-girdle muscular dystrophy includes several different illnesses, which can be inherited by both males and females, as can facioscapulohumeral muscular dystrophy.

International

The incidence of muscular dystrophies internationally is similar to that of the United States, however some types are especially frequent in certain populations and are rare elsewhere. For example, autosomal dominant distal muscular dystrophy occurs more often in Scandinavia than elsewhere, Fukuyama muscular dystrophy in Japan, oculopharyngeal muscular dystrophy in French Canada, and several autosomal recessive LGMD in communities in Brazil, North America, and the Middle East.

Causes and symptoms

All types of muscular dystrophy are inherited. They are caused by a defect in one or more of the genes that control muscle structure and function. Some types are inherited as a dominant gene abnormality, while others are inherited as a recessive gene abnormality or an X-linked recessive gene abnormality. In an X-linked recessive gene abnormality, the gene is on the X chromosome, one of the pair of chromosomes that determine a person's sex.

Both DMD and BMD are inherited X-linked recessive diseases affecting primarily skeletal muscle and the myocardium (heart muscle). Dystrophin, a large protein that stabilizes the plasma membrane during muscle contractions, is absent in DMD and reduced in BMD. This results

Jerry Lewis, talking with Sarah Schwegel, MDA National Goodwill Ambassador, during the Muscular Dystrophy Association Labor Day Telethon. *(Reproduced by permission of the Muscular Dystrophy Association.)*

in an unstable muscle cell membrane and impaired function in the cell. Muscle fibers continually deteriorate and regenerate until the capacity for repair is no longer sufficient. Muscle fiber tissue is eventually replaced by fat and connective tissue. The abnormal gene for DMD and BMD is on the short arm of the X chromosome at position Xp21.

Two types of MMD are well recognized: noncongenital (NC-MMD, not present at birth) and congenital (C-MMD, present at birth). In MMD, a DNA sequence within the gene on chromosome 19q 13.3, is repeated many times, leading to an enlarged, unstable area of the chromosome. Called a triplet repeat mutation, the flawed gene grows by sudden leaps when transmitted from generation to generation, causing the disease to occur at a younger age and in a more severe form (a phenomenon called anticipation). C-MMD patients have been shown to have substantially more repeats than those found in NC-MMD patients.

In FSHD, the abnormal gene is known to be near the end of chromosome 4. Exact DNA testing for diagnostic purposes is not yet available except in some cases, a detailed genetic analysis of a particular family can be accomplished.

Genetic studies with LGMD have identified one form linked to chromosome 15q, another form to chromosome 2p, and two more severe forms to 13ql2 and 17ql2-q21.

Symptoms can first appear during early childhood or late in adult life, depending on the type of muscular dystrophy.

- Duchenne muscular dystrophy—Symptoms usually begin between ages two and four. Because of a progressive weakening of leg muscles, the child falls frequently and has difficulty getting up from the ground. The child also has trouble walking or running normally. By age 12, most patients are unable to walk and are limited to a

wheelchair. As the illness progresses, there also is an abnormal curvature of the spine.

- Becker muscular dystrophy—Symptoms are similar to those of DMD, but they are milder and begin later, usually between ages five and fifteen.
- Myotonic muscular dystrophy—Muscle myotonia may develop soon after birth or begin as late as early adulthood, and especially affects the hands, wrists and tongue. There also is wasting and weakening of facial muscles, neck muscles, and muscles of the wrists, fingers and ankles. Involvement of the tongue and throat muscles causes speech problems and difficulty swallowing. If the diaphragm and chest muscle also are involved, there may be breathing problems.
- Limb-girdle muscular dystrophy—Symptoms begin in late childhood or early adulthood. They include progressive muscle weakness in the shoulders and hips, together with breathing problems (if the diaphragm is involved). If illness also affects the heart muscle, there may be heart failure or abnormal heart rhythms.
- Facioscapulohumeral muscular dystrophy—Symptoms may begin during infancy, late childhood, or early adulthood. Usually, the first sign is facial weakness with difficulty smiling, whistling and closing the eyes. Later, there is difficulty raising the arms or flexing the wrists and/or ankles.

Diagnosis

The diagnosis of muscular dystrophy is made with a physical examination and diagnostic testing by the child's physician. During the examination, the child's physician obtains a complete prenatal and birth history and asks if other family members are known to have MD. In addition to a clinical history and a physical exam, others exams may be suggested:

- Serum creatine kinase—Measurement of serum (a blood component) concentration of creatine kinase is a simple and inexpensive diagnostic test for severe forms of dystrophy known to be associated with high concentrations of creatine in the blood. In DMD, serum creatine kinase values are raised from birth, and testing in newborns for early diagnosis could reduce the possibility of further affected boys in a family and improve medical assistance before the onset of symptoms.
- Electromyography—This test is important in the establishment of the myopathic (muscle disease not caused by nerve dysfunction) nature of the disease and for the exclusion of neurogenic (from the nerves) causes of weakness, including peripheral nerve disorders. Because **electromyography** is an invasive technique involving a needle stick, it is becoming less favored in the investigation of children, but it still has an important role in the diagnosis of adult disease.
- Muscle histology—The one unifying feature of the dystrophies is their similar muscle histological (in the tissues) findings, such as variation in muscle fiber size, muscle fiber death, invasion by macrophages (a versatile immune cell), and ultimately, replacement by fat and connective tissue. This picture is aggravated in the more severe forms of dystrophy, such as Duchenne type. However, in FSHD and LGMD, inflammatory changes in tissues are often the main features.
- Immunohistochemistry and mutation analysis—In some muscular dystrophies, certain proteins are deficient in muscle tissue. Immunohistochemistry involves methods of detecting the presence of these specific proteins in muscle cells or tissues. A diagnosis can be made when these protein deficiencies are identified. Analysis of genetic mutations associated with muscular dystrophies is also important for genetic counseling and prenatal diagnosis.

Treatment team

There are many professionals available to help the child with muscular dystrophy, depending on the patient's needs. These include physicians, orthopedic surgeons (bone specialists), physical therapists, orthotists (specialists on equipment to maintain posture and mobility), occupational therapists, dietitians, nurses, **social workers**, psychologists, teachers, religious advisers, staff from the Muscular Dystrophy Association, parents, and other persons with MD.

Physical therapy involves a program of stretching exercises to maintain muscle length and the flexibility of joints. Physical therapists also work with orthotists. Night splints, calipers, swivel walkers, and braces are some of the aids employed. Physical therapists are the main professionals involved in teaching parents the appropriate exercises and in making sure that any mobility aids are comfortable. Both physical therapy and hydrotherapy (water therapy) contribute significantly to mobility and respiratory function.

Treatment

Although there is no known cure for muscular dystrophy, **exercise** and physical therapy are recommended to maintain mobility for as long as possible. Corticosteroid drugs and gene therapies are being studied to help relieve the symptoms.

Specific treatment for muscular dystrophy is determined by the child's physician based on age, overall

Key Terms

Autosomal dominant disorder A genetic disorder caused by a dominant mutant gene that can be inherited by either parent.

Autosomal recessive disorder A genetic disorder that is inherited from parents that are both carriers, but do not have the disorder. Parents with an affected recessive gene have a 25% chance of passing on the disorder to their offspring with each pregnancy.

Dystrophin A large protein that stabilizes the plasma membrane of a muscle cell during muscle contractions. Dystrophin is absent or reduced in the most common forms of muscular dystrophy.

Electromyography A test used to detect nerve function. It measures the electrical activity generated by muscles.

Immunohistochemistry A method of detecting the presence of specific proteins in cells or tissues.

Macrophage A large, versatile immune cell that acts as a scavenger, engulfing dead cells, foreign substances, and other debris.

Mutation A permanent, heritable change in a gene or chromosome structure.

Myopathy Refers to a disorder of the muscle, usually associated with weakness.

Myotonia Abnormally long muscular contractions.

health, medical history, extent of the condition, type of condition, child's tolerance for specific medications, procedures or therapies.

Drug therapies

In children with Duchenne muscular dystrophy, corticosteroids (such as prednisone) may be prescribed to temporarily delay progression of their illness; however, some patients cannot tolerate this medication because of side effects. Powerful medications that suppress the immune system have been reported to help some patients, but their use is controversial. In patients with MMD, myotonia (abnormally long muscular contractions) may be treated with medications such as **carbamazepine** or phenytoin.

Gene therapy

With advances in molecular biology techniques, another method of treatment currently under intense investigation is somatic **gene therapy**. The idea is to introduce healthy immature cells into affected muscles, which would fuse and stimulate production of enough dystrophin to reverse the degeneration already taking place. Although this has been achieved successfully in mice, the benefit may not translate into humans. The mice cannot demonstrate muscle strength, and the laboratory-raised mice were not able to mount a rejection response that may occur in humans.

Other therapies

The orthopedic problems in children with MD lead to progressive weakness with walking difficulties, soft-tissue contractures, and spinal deformities. The role of the orthopedic surgeon is to correct deformities and help maintain the child's ambulatory status for as long as possible. The modalities available to obtain these goals include: functional testing; physical therapy; use of orthoses (specialized aids); fracture management; soft tissue, bone, and spinal surgeries; use of a wheelchair when indicated; and genetic and/or psychological testing.

Recovery and rehabilitation

To date, there is no known treatment, medicine, or surgery that will cure MD, or stop the muscles from weakening. The goal of treatment is to prevent deformity and allow the child to function as independently as possible at home and in the community.

Physical therapy

In general, patients are given supportive care, together with leg braces and physical therapy to maximize their ability to function in daily life. Stretching limbs to avoid tightened tendons and muscles is particularly important. When tightness of tendons develops (called contractures), surgery can be performed. When chest muscles are involved, respiratory therapy may be used to delay the onset of breathing problems. In addition, people with MD are given age-appropriate dietary therapy to help them avoid obesity. Obesity is especially harmful to patients with MD because it places additional strain on their already weak muscles. Unfortunately, many MD patients are at a high risk of obesity because their limited physical activity prevents them from exercising.

Wheelchair prescription

If the person with MD becomes nonambulatory, wheelchair mobility is essential. The wheelchair should complement the patient's lifestyle, providing comfort, safety, and functionality. Special attention should be given to the frame, seat, backrest, front rigging, rear wheels, and casters because of the functional weakness and contractures in the upper and lower extremities of patients with limb-girdle dystrophy. An accessible home

and work environment and personal or public transportation with safe restraint systems for the wheelchair are also important.

Additional resources

Specific planning for vocational needs and desires may be coordinated with therapists. Resources within the community, such as the Parks and Recreation Department for activity programs, may be explored. Educational institutions, from public schools to community colleges and universities, have resources that may be used. Adaptive physical education program and Disabled Student Services generally are available for persons with MD.

Clinical trials

There are numerous open **clinical trials** for MD:

- An open-label pilot study of Oxatomide in steroid-naive DMD, sponsored by Cooperative International Neuromuscular Research Group;
- An open-label pilot study of Coenzyme Q10 in steroid-treated DMD, sponsored by Cooperative International Neuromuscular Research Group;
- Study of Inherited Neurological Disorders, sponsored by National Institute of Neurological Disorders and Stroke (NINDS);
- Study of Albuterol and Oxandrolone in Patients With FSHD, sponsored by the Food and Drug Administration Office of Orphan Products Development.

Updated information on clinical trials is available at the National Institutes of Health website for clinical trials at <www.clinicaltrials.org>.

Prognosis

The prognosis varies according to the type of MD and its progression. Some patients have only mild symptoms with a normal lifespan, whereas others have severe symptoms and die at a young age. For example, children with DMD often die before age 18 because of respiratory failure, heart failure, pneumonia or other problems. In persons with BMD, death tends to occur later. Some examples of complications associated with MD that lead to permanent, progressive disability are:

- deformities, such as scoliosis and joint contractures
- decreased mobility
- decreased ability to perform daily self-care tasks, such as bathing and dressing
- mental impairment (varies)
- cardiomyopathy (weakened heart muscle)
- respiratory failure

Special concerns

Genetic counseling is an important aspect of the care and evaluation of patients with DMD and BMD and their family members. A minority of female carriers have MD symptoms, but even in these symptomatic patients, correct diagnosis requires appropriate testing. In families in which an affected male has a known deletion or duplication of the dystrophin gene, testing for carrier status is performed accurately by testing possible carriers for the same mutation, the absence of which would exclude them as a carrier.

Resources

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"NINDS Muscular Dystrophy (MD) Information Page" National Institute of Neurological Disorders and Stroke. (March 20, 2004). <http://www.ninds.nih.gov/health_and_medical/disorders/md.htm>.

ORGANIZATIONS

Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718-3208. (520) 529-2000 or (800) 572-1717; Fax: (520) 529-5300. mda@mdausa.org. <http://www.mdausa.org/>.

Muscular Dystrophy Family Foundation. 2330 North Meridien Street, Indianapolis, IN 46208. (317) 923-6333 or (800) 544-1213; Fax: (317) 923-6334. mdff@mdff.org. <http://www.mdff.org/>.

Parent Project for Muscular Dystrophy Research. 1012 North University Blvd., Middletown, OH 45042. (413) 424-0696 or (800) 714-KIDS (5437); Fax: (513) 425-9907. ParentProject@aol.com. <http://www.parentprojectmd.org/>.

Francisco de Paula Careta
Iuri Drumond Louro, MD, PhD

Myasthenia, congenital

Definition

Congenital myasthenia is an inherited disorder that results in muscle weakness caused by a malfunction at the neuromuscular junction, the area where nerve cells communicate to muscle cells.

Key Terms

Myasthenia Muscular weakness, or a group of chronic muscular diseases characterized by muscle weakness.

Neuromuscular junction The junction between a nerve fiber and the muscle it supplies.

Ophthalmoplegia Paralysis of the motor nerves of the eye, resulting in wandering or floating eye movements.

Description

Congenital myasthenia is caused by a number of genetic defects that affect the ability of a nerve impulse to move from nerve to nerve, and from the nerve to muscle. The genetic abnormalities can be present in the fetus at the moment of conception or may occur during fetal development. This genetic cause of the disease separates the congenital form of myasthenia from **myasthenia gravis** and **Lambert-Eaton myasthenic syndrome**, both of which are caused by the malfunctioning of the immune system.

Demographics

Congenital myasthenia occurs in the young, and occurs with equal frequency in boys and girls. Symptoms tend to appear within the first two years of life. It is common to have siblings who are affected. The disease is extremely rare, occurring in only one to two per million live births.

Causes and symptoms

The root of congenital myasthenia are defects in various genes that play a role in the transmission of nerve impulses. At least a dozen genetic defects have been identified as causes of congenital myasthenic syndromes so far. The defects can affect the manufacture or the release of acetylcholine, a neurotransmitter, or molecule that acts as a communication bridge between adjacent nerves.

As a result of the varying genetic roots of the disease, different congenital myasthenic syndromes exist. These can produce different effects in those who are affected. The symptoms, which usually begin in infancy or toddlerhood, can include a poor sucking response, drooping eyelids (a condition called ptosis), eyes that appear to wander or float (ophthalmoplegia), weakness in facial muscles that is apparent as an abnormal appearance, weakness in the arms and legs, breathing difficulty, delayed development of muscle skills, and a feeling of **fatigue**. Usually, a parent may notice that the infant is experiencing delays in developmental milestones that require coordinated muscle strength, such as sitting up alone, crawling, or walking. All or just a few of these symptoms can be present in a person with congenital myasthenia. As well, the severity of the symptoms can vary from person to person. Some children may be severely impaired, while others lead near normal lives. Even though children display symptoms, their parents may not be similarly affected.

Diagnosis

The disease is usually diagnosed in the early years of childhood by the abnormal appearance of the face and/or by the noticeable weakening of the arms or legs. A test of muscle strength known as the tensilon test that is considered to be accurate in diagnosis of other forms of myasthenia is usually not specific for congenital myasthenia. Congenital myasthenia is often misdiagnosed as myasthenia gravis or other neuromuscular diseases.

Accurate diagnosis of congenital myasthenia requires specialized testing. These include testing specific nerves to determine if the nerves fatigue more quickly than is normal. While at least a dozen genes that are responsible for the disease are known, genetic testing technology is not currently routinely available. Only a handful of centers in the United States are able to test the anconeus and intercostal muscles to detect the abnormal genes. However, as such technology becomes routine (i.e., gene chips), genetic testing will no doubt become one of the principle means of diagnosis.

Treatment team

Treatment can involve the family physician, a **neurologist**, family members, and physical therapists. The latter can provide exercises that assist in maximizing muscular strength.

Treatment

Treatment for most types of congenital myasthenia typically involves the use of drugs that help promote the transmission of nerve impulses. Drugs that retard the breakdown of acetylcholine can be used. An example of an acetylcholinesterase is mestinon. Other drugs that show merit in some cases include guanidine, ephedrine sulfate,

and albuterol. People may build up a tolerance to ephedrine, which decreases its effectiveness.

Recovery and rehabilitation

As there is no recovery from congenital myasthenia, treatment is aimed at maximizing muscle function through drug therapy and physical therapy.

Clinical trials

As of mid-2004, there were no **clinical trials** underway or in the planning stages specific for congenital myasthenia. However, agencies such as the National Institute for Neurological Diseases and Stroke continue to fund research that seeks to better understand the underlying genetic bases of congenital myasthenia, and to discover more effective means of increasing nerve signal transmission. Updated information on clinical trials related to congenital myasthenia can be located at the National Institutes of Health website for clinical trials at www.clinicaltrials.org.

Prognosis

With accurate diagnosis, most types of congenital myasthenia can be improved or at least stabilized by the use of drug therapy. More severe forms of the disease may weaken respiratory muscles and result in a reduced lifespan.

Resources

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ORGANIZATIONS

National Institute for Neurological Diseases and Stroke (NINDS). P.O. Box 5801, Bethesda, MD 20824. (301) 496-5751. (800) 352-9424. <http://www.ninds/nih.gov>.

National Organization for Rare Disorders (NORD). 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Myasthenia Gravis Foundation of America, Inc. 1821 University Ave. W., Suite S256, St. Paul, MN 55104. (651) 917-6256 or (800) 541-5454; Fax: (651) 917-1835. mgfa@myasthenia.org. <http://www.myasthenia.org>.

Brian Douglas Hoyle, PhD

Myasthenia gravis

Definition

Myasthenia gravis (MG) is a chronic autoimmune disease characterized by **fatigue** and muscular weakness, especially in the face and neck, that results from a breakdown in the normal communication between nerves and muscles caused by the deficiency of acetylcholine at the neuromuscular (nerve-muscle) junctions. MG is the most common primary disorder of neuromuscular transmission.

Description

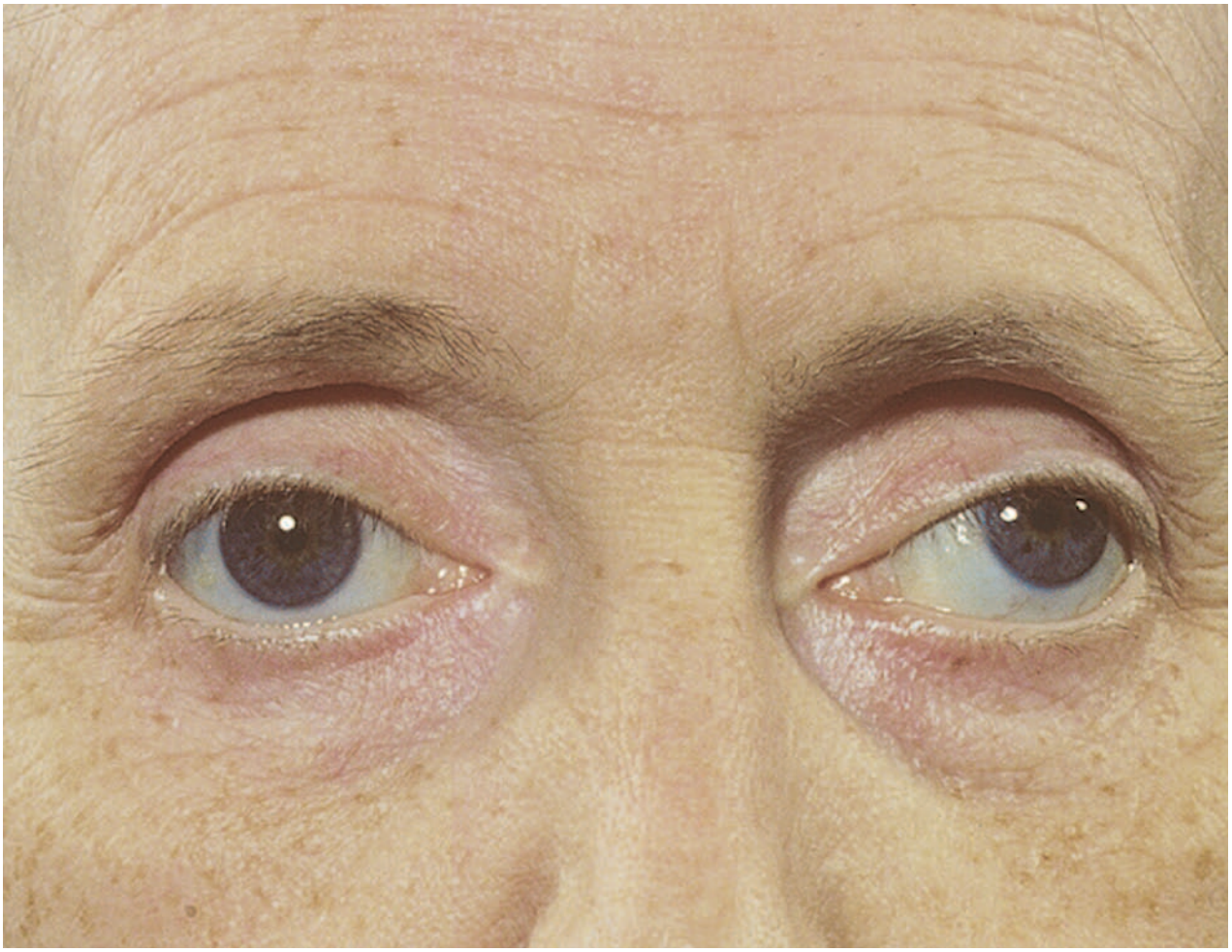
MG is a chronic autoimmune neuromuscular disease characterized by varying degrees of weakness of the skeletal (voluntary) muscles of the body. The hallmark of this disease is muscle weakness that increases during periods of activity and improves after periods of rest. Muscles that control eye and eyelid movements, facial expression, chewing, talking, and swallowing are often, but not always, involved. The muscles that control breathing and neck and limb movements may also be affected.

Myasthenia gravis can be classified according to which skeletal muscles are affected. Within a year of onset, approximately 85–90% of affected persons develop generalized MG, which is characterized by weakness in the trunk, arms, and legs. About 10–15% of patients have weakness only in muscles that control eye movement. This type is called ocular myasthenia gravis.

Other types of MG include congenital MG, an inherited condition caused by a genetic defect, and transient neonatal, which occurs in infants born from mothers who have MG. Congenital MG develops at or shortly after birth and causes generalized symptoms.

Demographics

Myasthenia gravis occurs in all ethnic groups and both genders. The prevalence of MG in the United States is estimated to be 14 per 100,000 population, which equals approximately 36,000 cases in the United States. However, this disease is probably under diagnosed and the prevalence may be higher. Previous studies showed that women are more often affected than men. The most common age at onset is the second and third decades in women



Although myasthenia gravis may affect any voluntary muscle, muscles that control eye and eyelid movement, facial expression, and swallowing are most frequently affected. *(Custom Medical Stock Photo. Reproduced by permission.)*

and the seventh and eighth decades in men. As the population ages, the average age of onset has increased correspondingly, and now males are considered to be more often affected than females, and the onset of symptoms is usually after age 50.

Causes and symptoms

Myasthenia gravis is an autoimmune disease caused by abnormal antibodies carried in the blood stream. Nerves release a chemical called acetylcholine (ACh) that activates receptors on muscles to trigger contraction. The normal neuromuscular junction releases ACh from the motor nerve terminal in discrete packages (quanta). The ACh quanta diffuse across the synaptic cleft and bind to receptors on the folded muscle end-plate membrane. Stimulation of the motor nerve releases many ACh quanta that depolarize the muscle end-plate region and then the muscle membrane, causing muscle contraction.

The myasthenia antibodies interfere with this process by binding to specific sites on the surface of the muscles, the post-synaptic muscle membrane is distorted and simplified, having lost its normal folded shape. The most common antibodies are directed against the muscle acetylcholine receptor (AChR). ACh is released normally, but its effect on the post-synaptic membrane is reduced. The post-junctional membrane is less sensitive to applied ACh, and the probability that any nerve impulse will cause a muscle action potential is reduced.

Ten percent of patients with MG have a tumor in the thymus, (a thymoma) that is usually benign, and 70% have changes (germinal centers) that indicate an active immune response. These are areas within lymphoid tissue where B-cells interact with helper T-cells to produce antibodies. Because the thymus is the central organ for immunological self-tolerance, it is reasonable to suspect that thymic abnormalities cause the breakdown in tolerance that leads to

an immune-mediated attack on AChR in this disease. The thymus contains all the necessary elements for the beginnings of MG: myoid cells that express the AChR antigen, antigen presenting cells, and immunocompetent T-cells. However, it is still uncertain whether the role of the thymus in the pathogenesis of disease is primary or secondary.

There are very rare genetic abnormalities that cause problems similar to myasthenia gravis. These diseases are called congenital or inherited myasthenias and usually are present in infants. MG is not directly inherited, nor is it contagious. Occasionally, the disease may occur in more than one member of the same family. Rarely, children may show signs of congenital (present at birth) myasthenia or congenital myasthenic syndrome. These are not autoimmune disorders, but are caused by defective genes that control proteins in the acetylcholine receptor or in acetylcholinesterase. In neonatal myasthenia that develops in 10–20% of infants born to mothers who have MG, the fetus may acquire immune proteins (antibodies) from a mother affected with MG. Generally, cases of neonatal myasthenia are transient and the child's symptoms usually disappear within few weeks after birth.

Although MG may affect any voluntary muscle, muscles that control eye and eyelid movement, facial expression, and swallowing are most frequently affected. The onset of the disorder may be sudden. Symptoms often are not immediately recognized as myasthenia gravis. In most cases, the first noticeable symptom is weakness of the eye muscles. In others, difficulty in swallowing and slurred speech may be the first signs. The degree of muscle weakness involved in this disease varies greatly among patients, ranging from a localized form, limited to eye muscles (ocular myasthenia), to a severe or generalized form in which many muscles, sometimes including those that control breathing, are affected. Symptoms, which vary in type and severity, may include a drooping of one or both eyelids (ptosis), blurred or double vision (diplopia) due to weakness of the muscles that control eye movements, unstable or waddling gait, weakness in arms, hands, fingers, legs, and neck, a change in facial expression, difficulty in swallowing and shortness of breath, and impaired speech (**dysarthria**).

Diagnosis

A delay in diagnosis of one or two years is not unusual in cases of MG. Because weakness is a common symptom of many other disorders, the diagnosis is often missed in people who experience mild weakness or in those individuals whose weakness is restricted to only a few muscles. The first steps of diagnosing MG include a review of the individual's medical history, and physical and neurological examinations. The signs a physician must look for are impairment of eye movements or muscle weakness without any changes in the individual's ability to feel things. If the physician suspects MG, several tests are available to confirm the diagnosis.

The Edrophonium Chloride (Tensilon) Test

This approach requires the intravenous administration of edrophonium chloride or Tensilon(r), a drug that temporarily increases the levels of acetylcholine at the neuromuscular junction. In people with myasthenia gravis involving the eye muscles, the drug will chloride will briefly relieve weakness.

Antibodies Against Acetylcholine Receptor (AChR)

In general, an elevated concentration of AChR binding antibodies in a patient with compatible clinical features confirms the diagnosis of MG, but normal antibody concentrations do not exclude the diagnosis.

Repetitive Nerve Stimulation (RNS)

This test records weakening muscle responses when the nerves are repetitively stimulated, and helps to differentiate nerve disorders from muscle disorders. Repetitive stimulation of a nerve during a **nerve conduction study** may demonstrate faults of the muscle action potential (CMAP) due to impaired nerve-to-muscle transmission. A significant decrement to RNS in either a hand or shoulder muscle is found in about 60% of patients with MG.

Single fiber electromyogram (SFEMG)

SFEMG is the most sensitive clinical test of neuromuscular transmission and shows increased jitter in some muscles in almost all patients with myasthenia gravis. Jitter is greatest in weak muscles, but may be abnormal even in muscles with normal strength. Patients with mild or purely ocular (eye) muscle weakness may have increased jitter only in facial muscles. Increased jitter is a nonspecific sign of abnormal neuromuscular transmission and can also be seen in other motor diseases.

Computed tomography (CT) or magnetic resonance imaging (MRI)

Computed tomography (**CT**) or **magnetic resonance imaging (MRI)** may be used to identify an abnormal thymus gland or the presence of a thymoma. Pulmonary function testing, which measures breathing strength, helps to predict whether respiration may fail and lead to a myasthenic crisis.

Treatment team

The treatment team is normally composed of a **neurologist**, a nutritionist (dietary advice), a speech pathologist, a pulmonologist, a geneticist, a neurologist, a

dentist, a otolaryngologist, a physical therapist, and nurses.

Key Terms

Acetylcholine A chemical called a neurotransmitter that functions primarily to mediate activity of the nervous system and skeletal muscles.

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

Thymoma A tumor that originates in the thymus, a small gland located in the upper chest just below the neck, that produces hormones necessary for the development of certain components of the immune system.

Treatment

Treatment regimens for myasthenia gravis are practical rather than curative. Treatment decisions are based on knowledge of the natural history of disease in each patient and the predicted response to a specific form of therapy. Treatment goals must be individualized according to the severity of disease, the patient's age and sex, and the degree of functional impairment. The response to any form of treatment is difficult to assess because the severity of symptoms fluctuates. Spontaneous improvement, even remissions, occur without specific therapy, especially during the early stages of the disease.

Cholinesterase inhibitors

Cholinesterase inhibitors result in increased ACh accumulation at the neuromuscular junction and prolongs its effect. These drugs cause considerable improvement in some patients and little to none in others. Pyridostigmine bromide (Mestinon) and neostigmine bromide (Prostigmin) are the most commonly prescribed cholinesterase inhibitors. No fixed dosage schedule suits all patients. The need for cholinesterase inhibitors varies from day to day and during the same day in response to infection, menstruation, emotional stress, and hot weather. Different muscles respond differently; with any dose, certain muscles become stronger, others do not change, and still others become weaker. Adverse effects of cholinesterase inhibitors include gastrointestinal complaints: queasiness, loose stools, nausea, vomiting, abdominal cramps, and diarrhea.

Thymectomy

Thymectomy (removal of the thymus) is recommended for most people with myasthenia gravis. The greatest benefit from the surgery generally occurs two to five years afterwards. However, the response is relatively unpredictable and significant impairment may continue for months or years after surgery. The best responses to thymectomy are in young people early in the course of the disease, but improvement can occur even after 30 years of symptoms. Persons with disease onset after the age of 60 rarely show substantial improvement from thymectomy. Patients with thymomas (tumor on the thymus) do not respond as well to thymectomy as do patients without them.

Corticosteroids

Marked improvement or complete relief of symptoms occurs in more than 75% of people treated with prednisone, and some improvement occurs in most of the rest. Much of the improvement occurs in the first six to eight weeks of therapy, but strength may increase to total remission in the months that follow. The best responses occur in patients with recent onset of symptoms, but patients with chronic disease may also respond. The severity of disease does not predict the ultimate improvement. Patients with thymoma have an excellent response to prednisone before or after removal of the tumor. About one-third of patients become weaker temporarily after starting prednisone, usually within the first seven to ten days, but this temporary weakness lasts for only a few days. The major disadvantages of chronic corticosteroid therapy are the side effects, such as weight gain and fluid retention.

Immunosuppressant drugs

Azathioprine reverses symptoms in most patients with myasthenia gravis, but the benefits are delayed by four to eight months. Once improvement begins, it is maintained for as long as the drug is given. Symptoms recur two to three months after the drug is discontinued or the dose is reduced below therapeutic levels. Patients who experience no improvement on corticosteroids may respond to azathioprine, and the reverse is also true. Sometimes, people with MG respond better to treatment with both drugs than to either one alone. Because the response to azathioprine is delayed, both drugs may be started simultaneously with the intent of rapidly tapering prednisone when azathioprine becomes effective. Approximately one-third of patients have mild dose-dependent side effects that may require dose reductions, but do not require stopping treatment.

Cyclosporine is sometimes beneficial in treating MG. Most patients with myasthenia gravis improve within two months after starting cyclosporine and improvement is maintained as long as therapeutic doses are given. Maximum improvement is achieved six months or longer after starting treatment. After achieving the maximal response,

the dose is gradually reduced to the minimum that maintains improvement. Toxicity to the kidneys and hypertension are important adverse reactions of cyclosporine. Many drugs interfere with cyclosporine metabolism and should be avoided or used with caution.

Cyclophosphamide is also given intravenously and orally for the treatment of myasthenia gravis. More than half of patients receiving cyclophosphamide experience a dramatic improvement in their symptoms after one year; however, side effects are common. Life-threatening infections are an important risk for all persons taking immunosuppressant drugs.

Plasma exchange

Plasma exchange is used as a short-term intervention for patients with sudden worsening of myasthenic symptoms, to rapidly improve strength before surgery, and as a chronic intermittent treatment for patients who are refractory to all other treatments. The need for plasma exchange and its frequency of use is determined by the clinical response in the individual patient. Almost all patients with acquired MG improve temporarily following plasma exchange. Maximum improvement may be reached as early as after the first exchange or as late as the fourteenth. Improvement lasts for weeks or months and then the effect is lost unless the exchange is followed by thymectomy or immunosuppressive therapy. Most patients who respond to the first plasma exchange will respond again to subsequent courses. Repeated exchanges do not have a cumulative benefit.

Intravenous immune globulin (IVIG)

Immune globulin given intravenously results in improvement in more than half of MG patients, usually beginning within one week of therapy and lasting for several weeks or months.

Recovery and rehabilitation

Physical and occupational therapists provide strategies to help people with myasthenia gravis maintain daily activities during almost all phases of the disease. As the progression of symptoms occurs over months or years, these strategies adapt to the changing needs of the person with myasthenia gravis. For example, wheelchairs, specialized eating utensils, and positioning aids might be required during the progressive phase. When improvement is made, shower stools, rolling carts for carrying shopping items, and exercises to promote maintenance of posture can all help avoid fatigue. While the symptoms of the disease may go into remission, recovery is not said to be complete, as symptoms may recur. The longer the person remains in remission; however, the greater is the chance that the disease will not recur

Clinical trials

As of February 2004, there were two open **clinical trials** for MG, both sponsored by the Rush University Medical Center in Chicago, Illinois:

- Study of CellCept in the Treatment of MG: This is a multicenter, placebo-controlled study testing CellCept and prednisone as the initial form of immunotherapy in the treatment of MG. The purpose of the study is to determine if the combination of these two medications provides better control of MG symptoms compared with prednisone alone.
- Study of Etanercept Among Individuals With MG: The purpose of the study is to determine if Etanercept improves muscle strength in patients with MG.

Up-to-date information on clinical trials can be found at the United States government website for clinical trials located at <www.clinicaltrials.org>.

Prognosis

Symptoms of myasthenia gravis usually progress to maximum severity within three years. After that time, persons with MG normally stabilize or improve. With treatment, the outlook for most patients with MG is bright: they will have significant improvement of their muscle weakness and they can expect to lead normal or nearly normal lives.

Many people's MG symptoms may go into remission temporarily and muscle weakness may disappear completely, so that medications can be discontinued. Stable, long-lasting complete remissions are the goal of thymus removal (thymectomy). In a few cases, the severe weakness of MG may cause a crisis (respiratory failure), which requires immediate emergency medical care. Advances in medical care have reduced the mortality rate from respiratory failure in myasthenia gravis patients to approximately three percent. Patients over the age of 40, those with a short history of severe disease, and those with thymoma tend to have less significant improvement.

Special concerns

Myasthenia gravis cannot be prevented, but avoiding the following triggers may help patients prevent exacerbations (worsening of symptoms):

- emotional stress
- exposure to extreme temperatures
- fever
- illness (e.g., respiratory infection, pneumonia, tooth abscess)
- low levels of potassium in the blood (hypokalemia; caused by diuretics, frequent vomiting)

• some medications, such as muscle relaxants, **anticonvulsants**, and certain antibiotics

Resources

BOOKS

Henderson, Ronald E. *Attacking Myasthenia Gravis.* Seattle: Court Street Press, 2002.

Icon Health Publications. *The Official Patient's Sourcebook on Myasthenia Gravis: A Revised and Updated Directory for the Internet Age.* San Diego: Icon Grp. Int., 2002.

OTHER

National Institute of Neurological Disorders and Stroke. "Myasthenia Gravis Fact Sheet." <http://www.ninds.nih.gov/health_and_medical/pubs/myasthenia_gravis.htm> (February 11, 2004).

ORGANIZATIONS

Myasthenia Gravis Foundation of America, Inc. 5841 Cedar Lake Road Suite 204, Minneapolis, MN 55416. (952) 545-9438 or (800) 541-5454; Fax: (952) 646-2028. myastheniagravis@msn.com. <http://www.myasthenia.org>.

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Myelinoclastic diffuse sclerosis *see* **Schilder's disease**

Myoclonic encephalopathy of infants *see* **Opsoclonus myoclonus**

Myoclonus

Definition

Myoclonus is a brief, rapid, shock-like jerking movement.

Description

Myoclonus can be a symptom of a separate disorder, or can be the only or primary neurological finding, in which case it is termed "essential myoclonus." Myoclonus may occur in **epilepsy**, or following many different types of brain injury, such as lack of oxygen, **stroke**, trauma, or poisoning. Myoclonus can occur in one or more limbs, or may be generalized, involving much of the body.

Demographics

Because myoclonus is so often part of another disorder, the prevalence of myoclonus is not known with certainty. One study indicates that the prevalence of all types of myoclonus may be approximately 10 per 100,000 population.

Key Terms

Hypoxia A condition characterized by insufficient oxygen in the cells of the body.

Causes and symptoms

Myoclonus can be a symptom of a very wide variety of disorders. A partial list includes:

• epilepsy (several types)
• **Tay-Sachs** disease and other storage diseases
• spinocerebellar degenerative diseases
• **Hallervorden-Spatz** syndrome
• **Huntington's disease**
• **multiple system atrophy**
• **corticobasal degeneration**
• **Creutzfeldt-Jakob disease**
• brain infections, including HIV
• focal brain damage, including from stroke or tumor
• heat stroke
• electrical shock
• **hypoxia** (oxygen deprivation)
• toxins and drugs

Myoclonus also occurs normally, as a person falls asleep or while sleeping. This type of myoclonus is not associated with disease.

Diagnosis

The diagnosis of myoclonus is not difficult, and depends on careful patient description of the symptoms. Much more effort is devoted to determining the underlying cause. Blood tests, neuroimaging studies, genetic tests, **electroencephalography** (EEG) and other types of studies may be performed in order to determine the underlying disorder.

Treatment team

Myoclonus is treated by a **neurologist**.

Treatment

If an underlying disorder can be identified, this is treated with the expectation that successful treatment may diminish the myoclonus. In many cases this is not possible, however. Alternatively, the underlying disorder may

be discovered, but may be impossible to treat. Such is the case with hypoxic myoclonus, or damage done by a stroke or trauma.

Several medications can be used to reduce the severity or frequency of the myoclonus. Valproic acid and clonazepam are the two most widely used drugs. Anticholinergic drugs, such as benztropine or trihexyphenidyl, may be useful. **Anticonvulsants** may be helpful, as may **benzodiazepines**, depending on the type of myoclonus. **Deep brain stimulation** has been reported to help at least one patient. **Botulinum toxin** injection may be useful in focal myoclonus.

Recovery and rehabilitation

Treatment of myoclonus is rarely entirely successful. The patient is likely to have some residual myoclonus even with the most successful treatments. Nonetheless, treatment may reduce frequency and severity, allowing more normal function.

Prognosis

Myoclonus is not a life-threatening disorder, but may continue to have a significant impact on quality of life and activities of daily living.

Resources

WEBSITES

Myoclonus Research Foundation. <http://www.myoclonus.com/index.htm>.

WE MOVE. <http://www.wemove.org>.

Richard Robinson

Myofibrillar myopathy

Definition

Myofibrillar myopathies (MFMs) are a group of skeletal muscle diseases that are frequently associated with involvement of the heart muscle. Myofibrillar myopathies can be hereditary or occur sporadically (spontaneously). The hallmark of myofibrillar disease is the abnormal accumulation of the protein desmin in the muscles, causing progressive weakness.

Description

The term myofibrillar **myopathy** was proposed in 1996 as a broad term for an abnormal pattern of muscle deterioration associated with the excess accumulation of multiple proteins that include desmin. Desmin, the main muscle intermediate fiber of the cytoskeleton (the fibrous network that provides structure for the cell), is a protein in cardiac, skeletal, and smooth muscles. This protein interacts with other proteins to form a network that maintains the structure of the cell.

The main features of myofibrillar myopathies include shoulder and hip muscle deterioration, often called "limb-girdle" myopathy, along with weakness of muscles farther away from the center of the body, called distal muscle weakness. The muscles involved often include the heart, and complications such as conduction blocks, arrhythmias, and congestive heart failure are often experienced.

Most persons with myofibrillar myopathy develop the disorder due to an autosomal-dominant or autosomal-recessive inheritance pattern, which means that males and females are equally affected, and there is a 50% chance of passing on the disorder in each pregnancy. In an autosomal-recessive inheritance pattern, the affected gene is recessive and one parent is its carrier. The risk of a child being affected with myofibrillar myopathy in an autosomal-recessive inheritance pattern is 25% for each pregnancy. A lesser number of myofibrillar myopathy cases are sporadic, meaning no inheritance pattern can be found.

The pattern of weakness in this condition is often similar to patients with the other limb-girdle muscular dystrophies, but some patients have more weakness in the hands and ankles in addition to the more typical shoulder and hip weakness. Myofibrillar myopathy, like limb-girdle **muscular dystrophy**, slowly worsens over time, but the rate of progression is variable and some affected persons remain functional for many years.

Desmin-related myopathy (DRM) is a subgroup of myofibrillar myopathy and is the most clearly recognized type among this group. DRM was originally described as a skeletal and cardiac myopathy characterized by abnormal accumulation of desmin within muscle fibers. This definition focused attention on desmin as a key molecule associated with a diverse group of clinically and pathologically related disorders.

Demographics

The true incidence of myofibrillar myopathy is unknown, but it is very rare. Both sexes are affected equally in MFM, since inheritance is usually autosomal recessive or autosomal dominant.

Causes and symptoms

Two gene mutations have been described in myofibrillar myopathy. Mutations on chromosome 2 in the gene for desmin are transmitted in an autosomal-dominant or autosomal-recessive inheritance pattern. Mutations on chromosome 11 in the gene for αBC (alpha-B-crystallin) are transmitted in an autosomal-dominant inheritance pattern, which can also cause a desmin storage myopathy.

Key Terms

Cardiomyopathy A disease of the heart muscle that leads to generalized deterioration of the muscle and its pumping ability.

Cytoskeleton A network of filaments that give structure and shape to the cell.

Desmin A protein that provides part of the structure to heart, skeletal, and smooth muscle cells.

Limb-girdle myopathy A muscular dystrophy-type disorder characterized by weakness in the muscles of the shoulders, trunk, and pelvic girdle, often progressing to respiratory or cardiac failure.

Myopathy A disorder of the muscles.

Defects in the function of desmin, as well as in other proteins, cause fragility of the myofibrils (structures in muscles that help them contract). In the heart, normal desmin protects the structural integrity of myofibrils during repeated muscle contractures over time. When desmin accumulates in abnormal amounts and locations of the heart muscle cell, myofibrils degrade and lose their ability to contract efficiently, resulting in weakness and inefficient pumping ability of the heart.

Myofibrillar myopathy becomes apparent in early to middle adulthood when muscle weakness in the lower extremities and gait (manner of walking) disturbances develop. The myopathy slowly progresses to also involve respiratory, facial, and heart muscles. Occasionally, this pattern is reversed and the heart muscle shows weakness before the skeletal muscles. Symptoms of alterations in the heart include abnormal rhythms that may cause **fainting** or, rarely, sudden death.

Diagnosis

Diagnostic difficulties arise from the fact that the disease has many variations: in some cases, myofibrillar myopathy is a relentlessly progressive skeletal disorder with no signs of cardiac involvement, while in others, cardiomyopathy (weak heart muscle action) is the leading or even exclusive feature. Respiratory muscle insufficiency may also be a major factor in myofibrillar myopathy and is a leading cause of death.

Most of the known genetic mutations responsible for myofibrillar myopathy are autosomal dominant, but some are autosomal recessive. A significant number of the mutations also occur spontaneously without inheritance pattern. For this reason, genetic testing is critical for establishing an accurate diagnosis. The true prevalence of myofibrillar myopathy may be assessed only when most or all persons with characteristic symptoms are tested genetically.

Electromyography (EMG) and nerve conduction studies (NCSs) should be performed in all persons in whom a myofibrillar myopathy is suspected. EMG and NCSs are important to exclude causes of weakness that result from nerve malfunction, including peripheral nerve disorders. Because electromyography involves inserting a needle into a muscle, it is becoming less favored in investigating muscle weakness in children, but it still has an important role in the diagnosis of the adult disease. In myofibrillar myopathy, **nerve conduction study** findings are normal and EMG findings are either normal or show typical patterns of myopathies.

Muscle **biopsy** is an important part of the diagnostic approach because it shows myofibrillar myopathy's histologic features (i.e., its organization and effect on tissue structure). In the typical diagnostic sequence, muscle biopsy is done first, then genetic studies are pursued.

Treatment team

The treatment team of hereditary muscle diseases, depending on the needs of a particular patient, includes a **neurologist**, pulmonologist, cardiologist, orthopedic surgeon, physiatrist, physical therapist, orthotist, and genetic counselors.

Because the diagnosis of hereditary myopathy is often difficult, interpretation of muscle biopsy, laboratory tests, and electrodiagnostic studies should be performed by a clinician experienced in the diagnosis and treatment of neuromuscular diseases.

Treatment

No specific treatment is available for any of the myofibrillar myopathies, but aggressive supportive care is essential to preserve muscle activity, to allow for maximal functional ability, and to prolong life expectancy.

The primary concerns are preventing and correcting skeletal abnormalities (e.g., scoliosis, foot deformities, and contractures) and maintaining ambulation. Aggressive use of passive stretching, bracing, and orthopedic procedures allows the affected person to remain independent for as long as possible.

Complications with the heart and lungs are the other chief concern. Early intervention to treat cardiac and respiratory insufficiency, at times requiring intermittent positive pressure ventilation (BiPAP/CPAP), can help improve function and prolong life expectancy.

Orthopedic surgery may be needed to help correct or prevent contractures (rigid muscles near joints), foot deformities, and scoliosis.

While no dietary restrictions are indicated for persons with myopathies, the diet should be tailored to the caloric needs of the patient. This may include restricting calories, especially in children with minimal mobility.

Recovery and rehabilitation

To date, there is no known treatment, medicine, or surgery that will cure MFM or stop the muscles from weakening. The goal is to prevent deformity and allow the patient to function as independently as possible. Since myofibrillar myopathy is a life-long condition that is not correctable, management includes focusing on preventing or minimizing deformities and maximizing the patient's functional ability at home and in the community.

In general, patients are given supportive care, together with leg braces and physical therapy, to maximize their ability to function in daily life. Stretching limbs to avoid tightened tendons and muscles is particularly important.

Clinical trials

As of mid-2004, there were no **clinical trials** recruiting participants specific for myofibrillar myopathy.

Prognosis

Myofibrillar myopathies are among a large group of related but distinct diseases. In general, it is expected that there will be slow progression of weakness, which worsens in affected muscles, then spreads, and progresses with time.

Heart muscle weakness and the tendency to have abnormal electrical activity of the heart can increase the risk of palpitations, fainting, and sudden death. Most patients with this group of diseases live into adulthood, but do not reach their full life expectancy.

Special concerns

Genetic counseling is often helpful to assist patients with family-planning decisions.

Vigorous physical activity is often impossible (or impractical) for patients with significant weakness, but activities like swimming, water aerobics, and low-resistance **exercise** equipment are often tolerated very well. The goal of these activities should be to increase the number of calories burned, but not to build strength.

Maintaining ambulation and functional ability with the aggressive use of physical therapy and bracing is highly recommended. Children and young adults are often encouraged continue with school in regular classes, with modifications designed to meet their specific physical needs.

Resources within the community may be explored. Educational institutions have resources that may be used. Adaptive physical education programs and disabled student services are generally available for qualified individuals. Access and mobility concerns in the community invariably touch upon the adjustment issues faced by individuals with a progressive disability.

Resources

BOOKS

Emery, Alan E. H. *Muscular Dystrophy: The Facts.* Oxford, UK: Oxford University Press, 2000.

Parker, James N., and Philip M. Parker, eds. *The 2002 Official Patient's Sourcebook on Muscular Dystrophy.* San Diego: Icon Group International, 2002.

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Selcen, D., et al. "Myofibrillar Myopathy: Clinical, Morphological and Genetic Studies in 63 Patients." *Brain* 127 (February 2004): 439–451.

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"Myofibrillar Myopathy; MDA-Ask the Experts." *Muscular Dystrophy Association.* July 2001. (May 4, 2004 [June 2, 2004].) <http://www.mdausa.org/experts/question.cfm?id=428>.

"Myopathy, Desmin Storage." *WebMD Health.* May 4, 2004 (June 2, 2004). <http://webcenter.health.webmd.netscape.com/hw/health_guide_atoz/nord1008.asp>.

ORGANIZATIONS

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Bldg. 31, Rm. 4C05, Bethesda, MD 20892-2350 or (877) 22-NIAMS (226-4267); Fax: (301) 496-8188. NIAMSInfo@mail.nih.gov. <http://www.nih.gov/niams>.

Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718-3208. (520) 529-2000 or (800) 572-1717; Fax: (520) 529-5300. mda@mdausa.org. <http://www.mdausa.org/>.

American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231-4596. (214) 373-6300 or (800) 242-8721; Fax: (214) 373-0268. inquire@heart.org. <http://www.americanheart.org>.

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Myopathy

Definition

Myopathy is a general term referring to any skeletal muscle disease or neuromuscular disorder. Myopathy can be acquired or inherited, and can occur at birth or later in life. Myopathies can result from endocrine disorders,

metabolic disorders, muscle infection or inflammation, drugs, and mutations in genes.

Description

Skeletal muscle diseases, or myopathies, are disorders with structural changes or functional impairment of the muscle. These conditions can be differentiated from other diseases of the motor unit by characteristic clinical and laboratory findings. The main symptom is muscle weakness that can be either intermittent or persistent. Different myopathy types exist with different associated causes. The main types include congenital myopathy, **muscular dystrophy**, **inflammatory myopathy**, and drug-induced myopathy.

Congenital myopathy (CM) is a term used for muscle disorders present at birth. According to this definition, the CMs could include hundreds of distinct neuromuscular syndromes and disorders. In general, this disease causes loss of muscle tone and muscle weakness in infancy and delayed motor skills, such as walking, later in childhood. Four distinct disorders are classified as CMs: central core disease, nemaline rod myopathy, centronuclear (myotubular) myopathy, and multicore myopathy.

Muscular dystrophy (MD) refers to a group of genetic diseases characterized by progressive weakness and degeneration of the skeletal or voluntary muscles that control movement. The muscles of the heart and some other involuntary muscles are also affected in some forms of MD, and a few forms involve other organs as well. The major forms of MD include myotonic, Duchenne, Becker, limb-girdle, facioscapulohumeral, congenital, oculopharyngeal, distal, and Emery-Dreifuss.

Inflammatory myopathies (IM) are a group of muscle diseases involving the inflammation and degeneration of skeletal muscle tissues. They are thought to be autoimmune disorders. In IMs, inflammatory cells surround, invade, and destroy normal muscle fibers as though they were defective or foreign to the body. This eventually results in discernible muscle weakness. This muscle weakness is usually symmetrical and develops slowly over weeks to months or even years. The IMs include **dermatomyositis**, **polymyositis**, and **inclusion body myositis**.

Drug induced myopathy (DIM) is a muscle disease caused by toxic substances that produce muscle damage. The toxic substances may act directly on muscle cells, but muscle damage can also be secondary to electrolyte disturbances, excessive energy requirements, or the inadequate delivery of oxygen and nutrients due to muscle compression. Drug use may also result in development of an immunologic reaction directed against the muscle. Muscle damage can be generalized or local, as occurs when a drug is injected into a muscle.

Demographics

Worldwide, CMs account for about 14% of all myopathies. Central core disease accounts for 16% of cases; nemaline rod myopathy for 20%; centronuclear myopathy for 14%; and multicore myopathy for 10%. Prevalence of MD is higher in males. In the United States, Duchenne and Becker MD occur in approximately one in 3,300 boys. Overall incidence of MD is about 63 per one million people.

Worldwide incidence of IM is about five to 10 per 100,000 people. These disorders are more common in women. Incidence and prevalence of DIM are unknown. Myopathy caused by corticosteroids is the most common disorder, and it is more common in women.

Causes and symptoms

CMs and MDs are caused by a genetic defect. In both conditions, mutations have been identified in genes that encode for muscle proteins. The loss or dysfunction of these proteins presumably leads to the specific morphological feature in the muscle and to clinically noticeable muscle disease. For example, in Becker dystrophy, there is a less-active form of dystrophin (a protein involved in the complex interactions of the muscle membrane and extracellular environment) that may not be effective as a gateway regulator, allowing some leakage of intracellular substances, resulting in the myopathy.

The causes of IM are not known. An autoimmune process is likely, as these conditions are often associated with other autoimmune diseases and because they respond to immunosuppressive medication. Muscle **biopsy** typically shows changes attributed to destruction by infiltrating lymphocytes (white blood cells).

In DIMs, there are a number of causative agents. Drugs such as lipid-lowering agents (statins, clofibrate and gemfibrizol), agents that cause hypokalemia (diuretics, theophylline, amphotericin B), lithium, succinylcholine, antibiotics (trimethoprim, isoniazid), **anticonvulsants** (valproic acid, **lamotrigine**, prolonged propofol infusion), vasopressin, colchicine, episilon, aminocaproic acid, high dose alfa-interferon, and illicit drugs (cocaine, heroin, phencyclidine, amphetamines) are possible myopathy inducers.

Although symptoms depend on the type of myopathy, some generalizations can be made. Skeletal muscle weakness is the hallmark of most myopathies. In most myopathies, weakness occurs primarily in the muscles of the shoulders, upper arms, thighs, and pelvis (proximal muscles). In some cases, the distal muscles of the hands and

Key Terms

Autoimmune disorder A large group of diseases characterized by abnormal functioning of the immune system that produces antibodies against its own tissues.

Congenital Present at birth.

Myopathy Disease of the muscle, most often associated with weakness.

feet may be involved during advanced stages of the disease. Other typical symptoms of muscle disease include the following:

- muscle aching
- muscle cramping
- muscle pain
- muscle stiffness
- muscle tenderness
- muscle tightness

Initially, individuals may feel fatigued during very light physical activity. Walking and climbing stairs may be difficult because of weakness in the pelvic and leg muscles that stabilize the trunk. Patients often find it difficult to rise from a chair. As the myopathy progresses, there may be muscle wasting.

Diagnosis

Generally, diagnosis involves several outpatient tests to determine the type of myopathy. Sometimes it is necessary to wait until the disease progresses to a point at which the syndrome can be identified.

A blood serum enzyme test measures how much muscle protein is circulating in the blood. Usually, this is helpful only at the early stages of the disease, when the sudden increase of muscle protein in the blood is conspicuous. Antibodies found in the blood might indicate an IM. DNA may be collected to evaluate whether one of the known genetic defects is present.

An electromyogram (EMG) measures the electrical activity of the muscle. It involves placing a tiny needle into the muscle and recording the muscular activity on a monitor (oscilloscope). This helps identify which muscles are weakened.

A muscle tissue biopsy involves surgically removing a very small amount of tissue to be examined under the microscope and analyzed for abnormalities.

Treatment team

A multidisciplinary team is involved in the treatment of myopathy patients. This team may include a **neurologist**, a rheumatologist, an orthopedic surgeon, a pulmonologist, a cardiologist, an orthopedist, a dermatologist, and a genetic counselor. It can also include physical and occupational therapists.

Treatment

Treatment depends on the cause, and goals are to slow progression of the disease and relieve symptoms. Treatments range from drug therapy for MD and IM to simply avoiding situations that work the muscles too hard. Some physicians recommend that patients keep their weight down (a lighter body demands less work from the muscles) and avoid overexerting their muscles. For MD, the corticosteroids deflazacort and prednisone seem to be the most effective medications. Calcium supplements and antidepressants may be prescribed to counteract the side effects. The IMs are usually treated with drugs that suppress the action of the immune system such as methotrexate, cyclosporine, and azathioprine, all of which have potentially serious side effects. For CM, treatment involves supportive measures to help patients cope with the symptoms.

Recovery and rehabilitation

Physical therapy can prevent weakening in a patient's healthy muscles, however, it cannot restore already weakened muscles. Occupational and respiratory therapy help patients learn how to use special equipment that can improve their quality of life.

Clinical trials

There are numerous open **clinical trials** for myopathies, including:

- Study and Treatment of Inflammatory Muscle Diseases and Infliximab to Treat Dermatomyositis and Polymyositis, sponsored by National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
- Diagnostic Evaluation of Patients with Neuromuscular Disease and Screening Protocol for Patients with Neurological Disorders with Muscle Stiffness, sponsored by National Institute of Neurological Disorders and Stroke (NINDS)
- Physiologic Effects of PRMS & Testosterone in the Debilitated Elderly, sponsored by Department of Veterans Affairs Medical Research Service
- Myositis in Children, sponsored by National Institute of Environmental Health Sciences (NIEHS)

More updated information on clinical trials can be found on the National Institutes of Health clinical trials website at <www.clinicaltrials.gov>.

Prognosis

The prognosis for persons with myopathy varies. Some individuals have a normal life span and little or no disability. In others, however, the disorder may be progressive, severely disabling, life threatening, or fatal. If the underlying cause of the disorder can be treated successfully, the prognosis is usually good. Progressive myopathies that develop later in life usually have a better prognosis than conditions that develop during childhood. Persons with Duchenne MD rarely live beyond their middle to late 20s, and persons with Becker MD may live until middle age.

Special concerns

If the cardiac muscle is affected in later disease stages, abnormal heart rhythms or heart muscle insufficiency (cardiomyopathy) may develop. Cardiomyopathy patients are at risk for congestive heart failure.

When muscles involved in breathing weaken, there may be significant breathing difficulties and increased risk for pneumonia, flu, and other respiratory infections. In severe cases, patients may require a respirator. When swallowing muscles are affected, persons are at increased risk for choking and malnutrition.

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Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718-3208. (520) 529-2000 or (800) 572-1717; Fax: (520) 529-5300. mda@mdausa.org. <http://www.mdausa.org/>.

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Myotonic dystrophy

Definition

Myotonic dystrophy is an inherited disorder that affects muscle tone, and hair loss and can involve varying degrees of impaired cognitive abilities. It is inherited as a dominant disorder, which means that individuals that carry the defective gene have the disease. The amount of symptoms exhibited in persons with myotonic dystrophy varies.

Description

Physical limitations resulting from myotonic dystrophy can be significant, involving muscle weakness and difficulty lifting items and performing certain routine daily tasks. There are many cases in which affected persons experience mental delays, and this usually correlates with the extent of the genetic defect. Myotonic dystrophy is a progressive disorder in terms of muscle weakness and muscle wasting.

Demographics

Myotonic dystrophy is relatively rare, occurring approximately once in 8,000 people. There is also a more rare, severe congenital form that occurs with an incidence of about 1 in 100,000.

Causes and symptoms

Myotonic dystrophy involves many different tissues within the body, including the eye, the heart, the endocrine system, and the **central nervous system**. The clinical manifestations in myotonic dystrophy span from mild to severe, leading to three separate categories with somewhat overlapping characteristics: mild, classical, and congenital (in which the clinical manifestations are evident at birth).

Mild myotonic dystrophy

In the mild form, persons usually develop cataracts and experience mild muscle tone dysfunction (myotonia). They normally do not experience clinical manifestations

until they reach 20 years of age. Some patients do not develop symptoms until 70 years of age.

Classical myotonic dystrophy

In the classical form, patients can have generalized weakness, myotonia that is more severe than the mild form, cataracts, balding, and heart rhythm disturbances. The age of onset can be from 10 years until they are 30 years old.

Congenital myotonic dystrophy

Symptoms in the congenital form of myotonic dystrophy are evident at birth. Affected infants show muscle weakness, respiratory defects, and eventually, **mental retardation**. There are cases that appear after birth but before 10 years of age, although the symptoms might be slight and remain unnoticed. Congenital myotonic dystrophy is almost always inherited from the mother; however, inheritance from the father has occurred. Mental retardation is thought to be associated with early respiratory failure and the effects of the mutated gene on the brain.

Causes of myotonic dystrophy

Myotonic dystrophy is caused by a DNA alteration the in the Myotonin-protein kinase (DMPK) gene. This gene has been found to localize to specialized structures of the heart and skeletal muscle. Normal function is important for intercellular conduction and impulse transmission. It interacts with a variety of proteins that are important in signaling neurological messages. The abnormal gene product leads to disease but the mechanism is complex and in some tissues, it is relatively unclear. The alteration in the DNA leads to abnormal RNA processing, an important step in the production of proteins. This abnormal processing is felt to result in functional alterations of this protein that can lead to disease.

Diagnosis

Myotonic dystrophy is diagnosed clinically in individuals that have a specific type of muscle weakness. This is confirmed with molecular genetics testing, where the DMPK is analyzed. This gene is located on chromosome 19q13.2-13.3. Within the gene, there is a DNA sequence that is a string of three letters in the DNA alphabet (GTC, which are abbreviations for the nucleotides guanine, thymine, and cytosine) that are normally repeated up to 37 times. CTG repeats repeated greater than 50 times alters the function of the protein and can lead to disease. Individuals that have repeats from 38–49 times are considered to have permutations and in this range they generally do not produce symptoms, but their children are at risk for having repeats that expand into the disease causing range. Patients have more symptoms when they have repeat sizes greater than 50. DNA testing is 100% sensitive (able to determine the defect) and widely available. Prenatal diagnosis to determine if a fetus is affected is also available.

Key Terms

Myotonia Abnormally long muscular contractions; slow relaxation of a muscle after a contraction.

Premutation carriers Individuals who have the genetic protein repeats associated with a particular disorder, but not in sufficient numbers to cause the disorder. The repeats may expand in these carriers' offspring, causing the disorder to occur.

Myotonic dystrophy is suspected by physicians if patients experience muscle weakness in the lower legs, hands, neck, and face. The will experience a characteristic sustained muscle contraction whereby they have difficulty in quickly releasing their hand grip during a handshake. They also develop cataracts. Newborns usually have generalized and facial muscle weakness, club foot, and respiratory difficulties. Their muscles usually appear hypotonic (floppy).

Treatment team

A general practitioner may not see very many cases of myotonic dystrophy during his career, but may be the first physician to observe a patient. Usually, a **neurologist** and a geneticist are consulted. Depending on the age of onset, the extent of professional help varies. When the age of onset is a birth or infancy, a cardiologist and a pulmonologist will be necessary to evaluate and heart or respiratory deficiencies, respectively. These individuals usually also require special education, depending on the extent of the cognitive deficits.

Treatment

There is no specific treatment that has been identified to help the muscle weakness or prevent muscle wasting in myotonic dystrophy. Ankle and/or leg braces can be used to help support the muscles as the disease worsens. Heart problems, cataracts, and other abnormalities can often be treated. There are also medications that can help relieve the myotonia.

Recovery and rehabilitation

Although patients with this disorder do not recover, occupational and physical therapy is felt to be of benefit in many cases to help maintain optimum function for as long as possible.

Clinical trials

As of May 2004, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Neurological Disorders and Stroke (NINDS) were recruiting patients for a registry that will connect people with myotonic dystrophy with researchers studying these diseases. (Contact information: Colleen M. Donlin-Smith, MA, telephone: 585-275-6372, email: Colleen_DonlinSmith@urmc.rochester.edu; Eileen Eastwood, telephone 585-275-6372; email: Eileen_Eastwood@urmc.rochester.edu).

Prognosis

The prognosis for patients that are diagnosed with the mild form of the disease is quite good. They usually do not have mental retardation and can live a close to normal lifespan. Affected individuals that have the classic form have a more severe prognosis. They have more clinical manifestations and lifespan usually ranges 48–55 years. The congenital form is the most severe, although patients live, on average, until they are 45 years old. They have more severe mental retardation, respiratory deficits, and have clinical manifestations at birth.

Special concerns

As this disorder can be inherited, genetic counseling for at-risk families is recommended. Offspring of an affected individual, regardless of gender, have a 50% chance of inheriting the mutant gene. It is important to recognize that expanded repeats within the gene can expand even more in the gametes (sex cells—sperm or egg) from individuals with expansions, resulting in the transmission of even longer trinucleotide repeat genes. This expansion leading to longer repeats is associated with more severe disease that is observed in the parent. Therefore, affected individuals are more likely to have more offspring with a more serious form of the disorder. Premutation carriers, or individuals that have repeats that do not usually cause disease but are likely to expand in their offspring, should be identified (if possible) in cases where there is a family history of the disorder. These individuals are at risk for having affected offspring, although they may not themselves have the disorder.

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Muscular Dystrophy Association (MDA). 3300 East Sunrise Drive, Tucson, AZ 85718-3208. (800) 572-1717 or (520) 529-2000; Fax: (520) 529-5300. mda@mdausa.org. <www.mdausa.org>.

Muscular Dystrophy Campaign. 7-11 Prescott Place, London SW4 6BS, UK. (+44) 0 020 7720 8055; Fax: (+44) 0 020 7498 0670. info@muscular-dystrophy.org. <http://www.muscular-dystrophy.org>.

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N

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, even in the middle of a conversation. These sleep attacks can last from a few seconds to more than an hour. Depending on where the sleep attacks occur, they may be mildly inconvenient or even dangerous to the person, particularly if they occur while driving. Some people continue to function outwardly during the sleep episodes, such as continuing a conversation or putting things away. But when they wake up, they have no memory of the event.

Sleep researchers have identified several different types of sleep in humans. One type of sleep is called rapid eye movement (REM) sleep, because the person's eyes move rapidly back and forth underneath the closed eyelids. REM sleep is associated with dreaming. Normally, when people fall asleep, they experience 90 minutes of non-REM sleep, which is then followed by a phase of REM sleep. People with narcolepsy, however, enter REM sleep immediately. In addition, REM sleep occurs inappropriately throughout the day in patients with narcolepsy.

Demographics

There has been debate over the incidence of narcolepsy. It is thought to affect between one in every 1,000–2,000 Americans. The known prevalence in other countries varies, from one in 600 in Japan to one in 500,000 in Israel. The reasons for these demographic differences are not clear. In about 8–12% of cases, people diagnosed with narcolepsy know of other family members with similar symptoms.

Causes and symptoms

One of the causes of narcolepsy is a genetic mutation. In 1999, researchers identified the gene that causes the disorder. The narcolepsy gene allows cells in the hypothalamus (the part of the brain that regulates sleep behavior) to receive messages from other cells. As a result of the mutation, the cells cannot communicate properly, and abnormal sleeping patterns develop.

Researchers are also looking into the possibility that narcolepsy may be caused by some kind of autoimmune disorder. This theory suggests that the person's immune system accidentally turns against the specific area of the brain that controls alertness and sleep, injuring or destroying it.

The disorder sometimes runs in families, but most people with narcolepsy have no family members with the disorder. Researchers believe that the inheritance of narcolepsy is similar to that of heart disease, in which several genes play a role in being susceptible to the disorder. But heart disease does not usually develop without an environmental trigger of some sort.

While the symptoms of narcolepsy usually appear during a person's late teens or early 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 of the disorder appear.

Cataplexy is the most dramatic symptom of narcolepsy, affecting 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 it is frightening.

Key Terms

Cataplexy A symptom of narcolepsy marked by a sudden episode of muscle weakness triggered by strong 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 a person is falling asleep.

Hypothalamus A part of the forebrain that controls heartbeat, body temperature, thirst, hunger, blood pressure, blood sugar levels, and other functions.

Polysomnogram A machine that is used to diagnose sleep disorders by measuring and recording a variety of body functions related to sleep, including heart rate, eye movements, brain waves, muscle activity, breathing, changes in blood oxygen concentration, and body position.

Rapid eye movement (REM) sleep A type of sleep during which the person's eyes move back and forth rapidly underneath their closed eyelids. REM sleep is associated with dreaming.

Sleep paralysis An abnormal episode of sleep in which the patient cannot move for a few minutes, usually occurring while falling asleep or waking up. Sleep paralysis is often found in patients with narcolepsy.

A narcoleptic has lost consciousness while reading the paper. *(© Bannor/Custom Medical Stock Photo. Reproduced by permission.)*

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

The diagnosis of narcolepsy can be made by a general practitioner familiar with the disorder as well as by a psychiatrist. If a person comes to the doctor with reports of both excessive daytime sleepiness and cataplexy, a diagnosis may be made on the patient's history alone. Laboratory tests, however, can confirm a diagnosis of narcolepsy. These tests may include an overnight polysomnogram, which is a test in which sleep is monitored with a variety of electrodes that record information about heart rate, eye movements, brain waves, muscle activity, breathing, changes in blood oxygen concentration, and body position. A multiple sleep latency test, which measures sleep latency (onset) and how quickly REM sleep occurs, may also be used. People who have narcolepsy usually fall asleep in less than five minutes.

If the diagnosis is still open to 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, that the patient has narcolepsy.

Narcolepsy is a complex disorder, and it is often misdiagnosed. Many people with the disorder struggle with symptoms for an average of 14 years before being correctly diagnosed.

Treatment team

Sleep disorder specialists are experts in management of narcolepsy. Other team members may include neurologists, psychiatrists, or psychologists.

Treatment

There is no cure for narcolepsy. It is not progressive, and it is not fatal, but it is a chronic disorder. The symptoms can be managed with lifestyle adjustments and/or medication.

People with narcolepsy must plan their days carefully. Scheduling regular naps (either several short, 15-minute naps or one long nap in the afternoon) can help boost alertness and wakefulness. A full eight hours of nighttime sleep should also be a goal. **Exercise** can often help people with narcolepsy feel more alert and energetic, although they should avoid exercising within a few hours of bedtime. Substances that contain alcohol, nicotine, and caffeine should be avoided because they can interfere with refreshing sleep and with daytime alertness.

Medications for narcolepsy may include the use of antidepressants (tricyclic antidepressants or selective serotonin-reuptake inhibitors [SSRIs]) to treat such symptoms of the disorder as cataplexy, hypnagogic hallucinations, and/or sleep paralysis.

Stimulants (amphetamines) may also be used to help individuals with narcolepsy stay awake and alert.

With the recent discovery of the gene that causes narcolepsy, researchers are hopeful that other treatments can be designed to relieve the symptoms of the disorder.

Clinical trials

A number of **clinical trials** are underway to investigate a number of drugs that may help improve daytime sleepiness in narcolepsy patients. For more information visit <http://www.clinicaltrials.gov>.

Prognosis

Narcolepsy is not a degenerative disease, and patients do not develop other neurologic symptoms. Narcolepsy can, however, interfere with a person's ability to work, play, drive, socialize, 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.

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American Sleep Disorders Association. 1610 14th St. NW, Suite 300, Rochester, MN 55901. (507) 287-6006.

Narcolepsy Network. P. O. Box 42460, Cincinnati, OH 45242. (973) 276- 0115.

National Center on Sleep Disorders Research. Two Rockledge Centre, 6701 Rockledge Drive, Bethesda, MD 20892. (301) 435-0199.

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Neostigmine *see* **Cholinergic stimulants**

Nerve compression

Definition

Nerve compression is the restriction in the space around a nerve that can occur due to several reasons. Functioning of the nerve is compromised.

Description

There are a variety of circumstances that cause nerve compression. Despite this variety, the resulting damage to the nerve produces a similar diminished functioning of the nerve.

Demographics

The incidence of brachial plexus palsy, usually a result of birth injury to the nerves that conduct signals from the spine to the shoulder and resulting in a limp or paralyzed arm, is low, on the order of one to two births out of

every 1,000. Brachial plexus palsy is associated with a difficult labor, especially compression on the baby's shoulders. Intervention or assistance during labor can lessen the chance of the physical trauma that causes the nerve damage. However, the condition cannot be totally eliminated, especially in times where an emergency response is needed to speed the birth of a fetus in distress.

Meralgia parasthetica, a condition involving compression of the lateral femoral cutaneous nerve, results in paresthesia, or tingling, numbness, and burning **pain** in the outer side of the thigh. Meraglia paresthetica has traditionally affected men more than women. The condition is not rare, but its overall prevalence is unknown. **Meralgia paresthetica** may occur after abdominal surgery or significant weight gain, in military members who often march, soccer players, or for no apparent reason in the general population. Other nerve compression maladies such as **carpal tunnel syndrome** can be quite common.

Causes and symptoms

There are a variety of conditions that lead to nerve compression, according to the affected nerve.

Carpal tunnel syndrome

In carpal tunnel syndrome, the nerves that pass through the wrist are pinched due to the enlargement of local tendons and ligaments. The enlargement occurs due to inflammation, which can be associated with the strain of performing a repetitive task such as typing. Carpal tunnel syndrome is also associated with maladies like diabetes, and with the restricted space that can develop in the wrist as weight is gained during pregnancy or in someone who is obese. The enlargement of the tendons and ligaments restricts the space available for the nerves that reach to the finger and also for the muscle that connects to the base of the thumb. As a consequence, the ability of the nerve to properly transmit impulses to the muscles in the fingers and thumb is affected.

The initial symptoms of carpal tunnel syndrome tend to be felt at night because the hand is at rest. The symptoms can be a burning or a tingling numbness in the fingers, in particular the thumb, along with the index and middle fingers. As well, the reduced transmission of nerve impulses to the muscles decrease muscle strength. It can become difficult to grip an object or make a fist.

Thoracic outlet syndrome

In **thoracic outlet syndrome**, nerve compression can occur as a result of stresses on the neck and shoulders that cause these areas to impinge on local nerves. While the underlying cause of the syndrome is not clear, there seems to be an association between thoracic outlet syndrome and physical labor, in particular the repeated lifting of heavy objects onto the shoulders, causing the shoulders to pull back and down. Reaching for objects that are positioned above shoulder level can also be irritating to muscles in the shoulders and the upper arms. Swelling and inflammation of the muscles can compress nerves between the neck and shoulders.

The symptoms of thoracic outlet syndrome include weakness of the arms, pain, and numbness of the arms and fingers. In more extreme cases, the sense of touch and ability to sense temperature changes can be lost in the fingers.

Brachial plexus palsy

Palsy is a term meaning the inability to purposely move a body part. Brachial plexus palsy refers to paralysis that is associated with compression and tearing of a group of nerves called the brachial plexus. These nerves are a connection between the spinal cord and the nerves that run into the arms neck, and shoulders. The nerves can become compressed and even torn when the neck is stretched. This can occur in an infant born following a difficult delivery, which can occur if the baby is large, in a breech position, or if the period of labor is long. In these situations, the baby's neck can be abnormally flexed. The abnormal position damages the brachial plexus nerves.

The brachial plexus affects certain segments of the spinal cord. When viewed in a x ray, the spinal cord is reminiscent of Lego blocks stacked on each other. Each 'block' represents a segment. Typically, brachial nerves that originate from upper segments of the spinal column (segments C5 and C6) are affected. This condition is also called Erb's palsy. Less commonly, nerves associated with lower segments (C7 and T1) can be deranged. This condition is called Klumke's paralysis. In some cases, all the nerves of the brachial plexus can be affected.

The causes of nerve damage can also involve injuries to the shoulder, arm, and the collarbone (clavicle). The main symptom of brachial plexus palsy, paralysis in an arm, is evident immediately after birth. A newborn will lie with the affected arm by its side, with the elbow extended. While the other arm will be capable of a normal range of motion, the affected arm will be immobile.

Meralgia paresthetica

This painful condition is due to the pinching of the lateral femoral cutaneous nerve as the nerve exits the pelvis. The nerve can become pinched as the position of the pelvic region changes due to weight gain, injury, pregnancy, or extended periods of standing of walking (i.e., military marching). The affected nerve becomes compressed as it crosses a region of the pelvis called the iliac crest. As well, the nerve can be rubbed during the pelvic motions that occur with walking. This friction increases the nerve damage.

A person with meralgia paresthetica experiences an ache, numbness, tingling, or burning sensations in their thigh. The ache can be mild or severe, and generally eases during rest and returns with resumption of activity.

Cubital tunnel syndrome

This syndrome results from pressure that compresses the ulnar nerve. The ulnar nerve is one of the main nerves of the hand, which connects the muscles of the forearm and hand with the spinal cord. The nerve passes across the back of the elbow behind a bump called the medial epicondyle. The sensation that is described as the funny bone is actually the transient sensation that occurs when the ulnar nerve is compressed in a bump.

Cubital tunnel syndrome is a more protracted from of the nerve compression. It results from the stretching or pushing of the nerve against the medial epicondyle when the elbow is bent. The condition is aggravated over time by the bending of the elbow. Symptoms of cubital tunnel syndrome are typically a numb feeling in the ring finger and small finger, weakness in muscles of the hand and forearm, and elbow pain. Without intervention, more serious nerve damage can occur.

Diagnosis

Carpal tunnel syndrome is diagnosed based on the pattern of the symptoms, the location of the symptoms, and a history of repetitive activity that might predispose to the syndrome. Similarly, thoracic outlet syndrome is diagnosed by the location of the symptoms and a person's work history (i.e., a job involving a lot of lifting).

The diagnosis of brachial plexus palsy is prominently based on the visual observation of the motion difficulties experienced by the newborn. X rays may be taken to discount any other injuries such as fractures of the spine, clavicle (collarbone), humerus (the large bone in the upper arm), or a dislocation of the shoulder.

Meralgia paresthetica is diagnosed by the nature of the symptoms and the occupation of the person. For example, hip and thigh pain in a soldier can alert a clinician to the possibility of this malady. As well, people usually experience tenderness in a specific spot over a ligament in the hip, and symptoms can be made worse by extending the hip in the Nachlas test.

Diagnosis of meralgia paresthetica needs to rule out other maladies to the pelvis and spine, as well as diabetes mellitus. For example, damage to spinal discs will impair reflexes, while reflexes are normal in meralgia paresthetica.

Cubital tunnel syndrome is diagnosed by the type and location of the symptoms.

Key Terms

Palsy Paralysis or uncontrolled movement of controlled muscles.

Paresthesia Abnormal physical sensations such as numbness, burning, prickling, or tingling.

Treatment team

Treatment often involves the family physician, family members, and physical and occupational therapists. In severe cases, a surgeon may be consulted for many types of nerve compression.

Treatment

Carpal tunnel syndrome responds to immobilization of the affected area. Often, a person will wear a splint that keeps the wrist from flexing. This reduces the strain and pressure on the nerves. Another option is to administer anti-inflammatory drugs or injections of cortisone. These compounds help reduce the swelling in the wrist. In a small number of cases of carpal tunnel syndrome, surgery can be a useful option. The ligament that connects to the bottom of the wrist is cut.

Persons with thoracic outlet syndrome are put on a planned program of **exercise** therapy designed to relieve the inflammation. Avoiding the repetitive activities that caused the muscle inflammation, at least temporarily, is a must. Re-design of the workplace so that heavy objects do not have to be placed above shoulder level can be a wise strategy. Anti-inflammatory drugs may be prescribed. Finally, if these efforts have not produced a satisfactory response, surgery may be an option.

Treatment for brachial plexus palsy consists of physical therapy that relieves the strain on the affected nerves. The therapy usually involves a gentle range of motions and the use of electrical stimulation of the muscles that are associated with the damaged nerves. Keeping the muscles supple and strong is an important part of the treatment. When a nerve has been more seriously damaged, surgery may be necessary to repair the tear or other damage. This is usually evident within three months of birth. Surgery can involve the grafting of a new section of nerve to replace the damaged and now-defective region of the original nerve.

Treatment for meralgia paresthetica can involve relief of the stress on the pelvis through weight loss or modifying the activity that causes the stress. Treatment for cubital tunnel syndrome can involve the use of medications that reduce inflammation. These include non-steroidal anti-inflammatory medications such as aspirin and ibuprofen.

Some people gain relief by wearing a special brace while sleeping that prevents the elbow from bending.

Recovery and rehabilitation

Rehabilitation and recovery from carpal tunnel syndrome can be complete for some people. Avoiding the activity that inflamed the wrist can help ensure that the inflammation and nerve injury does not reoccur. Other people do recover, but more slowly. For others, the syndrome becomes a chronic concern.

Recovery from brachial plexus palsy ranges from limited to complete. Most recovery occurs by two years of age. The Erb's type of palsy is a milder form, and recovery can occur in three to four months. With the more serious Klumke's paralysis, 18–24 months of physical therapy can be required to achieve significant improvement.

Clinical trials

Rather than specific **clinical trials**, research is ongoing to try to better understand the triggers for the various nerve compression syndromes, and to find better and more efficient rehabilitation techniques. In the United States, organizations including the National Institute of Arthritis and Musculoskeletal and Skin Diseases fund such research.

Prognosis

For carpal tunnel syndrome, the outlook for many people is quite good. Once the inflammation has been dealt with, avoiding the cause of the irritation can prevent a reoccurrence of the trouble. However, for about 1% of those with carpal tunnel syndrome, permanent injury develops.

The prognosis for brachial plexus palsy varies upon the nature of the nerve damage. Some cases resolve quickly and completely without intervention, others require extended time and therapy, and in the worst-cases, impaired use of an arm can be permanent.

Meralgia paresthetica due to pregnancy, obesity, and diabetes may resolve completely when the condition is properly treated. Other mechanically-related causes of the malady can be less successfully treated. In the latter case, modification of life-style may be needed.

Most people with cubital tunnel syndrome respond well to conservative treatment, although surgery is necessary for some. For those resulting to surgery, permanent elbow numbness may result.

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ORGANIZATIONS

National Institute for Neurological Diseases and Stroke (NINDS). P.O. Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424. <http://www.ninds/nih.gov>.

National Chronic Pain Outreach Organization (NCPOA). P.O. Box 274, Millboro, VA 24460. (540) 862-9437; Fax: (540) 862-9485. ncpoa@cfw.org. <http://www.chronic-pain.org>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). 31 Centre Dr., Rm. 4Co2 MSC 2350, Bethesda, MD 20892-2350. (301) 496-8190 or (877) 226-4267. info@mail.nih.gov. <http://www.niams.nih.gov>.

American Chronic Pain Association (ACPA). P.O. Box 850, Rocklin, CA 95677-0850. (916) 632-0922 or (800) 533-3231; Fax: ACPA@pacbell.net. <http://www.theacpa.org>.

Brian Douglas Hoyle, PhD

Nerve conduction study

Definition

A nerve conduction study is a test that measures the movement of an impulse through a nerve after the deliberate stimulation of the nerve.

Purpose

The ability of a nerve to swiftly and properly transmit an impulse down its length, and to pass on the impulse to the adjacent nerve or to a connection muscle in which it is embedded, is vital to the performance of many activities in the body.

When proper functioning of nerves does not occur, as can happen due to accidents, infections, or progressive and genetically based diseases, the proper treatment depends on an understanding of the nature of the problem. The nerve conduction study is one tool that a clinician can use to assess nerve function. Often, the nerve conduction study is performed in concert with a test called an electromyogram. Together, these tests, along with other procedures that comprise what is known as electrodiagnostic testing,

provide vital information on the functioning of nerves and muscles.

Key Terms

Axon The long, slender part of a nerve cell that carries electrochemical signals to another nerve cell.

Electromyogram (EMG) Aa diagnostic used test to evaluate nerve and muscle function.

Nerve impulse The electrochemical signal carried by an axon from one neuron to another neuron.

Neuron A nerve cell.

Description

Nerve cells consist of a body, with branches at one end. The branches are called axons. The axons are positioned near an adjacent nerve or a muscle. Nerve impulses pass from the axons of one nerve to the next nerve or muscle. The impulse transmission speed can be reduced in damaged nerves.

Surrounding a nerve is a tough protective coat of a material called myelin. Nerve damage can involve damage or loss of myelin, damage to the nerve body, or damage to the axon region. The nerve conduction study, which was devised in the 1960s, can detect the loss of nerve function due to these injuries, and, from the nature of the nerve signal pattern that is produced, offer clues as to the nature of the problem.

Depending on the nature of the nerve damage, the pattern of signal transmission can be different. For example, in a normal nerve cell, sensors placed at either end of the cell will register the same signal pattern. But, in a nerve cell that is blocked somewhere along its length, these sensors will register different signal patterns. In another example, in a nerve cell in which transmission is not completely blocked, the signal pattern at the axon may be similar in shape, but reduced in intensity, to that of the originating signal, because not as much of the signal is completing the journey down the nerve cell.

Diseases of the nerve itself mainly affect the size of the responses (amplitudes); diseases of the myelin mainly affect the speed of the responses.

Nerve conduction studies are now routine, and can be done in virtually any hospital equipped with the appropriate machine and staffed with a qualified examiner. The nerve conduction study utilizes a computer, computer monitor, amplifier, loudspeaker, electrical stimulator, and filters. These filters are mathematical filters that can distinguish random, background electrical signals from the signal produced by an activated nerve. When the study is done, small electrodes are placed on the skin over the muscles being tested. Generally, these muscles are located in the arms or legs. Some of the electrodes are designed to record the electrical signal that passes by them. Other electrodes (reference electrodes) are designed to monitor the quality of the signals to make sure that the test is operating properly. If monitoring of the test is not done, then the results obtained are meaningless.

After the electrodes are in place, a small electrical current can be applied to the skin. The electrical stimulation is usually done at several points along the nerve, not just at a single point. This is done because conduction of an impulse through a nerve is not uniform. Some regions of a nerve conduct more slowly than other regions. By positioning the stimulating electrodes at several sites, a more accurate overall measurement of conduction velocity is obtained.

The electrical current activates nerves in the vicinity, including those associated with the particular muscle. The nerves are stimulated to produce a signal. This is known as the "firing" of the nerve. The nerve signal, which it also electric, can be detected by some of the electrodes and conveyed to the computer for analysis.

The analysis of the nerve signal involves the study of the movement of the signal through the nerve and from the nerve to the adjacent muscle. Using characteristics such as the speed of the impulse, and the shape, wavelength, and height of the signal wave, an examiner can assess whether the nerve is functional or defective.

Risks

A nerve conduction study can be done quite quickly. A person will experience some discomfort from the series of small electrical shocks that are felt. Otherwise, no damage or residual effects occur.

Normal results

Analysis of the results of a nerve conduction study

Under normal circumstances, the movement of the electrical impulse down the length of a nerve is very fast, on the order of 115–197 ft/sec (35–60 m/sec).

A number of aspects of the nerve impulse are measured in nerve conduction studies. The first aspect (or parameter) is known as latency. Latency is the time between the stimulus (the applied electrical current) and the response (the firing of the nerve). In damaged nerves, latency is typically increased.

Another parameter is known as the amplitude. Electrical signals are waves. The distance from the crest of one

wave to the bottom of the trough of the adjacent wave is the amplitude. Impulses in damaged nerves can have an abnormal amplitude, or may show different amplitudes in the undamaged and damaged sections of the same nerve.

The area under a wave can also vary if not all muscle fibers are being stimulated by a nerve or if the muscle fibers are not all reacting to a nerve impulse at the same time. The speed of a nerve impulse (the conduction velocity) can be also be determined and compared to data produced by a normally functioning nerve.

A number of other, more technically complex parameters can also be recorded and analyzed. A skilled examiner can tell from the appearance of the impulse waves on the computer monitor whether or not a nerve or muscle is functioning normally, and can even begin to gauge the nature of a problem. Examples of maladies that can be partially diagnosed using the nerve conduction study include **Guillain-Barré syndrome**, **amyotrophic lateral sclerosis** (ALS, or Lou Gehrig's disease, Charcot's disease), and **multifocal motor neuropathy**.

Conditions affecting the nerve conduction study

The nerve conduction study does not produce uniform results from person to person. Various factors affect the transmission of a nerve impulse and the detected signal.

Temperature affects the speed of impulse movement. Signals move more slowly at lower temperatures, due to the tighter packing of the molecules of the nerve. This variable can be minimized during the nerve conduction study by maintaining the skin temperature at 80–85° Fahrenheit (27–29° Celcius). Use of a controlled temperature also allows study runs done at different times to be more comparable, which can be very useful in evaluating whether muscle or nerve problems are worsening or getting better.

The speed of nerve impulse transmission changes as the body ages. In infants, the transmission speed is only about half that seen in adults. By age five, most people have attained the adult velocity. A gradual decline in conduction velocity begins as people reach their 20s, and continues for the remainder of life. Another factor that influences conduction velocity is the length of the nerve itself. An impulse that has to travel a longer distance will take longer. Some nerves are naturally longer than others. Measurement of nerve conduction takes into account the length of the target nerve.

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Brian Douglas Hoyle, PhD

Neurodegeneration with brain iron accumulation *see* **Pantothenate kinase-associated neurodegeneration**

Neurofibromatosis

Definition

Neurofibromatosis (NF) is a genetic condition in which fleshy tumors called neurofibromas grow throughout the body. Neurofibromatosis was first written up in the medical literature in 1882 by a German physician, Dr. Friedrich Daniel von Recklinghausen.

Description

Neurofibromas are tumors that are composed of the fibrous substance that covers nerve cells. These neurofibromas grow along the nerves in the body (the peripheral nerves), and cause skin and bone abnormalities. Furthermore, while neurofibromas initially start out as benign (non-cancerous) growths, 3–5% of all neurofibromas are converted into malignant (cancerous) tumors. Neurofibromatosis patients are also at risk of developing other types of cancerous tumors of the nervous system.

Neurofibromatosis is divided into two types, NF1 and NF2. NF1, also called Von Recklinghausen disease or peripheral neurofibromatosis, is the most common. Visible skin signs of NF1 tend to be present at birth, or certainly by about age 10. NF1 causes predominantly skin and bone changes, as well as problems due to the growing neurofibromas exerting damaging pressure on peripheral nerves. NF2, also called central neurofibromatosis or bilateral acoustic neurofibromatosis, is less common. Its predominant problem involves neurofibromas growing on the eighth cranial nerve (also known as the acoustic or auditory nerve). These tumors interfere with the functioning of the cranial nerve VIII, causing serious hearing impairment or even profound deafness, as well as a variety of symptoms due to pressure on adjacent nerves that serve the head and neck areas.

Demographics

NF1 occurs in one out of 4,000 births; NF2 occurs in one out of 40,000 births. Males and females are equally affected. In the United States, about 100,000 people are identified as having either NF1 or NF2.

Causes and symptoms

Neurofibromatosis is a genetic disease that is inherited in an autosomal dominant fashion, meaning that only one parent with neurofibromatosis is required to pass on the disease to offspring. Half of all cases of neurofibromatosis is inherited from a parent with the disorder; the other half of cases of neurofibromatosis does not have a history of the disease in a parent. They are considered to have developed the disease due to a spontaneous mutation, which can then be passed on to the patient's own offspring. When one parent has neurofibromatosis, each child has a 50% chance of inheriting the condition.

Neurofibromatosis 1

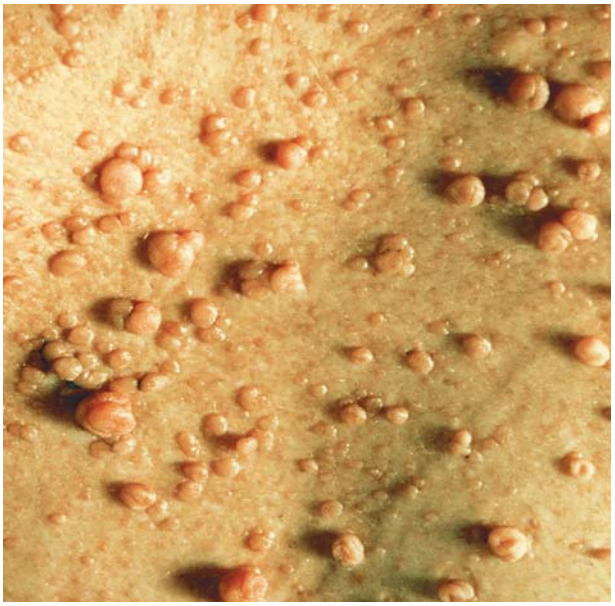
Patients with NF1 are most often diagnosed in childhood or even infancy. The most common characteristics of NF1 include:

- cafe-au-lait macules (light brown, flat skin patches)
- freckles in the armpit and groin areas (axillary and inguinal freckling)
- neurofibromas on and under the skin, ranging from millimeters to inches (centimeters) in size (an individual may have anywhere from several to thousands of these soft, rubbery, flesh-colored tumors)
- Lisch nodules, tumors within the iris of the eye
- vision problems, probably due to gliomas (tumors made of cells called glial cells that serve a supportive function within the **central nervous system**) located within or exerting pressure on the optic nerves
- learning problems or frank mental retardation
- scoliosis (side-to-side curvature of the spine)
- high blood pressure
- short adult height
- early (precocious) puberty
- increased risk of malignant brain and spinal cord tumors, kidney tumors (Wilms' tumor), adrenal tumors (pheochromocytoma), leukemia (cancer of blood cells), and tumors of the tendons, muscles, or connective tissue (rhabdomyosarcoma)

Neurofibromatosis 2

The most common characteristics of NF2 include:

- hearing problems due to neurofibromas in both acoustic nerves



Neurofibromatosis. Visible are large and small smooth, round, protruding growths scattered across a patient's back. *(Photograph by Michael English, M.D. Custom Medical Stock Photo. Reproduced by permission.)*

- cataracts, the abnormal clouding of the lens of the eye
- **headache**, **pain** or numbness in the face
- problems with balance and coordination when walking, resulting in unsteadiness
- ringing in the ears (tinnitus)
- cafe-au-lait macules (many fewer than in NF1)
- neurofibromas on and under the skin (many fewer than in NF1)

Diagnosis

NF1 is diagnosed when the patient has at least two of the following criteria:

- six or more cafe-au-lait macules that measure more than 0.2 in (5 mm) in children before puberty, or that measure more than 0.6 in (15 mm) in patients after puberty
- demonstration of two or more neurofibromas
- axillary or inguinal freckling
- presence of optic glioma
- presence of two or more Lisch nodules, diagnosed through slit-lamp examination (a slit-lamp is a microscope with an extremely strong light that can be focused into a slit in order to examine the eye)
- bone abnormalities such as defects of the skull bone (sphenoid wing) or abnormal thinning of the usually dense outer layer of the long thigh, leg, or arm bones

- a parent, sibling, or child who has been diagnosed with NF1

NF2 is diagnosed when the patient has at least one of the following criteria:

- gadolinium-enhanced **magnetic resonance imaging (MRI)** scan or other appropriate imaging study that demonstrates tumors of the two cranial nerves VIII
- a parent, sibling, or child who has been diagnosed with NF2, and has either a diagnosed tumor on one cranial nerve VIII or at least two of the following: neurofibroma, meningioma (tumor of the membrane that covers the spinal cord and brain [meninges]), glioma (tumor composed of the supportive cells called glial cells), schwannoma (tumor composed of the schwann cells that normally wrap around nerves throughout the body, creating a sheath that both insulates the nerves and allows nerve conduction to occur more quickly), or a specific type of cataract called a juvenile posterior subcapsular lenticular opacity

Treatment team

Treatment of neurofibromatosis requires a multidisciplinary team approach, with neurologists, ophthalmologists, otolaryngologists (ENTs), neurosurgeons, general surgeons, plastic surgeons, orthopedic surgeons, and dermatologists all collaborating. Depending on the kinds of challenges that the specific patient faces, other team members may include speech and language specialists, learning specialists, occupational therapists, and physical therapists.

Treatment

There is no known cure for either NF1 or NF2. Regular examinations are important in order to catch new developments early, such as the advent of high blood pressure, malignant transformation of a neurofibroma, or development of cataracts.

Treatment is purely supportive and depends on the specific manifestations of the disease in a given patient. For example, a patient with scoliosis may require bracing; patients with cataracts may require surgery; patients with auditory nerve tumors may require traditional scalpel surgery or gamma-knife surgery (also called stereotactic radiosurgery, this is a technique that allows a very focused, very high dose of **radiation** to be delivered to a carefully designated tissue location). Optic gliomas may be treated with radiation therapy. Any tumors that are impinging on nerves and causing symptoms or tumors that have undergone malignant transformation may require surgical removal, while tumors that are purely problematic from a cosmetic standpoint may be left alone.

Clinical trials

A variety of **clinical trials** are underway, including studies of several types of drugs such as drug R115777, tipifarnib, pirfenidone, and combination methotrexate/vinblastine therapy, each of which may be useful in shrinking tumors associated with neurofibromatosis. Information about these trials are available through the National Cancer Institute.

Prognosis

Even within the same family, the manifestations and severity of neurofibromatosis can differ widely.

Special concerns

Genetic counseling is crucial for families with a history of neurofibromatosis to help ascertain the risk of future offspring being born with neurofibromatosis.

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National Institute of Neurological Disorders and Stroke (NINDS). *Neurofibromatosis Fact Sheet.* (April 27, 2004). <http://www.ninds.nih.gov>.

ORGANIZATIONS

National Cancer Institute (NCI). 9000 Rockville Pike, Bethesda, MD 20892. gillesan@exchange.nih.gov or prpl@mail.cc.nih.gov.

The National Neurofibromatosis Foundation, Inc. 95 Pine Street, 16th Floor, New York, NY 10005. (212) 344-NNFF (6633) or (800) 323-7938. nnff@nf.org. <http://www.nf.org>.

Rosalyn Carson-DeWitt, MD

Neuroleptic malignant syndrome

Definition

Neuroleptic malignant syndrome is a rare, potentially life-threatening disorder that is usually precipitated by the use of medications that block the neurotransmitter called

Key Terms

Acoustic nerve The cranial nerve VIII, involved in both hearing and balance.

Axillary Referring to the armpit.

Cataracts Abnormal clouding or opacities within the lens of the eye.

Gamma-knife surgery A technique of focusing very intense radiation on an extremely well-defined area of abnormal tissue requiring treatment, thus allowing a very high dose of radiation to be used with less damage to neighboring, normal tissue.

Glial cell A type of cell in the nervous system that provides support for the nerve cells.

Glioma A tumor made up of abnormal glial cells.

Inguinal Referring to the groin area.

Iris In the eye, the colored ring that is located behind the cornea and in front of the lens.

Leukemia Cancer of a blood cell.

Lisch nodule A benign growth within the iris of the eye.

Macule A small, flat area of abnormal color on the skin.

Meninges The three-layered membranous covering of the brain and spinal cord.

Meningioma A tumor made up of cells of the lining of the brain and spinal cord (meninges).

Neurofibromas Soft, rubbery, flesh-colored tumors made up of the fibrous substance that covers peripheral nerves.

Pheochromocytoma A tumor of the adrenal glands that causes high blood pressure.

Posterior subcapsular lenticular opacity A type of cataract in the eye.

Rhabdomyosarcoma A tumor of the tendons, muscles, or connective tissue.

Schwann cell Cells that cover the nerve fibers in the body, providing both insulation and increasing the speed of nerve conduction.

Scoliosis Side-to-side curvature of the spine.

Sphenoid A bone of the skull.

Tinnitus The abnormal sensation of hearing a ringing or buzzing noise.

Wilms' tumor A childhood tumor of the kidneys.

dopamine. Most often, the drugs involved are those that treat psychosis, called neuroleptic medications. The syndrome results in dysfunction of the autonomic nervous system, the branch of the nervous system responsible for regulating such involuntary actions as heart rate, blood pressure, digestion, and sweating. Muscle tone, body temperature, and consciousness are also severely affected.

Description

Most cases of neuroleptic malignant syndrome develop between four to 14 days of the initiation of a new drug or an increase in dose. However, the syndrome can begin as soon as hours after the first dose or as long as years after medication initiation.

A variety of factors may increase an individual's risk of developing this condition, including:

- high environmental temperatures
- dehydration
- agitation or catatonia in a patient
- high initial dose or rapid dose increase of neuroleptic, and use of high-potency or intramuscular, long-acting (depot) preparations
- simultaneous use of more than one causative agent
- sudden discontinuation of medications for **Parkinson's disease**
- past history of organic brain syndromes, **depression**, or bipolar disorder
- past episode of neuromuscular malignant syndrome (risk of recurrence may be as high as 30%)

Because of heightened awareness of this syndrome and improved monitoring for its development, mortality rates have dropped from 20–30% down to 5–11.6%.

Demographics

Neuroleptic malignant syndrome is thought to affect about 0.02–12.2% of all patients using neuroleptic medications. Because more men than women take neuroleptic medications, the male-to-female ratio is about 2:1.

Causes and symptoms

Neuroleptic malignant syndrome occurs due to interference with dopamine activity in the **central nervous system**, either by depletion of available reserves of dopamine or by blockade of receptors that dopamine usually stimulates.

Neuroleptic malignant syndrome most commonly affects patients who are using neuroleptic or antipsychotic medications, including prochlorperazine (Compazine), promethazine (Phenergan), olanzapine (Zyprexa), clozapine (Clozaril), and risperidone (Risperdal). Other medications that block dopamine may also precipitate the syndrome, including metoclopramide (Reglan), amoxapine (Ascendin), and lithium. Too-fast withdrawal of drugs used to treat Parkinson's disease (levodopa, bromocriptine, and **amantadine**) can also precipitate neuroleptic malignant syndrome.

Symptoms of the disorder include:

- extremely high body temperature (hyperthermia), ranging from 38.6° to 42.3° C or 101° to 108° F
- heavy sweating
- fast heart rate (tachydardia)
- fast respiratory rate (tachypnea)
- rapidly fluctuating blood pressure
- impaired consciousness
- tremor
- rigid, stiff muscles (termed "lead pipe rigidity")
- catatonia (a fixed stuporous state)

Without relatively immediate, aggressive treatment, coma and complete respiratory and cardiovascular collapse will take place, followed by death.

Diagnosis

Diagnosis requires a high level of suspicion when characteristic symptoms appear in a patient treated with agents known to cause neuroleptic malignant syndrome.

The usual diagnostic criteria for neuroleptic malignant syndrome includes the presence of hyperthermia (temperature over 38° C or 101° F) with no other assignable cause, muscle rigidity, and at least five of the following signs or symptoms: impaired mental status, tremor, fast heart rate, fast respiratory rate, loss of bladder or bowel control, fluctuating blood pressure, metabolic acidosis, fluctuating blood pressure, excess blood acidity (metabolic acidosis), increased blood levels of creatanine phosphokinase (normally found in muscles and released into the bloodstream due to muscle damage), heavy sweating, drooling, or increased white blood cell count (leukocytosis).

Treatment team

Neuroleptic malignant syndrome usually requires treatment in an intensive care unit, with appropriate specialists, including intensivists, pulmonologists, cardiologists, psychiatrists.

Treatment

Treatment must be aggressive. Supportive treatment should include hydration with fluids, cooling, and supplemental oxygen. Causative medications should be immediately discontinued, and medications that restore dopamine levels (bromocriptine, amantadine) administered. Dantrolene can be given to more quickly resolve muscle rigidity and hyperthermia. **Benzodiazepines**, such as lorazepam, may help agitated patients, and may also help relax rigid muscles. Benzodiazepines may also aid in the reversal of catatonia. In severe or intractable cases of catatonia or psychosis that remains after other symptoms of neuroleptic malignant syndrome have resolved, electroconvulsive therapy may be required.

Prognosis

With quick identification of the syndrome and immediate supportive treatment, the majority of patients recover fully, although mortality rates are still significant. Signs that may warn of a poor prognosis include temperature over 104° F and kidney failure. In patients whose syndrome was precipitated by the use of oral medications, symptoms may last for seven to 10 days. In patients whose syndrome was precipitated by the use of long-acting, intramuscular preparation, symptoms may continue as long as 21 days.

Special concerns

Patients with a history of neuroleptic malignant syndrome are also at increased risk for a similar malignant hyperthermia syndrome that is precipitated by the administration of surgical anesthetics.

Resources

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Key Terms

Key Terms

Autonomic nervous system The divisions of the nervous system that control involuntary functions, such as breathing, heart rate, blood pressure, digestion, glands, smooth muscle.

Bipolar disorder A psychiatric illness characterized by both recurrent depression and recurrent mania (abnormally high energy, agitation, irritability).

Catatonia A fixed, motionless stupor.

Creatanine phosphokinase A chemical normally found in the muscle fibers, and released into the bloodstream when the muscles undergo damage and breakdown.

Depot A type of drug preparation and administration that involves the slow, gradual release from an area of the body where the drug has been injected.

Depression A psychiatric disorder in which the mood is low for a prolonged period of time, and feelings of hopelessness and inadequacy interfere with normal functioning.

Dopamine A brain neurotransmitter involved in movement.

Hyperthermia Elevated body temperature.

Leukocytosis An elevated white blood cell count.

Metabolic acidosis Overly acidic condition of the blood.

Neuroleptic Referring to a type of drug used to treat psychosis.

Neurotransmitter A chemical that transmits information in the nervous system.

Organic brain syndrome A brain disorder that is caused by defective structure or abnormal functioning of the brain.

Parkinson's disease A disease caused by deficient dopamine in the brain, and resulting in a progressively severe movement disorder (tremor, weakness, difficulty walking, muscle rigidity, fixed facial expression).

Receptor An area on the cell membrane where a specific chemical can bind, in order to either activate or inhibit certain cellular functions.

Tachycardia Elevated heart rate.

Tachypnea Elevated breathing rate.

ORGANIZATIONS

Neuroleptic Malignant Syndrome Information Service. PO Box 1069 11 East State Street, Sherburne, NY 13460. (607) 674-7920 or (888) 667-8367; Fax: (607) 674-7910. gillesan@exchange.nih.gov or info@nmsis.org. <http://www.nmsis.org/index.shtml>.

Rosalyn Carson-DeWitt, MD

Neurologist

Definition

A neurologist is a physician who has undergone additional training to diagnose and treat disorders of the nervous system.

Description

The training a neurologist receives enables the individual to recognize nervous system malfunctions, to accurately diagnose the nature of the dysfunction (such as disease or injury), and to treat the malady. While many people associate a neurologist with treating brain injuries, this is just one facet of a neurologist's responsibility and expertise. Diseases of the spinal cord, nerves, and muscles that affect the operation of the nervous system can also be addressed by a neurologist.

The training that is necessary to become a neurologist begins with the traditional medical background. From there, the medical doctor trains for several more years to acquire expertise in the structure, functioning, and repair of the body's neurological structures, including the area of the brain called the cerebral cortex, and how the various regions of the cortex contribute to the normal and abnormal functioning of the body.

Typically, a neurologist's educational path begins with premed studies at a university or college. These studies can last up to four years. Successful candidates enter medical school. Another four years of study is required for a degree as a doctor of medicine (MD). Following completion of the advanced degree, a one-year internship is usually undertaken in internal medicine; sometimes, internships in transitional programs that include pediatrics

and emergency-room training are chosen. Finally, another training period of at least three years follows in a neurology residency program. The latter program provides specialty experience in a hospital and can include research. Postdoctoral fellowships lasting one year or more offer additional opportunities for further specialization.

After completion of the more than decade-long training, medical doctors can become certified as neurologists through the American Board of Psychiatry and Neurology. Those with an osteopathy background can be certified through the American Board of Osteopathic Neurologists and Psychiatrists. Most neurologists belong to professional organizations such as the American Academy of Neurology (AAN), which is dedicated to setting practice standards, supporting research, providing continuing education, and promoting optimum care for persons with neurological disorders. Numerous professional publications specialize in neurology, including *Neurology Today*, *Neurology*, *Brain*, and *Archives of Neurology*.

A neurologist can sometimes be a patient's principle physician. This is true when the patient has a neurological problem such as **Parkinson's** or **Alzheimer's disease** or **multiple sclerosis**. As well, an important aspect of a neurologist's daily duties is to offer advice to other physicians on how to treat neurological problems. A family physician might consult a neurologist when caring for patients with **stroke** or severe **headache**.

When a neurologist examines a patient, details such as vision, physical strength and coordination, reflexes, and sensations like touch and smell are probed to help determine if the medical problem is related to nervous system damage. More tests might be done to help determine the exact cause of the problem and how to treat the condition. While neurologists can recommend surgery, they do not actually perform the surgery. That is the domain of the neurosurgeon.

One well-known neurologist is the English-born physician and writer Oliver Sacks (1933–). In addition to maintaining a clinical practice, Sacks has authored numerous popular books that describe patients' experiences with neurological disorders and neurologists' experiences in treating them. Another notable neurologist was Alois Alzheimer (1864–1915). A German neurologist, he first observed and identified the symptoms of what is now known as Alzheimer's disease.

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ORGANIZATIONS

American Board of Psychiatry and Neurology, Inc. 500 Lake Cook Road, Suite 335, Deerfield, IL 60015-5249. (847) 945-7900 or (800) 373-1166; Fax: (847) 945-1146. <http://www.abpn.com>.

American Academy of Neurology. 1080 Montreal Avenue, Saint Paul, MN 55116. (651) 695-2717 or (800) 879-1960; Fax: (651) 695-2791. memberservices@aan.com. <http://www.aan.com>.

Brian Douglas Hoyle, PhD

Neuromuscular blockers

Definition

Neuromuscular blocking agents are a class of drugs primarily indicated for use as an adjunct to anesthesia. Neuromuscular blocking drugs relax skeletal muscles and induce paralysis.

Purpose

Neuromuscular blockers are indicated for a wide variety of uses in a hospital setting, from surgery to trauma care. In surgery, they are used to prepare patients for intubation before being placed on a ventilator and to suppress the patient's spontaneous breathing once on a ventilator.

Description

Neuromuscular blockers relax skeletal muscle tone by blocking transmission of key **neurotransmitters** through the neuron receptors at the neuromuscular junction (NMJ). They are divided into two major categories, depolarizing and non-depolarizing neuromuscular blockers, corresponding to the manner in which they exert their therapeutic effect. Depolarizing neuromuscular blocking agents mimic the effects of the neurotransmitter acetylcholine (ACh) and change the interaction between ACh and neuron receptors. Blockade occurs because membranes surrounding the neuromuscular junction become unresponsive to typical ACh-receptor interaction. Non-depolarizing neuromuscular blockers bind to receptors to prevent transmission of impulses through ACh neurotransmitters.

Neuromuscular blockers are primarily used in a clinical or hospital setting. In the United States, they are

known by several generic and brand names, including atracurium (Tracurium), cisatracurium (Nimbex), doxacurium (Neuromax), mivacurium (Mivacron), pancuronium (Pavulon), pipecuronium (Arduan), rocuronium (Zemeron), succinylcholine (Anectine), tubocurarine, and vecuronium (Norcuron).

A physician will decide which neuromuscular blocking agent, or combination of neuromuscular blocker and other type of anesthesia, is appropriate for an individual patient. During surgical anesthesia, neuromuscular blockers are administered after the induction of unconsciousness, in order to avoid patient distress at the inability to purposefully move muscles. Neuromuscular blockers can be used on pediatric patients.

Recommended dosage

Neuromuscular blocking agents are most often administered though an intravenous (IV) infusion tube. Typically, the time in which the medicines begin to exert their effects and duration of action are more predictable when neuromuscular blocking agents are administered via IV. Dosages vary depending on the neuromuscular blocking agent used and the duration of action desired. The age, weight, and general health of an individual patient can also affect dosing requirements.

Depolarizing and non-depolarizing agents are grouped together into three categories based on the time in which they begin to exert their anesthetic effects, causing muscle relaxation or paralysis and desensitization, and the duration of those effects (duration of action). Short-acting neuromuscular blockers begin to work within 30 seconds to two-and-a-half minutes and have a typical duration of action ranging from five to twenty minutes. Short-acting agents include mivacurium, rocuronium, and succinylcholine. Intermediate-acting agents exert their effects within two to five minutes and typically last for twenty to sixty minutes. Atracurium, cisatracurium, pancuronium, and vecuronium are intermediate-acting neuromuscular blockers. Long-acting neuromuscular blocking agents take effect within two-and-a-half to six minutes and last as long as 75–100 minutes. Doxacurium, pipecuronium, and tubocurarine are long-acting neuromuscular blocking agents.

The duration of action of any neuromuscular blocking agent can be prolonged by administering smaller supplemental (maintenance) doses via IV following the initial blockade-creating dose.

Precautions

Each neuromuscular blocking agent has its own particular precautions, contraindications, and side effects. However, many are common to all neuromuscular blockers. Neuromuscular blocking agents may not be suitable for persons with a history of lung diseases, **stroke**, increased intracranial pressure, increased intraocular (within the eye) pressure as in glaucoma, liver or kidney disease, decreased renal function, diseases or disorders affecting the muscles, angina (chest **pain**), and irregular heartbeats and other heart problems. Neuromuscular blockers are not typically used on patients with recent, severe burns, elevated potassium levels, or severe muscle trauma. There is an increased risk of seizure in patients with seizure disorders such as **epilepsy**.

Neuromuscular blockers can be administered to patients who have suffered a **spinal cord injury** resulting in paraplegia (paralysis) immediately following the injury. But further use of neuromuscular blockers is typically avoided 10–100 days after the initial trauma.

Patients who are obese or have increased plasma cholinesterase activity may exhibit increased resistance to neuromuscular blocking agents. Some **cholinergic stimulants** that act as **cholinesterase inhibitors**, including medications used in the treatment of **Alzheimer's disease**, may enhance neuromuscular blockade and prolong the duration of action of neuromuscular blockers.

With careful supervision, neuromuscular blocking agents can be used in pediatric patients. However, rare but serious complications such as bradycardia (decreased heart rate) are more likely to develop in children than in adults.

Placental transfer (passing of the medication to the fetus) of neuromuscular blocking agents is minimal. Histamine release is associated with neuromuscular blocking agents tubocurare and succinylcholine. Complications such as bronchospasm, decreased blood pressure, and blood clotting problems could arise in patients especially sensitive or susceptible to changes in histamine levels.

Side effects

In some patients, neuromuscular blockers may produce mild or moderate side effects. Anesthesiologists (specialists in administering anesthesia and treating pain) may notice a slight red flushing of the face as neuromuscular blockers are administered to the patient. After completion of the surgical procedure, **headache**, nausea, muscle soreness, and muscle weakness are the most frequently reported side effects attributed to neuromuscular blockers. Most of these side effects disappear or occur less frequently after a few hours or days.

With depolarizing neuromuscular blocking agents, fasciculations (involuntary muscle contractions) may occur before the onset of muscle relaxation or paralysis. Some patients report generalized muscle soreness or pain after taking a neuromuscular blocking agent that causes fasciculations. Women and middle-aged patients reported this side effect more frequently.

Key Terms

Acetylcholine The neurotransmitter, or chemical that works in the brain to transmit nerve signals, involved in regulating muscles, memory, mood, and sleep.

Fasciculations Fine tremors of the muscles.

Neuromuscular junction The junction between a nerve fiber and the muscle it supplies.

Neurotransmitter Chemicals that allow the movement of information from one neuron across the gap between the adjacent neuron.

Other, uncommon side effects or complications associated with neuromuscular blockers can be serious or may indicate an allergic reaction. As neuromuscular blockers are most frequently used in trauma, surgical, and intensive hospital care, physicians may be able to counteract the following side effects or complications as they occur:

- bradycardia
- cessation of breathing
- severe bronchospasm
- prolonged numbness in the extremities
- extended paralysis
- jaw rigidity
- skeletal muscle atrophy or trauma
- impaired blood clotting
- severe decrease in blood pressure
- chest pain or irregular heartbeat

Interactions

Neuromuscular blocking agents may have negative interactions with some anticoagulants, **anticonvulsants** (especially those also indicated for use as skeletal muscle relaxants), antihistamines, antidepressants, antibiotics, pain killers (including non-prescription medications) and monoamine oxidase inhibitors (MAOIs).

Cholinergic stimulants, some insecticides, diuretics (furosemide), local anesthetics, magnesium, antidepressants, anticonvulsants, aminoglycoside antibiotics, high estrogen levels, and metoclopramide (Reglan) may affect the duration of action of neuromuscular blocking agents.

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Adrienne Wilmoth Lerner

Neuromyelitis optica *see* **Devic syndrome**

Neuronal ceroid lipofuscinosis *see* **Batten disease**

Neuronal migration disorders

Definition

Neuronal migration disorders are a diverse group of congenital brain abnormalities that arise specifically from defective formation of the **central nervous system**. During early brain development, neurons are born and move over large distances to reach their targets and thereby give rise to the different parts of the brain. The control of this process is highly orchestrated and dependent on the expression of various environmental and genetic factors that continue to be discovered in genetic studies of mice and humans. The critical role neuronal migration plays in brain development is evident from the variety of gross malformations that can occur when it goes wrong. Defective neuronal migration leads to a broad range of clinical syndromes, and most affected patients will have a combination of **mental retardation** and **epilepsy**.

Description

Neuronal migration disorders include **lissencephaly** as part of the agyria-pachygyria-band spectrum, cobblestone lissencephaly, periventricular heterotopia, and other variants such as Zellweger and Kallman syndrome. Patients may have only focal collections of abnormally located neurons known as heterotopias. The common factor in these disorders is a defect in neuronal migration, a key process in brain development that occurs during weeks 12 to 16 of gestation. Some disorders such as polymicrogyria and **schizencephaly** are presumably due to abnormal neuronal migration due to studies showing heterotopias in other parts of the brain, but the exact relationship is unclear. Early in brain development, neurons are born in specific locations in the brain and migrate to their final destinations to create distinct brain regions. Each step of this process, from starting, continuing, and stopping migration, is controlled by distinct molecular mechanisms that are regulated by the activity of genes. Defects in these

genes lead to the various presentations of neuronal migration disorders seen in clinical practice.

Lissencephaly

Lissencephaly is the most extreme example of defective neuronal migration. In lissencephaly or agyria, neuronal migration fails globally, causing the brain to appear completely smooth and have abnormal layering in the cortex. Various genes have been associated with varying levels of severity of lissencephaly giving rise to a spectrum of disorders ranging from classical lissencephaly to milder forms such as double cortex syndrome or pachygyria. Classical or type I lissencephaly differs from type II or cobblestone lissencephaly. In cobblestone lissencephaly, the defect is presumably an overmigration of neurons past their targets, giving rise to the abnormally bumpy surface.

Periventricular heterotopia

Periventricular heterotopia is a disorder where neurons fail to begin the process of migration. Neurons are generated near the ventricular zone but do not start the process of migration to their destinations. Instead, they are stuck and collect around the ventricles, giving rise to the distinct appearance on brain imaging.

Other neuronal migration disorders

Zellweger syndrome is a disorder of neuronal migration that may consist of abnormally large folds (pachygyria) and heterotopias spread throughout the brain. It is thought to be due to a defect in peroxisome metabolism, a pathway by which cells break down waste products. The relationship between this metabolic defect and neuronal migration is unclear at this time. Kallman syndrome is a disorder where cells fail to migrate to the portion of the brain controlling smell as well as the hypothalamus, a region that controls hormone secretion. The mechanism underlying this disease is unclear.

Schizencephaly is grouped as a neuronal migration disorder although the exact etiology is unknown. Schizencephaly is an example of abnormal neuronal migration that may occur locally rather than globally. In schizencephaly, an early insult to the brain in the form of an infection, **stroke**, or genetic defect leads to abnormal migration of neurons in a portion of the brain and subsequent lack of developed brain tissue, giving rise to the characteristic brain clefts that define this syndrome. Schizencephaly may show a wide range of presentations, with bilateral clefts that vary in size and extent of involvement.

Polymicrogyria refers to an abnormal amount of small convolutions (gyri) in affected areas of the cerebral cortex and is believed to be a neuronal migration disorder, although the exact etiology is unknown.

Demographics

Neuronal migration disorders are rare overall, but the exact incidence is unknown. Patients may have very mild degrees of the different disorders and may not be diagnosed if they do not manifest symptoms, making the actual incidence difficult to determine.

Causes and symptoms

The majority of neuronal migration disorders seen in clinical practice are thought to be genetic in cause. Much of what is known about neuronal migration disorders to date has been discovered from intense research identifying the genes affected in individuals with these diseases. The widespread abnormal expression of defective genes leads to the global nature of the disorders, contrary to acquired developmental brain insults, which lead to more localized defects. Several genes have been implicated in causing the various disorders, and they continue to be identified. The most well characterized genes include DCX on the X chromosome, responsible for double cortex syndrome, and LIS1 on chromosome 17, the first gene identified for lissencephaly. Cobblestone lissencephaly is associated with abnormalities in fukutin, a gene responsible for Fukuyama **muscular dystrophy**, a syndrome consisting of muscle weakness and cobblestone lissencephaly. Periventricular heterotopia is associated with abnormalities of the filamin1 gene on the X chromosome. DCX, LIS1, and filamin1 are genes responsible for controlling the mechanics of cell movement during neuronal migration. Schizencephaly has been associated with abnormalities in EMX2, a transcription factor gene whose role in neuronal migration is as yet unidentified. Neuronal migration disorders can also be associated with early insults to the brain from infections or damage from stroke.

Most neuronal migration disorders present with some combination of epilepsy, mental retardation, and abnormalities in head size, known as **microcephaly**. Some patients, such as those with small heterotopias, may have no symptoms at all since the severity of the defect is very mild. Patients may also have **cerebral palsy** or abnormalities in muscle tone. Depending on the severity of the malformation, the level of mental retardation may vary from mild to severe. Patients with lissencephaly are usually severely delayed, have failure to thrive, and are microcephalic. They may also have accompanying eye problems. Patients with double cortex syndrome or schizencephaly may have milder symptoms and may only present with **seizures**. Schizencephaly may have associated complications of increased fluid pressure in the brain, known as **hydrocephalus**. Periventricular heterotopia and polymicrogyria may present with only seizures. Some neuronal migration disorders such as lissencephaly may be

part of a larger syndrome affecting other body parts such as the muscle, eyes, or face.

Diagnosis

Diagnosis is usually made by neuroimaging. **CT scan** or **MRI** of the brain will show the characteristic abnormality. MRI has better resolution and may detect polymicrogyria or small heterotopias more easily than CT. Genetic testing is available for patients with lissencephaly to identify whether the DCX or LIS1 gene is defective. Knowledge of the genes affected allows for counseling and family planning. Laboratory tests are not useful in diagnosis.

Treatment team

Management of neuronal migration disorders involves a pediatrician, pediatric **neurologist** and physical therapists. With symptoms of later onset, an adult neurologist may be involved in treating symptoms of seizures. Rehabilitation specialists may help in prescribing medications for cerebral palsy or increased muscle tone. A case manager may be involved in coordinating care and resources.

Treatment

There are no known cures for the various neuronal migration disorders at this time. The majority of treatments are directed towards symptoms caused by the malformed brain. Seizures may be treated with anticonvulsant medications. Refractory seizures may respond to neurosurgical removal of abnormal brain tissue. Neurosurgery may be required to relieve hydrocephalus, by placement of a shunt. Increased muscle tone may respond to injections of **botulinum toxin** or muscle relaxants. Patients may require feeding through a tube due to inability to swallow normally.

Recovery and rehabilitation

Due to the congenital nature of neuronal migration disorders, most patients do not recover from their symptoms. The course of disease tends to be static. Physical and occupational therapists may help treat symptoms of weakness or increased tone that limit mobility and daily hand use.

Clinical trials

A clinical trial is currently under way and is funded by the National Institutes of Health to identify genes responsible for neuronal migration disorders such as lissencephaly and schizencephaly. For contact information for the Walsh Lab Site, see Resources below.

Prognosis

There is no known cure for any of the neuronal migration disorders. Due to the congenital nature of the diseases, the symptoms tend to be static and do not improve. The prognosis varies for each individual depending on the extent of the defect and the accompanying neurologic deficits. Most individuals with severe malformations such as classical lissencephaly or bilateral schizencephaly will die at an early age due to failure to thrive or infections such as pneumonia. Their cognitive development stays at the three month level. Patients with milder forms such as unilateral schizencephaly, periventricular heterotopia, or subcortical band heterotopia may have mild mental retardation and seizures only and live a normal life span.

Special concerns

Educational and Social Needs

Due to developmental disability, children with neuronal migration disorders who survive beyond the age of two may benefit from special education programs. Various state and federal programs are available to help individuals and their families with meeting these needs.

Resources

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ORGANIZATIONS

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605. (914) 428-7100 or

(888) 663-4637; Fax: (914) 428-8203. askus@marchofdimes.com. <http://www.marchofdimes.com>.

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Key Terms

Biopsy The surgical removal and microscopic examination of living tissue for diagnostic purposes or to follow the course of a disease. Most commonly the term refers to the collection and analysis of tissue from a suspected tumor to establish malignancy.

Histology The study of tissue structure.

Neuropathologist

Definition

A pathologist is a medical doctor who is specialized in the study and diagnosis of the changes that are produced in the body by various diseases. A neuropathologist is a specialized pathologist who is concerned with diseases of the **central nervous system** (the brain and spinal cord). Often a neuropathologist is concerned with the diagnosis of brain tumors.

A neuropathologist is also an expert in the various aspects of diseases of the nervous system and skeletal muscles. This range of disease includes degenerative diseases, infections, metabolic disorders, immunologic disorders, disorders of blood vessels, and physical injury. A neuropathologist functions as the primary consultant to neurologists and neurosurgeons.

Description

A neuropathologist is a medical doctor who has pursued specialized training. Aspects of this training include neurology, anatomy, cell biology, and biochemistry. Typically, a patient will not see a neuropathologist. Rather, the specialist works in the background, in the setting of the laboratory, to assist in the patient's diagnosis. In the path that leads to the diagnosis of a tumor, disease, or other malady, a neuropathologist typically becomes involved at the request of a **neurologist**. It is the neurologist who suspects a problem or seeks to confirm the presence of a tumor, based on tests such as **magnetic resonance imaging (MRI)** or a computed assisted tomography (CAT) scan. The neurologist can obtain some of the tissue of concern in a procedure known as a **biopsy**, as well as obtaining fluid or cell samples.

It is this material that is sent to the pathology lab where the neuropathologist seeks to identify the nature of the problem. The diagnosis of brain and spinal cord related damage often involves a visual look at the samples using the extremely high magnification of the electron microscope. The neuropathologist can assess from the appearance of the sample whether the sample is unaffected or damaged. For example, in brain tissue obtained from a patient with suspected **Alzheimer disease**, the neuropathologist will look for evidence of the presence of amyloid plaques, which are caused by abnormal folding of protein. As well, the neuropathologist will look for other diagnostic signs that support or do not support the suspected malady.

In the case of a tumor, part of a neuropathologist's responsibility is to identify the tumor and grade it as malignant or benign. This is no small task, as there are literally hundreds of different types of tumors. The correct identification greatly aids the subsequent treatment process and the patient's prognosis.

The neuropathological analysis of a tumor is concerned mainly with two areas. The first is the origin of the tumor in the brain. Determining the tumor's origin aids in naming the tumor. Secondly, the neuropathologist determines if the tumor displays signs of rapid growth. The speed of growth of the tumor can be quantified as a grade. A result such as "grade three astrocytoma" is very informative to the neurologist. Even if the neuropathologist determines that a brain or spinal cord tumor is benign, the location of the tumor may still pose serious health risks, and this important determination is also usually made by the neuropathologist.

Another important tool that a neuropathologist uses to examine tissue samples is histology. The treatment of a thin section of a sample with specific compounds that will bind to and highlight (stain) regions of interest in the specimen allows the neuropathologist to determine if the stained regions are normal or abnormal in character. The histological stains can be applied to a section that has been sliced from the sample at room temperature or at a very low temperature. The use of frozen sections can help preserve structural detail in the specimen that might otherwise be changed at a higher temperature.

The assessment of a stained specimen by the neuropathologist is typically done by examining the material using a light microscope. This type of microscope does not magnify the specimen nearly as much as does the electron microscope. But such high-power magnification is not necessary to detect the cellular changes in the stained specimen. By carefully selecting the stain regimen, a

skilled neuropathologist can reveal much detail about a specimen. Histological examinations can also be done much more quickly and easily than electron microscopic examinations. Saving time can be important in diagnosis and treatment, especially when dealing with brain tumors.

Finally, one of the consultative duties of a neuropathologist can also include legal testimony. Their expert knowledge can be useful in court cases in which the mental state or functional ability of a person is an important consideration.

Resources

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American Association of Neuropathologists (AANP). 2085 Adelbert Rd., Cleveland, OH 44106. (216) 368–2488; Fax: (216) 368–8964. aanp@cwru.edu. <http://www.aanp-jnen.com>.

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Neuropathy, hereditary *see* **Charcot-Marie-Tooth disorder**

Neuropsychological testing

Definition

Clinical neuropsychology is a field with historical origins in both psychology and neurology. The primary activity of neuropsychologists is assessment of brain functioning through structured and systematic behavioral observation. Neuropsychological tests are designed to examine a variety of cognitive abilities, including speed of information processing, attention, memory, language, and executive functions, which are necessary for goal-directed behavior. By testing a range of cognitive abilities and examining patterns of performance in different cognitive areas, neuropsychologists can make inferences about underlying brain function. Neuropsychological testing is an important component of the assessment and treatment of **traumatic brain injury**, **dementia**, neurological conditions, and psychiatric disorders. Neuropsychological testing is also an important tool for examining the effects of toxic substances and medical conditions on brain functioning.

Description

As early as the seventeenth century, scientists theorized about associations between regions of the brain and specific functions. The French philosopher Descartes believed the human soul could be localized to a specific brain structure, the pineal gland. In the eighteenth century, Franz Gall advocated the theory that specific mental qualities such as spirituality or aggression were governed by discrete parts of the brain. In contrast, Pierre Flourens contended that the brain was an integrated system that governed cognitive functioning in a holistic manner. Later discoveries indicated that brain function is both localized and integrated. Paul Broca and Karl Wernicke furthered understanding of localization and integration of function when they reported the loss of language abilities in patients with lesions to two regions in the left hemisphere of the brain.

The modern field of neuropsychology emerged in the twentieth century, combining theories based on anatomical observations of neurology with the techniques of psychology, including objective observation of behavior and the use of statistical analysis to differentiate functional abilities and define impairment. The famous Soviet **neuropsychologist** Alexander Luria played a major role in defining neuropsychology as it is practiced today. Luria formulated two principle goals of neuropsychology: to localize brain lesions and analyze psychological activities arising from brain function through behavioral observation. American neuropsychologist Ralph Reitan emphasized the importance of using standardized psychometric tests to guide systematic observations of brain-behavior relationships.

Before the introduction of neuroimaging techniques like the computed tomography (CAT or **CT**) scan and **magnetic resonance imaging (MRI)**, the primary focus of neuropsychology was diagnosis. Since clinicians lacked non-surgical methods for directly observing brain lesions or structural abnormalities in living patients, neuropsychological testing was the only way to determine which part of the brain was affected in a given patient. Neuropsychological tests can identify syndromes associated with problems in a particular area of the brain. For instance, a patient who performs well on tests of attention, memory, and language, but poorly on tests that require visual spatial skills such as copying a complex geometric figure or making designs with colored blocks, may have dysfunction in the right parietal lobe, the region of the brain involved in complex processing of visual information. When a patient complains of problems with verbal communication after a **stroke**, separate tests that examine

Key Terms

Abstraction Ability to think about concepts or ideas separate from specific examples.

Battery A number of separate items (such as tests) used together. In psychology, a group or series of tests given with a common purpose, such as personality assessment or measurement of intelligence.

Executive functions A set of cognitive abilities that control and regulate other abilities and behaviors. Necessary for goal-directed behavior, they include the ability to initiate and stop actions, to monitor and change behavior as needed, and to plan future behavior when faced with novel tasks and situations.

Hemisphere One side of the brain, right or left.

Psychometric Pertaining to testing and measurement of mental or psychological abilities. Psychometric tests convert an individual's psychological traits and attributes into a numerical estimation or evaluation.

Syndrome A group of symptoms that together characterize a disease or disorder.

production and comprehension of language help neuropsychologists identify the location of the stroke in the left hemisphere. Neuropsychological tests can also be used as screening tests to see if more extensive diagnostic evaluation is appropriate. Neuropsychological screening of elderly people complaining of memory problems can help identify those at risk for dementia versus those experiencing normal age-related memory loss.

As neuropsychological testing came to play a less vital role in localization of brain dysfunction, clinical neuropsychologists found new uses for their skills and knowledge. By clarifying which cognitive abilities are impaired or preserved in patients with brain injury or illness, neuropsychologists can predict how well individuals will respond to different forms of treatment or rehabilitation. Although patterns of test scores illustrate profiles of cognitive strength and weakness, neuropsychologists can also learn a great deal about patients by observing how they approach a particular test. For example, two patients can complete a test in very different ways yet obtain similar scores. One patient may work slowly and methodically, making no errors, while another rushes through the test, making several errors but quickly correcting them. Some individuals persevere despite repeated failure on a series of test items, while others refuse to continue after a few failures. These differences might not be apparent in test scores, but can help clinicians choose among rehabilitation and treatment approaches.

Performance on neuropsychological tests is usually evaluated through comparison to the average performance of large samples of normal individuals. Most tests include tables of these normal scores, often divided into groups based on demographic variables like age and education that appear to affect cognitive functioning. This allows individuals to be compared to appropriate peers.

The typical neuropsychological examination evaluates sensation and perception, gross and fine motor skills, basic and complex attention, visual spatial skills, receptive and productive language abilities, recall and recognition memory, and executive functions such as cognitive flexibility and abstraction. Motivation and personality are often assessed as well, particularly when clients are seeking financial compensation for injuries, or cognitive complaints that are not typical of the associated injury or illness.

Some neuropsychologists prefer to use fixed test batteries like the Halstead-Reitan battery or the Luria-Nebraska battery for all patients. These batteries include tests of a wide range of cognitive functions, and those who advocate their use believe that all functions must be assessed in each patient in order to avoid diagnostic bias or failure to detect subtle problems. The more common approach today, however, is to use a flexible battery based on hypotheses generated through a clinical interview, observation of the patient, and review of medical records. While this approach is more prone to bias, it has the advantage of preventing unnecessary testing. Since patients often find neuropsychological testing stressful and fatiguing, and these factors can negatively influence performance, advocates of the flexible battery approach argue that tailoring test batteries to particular patients can provide more accurate information.

Resources

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American Psychological Association. Division 40, 750 First Street, NE, Washington, DC 20002-4242. <http://www.div40.org/>.

International Neuropsychological Society. 700 Ackerman Road, Suite 550, Columbus, OH 43202. <http://www.acs.ohio-state.edu/ins/>.

National Academy of Neuropsychology. 2121 South Oneida Street, Suite 550, Denver, CO 80224-2594. <http://nanonline.org/>.

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Neuropsychologist

Definition

A clinical psychologist is a licensed or certified professional who holds a doctoral degree in psychology and works in the area of prevention and treatment of emotional and mental disorders. A neuropsychologist is typically a clinical psychologist with additional training and experience in neuropsychology, an area of psychology that focuses on brain-behavior relationships.

Description

Neuropsychologists are licensed professionals within the field of psychology. Most have a doctorate (PhD) in psychology with additional years of post-doctoral training in clinical neuropsychology. The graduate education and training for neuropsychologists emphasizes **brain anatomy**, brain function, and brain injury or disease. The neuropsychologist also learns how to administer and interpret certain types of standardized tests that can detect effects of brain dysfunction. Neuropsychologists may receive certification from the American Board of Clinical Neuropsychology (ABCN), the member board of the American Board of Professional Psychology (ABPP) that administers the competency exam in the specialty of clinical neuropsychology.

Neuropsychologists are not medical doctors; they are consultants who work closely with physicians, teachers, and other professionals to assess an individual's brain functioning. With the aid of standardized tests, neuropsychologists help to diagnose and assess patients with a variety of medical conditions that impact intellectual, cognitive, or behavioral functioning. They may also provide psychotherapy or other therapeutic interventions.

Neuropsychologists usually work in private practice or in institutional settings such as hospitals or clinics. Most neuropsychologists are in clinical practice; that is, their primary responsibilities include evaluation and treatment of patients. A neuropsychologist's practice may include pediatric neuropsychology, a specialty that concerns the relationship between learning and behavior and a child's brain, and forensic neuropsychology, an area that deals with determination of disability for legal purposes. In addition to seeing patients, neuropsychologists may also engage in professional activities such as teaching, research, and administration.

Reasons for referral

Neuropsychological evaluation is generally warranted for patients who show signs of problems with memory or thinking. Such problems may manifest as changes in language, learning, organization, perception, coordination, or personality. These symptoms can be due to a variety of medical, neurological, psychological, or genetic causes. Examples of conditions that may prompt a referral to a neuropsychologist include **stroke**, brain trauma, **dementia** (such as **Alzheimer's disease**), **seizures**, psychiatric illness, toxic exposures (such as to lead), or an illness that increases the chance of brain injury (such as diabetes or alcoholism).

Neuropsychological evaluation

The purpose of a neuropsychological evaluation is to provide useful information about an individual's brain functioning. Such information may help a physician, teacher, or other professional:

- make or confirm a diagnosis
- find problems with brain functioning
- determine individual thinking skill strengths and weaknesses
- guide treatment decisions such as rehabilitation, special education, vocational counseling, or other services
- track changes in brain functioning over time

Neuropsychological evaluation can reveal abnormalities or even subtle difference in brain functioning that may not be detected by other means. For example, testing can help determine if a person's mild memory changes represent the normal aging process or if they signify a neurological disorder such as Alzheimer's disease.

During the evaluation, a neuropsychologist may take a medical history, review medical records, and administer and interpret a series of standardized tests. Though the time required to conduct a neuropsychological exam varies, the exam can last six to eight hours and may span the course of several visits. The standardized tests used in

Key Terms

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.

a neuropsychological assessment involve answering questions ("paper and pencil" or computerized tests) or performing hands-on activities at a table. The goal of testing is to evaluate how well the brain functions when it performs certain tasks. A trained examiner, also called a technician, may give or score the tests. Testing does not include x rays, electrodes, needles, or other invasive procedures. Tests used may examine one or more of the following areas:

- general intellect
- attention, memory, and learning
- reasoning and problem-solving
- planning and organization
- visual-spatial skills (perception)
- language
- sensory skills
- motor functions
- academic skills
- emotions
- behavior
- personality

Neuropsychologists tailor their services to the patient's needs and the reason for referral. For example, in a child who is having difficulty reading, the neuropsychologist will try to determine if this difficulty is related to a problem with attention, language, auditory processing, or another cause.

The neuropsychologist's conclusions about an individual's brain functioning may complement findings from brain imaging studies such as a computerized topography (CT) scan or **magnetic resonance imaging (MRI)**, or the results of blood tests. Depending on the circumstances, a neuropsychologist may treat the patient with interventions such as cognitive rehabilitation, behavior management, or psychotherapy. A neuropsychologist may also recommend referrals to other health care specialists, including neurologists, psychiatrists, psychologists, **social workers**, nurses, special education teachers, therapists, or vocational counselors.

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Dawn Cardeiro, MS, CGC

Neurosarcoidosis

Definition

Neurosarcoidosis refers to an autoimmune disorder of unknown cause, which causes deposition of inflammatory lesions called granulomas in the **central nervous system**.

Description

Sarcoidosis is a multisystem disease of unknown cause. It is thought that the disorder is caused by an inflammatory reaction in the body which forms a lesion called a granuloma. Neurosarcoidosis is characterized by formation of granulomas in the central nervous system. The granulomas consist of inflammatory cells (lymphocytes, mononuclear phagocytes) which function during inflammatory reactions. The disorder is often unrecognized since most patients do not exhibit symptoms. Typically the disease is diagnosed by routine chest x ray. If symptoms are present they usually include respiratory problems (shortness of breath, cough) since the lungs are affected most frequently.

Neurological description

Patients can have a broad range of clinical signs and symptoms that typically could involve mononeuropathy, **peripheral neuropathy**, or central nervous system involvement. Mononeuropathy problems can include facial nerve palsy, impaired taste and smell, blindness (or other eye problems such as double vision, visual field defects, blurry vision, dry/sore eyes), or speech problems (impaired swallowing or hoarseness). Patients can also develop vertigo, weakness of neck muscles and tongue deviation and atrophy.

Peripheral nerve involvement

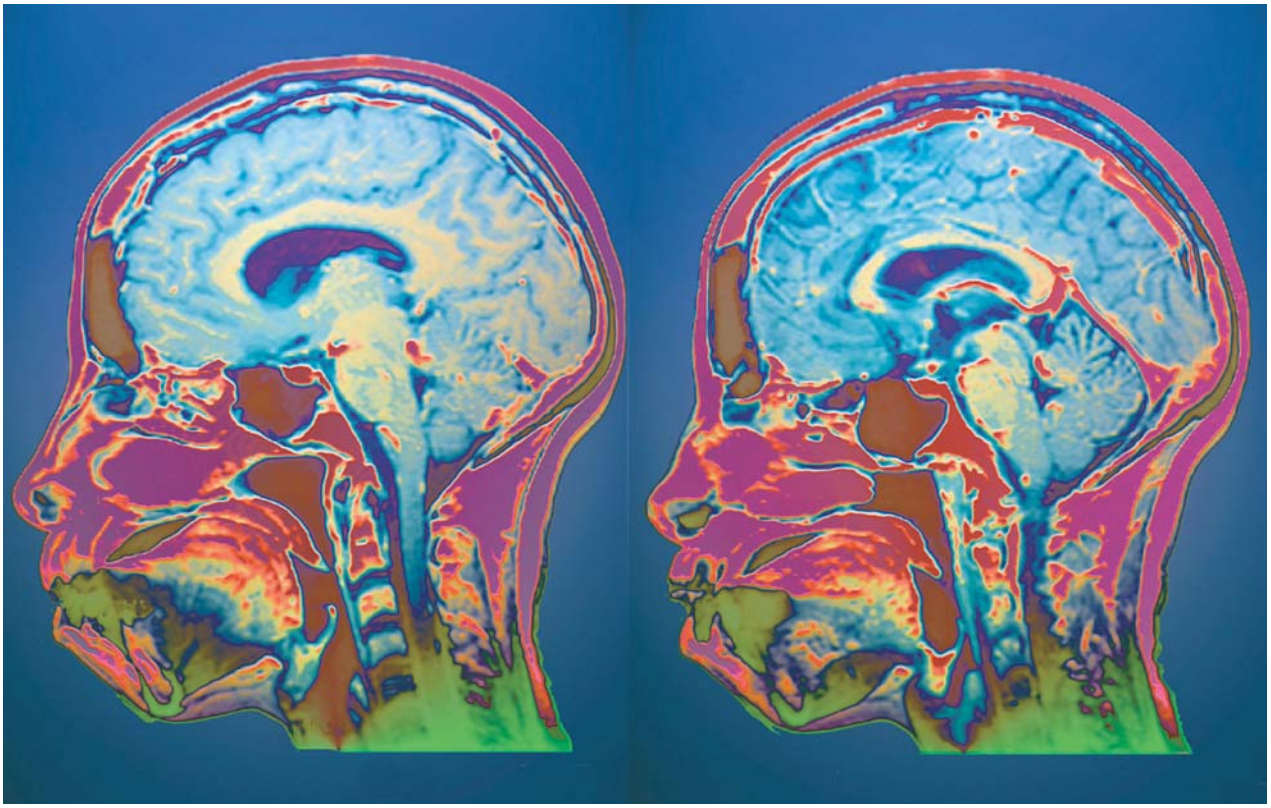
Neurosarcoidosis can cause damage to peripheral nerves that can affect motor nerves (responsible for movement of muscles) and sensory nerves (responsible for sensation). Symptoms of sensory loss include loss of sensation and abnormal sensation (numb, painful, tingling sensations) over the thorax (chest) and the areas where stockings and gloves are usually worn. Motor neurosarcoidosis is characterized by weakness that can progress to immobility and joint stiffness.

Central nervous system (CNS) involvement can affect the pituitary gland, **cerebellum**, or cerebral cortex. The spinal cord is rarely involved. Signs and symptoms of CNS involvement can include polyuria, polydipsia, obesity, impotence, amenorrhea, confusion/amnesia (short and long term memory), meningitis, and **seizures** (focal seizures).

Demographics

Sarcoid disorders are more prevalent in African Americans, and in the United States there seems to be a variable prevalence within different states. The prevalence is much higher in the southeastern United States among both Caucasian and African Americans. The prevalence is high in Puerto Rico, reaching approximately 175 cases per 100,000 persons. The frequency for neurological involvement for all cases of sarcoid disease is 5%. However, neurological involvement has been reported to occur in up to 5% to 16% of cases. Internationally the incidence of sarcoid varies widely. In Spain the incidence is low (0.04 per 100,000) whereas in Sweden the incidence is high, representing 64 cases per 100,000 persons. Studies reveal the prevalence in London is 27 per 100,000 and 97 per 100,000 among Irish men. In the Caribbean, studies indicate that the prevalence is as high as 200 per 100,000 in men from the West Indies and 13% of individuals from Martinique.

There does not seem to be a racial predilection for the development of sarcoid neuropathy. Sarcoid disease is uncommon in Chinese, Inuits, Southeast Asians, Canadian Indians, New Zealand Maoris and native Japanese. Death from neurosarcoidosis is unusual. About 66% of patients with neurosarcoidosis have self-limited monophasic illness. Approximately 33% have a chronic remitting and relapsing course. Neurosarcoidosis commonly occurs in adults aged 25-50 years. Neurosarcoidosis is not common in children, but if it does occur, it affects children age 9-15 years. The clinical signs in children are different than in adults. When neurosarcoidosis is present in children over the age of eight, there is usually a triad of signs which include arthritis, uveitis, and cutaneous nodules. In children ocular (eye) problems occur in approximately 100% of cases, which typically manifest as iritis and/or anterior vitreitis. For all cases, if the nervous system is involved it usually occurs within two years of disease onset.



Cerebral MRIs of a 52-year-old patient with neurosarcoidosis. The MRIs show the presence of numerous granulomas in the meninges and cisterns. *(Phototake, Inc. All rights reserved.)*

Causes and symptoms

The causes of sarcoid disease are not clear. Current evidence suggests that sarcoidosis is due to the abnormal proliferation of a certain cell called a T-helper cell, which functions to help immune cells attack a foreign substance. The abnormal proliferation of T-helper cells is thought to result from an exaggerated response to a foreign substance or to self cells (a condition referred to as autoimmunity, in which for unknown reasons, the body's natural defense cells attack normal cells in organs).

During physical examination patients may exhibit weakness, absence of tendon reflexes, lack of sensation in a stocking and glove distribution, atrophy of muscles, and focal mononueropathies that may affect the cranial nerves (causing problem with hearing, vision, smell, balance, or paralysis of facial muscles). Some patients may develop Heerfordt syndrome characterized by fever, uveitis, swelling of the parotid gland, and facial palsy.

Diagnosis

Blood analysis is essential since patients may have increased erythrocyte sedimentation rate (ESR) or anemia (hypochromic microcytic type). Blood analysis can provide information concerning multiple organs (kidney, liver, blood) and this is important since sarcoidosis is a multisystem disease (affects many different organs in the body). **CT** and **MRI** scans are important in assessing neurosarcoidosis. MRI is the imaging tool of choice in cases of neurosarcoidosis, because of the high quality superior images obtained. The presence of a mass or lesion in the CNS can be visualized by MRI images. To confirm the diagnosis it is necessary to take a **biopsy** of either muscle or nerve tissue. Examination of the tissue specimen with a microscope reveals the characteristic granuloma within tissues.

Treatment team

The effects of neurosarcoidosis can involve several symptoms from different organ systems. The treatment team consists of a **neurologist**, neurosurgeon, endocrinologist, rheumatologist, and pulmonologist.

Treatment

There is no definitive treatment, but corticosteroids remain the standard treatment. The most commonly used oral corticosteroid is prednisone, which works to decrease inflammatory actions in the body that are responsible for granuloma formation. Doses are usually tapered down.

Key Terms

Amenorrhea The absence or abnormal stoppage of menstrual periods.

Anterior vitreitis Inflammation of the corpus vitreum, which surrounds and fills the inner portion of the eyeball between the lens and the retina.

Atrophy The progressive wasting and loss of function of any part of the body.

Iritis Inflammation of the iris, the membrane in the pupil, the colored portion of the eye. It is characterized by photophobia, pain, and inflammatory congestion.

Mononeuropathy Disorder involving a single nerve.

Pituitary gland The most important of the endocrine glands (glands that release hormones directly into the bloodstream), the pituitary is located at the base of the brain. Sometimes referred to as the "master gland," it regulates and controls the activities of other endocrine glands and many body processes including growth and reproductive function. Also called the hypophysis.

Polydipsia Excessive thirst.

Polyuria Excessive production and excretion of urine.

Uveitis Inflammation of all or part the uvea. The uvea is a continuous layer of tissue which consists of the iris, the ciliary body, and the choroid. The uvea lies between the retina and sclera.

Vertigo A feeling of dizziness together with a sensation of movement and a feeling of rotating in space.

Additionally, patients can be given immunosuppressant agents (e.g., cyclosporine) which can suppress autoimmune responses (which are responsible for granuloma formation). Surgery is rare and reserved for cases that require removal of a mass (space-occupying lesion) in the brain.

Recovery and rehabilitation

Neurosarcoidosis is a slowly chronic disease with a progressive course, which is fatal in about 50% of patients. Follow-up visits with a neurologist every three to six months are advisable. During visits the neurologist will monitor progress and make recommendations.

Clinical trials

There are several studies currently active concerning sarcoidosis. The National Heart, Lung and Blood Institute Drug study are conducting clinical research trials with patients who have lung involvement (pulmonary sarcoidosis). Contact Pauline Barnes, RN (1-877-644-5864) or visit their website: <http://www.sarcoidresearch.org>.

Prognosis

Spontaneous resolution of neurosarcoidosis can occur but it is not common. Many patients with neurosarcoidosis have a slow chronic and progressive course with intermittent exacerbations. Neurosarcoidosis responds to steroid therapy, but long-term outcome of neurologic impairment is unknown.

Special concerns

Sarcoidosis is difficult to diagnose, and sometimes a delay can cause patients to get sicker before proper treatment is initiated. On rare occasions a patient may even die because the diagnosis was not suspected. Caution must be taken to exclude other diseases before a final diagnosis is made. Additionally, before corticosteroid therapy is initiated, the clinician must rule out an infectious cause.

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Neurotransmitters

Definition

Neurotransmitters are chemicals that allow the movement of information from one neuron across the gap between it and the adjacent neuron. The release of neurotransmitters from one area of a neuron and the recognition of the chemicals by a receptor site on the adjacent neuron causes an electrical reaction that facilitates the release of the neurotransmitter and its movement across the gap.

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.

Synapse A junction between two neurons. At a synapse the neurons are separated by a tiny gap called the synaptic cleft.

Description

The transmission of information from one neuron to another depends on the ability of the information to traverse the gap (also known as the synapse) between the terminal end of one neuron and the receptor end of an adjacent neuron. The transfer is accomplished by neurotransmitters.

In 1921, an Austrian scientist named Otto Loewi discovered the first neurotransmitter. He named the compound "vagusstoff," as he was experimenting with the vagus nerve of frog hearts. Now, this compound is known as acetylcholine.

Neurotransmitters are manufactured in a region of a neuron known as the cell body. From there, they are transported to the terminal end of the neuron, where they are enclosed in small membrane-bound bags called vesicles (the sole exception is nitric oxide, which is not contained inside a vesicle, but is released from the neuron soon after being made). In response to an action potential signal, the neurotransmitters are released from the terminal area when the vesicle membrane fuses with the neuron membrane. The neurotransmitter chemical then diffuses across the synapse.

At the other side of the synapse, neurotransmitters encounter receptors. An individual receptor is a transmembrane protein, meaning part of the protein projects from both the inside and outside surfaces of the neuron membrane, with the rest of the protein spanning the membrane. A receptor may be capable of binding to a neurotransmitter, similar to the way a key fits into a lock. Not all neurotransmitters can bind to all receptors; there is selectivity within the binding process.

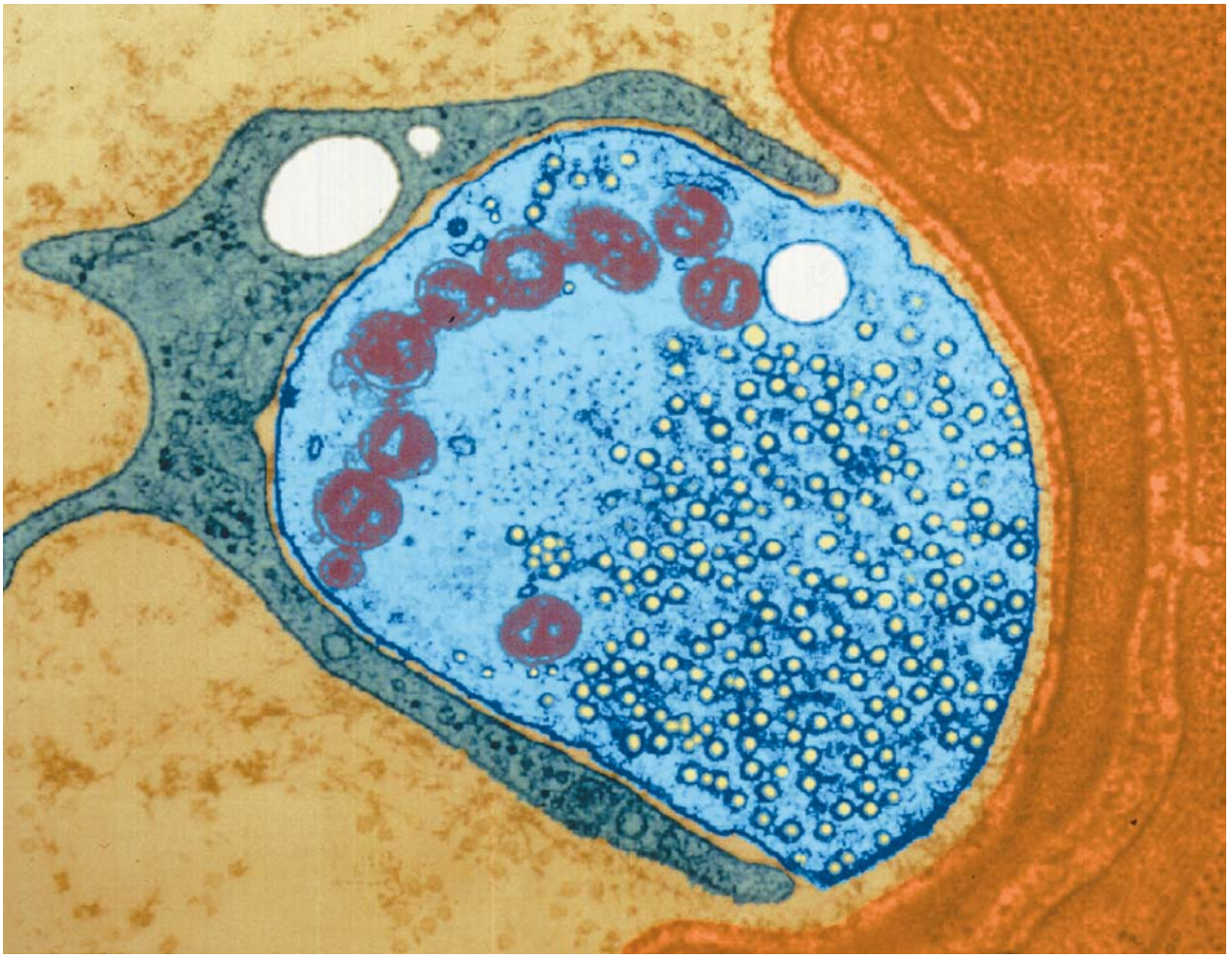
When a receptor site recognizes a neurotransmitter, the site is described as becoming activated. This can result in depolarization or hyperpolarization, which acts directly on the affected neurons, or the activation of another molecule (second messenger) that eventually alters the flow of information between neurons.

Depolarization stimulates the release of the neurotransmitter from the terminal end of the neuron. Hyperpolarization makes it less likely that this release will occur. This dual mechanism provides a means of control over when and how quickly information can pass from neuron to neuron. The binding of a neurotransmitter to a receptor triggers a biological effect. However, once the recognition process is complete, its ability to stimulate the biological effect is lost. The receptor is then ready to bind another neurotransmitter.

Neurotransmitters can also be inactivated by degradation by a specific enzyme (e.g., acetylcholinesterase degrades acetylcholine). Cells known as astrocytes can remove neurotransmitters from the receptor area. Finally, some neurotransmitters (norepinephrine, dopamine, and serotonin) can be reabsorbed into the terminal region of the neuron.

Since Loewi's discovery of acetylcholine, many neurotransmitters have been discovered, including the following partial list:

- Acetylcholine: Acetylcholine is particularly important in the stimulation of muscle tissue. After stimulation, acetylcholine degrades to acetate and choline, which are absorbed back into the first neuron to form another acetylcholine molecule. The poison curare blocks transmission of acetylcholine. Some nerve gases inhibit the breakdown of acetylcholine, producing a continuous stimulation of the receptor cells, and spasms of muscles such as the heart.
- Epinephrine (adrenaline) and norepinephrine: These compounds are secreted principally from the adrenal gland. Secretion causes an increased heart rate and the enhanced production of glucose as a ready energy source (the "fight or flight" response).
- Dopamine: Dopamine facilitates critical brain functions and, when unusual quantities are present, abnormal dopamine neurotransmission may play a role in **Parkinson's disease**, certain addictions, and schizophrenia.
- Serotonin: Synthesized from the amino acid tryptophan, serotonin is assumed to play a biochemical role in mood and mood disorders, including anxiety, **depression**, and bipolar disorder.



Nerve teminal synapses with muscle fiber (red). *(© Don Fawcett/Photo Researchers, Inc. Reproduced by permission.)*

- Aspartate: An amino acid that stimulates neurons in the **central nervous system**, particularly those that transfer information to the area of the brain called the cerebrum.
- Oxytocin: A short protein (peptide) that is released within the brain, ovary, and testes. The compound stimulates the release of milk by mammary glands, contractions during birth, and maternal behavior.
- Somatostatin: Another peptide, which is inhibitory to the secretion of growth hormone from the pituitary gland, of insulin, and of a variety of gastrointestinal hormones involved with nutrient absorption.
- Insulin: A peptide secreted by the pancreas that stimulates other cells to absorb glucose.

As exemplified above, neurotransmitters have different actions. In addition, some neurotransmitters have different effects depending upon which receptor to which they bind. For example, acetylcholine can be stimulatory when bound to one receptor and inhibitory when bound to another receptor.

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Brian Douglas Hoyle, PhD

Nevus cavernosus *see* **Cerebral cavernous malformation**

Niemann-Pick disease

Definition

Niemann-Pick disease (NPD) is a term that defines a group of diseases that affect metabolism and which are caused by specific genetic mutations. Currently, there are three categories of Niemann-Pick diseases: type A (NPD-A), the acute infantile form; type B (NPD-B), a less common, chronic, non-neurological form; and type C (NPD-C), a biochemically and genetically distinct form of the disease.

Description

NPD-A is a debilitating neurodegenerative (progressive nervous system dysfunction) childhood disorder characterized by failure to thrive, enlarged liver, and progressive neurological deterioration, which generally leads to death by three years of age. In contrast, NPD-B patients have an enlarged liver, no neurological involvement, and often survive into adulthood. NPD-C, although similar in name to types A and B, is very different at the biochemical and genetic level. People with NPD-C are not able to metabolize cholesterol and other lipids properly within the cells. Consequently, excessive amounts of cholesterol accumulate in the liver and spleen. The vast majority of children with NPD-C die before age 20, and many before the age of 10. Later onset of symptoms usually leads to a longer life span, although death usually occurs by age forty.

Demographics

Both Niemann-Pick disease types A and B occur in many ethnic groups; however, they occur more frequently among individuals of Ashkenazi Jewish descent than in the general population. NPD-A occurs most frequently, and it accounts for about 85% of all cases of the disease. NPD-C affects an estimated 500 children in the United States.

Causes and symptoms

All forms of NPD are inherited autosomal recessive disorders, requiring the presence of an inherited genetic mutation in only one copy of the gene responsible for the disease. Both males and females are affected equally. Types A and B are both caused by the deficiency of a specific enzyme known as the acid sphingomyelinase (ASM). This enzyme is ordinarily found in special compartments within cells called lysosomes and is required to metabolize a certain lipid (fat). If ASM is absent or not functioning properly, this lipid cannot be metabolized and is accumulated within the cell, eventually causing cell death and the malfunction of major organs and systems.

NPD-C disease is a fatal lipid storage disorder characterized by cholesterol accumulation in the liver, spleen, and **central nervous system**. Mutations in two independent genes result in the clinical features of this disease.

Symptoms of all forms of NPD are variable; no single symptom should be used to include or exclude NPD as a diagnosis. A person in the early stages of the disease may exhibit only a few of the symptoms, and even in the later stages not all symptoms may be present.

NPD-A begins in the first few months of life. Symptoms normally include feeding difficulties, abdomen enlargement, progressive loss of early motor skills, and cherry red spots in the eyes.

NPD-B is biochemically similar to type A, but the symptoms are more variable. Abdomen enlargement may be detected in early childhood, but there is almost no neurological involvement, such as loss of motor skills. Some patients may develop repeated respiratory infections.

NPD-C usually affects children of school age, but the disease may strike at any time from early infancy to adulthood. Symptoms commonly found are jaundice, spleen and/or liver enlargement, difficulties with upward and downward eye movements, gait (walking) unsteadiness, clumsiness, **dystonia** (difficulty in posturing of limbs), **dysarthria** (irregular speech), learning difficulties and progressive intellectual decline, sudden loss of muscle tone which may lead to falls, **tremors** accompanying movement, and in some cases **seizures**.

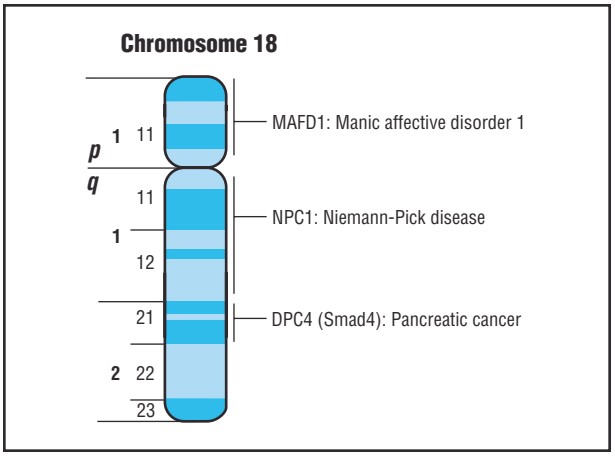
Diagnosis

The diagnosis of NPD-A and B is normally clinical, helped by measuring the ASM activity in the blood (white blood cells). While this test will identify affected individuals with the two mutated genes, it is not very reliable for detecting carriers, who have only one mutated gene.

NPD-C is diagnosed by taking a small skin **biopsy**, growing the cells (fibroblasts) in the laboratory, and studying their ability to transport and store cholesterol. Cholesterol transport in the cells is tested by measuring conversion of the cholesterol from one form to another. The storage of cholesterol is assessed by staining the cells with a compound that glows under ultraviolet light. It is important that both of these tests are performed, as reliance on one or the other may lead to the diagnosis being missed in some cases. NPD-C is often incorrectly diagnosed, and misclassified as attention deficit disorder (ADD), learning disability, retardation, or delayed development.

Treatment team

The treatment team is normally composed of a nutritionist, a physical therapist and/or occupational therapist (walking and balance, motor skills and posturing), a **neurologist** (seizure medications and neurological assessments), a speech therapist, pulmonologist, a geneticist, a



Niemann-Pick disease, on chromosome 18. *(Gale Group.)*

gastroenterologist, a psychologist, a social worker, and nurses.

Treatment

No specific definitive treatment is available for patients with any NPD type, and treatment is purely supportive. For NPD-C, a healthy, low-cholesterol diet is recommended. However, research into low-cholesterol diets and cholesterol-lowering drugs do not indicate that these halt the progress of the disease or change cholesterol metabolism at the cellular level.

Recovery and rehabilitation

All types of NPD require continuous family care and medical follow-up. Long-term survival and life quality will vary from patient to patient and seem to be directly related to the nature of the disease (genetic mutation) and the medical support provided.

Clinical trials

Enzyme replacement has been tested in mice and shown to be effective for type NPD type B. It has also been used successfully in other storage diseases, such as Gaucher type I. Genzyme Corporation and Mount Sinai Medical Center have announced plans for a clinical trial using enzyme replacement therapy to begin late 2003.

A clinical trial with a drug known as Zavesca for NPD type C is underway in the United States and Europe. The drug slowed, but did not stop, the neurological decline when tested on NPD mice.

Laboratory studies of neurosteroids have recently shown encouraging results when tested on mice, but more work needs to be done before a clinical trial can be considered.

Key Terms

Autosomal recessive A pattern of inheritance in which both copies of an autosomal gene must be abnormal for a genetic condition or disease to occur. An autosomal gene is a gene that is located on one of the autosomes or non-sex chromosomes. When both parents have one abnormal copy of the same gene, they have a 25% chance with each pregnancy that their offspring will have the disorder.

Hepatosplenomegaly Enlargement of the liver and spleen.

Lipids Organic compounds not soluble in water, but soluble in fat solvents such as alcohol. Lipids are stored in the body as energy reserves and are also important components of cell membranes. Commonly known as fats.

Prognosis

Patients with NPD-A commonly die during infancy. NPD-B patients may live for a few decades, but many require supplemental oxygen because of lung impairment. The life expectancy of patients with type C is variable. Some patients die in childhood while others, who appear to be less drastically affected, live into adulthood.

Special concerns

All types of NPD are autosomal recessive, which means that both parents carry one copy of the abnormal gene without having any signs of the disease. When parents are carriers, in each pregnancy, there is a 25% risk of conceiving a child who is affected with the disease and a 50% risk that the child will be a carrier.

For NPD-A and B the ASM gene has been isolated and extensively studied. DNA testing and prenatal diagnosis is currently available. Research into treatment alternatives for these types has progressed rapidly since the early 1990's. Current research focuses on bone marrow transplantation, enzyme replacement therapy, and **gene therapy**. All of these therapies have had some success against NPD-B in a laboratory environment. Unfortunately, none of the potential therapies has been effective against NPD-A.

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Nutritional deficiency *see* **Vitamin/nutritional deficiency**

O

O'Sullivan-McLeod syndrome *see* **Monomelic amyotrophy**

Occipital neuralgia

Definition

Occipital neuralgia is a persistent **pain** that is caused by an injury or irritation of the occipital nerves located in the back of the head.

Description

The greater and lesser occipital nerves run from the region where the spinal column meets the neck (the suboccipital region) up to the scalp at the back of the head. Trauma to these nerves can cause a pain that originates from the lower area of the neck between the shoulder blades.

Demographics

Although statistics indicating the frequency of persons with occipital neuralgia are unknown, the condition is more frequent in females than males.

Causes and symptoms

Occipital neuralgia is caused by an injury to the greater or lesser occipital nerves, or some irritation of one or both of these nerves. The repeated contraction of the neck muscles is a potential cause. Spinal column compression, localized infection or inflammation, gout, diabetes, blood vessel inflammation, and frequent, lengthy periods of maintaining the head in a downward and forward position have also been associated with occipital neuralgia. Less frequently, the growth of a tumor can be a cause, as the tumor puts pressure on the occipital nerves.

The result of the nerve damage or irritation is pain, which is typically described as continuously aching or throbbing. Some people also have periodic jabs of pain in addition to the more constant discomfort. The level of pain can be intense, and similar to a migraine. This intense pain can cause nausea and vomiting.

The pain typically begins in the lower area of the neck and spreads upward in a "ram's horn" pattern on the side of the head. Ultimately, the entire scalp and forehead can be painful. The scalp is also often tender to the touch. Additionally, persons with occipital neuralgia may have difficulty rotating or flexing the neck, and pain may radiate to the shoulder. Pressure or pain may be felt behind the eyes, and eyes are sensitive to light, especially when **headache** is present.

Diagnosis

Diagnosis is based on the symptoms, and especially on the location of the pain. Medical history is also useful. A history of muscle tension headaches over a long period of time is a good indicator that the current pain could be a neuralgic condition such as occipital neuralgia. While many people experience a tension headache due to the contraction of neck and facial muscles, few people experience the true neuralgic pain of occipital neuralgia. Nevertheless, physical and emotional tension can be contributing factors to the condition.

Treatment team

The treatment team typically is made up of someone capable of giving a massage, and a family physician. A **neurologist** and pain specialist may also be consulted. In the rare cases that surgery is required, a neurosurgeon is also involved.

Treatment

Treatment usually consists attempting to relieve the pain. This often involves a massage to relax the muscles in the area of the occipital nerves. Bed rest may relieve acute pain. In cases in which the nerve pain is suspected of being

Key Terms

Neuralgia Pain along a nerve pathway.

Occipital nerves Two pairs of nerves that originate in the area of the second and third vertebrae of the neck, and are part of a network that innervate the neck, upper back, and head.

caused by a tumor, a more specialized examination is done using the techniques of nuclear imaging or computed tomography (**CT**). These techniques provide an image that can reveal a tumor. If present, the tumor can be removed surgically, which usually cures the condition.

In cases in which the pain is especially intense, as in a migraine type of pain, pain-relieving drugs and antidepressants can be taken. Other treatments involve the blocking of the impulses from the affected nerve by injection of compounds that block the functioning of the nerve. Steroids can also be injected at the site of the nerve to try to relieve inflammation. However, the usefulness and long-term effects of this form of steroid therapy are not clear.

In extreme cases where pain is frequent, the nerves can be severed at the point where they join the scalp. The person is pain-free, but sensation is permanently lost in the affected region of the head.

Recovery and rehabilitation

Recovery is usually complete after the bout of pain has subsided and the nerve damage has been repaired or lessened.

Clinical trials

As of April 2004, there were no **clinical trials** in the United States that are directly concerned with occipital neuralgia. However, research is being funded through agencies such as the National Institute of Neurological Disorders and Stroke to try to find new treatments for pain and nerve damage, and to uncover the biological processes that result in pain.

Prognosis

The periodic nature of mild occipital neuralgia usually does not interfere with daily life. The prognosis for persons with more severe occipital neuralgia is also good, as the pain is usually lessened or eliminated by treatment.

Resources

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"NINDS Occipital Neuralgia Information Page." *National Institute of Neurological Disorders and Stroke.* April 12, 2004 (June 2, 2004). <http://www.ninds.nih.gov/health_and_medical/disorders/occipitalneuralgia.htm>.

ORGANIZATIONS

National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders. 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). 31 Center Dr., Rm. 4C02 MSC 2350, Bethesda, MD 20892-2350. (301) 496-8190 or (877) 226-4267. NIAMSinfo@mail.nih.gov. <http://www.niams.nih.gov>.

Brian Douglas Hoyle, PhD

Occulocephalic reflex *see* **Visual disturbances; Traumatic brain injury**

Occult spinal dysraphism sequence *see* **Tethered spinal cord syndrome**

Olivopontocerebellar atrophy

Definition

Olivopontocerebellar atrophy (OPCA) is a group of disorders characterized by degeneration of three brain areas: the inferior olives, the pons, and the **cerebellum**. OPCA causes increasingly severe **ataxia** (loss of coordination) as well as other symptoms.

Description

Two distinct groups of diseases are called OPCA, leading to some confusion. Non-inherited OPCA, also called sporadic OPCA, is now considered a form of **multiple system atrophy** (MSA). Hereditary OPCA, also called inherited OPCA and familial OPCA, is caused by inheritance of a defective gene, which is recognized in some forms but not in others.

Demographics

Hereditary OPCA affects approximately 10,000 people in the United States, with males affected approximately twice as often as females. The average age of onset is 28 years.

Causes and symptoms

By definition, hereditary OPCA is caused by the inheritance of a defective gene. Several genes have been identified. The two most common are known as SCA-1 and SCA-2 (SCA stands for **spinocerebellar ataxia**). These genes cause similar, though not identical, diseases. Besides these two genes, there are at least 20 other genetic forms of the disease. For reasons that are not understood, these gene defects cause degeneration (cell death) in specific parts of the brain, leading to the symptoms of the disorder. The cerebellum is a principal center for coordination, and its degeneration leads to loss of coordination.

The most common early symptom of OPCA is ataxia, or incoordination, which may be observed in an unsteady gait or over-reaching for an object with the hand. Other common symptoms include **dysarthria** (speech difficulty), dysphagia (swallowing difficulty), nystagmus (eye tremor), and abnormal movements such as jerking, twisting, or writhing. Symptoms worsen over time.

Diagnosis

An initial diagnosis of OPCA can be made with a careful neurological examination (testing of reflexes, balance, coordination, etc.), plus a magnetic resonance image (**MRI**) of the brain to look for atrophy (loss of tissue) in the characteristic brain regions. Genetic tests exist for SCA-1 and SCA-2 forms. Many other types of tests are possible, although they are usually done only to rule out other conditions with similar symptoms or to confirm the diagnosis in uncertain cases. Because the symptoms of OPCA can be so variable, especially at the beginning of the disease, it may be difficult to obtain a definite diagnosis early on.

Treatment team

The treatment team is likely to consist of a **neurologist**, physical therapist, occupational therapist, speech/language pathologist, genetic counselor, and nursing care specialist.

Treatment

There are no treatments that reverse or delay the progression of OPCA.

Very few medications have any beneficial effect on OPCA symptoms. In some patients, Levodopa, also prescribed for **Parkinson's disease**, may initially help. Some anti-tremor medications, including propranolol, may also slightly help. **Acetazolamide** may be useful in some forms of the disease.

Treatment of OPCA is primarily directed toward reducing the danger of ataxia, and minimizing the impact of the disease on activities of daily living. Falling is the major danger early in the disease, and **assistive mobile devices** such as walkers and wheelchairs are often essential to prevent falling.

As the disease progresses, swallowing difficulties present the greatest danger. Softer foods and smaller mouthfuls are recommended. A speech-language pathologist can help devise swallowing strategies to lessen the risk of choking, and can offer advice on assisted communication as well. Late in the disease, a feeding tube may be needed to maintain adequate nutrition.

Prognosis

The life expectancy after diagnosis is approximately 15 years, although this is an average and cannot be used to predict the lifespan of any individual person.

Special concerns

Because OPCA is an inherited disease with identified genetic causes, it is reasonable to have other family members tested for the genes to determine if they, too, are at risk. This information may help family members to make personal decisions about their future, including decisions about family planning.

Resources

WEBSITES

National Ataxia Foundation. (April 19, 2004). <http://www.ataxia.org>.

National Organization for Rare Disorders. (April 19, 2004). <http://www.rarediseases.org>

Richard Robinson

Opsoclonus myoclonus

Definition

Opsoclonus **myoclonus** is a syndrome in which the eyes dart involuntarily (opsoclonus or dancing eyes) and muscles throughout the body jerk or twitch involuntarily (myoclonus).

Description

Opsoclonus myoclonus is a very rare syndrome that strikes previously normal infants, children, or adults, often occurring in conjunction with certain cancerous tumors,

viral infections, or medication use. Onset can be very sudden and dramatic, with a quick progression.

Demographics

Most children who develop opsoclonus myoclonus are under the age of two when they are diagnosed. Boys and girls are affected equally.

Causes and symptoms

Many cases of opsoclonus myoclonus follow a bout of a viral illness such as infection with influenza, Epstein-Barr or Coxsackie B viruses, or after St. Louis encephalitis. About half of all cases are associated with a cancerous tumor; this kind of symptom that occurs due to cancer is termed a paraneoplastic syndrome. In children, the most common type of tumor that precipitates opsoclonus myoclonus is called neuroblastoma. Neuroblastoma can cause tumors in the brain, abdomen, or pelvic area. The cancerous cells develop from primitive nerve cells called neural crest cells. When opsoclonus myoclonus occurs in adults, it is usually associated with tumors in the lung, breast, thymus, lymph system, ovaries, uterus, or bladder. Rarely, opsoclonus myoclonus can occur after the use of certain medications such as intravenous phenytoin or **diazepam**, or subsequent to an overdose of the antidepressant amitriptyline.

No one knows exactly why opsoclonus myoclonus occurs. It is postulated that the presence of a viral infection or tumor may kick off an immune system response. The immune system begins trying to produce cells that will fight the invaders, either viruses or cancer cells. However, the immune cells produced may accidentally also attack areas of the brain, producing the symptoms of opsoclonus myoclonus.

Patients with opsoclonus myoclonus all have both opsoclonus and myoclonus. They experience involuntary, rapid darting movements of their eyes, as well as lightning-quick jerking of the muscles in their faces, eyelids, arms, legs, hands, heads, and trunk. Many individuals with opsoclonus myoclonus also experience weak and floppy muscles and a tremor. The movement disorder symptoms are incapacitating enough to completely interfere with sitting or standing when they are at their most severe. Difficulties eating, sleeping, and speaking also occur. Other common symptoms include mood changes, rage, irritability, nervousness, anxiety, severe drowsiness, confusion, and decreased awareness and responsiveness.

Diagnosis

Diagnosis is primarily arrived at through identification of concurrent opsoclonus and myoclonus. Laboratory testing of blood and spinal fluid may reveal the presence of certain immune cells that could be responsible for attacking parts of the nervous system, such as autoantibodies. When opsoclonus myoclonus is diagnosed, a search for a causative condition such as tumor should be undertaken.

Key Terms

Apheresis A procedure in which the blood is removed and filtered in order to rid it of particular cells, then returned to the patient.

Autoantibodies Antibodies that are directed against the body itself.

Immunoadsorption A procedure that can remove harmful antibodies from the blood.

Myoclonus Lightning-quick involuntary jerks and twitches of muscles.

Neuroblastoma A malignant tumor of nerve cells that strikes children.

Opsoclonus Often called "dancing eyes," this symptom involves involuntary, quick darting movements of the eyes in all directions.

Paraneoplastic syndrome A cluster of symptoms that occur due to the presence of cancer in the body, but that may occur at a site quite remote from the location of the cancer.

Treatment team

The treatment team will include a **neurologist** and neurosurgeon. A physical therapist, occupational therapist, and speech and language therapist may help an individual with opsoclonus myoclonus retain or regain as much functioning as possible.

Treatment

If opsoclonus myoclonus is due to the presence of a tumor, the first types of treatment will involve tumor removal and appropriate treatment of the cancer. Some adult cases of opsoclonus myoclonus resolve spontaneously, without specific treatment.

Treatment of the symptoms of opsoclonus myoclonus include clonzaepam or valproate. These may decrease the severity of both the opsoclonus and the myoclonus.

Other treatments for opsoclonus myoclonus include the administration of the pituitary hormone, called adrenocorticotropic hormone (ACTH). ACTH prompts the production of steroid hormones in the adrenal glands. When ACTH is given in high intravenous (IV) doses for about 20

weeks, the body produces large quantities of steroids, which can help quell any immune response that may be responsible for the opsoclonus myoclonus. Intravenous immunoglobulin treatment (IVIG), Azathioprine, and intravenous steroid treatments may also be given in an effort to suppress the immune system's response.

Two treatments that filter the blood in an effort to remove potentially damaging immune cells may also be attempted, although they are generally only able to be performed on adults. These include therapeutic apheresis and immunoadsorption. In these procedures, the patient's blood or plasma is processed to extract certain immune cells; the blood or plasma is then returned to the patient. These procedures may need to be repeated five or six times, but improvement is often rapid and may last up to two to three months.

Prognosis

The prognosis for opsoclonus myoclonus is varied. The milder the case prior to treatment, the more likely full recovery may occur. When opsoclonus myoclonus is due to a viral illness, there is a higher possibility for resolution of symptoms than when the condition results from neuroblastoma. Furthermore, although the degree of myoclonus may decrease, there are still often some residual coordination problems, difficulties with learning, behavior and/or attention, and obsessive-compulsive disorder. Children with very severe cases of opsoclonus myoclonus are likely to continue to have severe problems, and will probably never have normal intelligence or the ability to live independently.

Many children have flares of their symptoms or actual relapses of the disease when they suffer from viral illnesses, even years later. The treatments for such relapses are the same as for the initial illness.

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ORGANIZATIONS

Opsoclonus-Myoclonus USA and International. SIU School of Medicine, 751 North Rutledge, Suite 3100, Springfield, IL 62702. (217) 545-7635; Fax: (217) 545-1903. omsusa@siumed.edu. <http://www.omsusa.org/index.htm>.

Rosalyn Carson-DeWitt, MD

Organic voice tremor

Definition

Organic voice tremor is a neurogenic voice disorder of adulthood that most often occurs as a component of essential or hereditofamilial tremor; it may occur by itself, however. Organic voice tremor must be distinguished from other conditions, which also present with voice disturbances in the early stages. These include Parkinsonism, cerebellar disease, thyrotoxicosis, and anxiety.

Description

Organic voice tremor is a disorder of voice production characterized by unsteadiness of pitch and loudness and quavering intonation. In some patients, it may result in rhythmic arrests of voicing that occur at a rate of four to six per second. Voice quality is characterized by harshness, vocal strain, abnormally low pitch, and voice stoppages. Laryngeal examination typically reveals vocal folds of normal appearance, with no evidence of aberrant innervation. The abnormal oscillations of the larynx occur as a result of vigorous up-and-down vertical movements that occurred synchronously with the oscillation of the tremor. The quavering speech quality that characterizes organic voice tremor has been thought to include extralaryngeal influences arising from **tremors** in the diaphragm, lips, and tongue (Critchley, 1949; Tomoda, et al., 1985).

The origin of organic voice tremors has not been conclusively determined, though aging and occlusive arterial disease are thought to contribute significantly to the effects. Critchley (1949) showed that essential tremor occurred in persons with confirmed lesions in the brain stem, basal ganglia (e.g., putamen and lentiform nuclei) and within neural connections joining the red nucleus, dentate nucleus, and inferior olive. Vocal tremors usually coexist with tremors in the head and limbs, but may be localized entirely

Key Terms

Dysphonia Disordered phonation or voice production.

Dystonia Abnormalities of muscle tone involving involuntary twisting or distortions of the trunk or other body parts.

Endoscopy A clinical technique using an instrument called an endoscope, used for visualization of structures within the body.

Extra-laryngeal Actions of muscles outside the larynx, but usually in its vicinity, which influence its functioning.

Extrapyramidal system Functional, rather than anatomical unit, comprised of nuclei and nerve fibers that are chiefly involved with subconscious, automatic aspects of motor coordination, but which also assist in regulation of postural and locomotor movements.

Hyperfunction Term used to describe excess effort or strain involved in producing an action.

Innervation Distribution or supply of nerves to a structure.

Neurogenic Of neurological origin.

Otolaryngologist A physician who specializes in medical and surgical treatment of disorders of the ear, nose, throat, and larynx.

Resonator As used in regard to the human speech mechanism, it is the cavity extending from the vocal folds to the lips, which selectively amplifies and modifies the energies produced during speech and voice production. It is synonymous with the term vocal tract.

Speech-language pathologist A non-physician health care provider who evaluates and treats disorders of communication and swallowing.

Thyrotoxicosis A condition caused by excess amounts of thyroid hormone.

Tremor Involuntary rhythmic movements, which may be intermittent or constant, involving an entire muscle or only a circumscribed group of muscle bundles.

within the larynx. Disturbed central innervation to the larynx is thought to disturb coordination between abductor and adductor groups of laryngeal muscles, which may affect the symmetry of vibration of the vocal folds, and result in excess force of approximation or abruptness of vocal fold separation during conversational speech. Symptoms may be difficult to fully appreciate in conversational speech but become quite evident in sustained vowel production (Brown and Simonson, 1963). This finding is significant for differential diagnosis of essential tremor from spasmodic dysphonia, a focal **dystonia** affecting voicing.

Demographics

Organic voice tremor is a condition that usually occurs in persons over age 50. Males and females appear to be affected equally. Specific incidence data are not available.

Causes and Symptoms

Organic voice tremor is thought to result from neural degeneration in one or more regions of the extrapyramidal system. It usually is part of a more general condition of tremor involving the head, neck, and limbs called essential tremor. For some individuals, these changes are inherited and may occur in several members of the same family, sometimes occurring in successive generations. These persons are said to have hereditofamilial tremor. When the onset of organic voice tremor is rapid, the etiology may result from occlusive vascular disease (Brown and Simonson, 1963). When it is gradual, the etiology is likely related to progressive changes in several locations in the brain stem or basal ganglia.

Persons with organic voice tremor usually experience changes in voice slowly. In addition to changes in voice quality and reduced stability in pitch, loudness, and vocal flexibility, some patients may experience tremor in the pharynx, lips, and jaw. Some patients experience difficulties in initiating or maintaining voicing or experience sudden loss of voice during conversation. In addition to vocal tremor, some patients experience spasms in the diaphragm and expiratory musculature (Tomoda, et al.,1987), which may contribute to instability within the vocal tract and add to the quavering property of the voice.

Diagnosis

Organic voice tremor is usually made by examination of a **neurologist** and speech-language pathologist. Detailed history and medical examination is essential to determine if disruptions in voice functioning are related to other neurological conditions such as Parkinsonism, cerebellar disease,

and systemic conditions such as thyrotoxicosis. Differential diagnosis needs to be made between organic voice tremor and spasmodic dysphonia, which is a focal dystonia. A complete laryngeal examination should be obtained from an otolaryngologist and include endoscopic and videostroboscopic examinations of the larynx. A battery of objective tests to assess the aerodynamic and acoustic properties of voice production should be obtained from a speech pathologist, who usually works with the otolaryngologist. In addition, neuromotor intactness of the speech mechanism (the motor speech examination), should be undertaken. In this examination attention is given to assessment of muscle strength, speed of movement, range of motion, accuracy of movement, motor steadiness, and muscle tone in the speech articulators, larynx, and resonatory systems.

Treatment Team

The treatment team for organic voice tremor consists of a neurologist, otolaryngologist, and speech-language pathologist.

Treatment

There is no cure for organic voice tremor. Medications (Sinemat or Inderal) used to treat essential tremor have not emerged as a reliable treatment modality for organic voice tremor. Koller, et al. (1985) used propranolol to treat organic voice tremor and found that voice tremor was more resistant to drug treatment than tremor in the hand. Others (Massey and Paulson, 1982; Hartman and Vishwanat, 1984; Tomoda, et al., 1987) report effective treatment of voice and hand tremors with clonazepan, and **diazepam**. **Botulinum Toxin** A (BOTOX) may be useful in treating some patients with organic voice tremor, in which vocal fold **spasticity** is a coexisting feature. Speech therapy may be useful in reducing laryngeal hyperfunction and in establishing improved respiratory support.

Recovery and Rehabilitation

Patients with organic voice tremor do not recover from the condition. They must learn to adapt or compensate for speech and voice deficits. Speech therapy may be useful in this regard.

Prognosis

Prognosis is very poor for clinically significant improvement of voice in those with organic voice tremor.

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ORGANIZATIONS

American Speech-Language and Hearing Association. 10801 Rockville Pike, Rockville, MD 20852-3279. (301) 897-5700. <http://www.asha.org>.

National Spasmodic Dysphonia Association. One East Wacker Drive, Suite 2430, Chicago, IL 60601-1905. 800-795-6732. NSDA@dysphonia.org. <http://www.dysphonia.org>.

Joel C. Kahane, PhD

Orthostatic hypotension

Definition

Orthostatic hypotension refers to a reduction of blood pressure (systolic blood pressure that occurs when the heart contracts) of at lest 20 mmHg or a diastolic pressure (pressure when the heart muscle relaxes) of at least 10 mmHg within three minutes of standing.

Description

Orthostatic hypotension is a decrease of blood pressure when standing, due to changes in the blood pressure regulation systems within the body. Normally in a healthy human there is an orthostatic pooling of venous blood in the abdomen and legs when shifting positions from the supine (lying on the back) to an erect position (standing up). This redistribution of blood flow is the result of normal physiological compensatory mechanisms built into

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.

Amyloidosis The accumulation of amyloid deposits in various organs and tissues in the body so that normal functioning is compromised. Primary amyloidosis usually occurs as a complication of multiple myeloma. Secondary amyloidosis occurs in patients suffering from chronic infections or inflammatory diseases such as tuberculosis, rheumatoid arthritis, and Crohn's disease.

Angina pectoris Chest pain caused by an insufficient supply of oxygen and decreased blood flow to the heart muscle. Angina is frequently the first sign of coronary artery disease.

Autonomic nervous system The part of the nervous system that controls so-called involuntary functions, such as heart rate, salivary gland secretion, respiratory function, and pupil dilation.

Brain stem The stalk of the brain which connects the two cerebral hemispheres with the spinal cord. It is involved in controlling vital functions, movement, sensation, and nerves supplying the head and neck.

Claudication Cramping or pain in a leg caused by poor blood circulation. This condition is frequently caused by hardening of the arteries (atherosclerosis). Intermittent claudication occurs only at certain times, usually after exercise, and is relieved by rest.

Diuretic drugs A group of medications that increase the amount of urine produced and relieve excess fluid buildup in body tissues. Diuretics may be used in treating high blood pressure, lung disease, premenstrual syndrome, and other conditions.

Levodopa A substance used in the treatment of Parkinson's disease. Levodopa can cross the blood-brain barrier that protects the brain. Once in the brain, it is converted to dopamine and thus can replace the dopamine lost in Parkinson's disease.

Mineralocorticoid A steroid hormone, like aldosterone, that regulates the excretion of salt, potassium, and water.

Monoamine oxidase inhibitors A class of antidepressants used to treat certain types of mental depression. MAO inhibitors are especially useful in treating people whose depression is combined with other problems such as anxiety, panic attacks, phobias, or the desire to sleep too much.

Myelopathy A disorder in which the tissue of the spinal cord is diseased or damaged.

Parkinson's disease A slowly progressive disease that destroys nerve cells in the basal ganglia and thus causes loss of dopamine, a chemical that aids in transmission of nerve signals (neurotransmitter). Parkinson's is characterized by shaking in resting muscles, a stooping posture, slurred speech, muscular stiffness, and weakness.

Syncope A loss of consciousness over a short period of time, caused by a temporary lack of oxygen in the brain.

Valsalva maneuver A strain against a closed airway combined with muscle tightening, such as happens when a person holds his or her breath and tries to move a heavy object. Most people perform this maneuver several times a day without adverse consequences, but it can be dangerous for anyone with cardiovascular disease. Pilots perform this maneuver to prevent black-outs during high-performance flying.

Vasodilator Any drug that relaxes blood vessel walls.

Vertigo A feeling of dizziness together with a sensation of movement and a feeling of rotating in space.

body systems to prevent any adverse outcome (decrease in blood pressure, or hypotension) during positional change. Compensatory mechanisms include sympathetic nervous system activation and parasympathetic inhibition and increased heart rate and vascular resistance. Compensation responses restore cardiac output to vital organs and return blood pressure to normal. Orthostatic hypotension can occur if normal physiological mechanisms become faulty, such as inadequate cardiovascular compensation when shifting positions (i.e. change from supine to erect position), or due to excessive reduction in blood volume. Elderly persons seemed predisposed to orthostatic hypotension because of age-related changes; possible cardiovascular disease and the medications commonly taken by the elderly all predispose autonomic nervous system (ANS) functions. Additionally, hypertension present in 30% of persons over 75 years of age also predisposes a person to orthostatic hypotension, since hypertension re-

duces baroreflex sensitivity. Hypertension and the normal aging process (which typically causes blood vessel stiffness) decrease the sensitivity of specialized structures called baroreceptors, which function to maintain blood pressure, but initiating compensatory mechanisms such as increasing heart rate and vascular resistance. Persons affected with symptomatic orthostatic hypotension have symptoms when tilting head upward or when moving toward an erect position. Symptom severity varies among affected persons, but can include blurred vision, lightheadedness, weakness, vertigo, tremulousness and cognitive impairment. Symptoms can be relieved within one minute of lying down. Some persons have orthostatic hypertension without symptoms.

Demographics

The demographics of orthostatic hypotension are different due to variables that include the subject's position change, the specific population, and when measurements are taken. It is estimated that elderly in community living environments have prevalence rates of approximately 20% among individuals over 65 years of age and 30% in persons over 75 years of age. In frail elderly persons, the prevalence of orthostatic hypotension can be more than 50%. The disorder seems more prevalent among the elderly (especially if systolic blood pressure rises) with chronic diseases (i.e. hypertension and/or diabetes).

Causes and symptoms

Orthostatic hypotension can be caused by several different disorders that affect the entire body (systemic disorders), the **central nervous system** (CNS, consisting of the brain and spinal cord), and the autonomic nervous system (peripheral autonomic neuropathy) or as a result of taking certain medications that are commonly prescribed by clinicians. Systemic causes can include dehydration, prolonged immobility or an endocrine disorder called adrenal insufficiency. Diseases of the CNS that can cause orthostatic hypotension include MSA (multiple systems atrophy), **Parkinson's disease**, multiple strokes, brain stem lesions, myelopathy.

Medications that can cause orthostatic hypotension include Tricyclic antidepressants, antipsychotics, monoamine oxidase inhibitors, antihypertensives, diuretics, vasodilators, Levodopa, beta-blockers (heart medications), and blood pressure medications that inhibit a chemical called angiotensin (angiotensin-converting-enzyme inhibitors). Disorders that cause peripheral autonomic neuropathy include diabetes mellitus, amyloidosis, **tabes dorsalis** (late manifestations of syphilis infection), alcoholism, nutritional deficiency, pure autonomic failure or **paraneoplastic syndromes**.

The most common symptoms of orthostatic hypotension include weakness, lightheadedness, cognitive impairment, blurred vision, vertigo and tremulousness. Other symptoms that have been reported include **headache**, paracervical **pain**, lower **back pain**, syncope, palpitations, angina pectoris, unsteadiness, falling, and calf claudication.

Diagnosis

It is important that the clinician take numerous blood pressure measurements on different occasions, since blood pressure can vary (i.e. postural hypotension, another disorder causing hypotension, is often worse in the morning when rising from bed). A detailed history and physical examination is important. The clinician should focus medical evaluation on autonomic symptoms and diseases. There are bedside tests that can determine autonomic (baroreceptor) response (i.e. Valsalva maneuver). Measurements of a chemical in blood called norepinephrine while lying down and for five to 10 minutes after standing, can produce some useful information concerning deficits in autonomic nervous system functioning. Additionally, levels of another chemical in blood (called vasopressin) during upright tilting, can help to distinguish if the cause is due to ANS failure or from as a result of MSA. Pure ANS failure is characterized by increased vasopressin levels, whereas patients with MSA have no appreciable increase of vasopressin levels during head tilting.

Treatment team

Primary care practitioner (internist); or in complicated cases (severe orthostatic hypotension) a **neurologist** is consulted.

Treatment

Nonsymptomatic orthostatic hypotension is a threat for falls or syncope and could be treated by preventive measures that include avoiding warm environments and increasing one's blood pressure by squatting, stooping forward, or crossing one's leg. Additionally, persons affected with the nonsymptomatic variation should increase salt intake, sleep in the head-up position, wear waist-high compression stockings and withdraw from drugs that are known to cause orthostatic hypotension as a side effect. Treatment for symptomatic orthostatic hypotension is important since it is a manifestation of a new illness or as a result of medications. Intervention can initially be nonpharmacologic (preventive measures and adjustments) or pharmacologic therapy. Nonpharmacologic intervention includes a review of medications, since elderly patients may be taking either OTC or prescribed drugs that can induce orthostatic hypotension. Persons affected should rise slowly to the erect position after a long period of sitting or

lying down. They should avoid excess heat environments (i.e. in shower or central heating systems), coughing, straining or heavy lifting since these events can precipitate episodes of orthostatic hypotension. There are certain measures that can redirect blood to increase blood pressure and reduce symptoms associated with orthostatic hypotension. These measures include squatting, sitting down, crossing legs, and stooping forward.

Pharmacological Treatment

One of the most commonly prescribed medications for treating orthostatic hypotension is fludrocortisone acetate. This chemical is a synthetic mineralocorticoid which expands circulatory volume. This drug can cause a decrease of an important body element called potassium (hypokalemia, a decrease in potassium in plasma) which is important for normal heart contraction. Elderly persons should be monitored for blood levels of potassium and cardiac status. A drug called midodrine is useful for cases of orthostatic hypotension caused by peripheral **autonomic dysfunction**, usually in conjunction with fludrocortisone. However, midodrine is not recommended in persons with coronary or peripheral arterial disease. Other medications that may be helpful include clonidine or antihypertension medications. In severe cases of ANS deficits, a combination of medications may be indicated to provide brief periods of upright posture.

Recovery and rehabilitation

The recovery is variable and is also dependent on the cause. Recovery varies according to specific health status of affected person, age complications, and comorbidities (other existing disorders).

Clinical trials

Government-sponsored research includes studies concerning treatment of orthostatic hypotension. Details can be obtained from the website: <http://www.clinical trials.gov>

Prognosis

Careful evaluation and management is important for outcome. Identifying the source is an important first step. Preventive measures and posture modification techniques and avoidance of triggers can result in significant reduction of falls, fractures, functional decline, and syncope.

Special concerns

Special attention should be given to medications that are prescribed, which may cause orthostatic hypotension as a side effect.

Resources

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ORGANIZATIONS

American Academy of Neurology. 1080 Montreal Avenue, Saint Paul, MN 55116. 800-879-1960; Fax: (651) 695-2791. <http://www.aan.com>.

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Overuse syndrome *see* **Repetitive motion disorders**

Oxazolindinediones

Definition

Oxazolindinediones are **anticonvulsants**, indicated for the treatment of absence **seizures** (sometimes called petit mal seizures) associated with **epilepsy** and other seizure disorders.

Purpose

Oxazolindinediones are thought to decrease abnormal activity and excitement within the **central nervous system** (CNS) that may trigger seizures. While oxazolindinediones is often effective in controlling petit mal seizures associated with epilepsy, there is no known cure for the disorder. If

necessary, oxazolindinediones can be used in conjunction with other anti-epileptic drugs (AEDs) that prevent or control other types of seizures.

Description

In the United States, oxazolindinediones are sold under the generic name trimethadione and the brand name Tridione.

Recommended dosage

Oxazolindinediones are taken orally and are available in tablet, chewable tablet, or suspension forms. Oxazolindinediones are appropriate for pediatric and adult patients. Physicians prescribe the medication in varying total daily dosages. Typically, the total daily dosage is administered in three to four divided doses.

When beginning a course of treatment that includes oxazolindinediones, most physicians will prescribe a carefully scheduled dosing regimen. The physician will determine the proper initial dosage, and then gradually raise the patient's daily dosage over the course of several days or weeks until seizure control is achieved. Likewise, dosages are usually tapered down over time when ending treatment with oxazolindinediones.

It is important to not take a double dose of any anticonvulsant medication, including oxazolindinediones. If a daily dose is missed, it should be taken as soon as possible. However, if it is within four hours of the next scheduled dose, then the missed dose should be skipped.

Precautions

A physician should be consulted before taking oxazolindinediones with certain non-prescription medications. Patients should avoid alcohol and CNS depressants (medicines that can make one drowsy or less alert, such as antihistimines, sleep medications, and some **pain** medications) while taking oxazolindinediones or any other anticonvulsants, which can exacerbate the side effects of alcohol and other medications.

A course of treatment including oxazolindinediones may not be appropriate for persons with liver or kidney disease, anemia, eye disorders, mental illness, diabetes, high blood pressure, angina (chest pain), irregular heartbeats, or other heart problems. Periodic blood, urine, and liver function tests are advised for many patients (especially pediatric and elderly patients) using the medicine.

Persons taking oxazolindinediones should avoid prolonged exposure to sunlight and should wear protective clothing and sunscreen while outdoors. Oxazolindinediones may make skin sensitive to sunlight and prone to sunburn.

Key Terms

Absence seizure A type of generalized seizure in which the person may temporarily appear to be staring into space and/or have jerking or twitching muscles. Previously called a petit mal seizure.

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Seizure A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain, resulting in abnormal body movements or behaviors

Before beginning treatment with oxazolindinediones, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant, nursing, or plan on becoming pregnant. Anticonvulsant medications may increase the risk of some birth defects. Patients who become pregnant while taking oxazolindinediones should contact their physician.

Side effects

Patients should discuss with their physicians the risks and benefits of treatment with oxazolindinediones before taking the medication. Oxazolindinediones are usually well tolerated. However, in some patients, they may case a variety of usually mild side effects. **Dizziness**, nausea, and drowsiness are the most frequently reported side effects of anticonvulsants. Possible side effects that do not usually require medical attention, and may diminish with continued use of the medication include:

- unusual tiredness or weakness
- loss of appetite
- weight loss
- abdominal pain
- speech problems
- nausea
- diarrhea or constipation
- heartburn or indigestion
- dry mouth
- chills, joint aches, and other flu-like symptoms

If any symptoms persist or become too uncomfortable, the prescribing physician should be notified.

Other, uncommon side effects of oxazolindinediones can be serious or could indicate an allergic reaction. Patients who experience any of the following symptoms should contact a physician:

- purple spots on the skin
- jaundice (yellowing of the skin and eyes)
- bruising easily
- unusual bleeding
- dark urine, frequent urination, or burning sensation when urinating
- extreme mood or mental changes
- shakiness or unsteady walking
- severe unsteadiness or clumsiness
- excessive speech or language problems
- difficulty breathing
- chest pain
- faintness or loss of consciousness
- persistent, severe headaches
- persistent fever or pain

Interactions

Oxazolindinediones may have negative interactions with some antacids, heartburn or acid reflux prevention medications, anticoagulants, antihistamines, antidepressants, antibiotics, and monoamine oxidase inhibitors (MAOIs). Oxazolindinediones may be used in conjunction with other seizure prevention medications (anticonvulsants or anti-epileptic drugs) only if advised and monitored by a physician. Many anticonvulsants may decrease the effectiveness of oral contraceptives (birth control pills) or contraceptive injections or implants containing estrogen and progestins.

Resources

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ORGANIZATIONS

Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. <http://www.aesnet.org>.

Adrienne Wilmoth Lerner

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Pain

Definition and classification

Pain is a universal human experience. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Pain may be a symptom of an underlying disease or disorder, or a disorder in its own right.

At the same time that pain is a universal experience, however, it is also a complex one. While the physical sensations involved in pain may be constant throughout history, the ways in which humans express and treat pain are shaped by their respective cultures and societies. Since the 1980s, research in the neurobiology of pain has been accompanied by studies of the psychological and sociocultural factors that influence people's experience of pain, their use of health care systems, and their compliance with various treatments for pain. As of 2003, the World Health Organization (WHO) emphasizes the importance of an interdisciplinary approach to pain treatment that takes this complexity into account.

Types of pain

Pain can be classified as either acute or chronic. Acute pain is a direct biological response to disease, inflammation, or tissue damage, and usually lasts less than one month. It may be either continuous or recurrent (e.g., sickle cell disease). Acute pain serves the long-term well-being of humans and the higher animals by alerting them to an injury or condition that needs treatment. In humans, acute pain is often accompanied by anxiety and emotional distress; however, its cause can usually be successfully diagnosed and treated. Some researchers use the term "eudynia" to refer to acute pain.

In contrast, chronic pain has no useful biological function. It can be defined broadly as pain that lasts longer than a month following the healing of a tissue injury; pain that recurs or persists over a period of three months or longer; or pain related to a tissue injury that is expected to continue or get worse. Chronic pain may be either continuous or intermittent; in either case, however, it frequently leads to weight loss, sleep disturbances, **fatigue**, and other symptoms of **depression**. According to an article in the *New York Times*, chronic pain is the most common underlying cause of suicide. Unlike acute pain, chronic pain is resistant to most medical treatments. It is sometimes called "maldynia," and is considered a disorder in its own right.

Pain that is caused by organic diseases and disorders is known as somatogenic pain. Somatogenic pain in turn can be subdivided into nociceptive pain and neuropathic pain. Nociceptive pain occurs when pain-sensitive nerve endings called nociceptors are activated or stimulated. Most nociceptors in the human body are located in the skin, joints and muscles, and the walls of internal organs. There may be as many as 1,300 nociceptors in a square inch (6.4 square centimeter) of skin. However, there are fewer nociceptors in muscle tissue and the internal organs, as they are covered and protected by the skin. Nociceptors are specialized to detect different types of painful stimuli—some are sensitive to heat or cold, while others detect pressure, toxic substances, sharp blows, or inflammation caused by infection or overuse.

In contrast to nociceptive pain, neuropathic pain results from damage to or malfunctioning of the nervous system itself. It may involve the **central nervous system** (the brain and spinal cord); the **peripheral nervous system** (the nerve trunks leading away from the spine to the limbs, plus the 12 pairs of cranial nerves on the lower surface of the brain); or both. Neuropathic pain is usually associated with an identifiable disorder such as **stroke**, diabetes, or **spinal cord injury**, and is frequently described as having a "hot" or burning quality.

Psychogenic pain is distinguished from somatogenic pain by the influence of psychological factors on the intensity of the patient's pain or degree of disability. The patient is genuinely experiencing pain—that is, he or she is

not malingering—but the pain has either no organic explanation or else a weak one. Common psychogenic pain syndromes include chronic **headache** or low **back pain**; atypical facial pain; or pelvic pain of unknown origin.

Some cases of psychogenic pain belong to a group of mental disorders known as somatoform disorders. According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), somatoform disorders are defined by "the presence of physical symptoms that suggest a general medical condition," but cannot be fully explained by such a condition, by the direct effects of a drug or other substance, or by another mental disorder. The somatoform disorders include somatization disorder, characterized by chronic complaints of unexplained physical symptoms, often involving multiple sites in the body; hypochondriasis is a preoccupation with illness that persists in spite of the doctor's reassurance; and pain disorder, characterized by physical pain that is intensified by psychological factors, often becoming the focus of the patient's life and impairing his or her family relationships and ability to work.

It is important to recognize that some pain syndromes may involve more than one type of pain. For example, a cancer patient may suffer from neuropathic pain as a side effect of cancer treatment as well as nociceptive pain associated with pressure from the tumor itself on nociceptors in a blood vessel or hollow organ. In addition to the somatogenic pain, the patient may experience psychogenic pain related to the loss of physical functioning or attractiveness, coupled with anxiety about the progression or recurrence of the cancer. Other pain syndromes do not fit neatly into either somatogenic or psychogenic categories. A case in point would be certain types of chronic headache that involve the stimulation of nociceptors in the tissues of the head and neck as well as psychogenic factors related to the patient's handling of stress.

Description

How the body feels pain

A person begins to feel pain when nociceptors in the skin, muscles, or internal organs detect pressure, inflammation, a toxic substance, or another harmful stimulus. The pain message travels along peripheral nerve fibers in the form of electrical impulses until it reaches the spinal cord. At this point, the pain message is filtered by specialized nerve cells that act as gatekeepers. Depending on the cause and severity of the pain, the nerve cells in the spinal cord may either activate motor nerves, which govern the ability to move away from the painful stimulus; block out the painful message; or release chemicals that increase or lower the strength of the original pain message on its way to the brain. The part of the spinal cord that receives and "processes" the pain messages from the peripheral nerves is known as the dorsal horn.

After the pain message reaches the brain, it is relayed to an egg-shaped central structure called the thalamus, which transmits the information to three specialized areas within the brain: the somatosensory cortex, which interprets physical sensations; the limbic system, which forms a border around the brain stem and governs emotional responses to physical stimuli; and the frontal cortex, which handles thinking. The activation of these three regions explains why human perception of pain is a complex combination of sensation, emotional arousal, and conscious thought.

In addition to receiving and interpreting pain signals, the brain responds to pain by activating parts of the nervous system that send additional blood to the injured part of the body or that release natural pain-relieving chemicals, including serotonin, endorphins, and enkephalins.

Factors that affect pain perception

LOCATION AND SEVERITY OF PAIN Pain varies in intensity and quality. It may be mild, moderate, or severe. In terms of quality, it may vary from a dull ache to sharp, piercing, burning, pulsating, tingling, or throbbing sensations; for example, the pain from jabbing one's finger on a needle feels different from the pain of touching a hot iron, even though both injuries involve the same part of the body. If the pain is severe, the nerve cells in the dorsal horn transmit the pain message rapidly; if the pain is relatively mild, the pain signals are transmitted along a different set of nerve fibers at a slower rate.

The location of the pain often affects a person's emotional and cognitive response, in that pain related to the head or other vital organs is usually more disturbing than pain of equal severity in a toe or finger.

GENDER Recent research has shown that sex hormones in mammals affect the level of tolerance for pain. The male sex hormone, testosterone, appears to raise the pain threshold in experimental animals, while the female hormone, estrogen, appears to increase the animal's recognition of pain. Humans, however, are influenced by their personal histories and cultures as well as by body chemistry. Studies of adult volunteers indicate that women tend to recover from pain more quickly than men, cope more effectively with it, and are less likely to allow pain to control their lives. One explanation of this difference comes from research with a group of analgesics known as kappa-opioids, which work better in women than in men. Some researchers think that female sex hormones may increase the effectiveness of some analgesic medications, while male sex hormones may make them less effective. In

addition, women appear to be less sensitive to pain when their estrogen and progesterone levels are high, as happens during pregnancy and certain phases of the menstrual cycle. It has been noted, for example, that women with irritable bowel syndrome (IBS) often experience greater pain from the disorder during their periods.

FAMILY Another factor that influences pain perception in humans is family upbringing. Some parents comfort children who are hurting, while others ignore or even punish them for crying or expressing pain. Some families allow female members to express pain but expect males to "keep a stiff upper lip." People who suffer from chronic pain as adults may be helped by recalling their family's spoken and unspoken "messages" about pain, and working to consciously change those messages.

CULTURE AND ETHNICITY In addition to the nuclear family, a person's cultural or ethnic background can shape his or her perception of pain. People who have been exposed through their education to Western explanations of and treatments for pain may seek mainstream medical treatment more readily than those who have been taught to regard hospitals as places to die. On the other hand, Western medicine has been slower than Eastern and Native American systems of healing to recognize the importance of emotions and spirituality in treating pain. The recent upsurge of interest in alternative medicine in the United States is one reflection of dissatisfaction with a one-dimensional "scientific" approach to pain.

There are also differences among various ethnic groups within Western societies regarding ways of coping with pain. One study of African American, Irish, Italian, Jewish, and Puerto Rican patients being treated for chronic facial pain found differences among the groups in the intensity of emotional reactions to the pain and the extent to which the pain was allowed to interfere with daily functioning. However, much more work on larger patient samples is needed to understand the many ways in which culture and society affect people's perception of and responses to pain.

Demographics

Acute pain, particularly in its milder forms, is a commonplace experience in the general population; most people can think of at least one occasion in the past week or month when they had a brief tension headache, felt a little muscle soreness, cut themselves while shaving, or had a similar minor injury. On the other hand, chronic pain is more widespread than is generally thought; the American Chronic Pain Association estimates that 86 million people in the United States suffer from and are partially disabled by chronic pain. Two Canadian researchers evaluating a set of 13 studies of chronic pain done in North America, Europe, and Australia reported that the prevalence of severe chronic pain in these parts of the world is about 8% in children and 11% in adults. In terms of the economic impact of chronic pain, various productivity audits of the American workforce have stated that such pain syndromes as arthritis, lower back pain, and headache cost the United States between $80 and $90 billion every year.

The demographics of chronic pain depend on the specific disorder, including:

- Chronic pelvic pain (CPP) is more common in women than in men; it is thought to affect about 14% of adult women worldwide. In the United States, CPP is most common among women of reproductive age, particularly those between the ages of 26 and 30. It appears to be more common among African Americans than among Caucasians or Asian Americans. In addition, a history of sexual abuse before age 15 is a risk factor for CPP in adult life.
- Lower back pain (LBP) is the most common chronic disability in persons younger than 45. One researcher estimates that 80% of people in the United States will experience an episode of LBP at some point in life. About 3–4% of adults are disabled temporarily each year by LBP, with another 1% of the working-age population disabled completely and permanently. While 95% of patients with LBP recover within six to 12 weeks, the back pain becomes a chronic syndrome in the remaining 5%.
- Headaches in general are very common in the adult population in North America; about 95% of women and 90% of men in the United States and Canada have had at least one headache in the past twelve months. Most of these are tension headaches. Migraine headaches are less common than tension headaches, affecting about 11% of the population in the United States and 15% in Canada. Migraines occur most frequently in adults between the ages of 25 and 55; the gender ratio is about 3 F:1 M. Cluster headaches are the least common type of chronic headaches, affecting about 0.4% of adult males in the United States and 0.08% of adult females. The gender ratio is 7.5–5 M:1 F.
- Atypical facial pain is a less-common chronic pain syndrome, affecting one or two persons per 100,000 population each year. It is almost entirely a disorder of adults. Atypical facial pain is thought to affect men and women equally, and to occur with equal frequency in all races and ethnic groups.

Evaluation of pain

Patient description and history

A doctor's first step in evaluating a patient's pain is obtaining a detailed description of the pain, including:

Key Terms

Adjuvant A medication or other substance given to aid another drug, such as a tranquilizer given to ease the anxiety of a cancer patient in addition to an analgesic for pain relief.

Analgesic A medication that relieves pain without causing loss of consciousness. Over-the-counter analgesics include aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).

Bursa (plural, bursae) A fluid-filled sac or pouch located in joints or other pressure points between tendons and bones. Inflammation of a bursa is known as bursitis.

Capsaicin An alkaloid derived from hot peppers that can be used as a topical anesthetic.

Dorsal horn The part of the spinal cord that receives and processes pain messages from the peripheral nervous system.

Endorphins Neuropeptides produced by the body that are released in response to stress or injury and act as natural analgesics.

Enkephalins Polypeptides that serve as neurotransmitters and short-acting pain relievers. Enkephalins also influence a person's perception of painful sensations.

Eudynia The medical term for acute pain, or pain that is a symptom of an underlying disease or disorder.

Limbic system A group of structures found in the brains of all mammals that are associated with emotions, behavior, and such body functions as appetite and temperature regulation.

Maldynia The medical term for chronic pain, or pain that has become a disease in and of itself as a result of changes in the patient's nervous system.

Malingering Knowingly pretending to be physically or mentally ill in order to get out of some unpleasant duty or responsibility, or for economic benefit.

Narcotic Another term for opioid drugs that refers to their ability to produce drowsiness as well as relieve pain.

Neurotransmitter Any of a group of chemicals that transmit nerve impulses across the gap (synapse) between two nerve cells.

Nociceptor A specialized type of nerve cell that senses pain.

Opioid Any of a number of pain-relieving drugs derived from the opium poppy or from synthetic compounds that have the same effect as natural opioids.

Pain medicine The medical specialty that deals with the study and prevention of pain, and with the evaluation, treatment, and rehabilitation of patients with acute or chronic pain.

Somatoform disorders A group of psychiatric disorders in the DSM-IV classification that are characterized by external physical symptoms or complaints related to psychological problems rather than organic illness.

Thalamus An egg-shaped structure in the brain that integrates pain sensations and other sensory impulses, and relays them to other regions of the brain.

- severity
- timing (time of day; continuous or intermittent)
- location in the body
- quality (piercing, burning, aching, etc.)
- factors that relieve the pain or make it worse (temperature or humidity; body position or level of activity; foods or medications; emotional stress, etc.)
- its relationship to mood swings, anxiety, or depression

The doctor will then take the patient's medical history, including past illnesses, injuries, and operations as well as a family history. In some cases, the doctor may need to ask about experiences of emotional, physical, or sexual abuse. The doctor will also make a list of all the medications that the patient takes on a regular basis. Other information that may help the doctor evaluate the pain includes the patient's occupation and level of functioning at work; marriage and family relationships; social contacts and hobbies; and whether the patient is involved in a lawsuit for injury or seeking workers' compensation. This information may be helpful in understanding what the patient means by "pain" as well as what may have caused the pain, particularly because many people find it easier to discuss physical pain than anxiety, anger, depression, or sexual problems.

Some doctors may give the patient a brief written pain questionnaire to fill out in the office. There are a number of different instruments of this type, some of which are designed to measure pain associated with cancer, arthritis, HIV infection, or other specific diseases. Most of these rating questionnaires ask the patient to mark their pain

level on a scale from zero to 10 or zero to 100 with zero representing "no pain" and the higher number representing "worst pain imaginable" or "unbearable pain." The patient then answers a few multiple-choice questions regarding the impact of the pain on his or her employment, relationships, and overall quality of life.

Physical examination

A thorough physical examination is essential in identifying the specific disorders or injuries that are causing the pain. The most important part of pain management is removing the underlying cause(s) whenever possible, even when there is a psychological component to the pain.

Special tests

Although there are no laboratory tests or imaging studies that can demonstrate the existence of pain as such or measure its intensity directly, the doctor may order special tests to help determine the cause(s) of the pain. These studies may include one or more of the following:

- Imaging studies, usually x rays or **magnetic resonance imagings** (**MRIs**). These studies can detect abnormalities in the structure of bones or joints, and differentiate between healthy and diseased tissues.
- Neurological tests. These tests evaluate the patient's movement, gait, reflexes, coordination, balance, and sensory perception.
- Electrodiagnostic tests. These tests include **electromyography** (EMG), nerve conduction studies, and evoked potential (EP) tests. In EMG, the doctor inserts thin needles in specific muscles and observes the electrical signals that are displayed on a screen. This test helps to pinpoint which muscles and nerves are affected by pain. Nerve conduction studies are done to determine whether specific nerves have been damaged. The doctor positions two sets of electrodes on the patient's skin over the muscles in the affected area. One set of electrodes stimulates the nerves supplying that muscle by delivering a mild electrical shock; the other set records the nerve's electrical signals on a machine. EP tests measure the speed of transmission of nerve impulses to the brain by using two electrodes, one attached to the patient's arm or leg and the other to the scalp.
- Thermography. This is an imaging technique that uses infrared scanning devices to convert changes in skin temperature into electrical impulses that can be displayed as different colors on a computer monitor. Pain related to inflammation, nerve damage, or abnormalities in skin blood flow can be effectively evaluated by thermography.
- Psychological tests. Such instruments as the Minnesota Multiphasic Personality Inventory (MMPI) may be helpful in assessing hypochondriasis and other personality traits related to psychogenic pain.

Treatment

Treatment of either acute or chronic pain may involve several different approaches to therapy.

Medications

Medications to relieve pain are known as analgesics. Aspirin and other nonsteroidal anti-inflammatory drugs, or NSAIDs, are commonly used analgesics. NSAIDs include such medications as ibuprofen (Motrin, Advil), ketoprofen (Orudis), diclofenac (Voltaren, Cataflam), naproxen (Aleve, Naprosyn), and nabumetone (Relafen). These medications are effective in treating mild or moderate pain. A newer group of NSAIDs, which are sometimes called "superaspirins" because they can be given in higher doses than aspirin without causing stomach upset or bleeding, are known as COX-2 inhibitors. The COX-2 inhibitors include celecoxib (Celebrex), rofecoxib (Vioxx), and valdecoxib (Bextra).

For more severe pain, the doctor may prescribe an NSAID combined with an opioid, usually codeine or hydrocodone. Opioids, which are also called narcotics, are strong painkillers derived either from the opium poppy *Papaver somniferum* or from synthetic compounds that have similar effects. Opioids include such drugs as codeine, fentanyl (Duragesic), hydromorphone (Dilaudid), meperidine (Demerol), morphine, oxycodone (OxyContin), and propoxyphene (Darvon). They are defined as Schedule II controlled substances by the Controlled Substances Act of 1970, which means that they have a high potential for abuse in addition to legitimate medical uses. A doctor must have a special license in order to prescribe opioids. In addition to the risk of abuse, opioids cause potentially serious side effects in some patients, including cognitive impairment (more common in the elderly), disorientation, constipation, nausea, heavy sweating, and skin rashes.

If the patient's pain is severe and persistent, the doctor will give separate dosages of opioids and NSAIDs in order to minimize the risk of side effects from high doses of aspirin or acetaminophen. In addition, the doctor may prescribe opioids that are stronger than codeine—usually morphine, fentanyl, or levorphanol.

The "WHO Ladder" for the treatment of cancer pain is based on the three levels of analgesic medication. Patients with mild pain from cancer are given nonopioid medications with or without an adjuvant (helping) medication. For example, the doctor may prescribe a tranquilizer to relieve the patient's anxiety as well as the pain medication. Patients on the second "step" of the ladder are given a milder opioid and a nonopioid analgesic with or without an adjuvant drug. Patients with severe cancer pain are given stronger opioids at higher dosage levels with or without an adjuvant drug.

Acute pain following surgery is usually managed with opioid medications, most commonly morphine sulfate (Astromorph, Duramorph) or meperidine (Demerol). In some cases, NSAIDs that are available in injectable form (such as ketorolac) are also used. Patient-controlled analgesia, or PCA, allows patients to control the timing and amount of pain medication they receive. Although there are oral forms of PCA, the most common form of administration involves an infusion pump that delivers a small dose of medication through an intravenous line when the patient pushes a button. The PCA pump is preprogrammed to deliver no more than an hourly maximum amount of the drug.

Some types of chronic pain are treated by injections in specific areas of the body rather than by drugs administered by mouth or intravenously. There are three basic categories of injections for pain management:

- Joint injections. Joint injections are given to treat chronic pain associated with arthritis. The most common medications used are corticosteroids, which suppress inflammation in arthritic joints, and hyaluronic acid, which is a compound found in the joint fluid of healthy joints.
- Soft tissue injections. These are given to reduce pain in trigger points (areas of muscle that are hypersensitive to touch) and bursae, which are small pouches or sacs containing tissue fluid that cushions pressure points between tendons and bones. When a bursa becomes inflamed—a condition called bursitis—the person experiences pain in the nearby joint. Corticosteroids are the drugs most often used in soft tissue injections, although the doctor may also inject an anesthetic into a trigger point in order to relax the muscle.
- Nerve blocks. Nerve blocks are injections of anesthetic around the fibers of a nerve to prevent pain messages relayed along the nerve from reaching the brain. They may be used to relieve pain in specific parts of the body for a short period; a common example of this type of nerve block is the lidocaine injections given by dentists before drilling or extracting a tooth. Some nerve blocks are injected in or near the spinal column to control pain that affects a larger area of the body; an example is the epidural injection given to women in labor or to patients with **sciatica**. A third type of nerve block is administered to block the sympathetic nervous system as part of pain management in patients with complex chronic pain syndromes.

Medications used to treat neuropathic pain include tricyclic antidepressants, anticonvulsant medications, selective serotonin reuptake inhibitors, topical creams containing capsaicin or 5% lidocaine, and diphenhydramine (Benadryl).

Surgery

Because surgery is itself a cause of pain, few surgical treatments to relieve pain were available prior to the discovery of safe general anesthetics in the mid-nineteenth century. For most of human history, doctors were limited to procedures that could be completed within two to three minutes because the patients could not bear the pain of the operation. Ancient Egyptian doctors gave their patients wine mixed with opium, while early European doctors made their patients drunk with brandy, tied them to the benches that served as operating tables, or put pressure on a nerve or artery to numb a specific part of the body.

Modern surgeons, however, can perform a variety of procedures to relieve either acute or chronic pain, depending on its cause. These procedures include:

- removal of diseased or dead tissue to prevent infection
- removal of cancerous tissue to prevent the spread of the cancer and relieve pressure on nearby healthy organs and tissues
- correction or reconstruction of malformed or damaged bones
- insertion of artificial joints or other body parts to replace damaged structures
- organ transplantation
- insertion of pacemakers and other electrical devices that improve the functioning of damaged organs or help to control pain directly
- cutting or destroying damaged nerves to control neuropathic pain

PSYCHOTHERAPY Psychotherapy may be helpful to patients with chronic pain syndromes by exploring the connections between anger, depression, or anxiety and physical pain sensations. One type of psychotherapy that has been shown to be effective is cognitive restructuring, an approach that teaches people to "reframe" the problems in their lives—that is, to change their conscious attitudes and responses to these stressors. Some psychotherapists teach relaxation techniques, biofeedback, or other approaches to stress management as well as cognitive restructuring.

Another type of psychotherapy that is effective in treating some patients with chronic pain is hypnosis. Although there is some disagreement among researchers as to whether hypnosis works by distracting the patient's attention from painful sensations or whether it works by stimulating the release of endorphins (chemicals produced by the body that are released in response to stress or injury and act as natural analgesics), it has been approved by the American Medical Association since 1958 as a treatment for pain. Some therapists offer instruction in self-hypnosis to patients with chronic pain.

COMPLEMENTARY AND ALTERNATIVE (CAM) APPROACHES CAM therapies that are used in pain management include:

- **Acupuncture**. Studies funded by the National Center for Complementary and Alternative Medicine (NCCAM) since 1998 have found that acupuncture is an effective treatment for chronic pain in many patients. It is thought that acupuncture works by stimulating the release of endorphins, the body's natural painkillers.
- **Exercise**. Physical exercise stimulates the body to produce endorphins.
- Yoga. Practiced under a doctor's supervision, yoga helps to maintain flexibility and range of motion in joints and muscles. The breathing exercises that are part of a yoga practice also relax the body.
- Prayer and meditation. The act of prayer by itself helps many people to relax. In addition, prayer and meditation are ways to refocus one's attention and keep pain from becoming the center of one's life.
- Naturopathy. Naturopaths include dietary advice and nutritional therapy in their treatment, which is effective for some patients suffering from chronic pain syndromes.
- Hydrotherapy. Warm whirlpool baths ease muscular and joint pain.
- Music therapy. Music therapy may involve listening to music, making music, or both. Some researchers think that music works to relieve pain by temporarily blocking the "gates" of pain in the dorsal horn of the spinal cord, while others believe that music stimulates the release of endorphins.

Pain management

Pain management refers to a set of skills and techniques for coping with chronic pain. The goal of pain management is not complete elimination of pain; rather, the patient learns to keep the pain at a level that he or she can tolerate, and to make the most of life in spite of the pain. The American Chronic Pain Association (ACPA) lists seven coping skills that help in managing pain:

- not dwelling on physical pain symptoms
- emphasizing abilities rather than disabilities
- recognizing one's feelings about the pain and discussing them freely
- using relaxation exercises to ease the emotional tension that makes pain worse.
- doing mild stretching exercises every day (with medical approval)
- setting realistic goals for improvement and evaluating them on a weekly basis
- affirming one's basic rights: the right to make mistakes, the right to say no, and the right to ask questions

An important part of pain management is participation in a multidisciplinary pain program. Many hospitals and rehabilitation centers in the United States and Canada offer pain management programs. Ideally, the program will have its own unit apart from patient care areas. Good pain management programs offer comprehensive treatment that includes relaxation training and stress management techniques; group therapy, family therapy, personal counseling, and job retraining; physical therapy, including exercise and body mechanics; patient education regarding medications and other aspects of pain management; and aftercare or follow-up support.

The treatment team in a pain management program is usually headed by a **neurologist**, psychiatrist, or anesthesiologist with specialized training in pain management. Other members of the team include registered nurses, psychiatrists or psychologists, physical and occupational therapists, massage therapists, family therapists, and vocational counselors.

Clinical trials

As of December 2003, the National Institutes of Health (NIH) was sponsoring 35 studies related to various chronic pain conditions and the effectiveness of such treatments as acupuncture, hypnosis, yoga, COX-2 inhibitors, and several experimental drugs.

Special concerns

Pain management in special populations

Pain management in the elderly and in children poses additional challenges. Although 20% of adults over 65 take an analgesic on a regular basis, older people are more vulnerable to the drug's side effects, particularly the nausea and bleeding that sometimes results from long-term use of NSAIDs. Children require special attention because they do not have an adult's ability to describe their pain. New tools have been developed since the mid-1990s to measure pain in children and to help doctors understand their nonverbal cues.

Addiction and withdrawal

Doctors have debated the risk of opioid abuse for most of the past century. For many years, patients with severe chronic pain were not given enough of the drugs they needed to control their pain because of the fear that they would become addicted to the narcotics. In the mid-1980s, however, some experts in pain management argued that the risk of addiction was quite low, whether the patients suffered from cancer pain or from chronic pain unrelated to cancer. As a result, some synthetic narcotics—most notably oxycodone (OxyContin)—were widely prescribed

and a growing number of patients became addicted to these drugs. As of 2003, researchers estimate that 3–14% of the population may have an underlying undiagnosed vulnerability to abuse these substances.

In addition to the risk of abuse, there is a risk of withdrawal symptoms and a temporary increase in pain (known as rebound pain) if opioid medications are discontinued suddenly. Withdrawal symptoms include diarrhea, runny nose and watery eyes, restlessness, insomnia, anxiety, nausea, and abdominal cramps. These symptoms are usually treated with clonidine (Catapres), an antihypertensive drug, and NSAIDs or antihistamines. The various risks of long-term use of opioids in pain management are not yet fully understood.

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American Academy of Pain Medicine (AAPM). 4700 West Lake, Glenview, IL 60025. (847) 375-4731; Fax: (877) 734-8750. aapm@amctec.com. <http://www.painmed.org>.

American Chronic Pain Association. P. O. Box 850, Rocklin, CA 95677. (916) 632-3208 or (800) 533-3231. ACPA@pacbell.net. <http://www.theacpa.org>.

American Pain Foundation. 201 North Charles Street, Suite 710, Baltimore, MD 21201-4111. (888) 615-PAIN. <http://www.painfoundation.org>.

International Association for the Study of Pain (IASP) Secretariat. 909 NE 43rd Street, Suite 306, Seattle, WA 98105-6020. (206) 547-6409; Fax: (206) 547-1703. iaspdesk@juno.com. <http://www.iasp-pain.org>.

NIH Neurological Institute. P. O. Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

Rebecca J. Frey, PhD

Pallidotomy

Definition

Pallidotomy is the destruction of a small portion of the brain within the globus pallidus internus, or GPi. The GPi helps control voluntary movements.

Purpose

Pallidotomy is performed to treat the symptoms of **Parkinson's disease** (PD), which results from the death of cells in a part of the brain that controls movement, called the substantia nigra. Part of the normal function of the substantia nigra is to inhibit overactivity of the GPi, which itself communicates with other portions of the brain in

complex control circuits. In PD, the overactivity of the GPi is in part responsible for the slowed movements, tremor, and rigidity that are the classic symptoms of the disease. By destroying part of the GPi, some balance is restored to these movement-control circuits, allowing faster and more fluid movements.

Early on in PD, symptoms can be effectively treated with medication, especially levodopa and the dopamine agonists (drugs that act like levodopa). As the disease progresses, increasing amounts of drugs are needed to control symptoms, and the patient's response to the drugs declines. Typically, within 10 years of starting treatment, the patient will develop uncontrolled movements, called dyskinesias, in response to drug treatment. At this point, surgery is considered an option.

The GPi has two halves, which control movements on opposites sides of the body: right controls left, left controls right. Unilateral (one-sided) pallidotomy may be used if symptoms are markedly worse on one side or the other, or if the risks from bilateral (two-sided) pallidotomy are judged to be too great.

Precautions

Pallidotomy is major surgery on the brain. It may cause excessive bleeding, and care must be taken in patients susceptible to uncontrolled bleeding or who are on anticoagulant therapy.

Description

To destroy tissue in the GPi, a long needle-like probe is inserted deep into the brain, through a hole in the top of the skull. To make sure the probe reaches its target exactly, a rigid "stereotactic frame" is attached to the patient's head. This provides an immobile three-dimensional coordinate system, which can be used both to determine the precise position of the GPi and to track the probe on its way to the target.

A single "burr hole" is made in the top of the skull for a unilateral pallidotomy; two holes are made for a bilateral procedure. General anesthesia is not used for two reasons: first, the brain does not feel any **pain**; second, the patient must be awake and responsive in order to respond to the neurosurgical team as they monitor the placement of the probe. The GPi is close to the nerve that carries visual information from the eyes to the rear of the brain. Visual abnormalities during probe placement may indicate that it is too close to this region, and thus needs repositioning.

Other procedures may be used to ensure precise placement of the probe, including electrical recording and injection of a contrast dye into the spinal fluid. The electrical recording can cause some minor odd sensations, but is harmless.

When the probe is in the correct position, its tip is heated briefly. This destroys the surrounding tissue in an area about the size of a pearl. If bilateral pallidotomy is being performed, the localizing and lesioning will be repeated on the other side.

Preparation

A variety of medical tests are needed to properly locate the GPi and fit the frame. These may include computed tomography (**CT**) scans, **magnetic resonance imaging (MRI)**, and injection of dyes into the spinal fluid or ventricles (fluid-filled cavities) of the brain. The frame is attached to the head on the day of surgery, which may be somewhat painful, although the pain is lessened by local anesthetic. A mild sedative is given to ease anxiety.

Aftercare

Pallidotomy takes several hours to perform. In some medical centers, pallidotomy is performed as an outpatient procedure, and patients are sent home the same day. Most centers provide an overnight stay or longer for observation and recuperation. Movement usually improves immediately, and typically requires the reduction of medication to accommodate the improvement.

Risks

Pallidotomy carries significant risks, especially in patients who are in poor health or who are cognitively impaired. Brain hemorrhage is a possible complication, as is infection. Damage to the optic tract, which carries visual messages from the eye to the brain, is a small but significant risk, and is more significant in bilateral pallidotomy. Speech impairments may also occur, including difficulty retrieving words, and slurred speech.

All PD experts agree that risks are lowest when the surgery is performed by neurosurgeons with the most experience in the procedure. Among the best surgeons, the risk of serious morbidity or mortality (i.e., serious consequences or death) is 1–2%. Hemorrhage may occur in 2–6%, visual deficits in 0–6%, and weakness in 2–8%.

Normal results

Pallidotomy improves the patient's ability to move, especially between levodopa doses (so-called "off" periods). Studies show the surgery generally improves tremor, rigidity, and slowed movements by 25–60%. Dyskinesias typically improve by 75% or more. Improvements from unilateral pallidotomy are primarily on the side opposite the surgery. Balance does not improve, nor do "nonmotor" symptoms such as drooling, constipation, and **orthostatic hypotension** (lightheadness on standing).

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Richard Robinson

Key Terms

Dystonia Painful involuntary muscle cramps or spasms.

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

Neurodegeneration The deterioration of nerve tissues.

Pantothenate kinase-associated neurodegeneration

Definition

Pantothenate kinase-associated neurodegeneration (PKAN), long known as Hallervorden-Spatz syndrome (HSS), is a very rare childhood neurodegenerative disorder that is associated with the accumulation of iron in the brain, which causes progressively worsening abnormal movements and **dementia**.

Description

In addition to its original name, Hallervorden-Spatz syndrome, pantothenate kinase-associated neurodegeneration has also been called neurodegeneration with brain iron accumulation (NBIA). The name Hallervorden-Spatz is rapidly being discontinued by those who study and treat the disease, both because the new names indicate the nature of the underlying disorder, and because Julius Hallervorden, who described the syndrome, was involved in a "selective euthanasia" program in Nazi Germany to kill retarded children.

Demographics

PKAN is so rare that there is no reliable information on its prevalence. It affects boys and girls equally. Typical age of onset is in middle childhood to early adolescence, although onset in early adulthood may occur.

Causes and symptoms

PKAN occurs due to mutation in the gene for pantothenate kinase 2 (PANK2), which is an enzyme, a type of protein that regulates a reaction inside a cell. PANK2 helps regulates the production of coenzyme A, an important intermediate in the production of energy within all cells. Mutations in the gene for PANK2 lead to loss of function of this enzyme, the consequence of which is accumulation of iron and the amino acid cysteine within brain cells. It is not yet known how this leads to the disease, but it is possible that cysteine interacts with iron, leading to buildup of other molecules within brain cells that puts stress on the cells and causes them to degenerate.

PKAN causes **dystonia**, a sustained posturing of lower limbs due to excessive muscle contraction. Leg dystonia leads to gait difficulties and other limitations of movement. Dystonia may also affect the upper limbs and the muscles of the face and neck. Abnormal movements may also include writhing or tremor. Ability to walk is usually lost within 15 years. **Dysarthria**, or impairment of the ability to speak, is common, and is usually accompanied by swallowing difficulty. PKAN also causes progressive dementia, or impairment of normal intellectual function, although this is more variable among patients. PKAN may also cause a degenerative eye condition, retinitis pigmentosa.

An atypical form of PKAN has similar features, but with later age of onset and more variable and less severe symptoms. Speech difficulties tend to be more common in atypical patients. Atypical patients may or may not have a recognizable gene defect.

Diagnosis

Diagnosis of PKAN begins with a neurological exam, which is followed up by a **magnetic resonance imaging (MRI)** scan to reveal a characteristic signal from the affected portions of the brain. Genetic testing may be done to look for the mutation in the PKAN gene.

Treatment team

Treatment involves a pediatric **neurologist**, a speech-language pathologist, and physical and occupational therapists.

Treatment

There is no treatment that can halt or slow the degeneration of the brain that occurs in PKAN. The recent discovery of the gene defect may lead to a better

understanding of the neurodegenerative process, and thereby to better treatments.

Drug therapy for the **movement disorders** of PKAN is variably successful, and becomes less so with time. Drugs used for **Parkinson's disease** such as levodopa may be beneficial in some patients. Trihexyphenidyl may be useful. Oral antispasticity medications, including **diazepam** and dantrolene, can help reduce muscle stiffness and **spasticity**. Intrathecal baclofen has been successful in several patients. A **pallidotomy**, a type of brain surgery that destroys part of the globus pallidus internus, a structure in the brain that regulates movements, has shown some success at relieving painful dystonia and returning some function to the affected limbs.

Speech impairment may be the most severe consequence of PKAN. Assistive communication devices such as computers or letter boards offer the possibility of continued communication even as the disease worsens.

Recovery and rehabilitation

Clinical trials

PKAN is so rare there are few **clinical trials**. Some effort is underway to determine whether supplements with PANK2's normal products or related molecules may be effective.

Prognosis

The average duration of disease is 11 years. Death is usually caused by aspiration pneumonia, brought on by food inhaled into the airways.

Resources

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Richard Robinson

Papilledema *see* **Visual disturbances**

Paramyotonia congenita

Definition

Paramyotonia congenita is an inherited condition that causes stiffness and enlargement of muscles, particularly leg muscles.

Description

Paramyotonia congenita is passed on in families as an autosomal dominant trait. This means that males and females are affected equally; it also means that if one parent has the trait, the offspring have a 75% chance of also having the condition.

Demographics

Paramyotonia congenita is present from birth on. In some cases, the symptoms appear to grow more mild as the patient ages.

Causes and symptoms

Paramyotonia congenita is believed to be caused by a defect in the chloride channels of the muscles. As a result, the relaxation phase of the muscles is impaired, resulting in prolonged muscle contraction and stiffness. This "overuse" of the muscle results in the muscle becoming enlarged and bulky (called muscle hypertrophy).

Symptoms of paramyotonia congenita include stiffness and enlargement of various muscle groups, particularly those in the legs. The muscle stiffness of paramyotonia congenita is often exacerbated by cold temperatures and inactivity and relieved by warmth and **exercise**.

Diagnosis

Electromyographic (EMG) testing involves placing a needle electrode into a muscle and measuring its electrical activity. EMG testing in paramyotonia congenita may reveal differences between electrical activity in a warm muscle and electrical activity in a cooled muscle. There are a number of genetic defects that are associated with the chloride channel defect of paramyotonia congenita, some of which can be revealed through genetic testing.

Treatment team

Paramyotonia congenita is diagnosed and treated by neurologists.

Treatment

Paramyotonia congenita is usually mild enough not to require any treatment at all. If muscle stiffness is truly problematic, quinine or anticonvulsant medications (such as phenytoin) may improve functioning.

Prognosis

Paramyotonia congenita has an excellent prognosis. Although annoying, it does not cause significant disability, and the patient usually learns to make lifestyle adjustments that prevent exacerbations (for example, dressing warmly and avoiding exposure to cold).

Resources

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Paraneoplastic syndromes

Definition

Paraneoplastic syndromes (PS) are rare disorders triggered by the immune system's response to cancer cells, or by remote effects of tumor-derived factors. These syndromes are believed to occur when cancer-fighting antibodies or white blood cells, known as T-cells, mistakenly attack normal body cells. These disorders typically affect middle-aged to older people and are most common in patients with lung, ovarian, lymphatic, or breast cancer.

Description

Paraneoplastic syndromes are defined as clinical syndromes involving non-cancerous effects in the body that accompany malignant disease, and can affect any part of the nervous system from the cerebral cortex to peripheral nerves and muscles. In a broad sense, these syndromes are collections of symptoms that result from substances produced by the tumor, occurring far away from the tumor itself. When a tumor arises, the body may produce antibodies to fight it, by binding to and helping in the destruction of tumor cells. Unfortunately, in some cases, these antibodies cross-react with normal tissues and destroy them, which may stimulate the onset of PS. However, not all PS are associated with such antibodies.

Neurological symptoms generally develop over a period of days to weeks, and usually occur prior to the discovery of cancer, which can complicate diagnosis. In these cases, additional information should raise the possibility that the patient may have a hidden cancer and that neurological symptoms could be paraneoplastic. Symptoms include **fatigue**, weakness, muscular **pain** in upper arms, difficulty walking, burning, numbness or tingling sensations in the limbs (peripheral paresthesia), dry mouth, sexual function difficulty, and drooping eyelids.

Neurological signs may include **dementia** with or without brain stem signs, rapid and irregular eye movements, and ophthalmoplegia (weakness or paralysis in muscles that move the eye). Paraneoplastic syndromes involving the nervous system include: **Lambert-Eaton myasthenic syndrome** (LEMS), **stiff person syndrome** (SPS), encephalomyelitis (inflammation of the brain and spinal cord), **myasthenia gravis** (MG), cerebellar degeneration (CD), limbic and/or brain stem encephalitis, neuromyotonia, **opsoclonus myoclonus** (OM), and sensory neuropathy.

Demographics

Most paraneoplastic syndromes are rare, affecting less than 1% of persons with cancer. Exceptions include LEMS, which affects about 3% of patients with small-cell lung cancer; MG, which affects about 15% of persons with thymoma; and demyelinating **peripheral neuropathy**, which affects about 50% of patients with the rare osteosclerotic form of plasmacytoma. No race, age, or sex preference has been reported.

Causes and symptoms

Most or all paraneoplastic syndromes are activated by the body's immune system. In response to a tumor, the immune system produces an antigen that is normally expressed exclusively in the nervous system. The tumor antigen is identical to the normal antigen, but for unknown reasons the immune system identifies it as foreign and mounts an immune response.

In general (although not always), PS develops in an acute or subacute fashion, over days or weeks. Symptoms may include difficulty in walking and/or swallowing, loss of muscle tone, loss of fine motor coordination, slurred speech, memory loss, vision problems, sleep disturbances, dementia, **seizures**, sensory loss in the limbs, and vertigo. The nervous system disability is usually severe.

Diagnosis

Currently, paraneoplastic syndromes are diagnosed using two different technologies in testing blood. Blood testing with western blot using recombinant human antigens is a highly specific method; it can clearly distinguish between different paraneoplastic antibodies. Immunohistochemistry can detect paraneoplastic antibodies in blood

Key Terms

Antibodies A protein produced by the body's immune system to fight infection or harmful foreign substances.

Cytotoxic T-cells A type of white blood cells, T lymphocytes, that can kill body cells infected by viruses or transformed by cancer.

Dysarthria Problems with speaking caused by difficulty moving or coordinating the muscles needed for speech.

Nystagmus Rapid, involuntary eye movements.

Ophthalmoplegia Drooping eyelids.

serum, providing a general diagnosis, but cannot distinguish between the different PS antibodies.

The physician should search for cancer using the most sensitive technology available, including **magnetic resonance imaging (MRI)** and a fluorodeoxyglucose body **positron emission tomography (PET)** scan.

Treatment team

Due to the many manifestations of paraneoplastic syndromes, PS should be evaluated clinically by a coordinated team of doctors, including medical oncologists, surgeons, **radiation** oncologists, endocrinologists, hematologists, neurologists, and dermatologists.

Treatment

Because PS are considered to be immune-mediated disorders, two treatment approaches have been used: removal of the source of the antigen by treatment of the underlying tumor, and suppression of the immune response. For many PS, the first approach is the only effective treatment. In the LEMS and MG, plasma exchange or intravenous immune globulin is usually effective in suppressing the immune response.

Physicians often also prescribe a combination of either plasma exchange or intravenous immune globulin and immunosuppressive agents such as corticosteroids, cyclophosphamide, or tacrolimus. For most paraneoplastic syndromes, immunotherapy is not effective.

Recovery and rehabilitation

Some disorders such as the LEMS and MG respond well to immunosuppressant drugs and to treatment of the underlying tumor. The peripheral neuropathy associated with osteosclerotic myeloma generally resolves when the tumor is treated with radiotherapy. A few disorders may respond to treatment of the underlying tumor, immunosuppression, or both, or they may resolve spontaneously. In many instances, it is not clear whether the PS resolve spontaneously or in response to treatment. Disorders involving the **central nervous system**, such as encephalomyelitis associated with cancer or paraneoplastic cerebellar degeneration, usually respond poorly to treatment, although they may stabilize when the underlying tumor is treated.

Clinical trials

As of mid-2004, the numerous **clinical trials** recruiting participants for the study and treatment of paraneoplastic syndromes include:

- Interferon and Octreotide to Treat Zollinger-Ellison Syndrome and Advanced Non-B Islet Cell Cancer
- Evaluating Pancreatic Tumors in Patients with Zollinger-Ellison Syndrome
- Treatment of Zollinger-Ellison Syndrome
- The Use of Oral Omeprazole and Intravenous Pantoprazole in Patients with Hypersecretion of Gastric Acid

Updates information on these and other ongoing trials can be found at the National Institutes of Health website for clinical trials at <http://www.clinicaltrials.gov>.

Prognosis

The prognosis for persons with paraneoplastic syndromes depends on the specific type of PS, and the progression of the underlying cancer. LEMS and MG are neuromuscular junction diseases, which can recover function once the causal insult is removed, because there is no neuronal loss. Disorders such as CD are usually associated with neuronal damage, and because they evolve subacutely and treatment is often delayed, neurons die, making recovery much more difficult. Some central nervous system disorders such as OM may not involve cellular loss and, thus, patients with these disorders, like those with LEMS, have the potential for recovery.

Special concerns

It is important that caregivers for those with paraneoplastic syndromes receive adequate support. The disorder typically emerges suddenly and without warning. The neurological manifestations of PS are complex and often require 24-hour patient care. Many caregivers will require quick access to information on caring for a disabled person. This includes information on social security benefits, insurance coverage, handicapped license plates, evaluations for physical therapy; medical equipment such as hospital beds, ultra-light wheelchairs, handheld showerheads,

and home healthcare and visiting nurses; and **social workers** and other support services.

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American Autoimmune Related Diseases Association. 22100 Gratiot Avenue, Eastpointe, MI 48201-2227. (586) 776-3900 or (800) 598-4668; Fax: (586) 776-3903. aarda@aol.com. <http://www.aarda.org>.

National Cancer Institute (NCI)—National Institutes of Health. Bldg. 31, Rm. 10A31, Bethesda, MD 20892-2580. (301) 435-3848. cancermail@icicc.nci.nih.gov. <http://cancernet.nci.nih.gov>.

American Cancer Society. 1599 Clifton Road, NE, Atlanta, GA 30329-4251 or (800) ACS-2345 (227-2345). <http://www.cancer.org>.

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Parkinson's disease

Definition

Parkinson's disease (PD) is a neurodegenerative disorder that causes slowed movements, tremor, rigidity, and a wide variety of other symptoms. "Neurodegenerative" refers to the degeneration, or death, of neurons, the type of cell in the brain that is the basis for all brain activity.

Description

Parkinson's disease occurs when neurons (nerve cells) in a part of the brain called the substantia nigra degenerate, or die off. The loss of these cells disrupts the brain's normal control of movement, causing the person to experience slowed movements, stiffness or rigidity, and tremor.

Demographics

PD is one of the most common neurodegenerative diseases, second only to **Alzheimer's disease** in the number of people affected. Estimates suggest that approximately 750,000 Americans have PD. It affects older people much more than younger, and indeed, old age is the single greatest risk factor for PD. The average age at diagnosis is 62. Onset before age 40 is extremely rare. Men are slightly more likely to be affected than women.

Causes and symptoms

In the vast majority of cases, the cause of PD is unknown. Besides old age, there are several well-recognized risk factors. These include exposure to pesticides or herbicides, rural living, and drinking well water. Because of this, it is assumed that some type of environmental pollutant, either a pesticide or something associated with its use, is involved in causing PD. Other known risk factors include welding and exposure to manganese, further strengthening the case for an environmental toxin.

There is also evidence that genes play an important role in determining the risk of PD. PD can run in families, affecting members of the family at a much higher rate than expected by chance alone. Among identical twins, the situation is complex: if one twin develops the disease early, the other is more likely to as well; but if one twin has typical late-onset PD, the other is no more likely to develop the disease than would be expected by chance.

Several genes have been identified that cause PD in some people, but the number of people affected by these genes is quite small. Therefore, the interest of these genes is more in what they can reveal about the disease process than in providing the solution to the mystery of what causes PD in most people. Two of the genetic mutations identified involve a protein called alpha-synuclein, whose normal function is unknown. It is believed that the mutations prevent the normal breakdown of alpha-synuclein, leading it to accumulate in the neuron, where it then goes on to damage the cell. Another gene mutation that causes PD affects a protein called parkin, which normally helps break down proteins. It is believed that the loss of parkin causes build-up of proteins (though not of alpha-synuclein), again leading to damage. Researchers believe that environmental toxins may also cause similar problems, and it now seems likely that problems in protein breakdown are a significant step leading to PD, whether of genetic or environmental causation. Finally, a combination of genetic and environmental factors is likely to be important

in most cases. For instance, a person with a genetically weaker ability to dispose of proteins, who was also exposed to pesticides, might develop PD, whereas a person with different genes but the same exposure might not.

Whatever the ultimate cause, people with PD share the same pathology, or disease process, in their brains. The symptoms of PD arise when cells in the substantia nigra (SN) degenerate. The SN is located at the base of the brain, near the top of the spinal column. Neurons of the SN receive messages from, and send messages to, several other portions of the brain, all of which are involved in the control of movement. By interacting with these other regions, the SN helps to ensure that movements will be smooth, fluid, and controlled.

SN cells communicate with other cells by releasing the chemical dopamine. Dopamine released by SN cells stimulates cells in other brain regions to act. As SN cells die, they release less dopamine, and the receiving cells are not stimulated as much. This leads to the disordered movement of PD. The SN is also involved in regulating numerous other types of brain behaviors, and late-stage PD is marked by a wide variety of symptoms that probably reflect loss of this regulation.

The earliest symptoms of PD, and the most widely recognized, are tremor, slowed movements (bradykinesia), and stiffness or rigidity. Symptoms often begin on one side of the body, and progress over time to involve both sides. The tremor of PD is a rest tremor—the shaking occurs when the patient is not trying to use the limb, and diminishes when the limb is in use. Bradykinesia and stiffness, along with loss of some balance reflexes, can combine to cause postural instability, and increase the likelihood of falling down.

Other symptoms of PD include:

- **orthostatic hypotension**, or loss of blood pressure upon standing, which can cause **dizziness** and fainting
- painful foot cramps
- micrographia, or reduced size of handwriting
- reduced voice volume
- reduced facial expression
- excessive sweating
- constipation
- decreased ability to smell
- male impotence
- drooling
- sleep disturbance
- **depression**
- anxiety
- panic attacks
- late-stage **dementia**

Diagnosis

Parkinson's disease is diagnosed by a careful neurological examination, testing movements, coordination, reflexes, and other aspects of function. If the physician suspects PD, the patient will usually be referred to a **neurologist** for definitive diagnosis. Unilateral (one-sided) tremor, slowed movements, and muscle stiffness are generally enough to confirm the diagnosis; two of the three are usually considered definitive. Several specialized tests may be used, including imaging of the brain with **magnetic resonance imaging (MRI)** or **positron emission tomography (PET)**. These are not essential to diagnosis in most cases, but may help to confirm the diagnosis in difficult cases and to distinguish PD from similar diseases such as **progressive supranuclear palsy**, **corticobasal degeneration**, or **multiple system atrophy**. Clues that the disease is one of these, rather than PD, include early or rapidly progressing dementia, loss of coordination, or early and prominent orthostatic hypotension (lightheadedness upon standing).

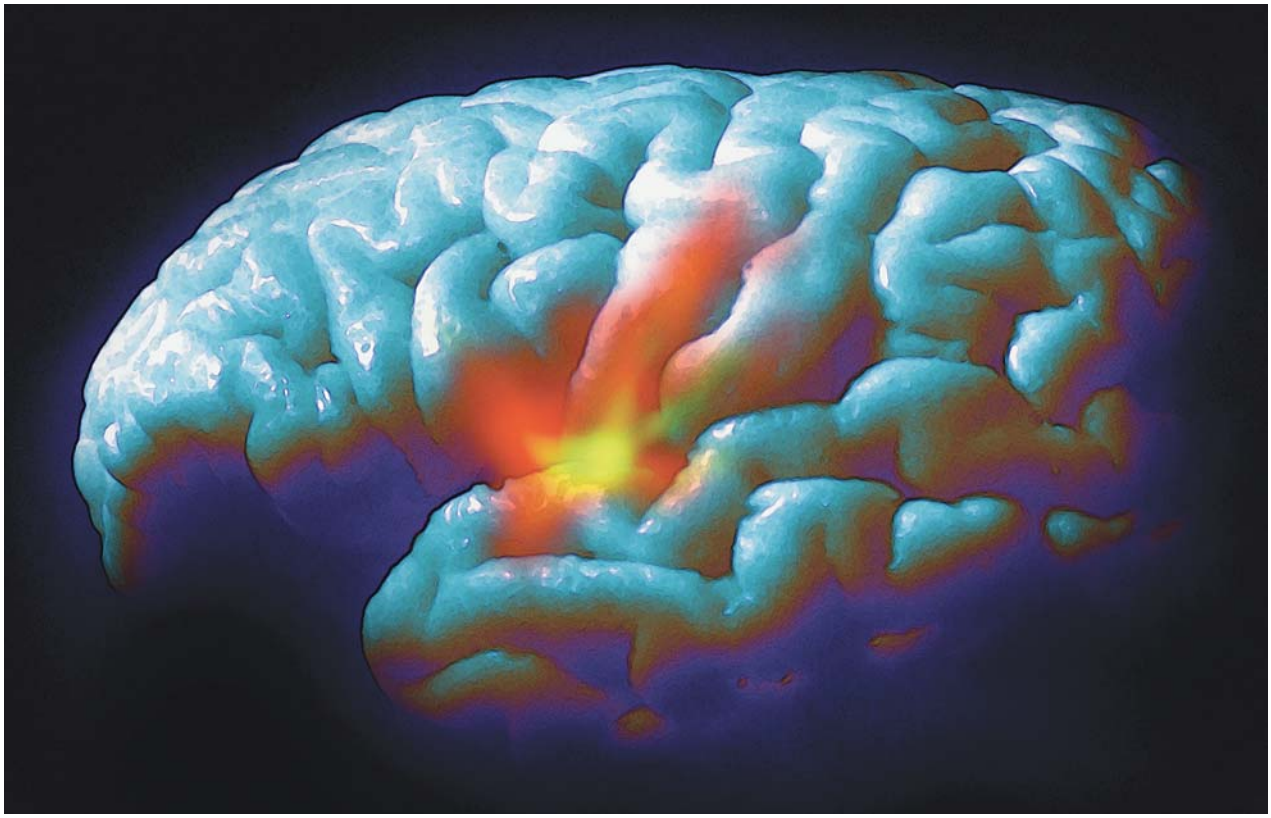
Certain medications can cause a PD-like syndrome, and it is important to rule these out. These drugs include certain antipsychotic medications (haloperidol) and antivomiting drugs (metoclopramide).

Treatment team

Treatment of PD is headed by a neurologist, who may be either a general neurologist or a **movement disorders** specialist. The movement disorders specialist is most likely to be aware of the most current trends in treatment. Since PD therapy continues to undergo rapid advances, it may be an advantage to see a specialist when possible. Other team members may include a speech/language pathologist for addressing voice and **swallowing disorders**, a geriatric medicine specialist to coordinate other medical and social issues, a **neuropsychologist** for expertise on cognitive aspects of PD and its treatment, and a neurosurgeon.

Treatment

There are no treatments that have been proven to slow the course of PD, although research published in 2003 suggested that coenzyme Q10 may offer a slight benefit in this regard. The study has not been replicated, and its authors noted it would be premature to recommend treatment with this very expensive supplement. Additional claims have been made that two medications used to treat PD symptoms—selegiline and dopamine agonists—may have



The highlight indicates the area of the brain affected by Parkinson disease. *(David Gifford / Photo Researchers, Inc.)*

some disease-slowing effects. These claims are not widely accepted.

The treatment of the symptoms of PD is complex for several reasons. First, PD is a progressive disease, getting worse over time, so that the medications and doses that work well early in the disease are insufficient later on. Second, the most effective drugs have long-term side effects that are troubling and difficult to control. Third, there are a lot of different treatment options, and finding the right combination can be time consuming. Fourth, the PD patient is likely being treated for other conditions associated with advancing age, and these conditions or their treatment may interfere with treatment of PD. Finally, a major treatment option for late-stage PD is surgery, but the risks of surgery are significant, and determining when and what kind of surgery to perform is a complicated decision.

Once the diagnosis of PD has been made, a central question is when to begin treatment. Treatment is typically not started right away (unless the patient elects to use coenzyme Q10), but instead is delayed until symptoms begin to interfere with his or her ability to work or engage in activities of daily living. This may be a year or even more after diagnosis.

Key Terms

Neurodegenerative Relating to the deterioration of nerve tissues.

Drug treatment

The next question is what drug to begin with. The most powerful treatment for the symptoms of PD is levodopa, which is taken into the brain and substitutes for the dopamine no longer being made by the substantia nigra. Similar in effect are the dopamine agonists, which mimic the effect of dopamine on the cells that normally receive dopamine from the SN. Three other medications also commonly used in PD, whose effects are not nearly as strong as either levodopa or the dopamine agonists, are **anticholinergics**, selegiline, and **amantadine**. These are often prescribed early on, when symptoms are not severe, saving the more powerful medications for later on.

Anticholinergics include benztropine and trihexyphenidyl. The loss of SN activity means that another

brain system that controls movement, the cholinergic system, is relatively overactive. Anticholinergics dampen the activity of this system, restoring some balance to the control of movement. Anticholinergics are usually well tolerated in younger patients, but their side effects can be a significant barrier to their use in the elderly. Side effects include sedation, confusion, hallucinations, **delirium**, dry mouth, constipation, and urinary retention.

Selegiline inhibits the action of monoamine oxidase B, an enzyme in the brain that breaks down dopamine. Thus, selegiline prolongs the activity of dopamine in the brain. It can cause insomnia and hallucinations, as well as orthostatic hypotension. It may also interact with certain types of antidepressants, and for this reason, selegiline may be discontinued when beginning treatment for depression. In the early 1990s, selegiline was examined for its potential for neuroprotection, or disease slowing. The results of that trial were inconclusive; selegiline had such a significant and long-lasting symptomatic benefit that it was difficult to examine its disease-slowing effects independently.

Amantadine improves PD symptoms through an unknown mechanism. It is beneficial for each of the major movement symptoms of PD, although its effects are not strong. It also can lessen dyskinesias, which are unwanted movements that develop late in PD due to treatment. Amantadine can cause orthostatic hypotension and confusion.

Most drugs have side effects, and drugs for PD are no exception. The most effective drugs for PD, levodopa and the dopamine agonists, cause a set of side effects called "dopaminergic" side effects, indicating they derive from mimicking the action of dopamine. Dopaminergic side effects include nausea and vomiting, orthostatic hypotension, excessive sleepiness, hallucinations, and dyskinesias (in more advanced patients). Nausea, vomiting, and orthostatic hypotension tend to lessen with use, and do not pose long-term problems for most patients. Excessive sleepiness is a problem for many patients. Dyskinesias are an unavoidable effect of dopaminergic treatments, although dopamine agonists tend to cause less of it than levodopa. Dyskinesias tend to appear after three or more years of successful treatment, and become worse over time. Episodes of dyskinesias can be lessened by reducing the dose of the dopaminergic drug, but may lose symptomatic benefit. Adjusting drugs to minimize dyskinesias while maintaining good symptom control is a central challenge of managing PD.

Levodopa is the most effective treatment for PD symptoms, and is the drug used most often at the beginning of disease in elderly patients, because it is less likely to cause hallucinations than dopamine agonists. It is given in a pill that also contains another medication, called carbidopa, which inhibits an enzyme that would act on dopamine in the bloodstream, thus allowing more of it to reach the brain. In order for levodopa to be taken up by the gut and to pass from the bloodstream to the brain, a carrier that also moves amino acids from food must transport the drug. For this reason, doctors typically suggest that patients avoid taking levodopa with or right after a protein-rich meal. Levodopa may also be given with another medication, called a COMT inhibitor, which further prevents its breakdown in the bloodstream. A new pill combines levodopa, carbidopa, and a COMT inhibitor.

Dopamine agonists are almost as effective as levodopa for combating PD symptoms, and have the advantage that their use does not lead to dyskinesias as frequently as levodopa does. For this reason, many movement disorder specialists begin their patients on a dopamine agonist rather than levodopa. This is especially true for younger patients, who can anticipate more years of dopaminergic therapy, and a higher likelihood of developing dyskinesias as a result. There are four major dopamine agonists available in the United States: pergolide, pramipexole, bromocriptine, and ropinirole. Each is taken as a pill, and can be taken alone or in combination with levodopa or other medications. Some patients respond better to one than another, and inadequate relief from one does not mean the same should be expected from another. The U.S. Food and Drug Administration was expected to approve a fifth dopamine agonist, called apomorphine, by mid-2004. Unlike the others, it is injected, and provides very rapid, short-term symptomatic relief when a dose of levodopa wears off.

Excessive sleepiness is a potentially dangerous side effect for all the dopaminergic drugs (levodopa and the dopamine agonists). This can take the form of predictable, peak-dose sleepiness, or general increase in sleepiness during the day, or a sudden, unpredictable "attack" of sleepiness and falling asleep. The latter can be dangerous if it occurs while driving or performing another activity requiring full awareness. Patients are cautioned to be aware of changes in sleepiness especially after changing a medication, and to avoid driving whenever possible if excessive sleepiness does become a side effect issue.

Complications of advanced disease

After several years of successful treatment, most patients begin to develop one or more motor complications. These often begin with "wearing off," a reduction in the duration of effect of a given dose of levodopa, which initially can be countered by dosing more frequently. Another complication is "on-off," in which the symptomatic benefit of a given dose suddenly switches off and the patient becomes rigid, with tremor and slowed movements emerging. When this occurs at home, the patient will typically just take another dose of medication, and wait for it

to begin to work. It is more of a problem when it occurs while the patient is out and about, and frequent on-off episodes may make the patient reluctant to leave the home. Apomorphine injection may be useful in this situation, since it works very rapidly (approximately seven minutes), and can therefore be used as a "rescue" for sudden off periods. Dyskinesias are a third motor complication. Dyskinesias are uncontrolled writhing movements that typically occur at the peak of effect of a levodopa dose. In some cases for some patients, dyskinesias are mild enough that they are not problematic. In other cases, they interfere with function, and attempting to reduce them becomes an important treatment issue. While drug adjustments can have some effect, as the disease progresses it becomes more and more difficult to maintain adequate symptom control while avoiding dyskinesias. At this stage, the patient may consider surgery for treatment of PD symptoms.

Other complications arise in advanced PD, especially in "non-motor" symptoms, those that do not affect movement. Low voice volume may be amenable to speech therapy treatment, with one of the most effective programs being **Lee Silverman voice treatment**, which focuses on conscious attempts to increase volume. Orthostatic hypotension may be treatable with increased salt intake, compression stockings, and medication. Drooling may become an issue in later-stage disease; there are both drug treatments and non-drug therapies available to reduce this problem. Constipation is a significant problem for many advanced PD patients, and can be treated with standard measures such as increasing the fiber in the diet and bulking laxatives.

Panic attacks and anxiety are common in PD. These can be addressed both through helping the patient understand that this is a feature of the disease, and through antianxiety medication. Depression affects many PD patients, and can worsen other aspects of the disease. It usually responds well to antidepressant medications. Dementia (loss of memory and impairment of other thinking functions) occurs more frequently in PD patients than in the population at large. Treatment is similar to that in non-PD patients, although some medications cannot be used because they have undesirable side effects for PD patients. Psychosis-hallucinations, paranoia, nightmares, and delusions may be a response to dopaminergic medications. If these side effects cannot be controlled through modification of treatments, an antipsychotic drug may be useful.

Surgery

Brain surgery is a treatment option in late-stage PD. The best candidate is the individual who continues to respond to levodopa, but whose treatment is complicated by unacceptable dyskinesias even after medication adjustment. Dementia or other significant health-related conditions may make the patient unsuitable for the rigors of surgery. The patient is usually evaluated by the neurologist, a neuropsychologist, and a neurosurgeon before deciding whether surgery is the right option.

There are two types of surgery for PD. An "ablative" lesion destroys a small portion of the brain, and in so doing, restores the balance of neural activity within the movement control circuits of the brain; ablation means to destroy or remove. The second option is **deep brain stimulation** (DBS), which accomplishes the same thing by implanting an electrode in the target brain region; electrical pulses shut the region down. Ablative lesions are simpler and less prone to long-term complications, but they are not adjustable after the lesion has been made. DBS is more complex, expensive, and time consuming, and carries a significant risk for infection or equipment malfunction, but it can be adjusted to more precisely target the brain region, thereby enhancing the surgical effect.

Three brain regions are targeted in PD surgery. Ablation of the thalamus (thalamotomy) is primarily effective in controlling tremor, and is not widely performed anymore since other, more effective targets are available. The globus pallidus internus (GPi) can either be ablated (**pallidotomy**) or stimulated (GPi DBS), which is effective for all the major motor symptoms of PD (tremor, bradykinesia, rigidity), and can improve them by 25–60%. It is also effective for reducing dyskinesias by up to 90%. The subthalamic nucleus can be stimulated in STN DBS, and is highly effective for all the major motor symptoms and dyskinesias, to a somewhat greater extent than GPi DBS. An additional advantage of STN DBS is that it is safer to do on both sides of the brain (left and right, termed bilateral) than GPi DBS. Therefore, if the patient is affected by disabling symptoms on both sides, as is often the case in advanced PD, bilateral STN DBS may be a better choice.

Clinical trials

Parkinson's disease is the subject of intense research, and there are usually several large and important **clinical trials** going on at any time. Trials may focus on slowing the disease, determining the best drug treatment, or refining surgical methods and targets.

Two experimental forms of surgery have been the subject of recent clinical trials. The first is the implantation of cells into the substantia nigra to replace the lost dopamine-producing cells. The implanted cells come from fetal tissue. Fetal-tissue transplants have led to success, but also to uncontrolled dyskinesias in some patients. For this reason, such trials on are on hold until a better understanding of this problem is discovered and methods are developed to avoid it.

The second form of surgery delivers a growth factor to the substantia nigra via an implanted pump and tube.

The growth factor, called GDNF, has been shown to slow cell death in experimental systems. A small group of patients undergoing this surgery has improved, although these results are quite preliminary.

Prognosis

PD is a progressive disease, and the loss of brain tissue in the SN is inevitable. PD patients tend to live almost as long as age-matched individuals without PD, although with an increasing level of disability. Loss of motor control can lead to an increased risk for falls, and swallowing difficulty can cause choking or aspiration (inhaling) of food. Aspiration pneumonia is a common cause of death in late-stage PD patients.

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Richard Robinson

Paroxysmal hemicrania

Definition

Paroxysmal hemicrania (PH) is a rare form of **headache**. Paroxysmal hemicrania usually begins in adulthood, and affected persons experience severe throbbing, claw-like, or boring **pain**. The pain is usually on one side of the face, near or in the eye, temple, and occasionally reaching to the back of the neck. Red and tearing eyes, a drooping or swollen eyelid on the affected side of the face, and nasal congestion may accompany this pain. Persons experiencing the headache pain of paroxysmal hemicrania may also feel dull pain, soreness, or tenderness between attacks.

Description

Paroxysmal hemicrania syndromes have two forms: chronic, in which persons experience attacks on a daily basis for a year or more, and episodic, in which the headaches do not occur for months or years. Episodic paroxysmal hemicrania is four times more common than the chronic form.

Chronic paroxysmal hemicrania (CPH), also known as Sjaastad syndrome, is a primary headache disorder first described by the Norwegian **neurologist** Ottar Sjaastad in 1974. In 1976, Sjaastad proposed the term chronic paroxysmal hemicrania after observing two patients, who had daily, solitary, severe headache pain that remained on one side of the head. The main feature of chronic paroxysmal hemicrania is frequent attacks of strictly one-sided severe pain localized in or around the eye or temple regions, lasting from 2–45 minutes in duration, and occurring 2–40 times per day.

Attacks of chronic paroxysmal hemicrania do not occur in recognizable time patterns. Episodic paroxysmal hemicrania (EPH), a more rare form of the disorder, is characterized by bouts of frequent, daily attacks with the same clinical features of CPH, but separated by relatively long periods without headache. Most episodic headaches in paroxysmal hemicrania occur at night or other recognizable time patterns.

Demographics

In the United States, CPH is a rare syndrome, but the number of diagnosed cases is increasing. The prevalence of CPH is not known, but it occurs more often than cluster headaches, a disorder of that can sometimes be confused with CPH. Internationally, many cases of CPH have been described throughout the world, in different races and different countries.

Chronic paroxysmal hemicrania affects more women than men. In the past, because of female preponderance, CPH was considered a disease exclusive to women. However, CPH has been reported in increasing numbers of men. A study conducted in 1979 reported a female-to-male ratio of 7:1, but a review of 84 patients in 1989 reported a female-to-male ratio of 2.3:1. Chronic paroxysmal hemicrania can occur at any age, and the mean age of onset is 34 years.

Episodic paroxysmal hemicrania occurs in both sexes, with a slight female preponderance (1.3:1). The age of onset is variable; studies show EPH onset is 12–51 years.

Causes and symptoms

No definite cause of paroxysmal hemicrania is known. Persons who experience these headaches usually do not have additional neurological disorders, with the exception of **trigeminal neuralgia**, which has been observed in a small number of persons also having paroxysmal hemicrania. History of head or neck trauma is reported in about 20% of persons with paroxysmal hemicrania, but

these findings are similar to cluster headache or migraine headaches. Occasionally, attacks may be provoked mechanically by bending or rotating the head and by applying external pressure against the back of the neck. There is no inheritable pattern or familial disposition known for paroxysmal hemicrania, and affected individuals do not have a higher incidence of other types of headaches, such as CH or migraine, than the general population.

Headache is the main symptom of both types of paroxysmal hemicrania. Chronic PH involves headaches that are one-sided, severe, affecting the eye or temple area, and lasting two to 45 minutes, occurring more than five times per day. Episodic paroxysmal hemicrania involves attacks of severe pain in the eye or temple area that last about one to 30 minutes, with a frequency of three or more events per day, and clear intervals between bouts of attacks that may last from months to years.

Both chronic and episodic paroxysmal hemicrania involve symptoms such as nasal congestion on the affected side, rhinorrhea (runny nose), and swelling of the eyelid on the affected side with tearing. Sweating, both on the forehead and generalized over the body, is also common.

Diagnosis

The diagnosis of paroxysmal hemicrania is based on a person's history and clinical symptoms. There are conditions involving underlying lesions in the brain (such as tumors or arteriovenous malformation) that can lead to symptoms similar to the headaches of paroxysmal hemicrania. Because of this, various tests of the brain are recommended to exclude structural abnormalities.

Laboratory studies such as routine blood tests can help identify metabolic and other causes of headache and facial pain. Imaging studies including computed tomography (**CT**) scan, or preferably **magnetic resonance imaging (MRI)** of the brain may be needed to rule out structural disorders of the eye, ear, nose, neck, skull, and brain.

Testing the effectiveness of the drug indomethiacin may also be a useful tool in the assessment of one-sided headaches. The response to indomethacin is part of the criteria for a diagnosis of paroxysmal hemicrania. During two different periods, the drug is administered intramuscularly, and patterns of headache pain are evaluated. In paroxysmal hemicranias, indomethiacin relieves pain, prevents recurring pain, and/or decreases the frequency of pain. As the effects of indomethacin clear the body, the pain returns in its usual form and pattern.

Treatment team

A neurologist is the primary consultant for PH treatment. An ophthalmologist is also important to evaluate any eye disorders such as glaucoma.

Key Terms

Cluster headache A painful recurring headache associated with the release of histamine from cells.

Migraine A severe recurring vascular headache; occurs more frequently in women than men.

Trigeminal neuralgia A condition resulting from a disorder of the trigeminal nerve resulting in severe facial pain.

Treatment

The nonsteroidal anti-inflammatory drug (NSAID) indomethacin often provides complete relief from symptoms. Other less effective NSAIDs, calcium-channel blocking drugs (such as verapamil), and corticosteroids may be used to treat the disorder. Patients with both PH and trigeminal neuralgia (a condition of the fifth cranial nerve that causes sudden, severe pain typically felt on one side of the jaw or cheek) should receive separate treatment for each disorder.

Recovery and rehabilitation

When headaches are severe enough or frequent enough to interfere with a person's daily activities such as work, family life, and home responsibilities, a specially trained physical therapist can provide a variety of treatment and education services to manage or reduce headaches, including:

- exercises (stretching, strengthening, and aerobic conditioning)
- safe sleep, standing, and sitting postures
- performing daily activities safely
- relaxation

Clinical trials

As of mid-2004, there were no ongoing **clinical trials** specific to the study or treatment of paroxysmal hemicrania. The National Institute for Neurological Disorders and Stroke (NINDS), however, carries out multifaceted research on headaches and their causes.

Prognosis

Many patients experience complete relief or near-complete relief of symptoms following medical treatment for paroxysmal hemicrania. PH headaches may occur throughout life, but have also been known to go into remission or stop spontaneously.

Special concerns

Chronic paroxysmal hemicrania headaches have been reported to improve during pregnancy; however, they often recur after delivery. In some persons, menstruation lessens the headaches, while in others, headaches are worse during menstruation. Birth control pills do not seem to influence the frequency of attacks, and the effects of menopause on paroxysmal hemicrania are unknown.

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ORGANIZATIONS

American Council for Headache Education. 19 Mantua Road, Mt. Royal, NJ 08061. (856)423-0258 or (800) 255-ACHE (255-2243); Fax: (856) 423-0082. achehq@talley.com. <http://www.achenet.org>.

National Headache Foundation. 820 N. Orleans, Suite 217, Chicago, IL 60610-3132. (773) 388-6399 or (888) NHF-5552 (643-5552); Fax: (773) 525-7357. info@headaches.org. <http://www.headaches.org>.

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Parsonage-Turner syndrome

Definition

Parsonage-Turner syndrome (PTS) is a rare syndrome of unknown cause, affecting mainly the lower motor neurons of the brachial plexus. The brachial plexus is a group of nerves that conduct signals from the spine to the shoulder, arm, and hand. PTS is usually characterized by the sudden onset of severe one-sided shoulder **pain**, followed by paralysis of the shoulder and lack of muscle control in the arm, wrist, or hand several days later. The syndrome can vary greatly in presentation and nerve involvement.

Description

PTS, also known as brachial plexus neuritis or neuralgic amyotrophy, is a common condition characterized by inflammation of a network of nerves that control and supply (innervate) the muscles of the chest, shoulders, and arms. Individuals with the condition first experience severe pain across the shoulder and upper arm. Within a few hours or days, weakness, wasting (atrophy), and paralysis may affect the muscles of the shoulder. Although individuals with the condition may experience paralysis of the affected areas for months or, in some cases, years, recovery is usually eventually complete.

Local pain around the shoulder girdle is the prevalent symptom of Parsonage-Turner syndrome. It is usually sudden and often severe, often awakening persons during the night. The pain worsens progressively for up to two days. Described as a constant, severe ache associated with tenderness of the muscles, the pain is not affected by coughing. However, it is accentuated by arm movements and muscular pressure, but almost unaltered by movements of the neck. The pain is commonly distributed across the back of the scapula (shoulder blade) and the tip of the shoulder. Pain often radiates down the outer side of the arm and up along the neck, and seldom spreads down as far as the outer side of the forearm, below the elbow. There is no exact correlation between the localization of the pain and the distribution of the subsequent muscle paralysis.

However, in general, pain radiating below the elbow is associated with involvement of the biceps or triceps, and **radiation** into the neck involves the sternocleidomastoid and trapezius muscles. Usually the severe pain lasts from a few hours to three weeks and then disappears rather suddenly; at the same time, muscular wasting and weakness are occurring. A less severe pain may persist considerably longer.

As the pain subsides, paralysis of some muscles of the shoulder girdle, and often of the arm, develops. Usually, muscle weakness appears suddenly, but sometimes gradually increases over two or three days, or up to one week in rare cases. The paralysis involves limpness and rapid wasting of the affected muscles. Tendon reflexes might be affected, depending on the severity and extent of muscular paralysis and wasting. Weakened reflexes are frequently encountered, and fasciculations (fine **tremors**) occasionally occur.

Demographics

In the United States, the incidence is approximately 1.64 cases per 100,000 people per year. Internationally, PTS has been described in many countries around the

Key Terms

Atrophy Degeneration or wasting of tissues.

Brachial plexus A group of nerves that exit the cervical (neck) and upper thoracic (chest) spinal column to provide muscle control to the shoulder, arms, and hands.

Scapula The bone also known as the shoulder blade.

Trapezius Muscle of the upper back that rotates the shoulder blade, raises the shoulder, and flexes the arm.

Triceps Muscle of the back of the upper arm, primarily responsible for extending the elbow.

world, although specific rates of incidence have not been reported. There is a male predominance in PTS with a male-to-female ratio ranging from 2:1–4:1. Individuals as young as three months or as old as 74 years can be affected with PTS; however, the prevalence is highest in young to middle-aged adults. When a child develops Parsonage-Turner syndrome, hereditary PTS should be considered.

Causes and symptoms

The exact cause of PTS is unknown, but the condition has been linked to many previous events or illnesses such as:

- viral infection (particularly of the upper respiratory tract)
- bacterial infection (e.g., pneumonia, diphtheria, typhoid)
- parasitic infestation
- surgery
- trauma (not related to shoulder)
- vaccinations (e.g., influenza, tetanus, diphtheria, tetanus toxoids, pertussis, smallpox, swine flu)
- childbirth
- miscellaneous medical investigative procedures (e.g., lumbar puncture, administration of radiologic dye)
- systemic illness (e.g., polyarteritis nodosa, lymphoma, systemic **lupus** erythematosus, **temporal arteritis**, Ehlers-Danlos syndrome)

In addition to these possible causes, a rare hereditary form of PTS has been localized to a defect on chromosome 17, and should be considered a distinct disorder. This form of the disorder occurs in a younger age group, affects males and females equally (autosomal-dominant inheritance), and is characterized by recurrent attacks that often cause pain on both sides of the body.

Acute pain in the shoulder girdle or arm is almost always the first symptom. Shortly thereafter, muscle weakness and wasting in the shoulder girdle and arm occur. The pain, which may be extraordinarily severe for a short time, eventually abates.

Diagnosis

PTS is a clinical syndrome, and therefore diagnosis is made by exclusion. Other disorders of the upper extremity or cervical spine have to be excluded, including abnormalities of the rotator cuff, acute calcific tendinitis, adhesive capsulitis, cervical **radiculopathy**, peripheral **nerve compression**, acute **poliomyelitis**, and **amyotrophic lateral sclerosis** (ALS). PTS may sometimes be confused with peripheral nerve compression or traction injury of the brachial plexus. Affected persons, however, do not experience the acute intense pain associated with PTS, and the loss of strength occurs simultaneously with the sensory changes.

In PTS, x rays of the cervical spine and shoulder show normal findings compatible with the patient's age. Nerve conduction studies and **electromyography** (EMG) are helpful in localizing the lesion. Three to four weeks after the onset of pain, EMG studies show changes consistent with PTS. Arthrography or ultrasound may be useful to rule out a tear of the rotator cuff. **MRI** may reveal muscles changes associated with PTS.

Treatment team

A specialist in neuromuscular disease may be consulted to confirm diagnosis and evaluate any potentially underlying causes. An orthopedic surgeon is important when nerve grafting or tendon transfer is necessary. Physical and occupational therapists may be asked to provide a comprehensive rehabilitation program.

Treatment

No specific treatment has yet been proved efficient in PTS. In the early stages, pain may require treatment. Common analgesic drugs are usually sufficient. Usually, steroidal medications do not relieve the pain or improve muscle function in PTS. Rest is recommended, and immobilization of the affected upper extremity may be helpful in relieving the pain and in preventing stretching of the affected muscles.

As pain subsides, physical therapy is recommended. Passive range of motion exercises of the shoulder and elbow are suggested to maintain full range of motion.

Surgical stabilization of the scapula to the thorax, or tendon transfers have been performed with benefit in persons with PTS who experience continuing pain and muscle weakness.

Recovery and rehabilitation

Physical therapy should focus on the maintenance of full range of motion (ROM) in the shoulder and other affected joints. Passive range of motion (PROM) and active range of motion (AROM) exercises should begin as soon as the pain has been controlled adequately, followed by regional conditioning of the affected areas. Strengthening of the rotator cuff muscles and scapular stabilization may be indicated. Passive modalities (e.g., heat, cold, transcutaneous electrical nerve stimulation) may be useful as adjunct pain relievers.

Another type of rehabilitation therapy in PTS is occupational therapy. Functional conditioning of the upper extremity may be helpful. Assistive devices and orthotics (such as splints or devices for grasping and reaching) may be used, depending on the particular disabilities present.

Clinical trials

As of mid-2004, there were no ongoing **clinical trials** specific for PTS.

Prognosis

The overall prognosis for persons with PTS is good, as recovery of strength and sensation usually begins spontaneously as early as one month after the onset of symptoms. Almost 75% of persons with PTS experience complete recovery within two years. However, the period of time for complete recovery is variable, ranging from six months to five years. It seems that the delay in recovering strength depends on the severity and duration of pain, weakness, or both. Furthermore, patients with involvement of upper trunk lesions have the most rapid recovery. Although not very common, relapse might occur within a few months to several years after full recovery. In general, complete restoration of normal strength and function usually occurs within five years.

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American Autoimmune Related Diseases Association. 22100 Gratiot Avenue, Eastpointe, MI 48021. (586) 776-3900. aarda@aarda.org. <http://www.aarda.org/>.

NIH/National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse. 1 AMS Circle, Bethesda, MD 20892-3675. (301) 495-4484 or (877) 226-4267. niamsinfo@mail.nih.gov. <http://www.niams.nih.gov>.

Greiciane Gaburro Paneto
Iuri Drumond Louro

Pellegra *see* **Vitamin/nutritional deficiency**

Pemoline *see* **Central nervous system stimulants**

Perineural cysts

Definition

Perineural cysts (also called Tarlov cysts) are abnormal fluid-filled sacs located in the sacrum, the base of the spine.

Description

Perineural cysts appear to be dilated or ballooned areas of the sheaths that cover nerve roots exiting from the sacral area of the spine. The spaces or cysts created by the dilated sheaths are directly connected to the subarachnoid area of the spinal column, the area through which cerebrospinal fluid flows. Many people have perineural cysts but no symptoms at all; in fact, the majority of people with these cysts are completely unaware of their existence. However, when conditions cause these perineural cysts to fill with cerebrospinal fluid and expand in size, they can begin to compress important neighboring nerve fibers, resulting in a variety of symptoms, including **pain**, weakness, and abnormal sensation.

Demographics

More women than men develop perineural cysts.

Causes and symptoms

A variety of conditions that can increase the flow of cerebrospinal fluid may cause perineural cysts to expand in size, creating symptoms. Such conditions include traumatic injury, shock, or certain forms of exertion (such as heavy lifting) or **exercise**. Prolonged sitting or standing may cause cysts to fill and retain fluid. Other research suggests that herpes simplex virus can cause the body chemistry to become more alkaline, which predisposes the

Key Terms

Cerebrospinal fluid A fluid that bathes the brain and the spinal cord.

Cyst A fluid-filled sac.

Sacrum An area in the lower back, below the lumbar region.

Subarachnoid The space underneath the layer of meningeal membrane called the arachnoid.

cerebrospinal fluid to fill the perineural cysts, thus prompting the advent of symptoms.

The symptoms of expanding perineural cysts occur due to compression of nerve roots that exit from the sacral area. Symptoms may include **back pain** and **sciatica**, a syndrome of symptoms that occur due to compression or inflammation of the sciatic nerve. Sciatica results in burning, tingling, numbness, stinging, or electric shock sensations in the lower back, buttocks, thigh, and down the leg to below the knee. Severe sciatica may also result in weakness of the leg or foot. Other more severe symptoms of perineural cysts include loss of bladder control and problems with sexual functioning.

Diagnosis

Because most perineural cysts don't cause symptoms, most perineural cysts are never diagnosed. When symptoms do develop that are suggestive of perineural cysts, **MRI** will usually demonstrate their presence, and CT myelography (a test in which dye is injected into the spine) may demonstrate the cerebrospinal fluid flow between the spinal subarachnoid area and the cyst.

Treatment team

Neurologists and neurosurgeons usually treat individuals with perineural cysts. A urologist may be called in to consult with individuals whose cysts are interfering with bladder or sexual functioning.

Treatment

Although using a needle to drain fluid from perineural cysts can temporarily relieve their accompanying symptoms, eventually the cysts will refill with cerebrospinal fluid and the symptoms will recur. Similarly, steroid injections can provide short-term pain relief. Pain may also be temporarily controlled by injecting the cysts with fibrin glue (a substance produced from blood chemicals involved in the clotting mechanism). Using diet or dietary supplements to decrease the body's alkalinity may prevent perineural cysts from filling with more fluid. Medications used to treat chronic nerve-related pain (such as **anticonvulsants** and antidepressants) may be helpful.

When pain is intractable despite a variety of interventions, or when weakness or other neurological symptoms become severe, surgery to remove the cysts may be necessary. This is the only permanent treatment for perineural cysts; once removed, they very rarely recur.

Prognosis

Most individuals with perineural cysts have no symptoms whatsoever. Those who do have symptoms run a risk of neurological damage if the cysts continue to compress nerve structures over time. Individuals who undergo neurosurgery to remove the cysts usually have an excellent outcome, with no cyst recurrence.

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Periodic paralysis

Periodic **paralysis** (PP) is the name for several rare, inherited muscle disorders marked by temporary weakness, especially following rest, sleep, or exercise.

Description

Periodic paralysis disorders are genetic disorders that affect muscle strength. There are two major forms, hypokalemic and hyperkalemic, each caused by defects in different genes.

In hypokalemic PP, the level of potassium in the blood falls in the early stages of a paralytic attack, while in hyperkalemic PP, it rises slightly or is normal. (The root of both words, "kali," refers to potassium.) Hyperkalemic PP is also called potassium-sensitive PP.

Causes and symptoms

Both forms of PP are caused by inheritance of defective genes. Both genes are dominant, meaning that only one copy of the defective gene is needed for a person to develop the disease. A parent with the gene has a 50% chance of passing it along to each offspring, and the likelihood of passing it on is unaffected by the results of previous pregnancies.

The gene for hypokalemic PP is present equally in both sexes, but leads to noticeable symptoms more often in men than in women. The normal gene is responsible for a muscle protein controlling the flow of calcium during muscle contraction.

The gene for hyperkalemic PP affects virtually all who inherit it, with no difference in male-vs.-female expression. The normal gene is responsible for a muscle protein controlling the flow of sodium during muscle contraction.

The attacks of weakness in hypokalemic PP usually begin in late childhood or early adolescence and often become less frequent during middle age. The majority of patients develop symptoms before age 16. Since they begin in the school years, the symptoms of hypokalemic PP are often first seen during physical education classes or after-school sports, and may be mistaken for laziness, or lack of interest on the part of the child.

Attacks are most commonly brought on by:

- strenuous **exercise** followed by a short period of rest
- large meals, especially ones rich in carbohydrates or salt
- emotional **stress**
- alcohol use
- infection
- **pregnancy**

The weakness from a particular attack may last from several hours to as long as several days, and may be localized to a particular limb, or might involve the entire body.

The attacks of weakness of hyperkalemic PP usually begin in infancy or early childhood, and may also become less severe later in life. As in the hypokalemic form, attacks are brought on by stress, pregnancy, and exercise followed by rest. In contrast, though, hyperkalemic attacks are not associated with a heavy meal but rather with missing a meal, with high potassium intake, or use of glucocorticoid drugs such as prednisone. (**Glucocorticoids** are a group of steroids that regulate metabolism and affect muscle tone.)

Weakness usually lasts less than three hours, and often persists for only several minutes. The attacks are usually less severe, but more frequent, than those of the hypokalemic form. Weakness usually progresses from the lower limbs to the upper, and may involve the facial muscles as well.

Key Terms

Gene A biologic unit of heredity transmitted from parents to offspring.

Diagnosis

Diagnosis of either form of PP begins with a careful medical history and a complete physical and neurological exam. A family medical history may reveal other affected relatives. Blood and urine tests done at the onset of an attack show whether there are elevated or depressed levels of potassium. Electrical tests of muscle and a muscle **biopsy** show characteristic changes.

Challenge tests, to aid in diagnosis, differ for the two forms. In hypokalemic PP, an attack of weakness can be brought on by administration of glucose and insulin, with exercise if necessary. An attack of hyperkalemic PP can be induced with administration of potassium after exercise during **fasting**. These tests are potentially hazardous and require careful monitoring.

Genetic tests are available at some research centers and are usually recommended for patients with a known family history. However, the number of different possible mutations leading to each form is too great to allow a single comprehensive test for either form, thus limiting the usefulness of **genetic testing**.

Treatment

Severe respiratory weakness from hypokalemic PP may require intensive care to ensure adequate ventilation. Potassium chloride may be given by mouth or intravenously to normalize blood levels.

Attacks requiring treatment are much less common in hyperkalemic PP. Glucose and insulin may be prescribed. Eating carbohydrates may also relieve attacks.

Prognosis

Most patients learn to prevent their attacks well enough that no significant deterioration in the quality of life occurs. Strenuous exercise must be avoided, however. Attacks often lessen in severity and frequency during middle age. Frequent or severe attacks increase the likelihood of permanent residual weakness, a risk in both forms of periodic paralysis.

Prevention

There is no way to prevent the occurrence of either disease in a person with the gene for the disease. The likelihood of an attack of either form of PP may be lessened by avoiding the triggers (the events or combinations of circumstances which cause an attack) for each.

Hypokalemic PP attacks may be prevented with use of **acetazolamide** (or another carbonic anhydrase inhibitor drug) or a diuretic to help retain potassium in the bloodstream. These attacks may also be prevented by avoiding such triggers as salty food, large meals, a high-carbohydrate diet, and strenuous exercise.

Attacks of hyperkalemic PP may be prevented with frequent small meals high in carbohydrates, and the avoidance of foods high in potassium such as orange juice or bananas. Acetazolamide or thiazide (a diuretic) may be prescribed.

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Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718. (800) 572-1717. <http://www.mdausa.org>.

The Periodic Paralysis Association. 5225 Canyon Crest Drive #71-351, Riverside, CA 92507. (909) 781-4401. <http://www.periodicparalysis.org>.

Richard Robinson

Peripheral nervous system

Definition

The peripheral nervous system (PNS) consists of all parts of the nervous system, except the brain and spinal cord, which are the components of the **central nervous system** (CNS). The peripheral nervous system connects the central nervous system to the remainder of the body, and is the conduit through which neural signals are transmitted to and from the central nervous system. Within the peripheral nervous system, sensory neurons transmit impulses to the CNS from sensory receptors. A system of motor neurons transmit neural signals from the CNS to effectors (glands, organs, and muscles).

Description

The peripheral nervous system is composed of nerve fibers that provide the cellular pathways for the various signals on which the proper operation of the nervous system relies. There are two types of neurons operating in the PNS. The first is the sensory neurons that run from the myriad of sensory receptors throughout the body. Sensory receptors provide the connection between the stimulus such as heat, cold, and **pain** and the CNS. As well, the PNS also consists of motor neurons. These neurons connect the CNS to various muscles and glands throughout the body. These muscles and glands are also known as effectors, meaning they are the places where the responses to the stimuli are translated into action.

The peripheral nervous system is subdivided into two subsystems: the sensory-somatic nervous system and the autonomic nervous system.

The sensory-somatic nervous system

The sensory-somatic nervous system is the sensory gateway between the environment outside of the body and the central nervous system. Responses tend to be conscious.

The sensory nervous system comprises 12 pairs of cranial nerves and 31 pairs of spinal nerves. Some pairs are exclusively sensory neurons such as the pairs involved in smell, vision, hearing, and balance. Other pairs are strictly made up of motor neurons, such as those involved in the movement of the eyeballs, swallowing, and movement of the head and shoulders. Still other pairs consist of a sensory and a motor neuron working in tandem such as those involved in taste and other aspects of swallowing. All of the spinal neuron pairs are mixed: they contain both sensory and motor neurons. This allows the spinal neurons to properly function as the conduit of transmission of the signals of the stimuli and the subsequent response.

The autonomic nervous system

The autonomic nervous system (ANS) consists of three subsystems: the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system. The ANS regulates the activities of cardiac muscle, smooth muscle, endocrine glands, and exocrine glands. The ANS functions involuntarily (i.e., reflexively)

Key Terms

Central nervous system (CNS) Composed of the brain and spinal cord.

Peripheral nervous system (PNS) All parts of the nervous system, except the brain and spinal cord.

in an automatic manner without conscious control. Accordingly, the ANS is the mediator of visceral reflex arcs.

In contrast to the somatic nervous system that always acts to excite muscle groups, the autonomic nervous systems can act to excite or inhibit innervated tissue. The autonomic nervous system achieves this ability to excite or inhibit activity via a dual innervation of target tissues and organs. Most target organs and tissues are innervated by neural fibers from both the parasympathetic and sympathetic systems. The systems can act to stimulate organs and tissues in opposite ways (antagonistically). For example, parasympathetic stimulation acts to decrease heart rate. In contrast, sympathetic stimulation results in increased heart rate. The systems can also act in concert to stimulate activity (e.g., both increase the production of saliva by salivary glands, but parasympathetic stimulation results in watery as opposed to viscous or thick saliva). The ANS achieves this control via two divisions of the ANS, the sympathetic nervous system and the parasympathetic nervous system.

The autonomic nervous system also differs from the somatic nervous system in the types of tissue innervated and controlled. The somatic nervous system regulates skeletal muscle tissue, while the ANS services smooth muscle, cardiac muscle, and glandular tissue.

Although the sympathetic systems share a number of common features (i.e., both contain myelinated preganglionic nerve fibers that usually connect with unmyelinated postganglionic fibers via a cluster of neural cells termed ganglia), the classification of the parasympathetic and the sympathetic systems of the ANS is based both on anatomical and physiological differences between the two subdivisions.

The sympathetic nervous system

The nerve fibers of the sympathetic system innervate smooth muscle, cardiac muscle, and glandular tissue. In general, stimulation via sympathetic fibers increases activity and metabolic rate. Accordingly, sympathetic system stimulation is a critical component of the fight or flight response.

The cell bodies of sympathetic fibers traveling toward the ganglia (preganglionic fibers) are located in the thoracic and lumbar spinal nerves. These thoraco-lumbar fibers then travel only a short distance within the spinal nerve (composed of an independent mixture of fiber types) before leaving the nerve as myelinated white fibers that synapse with the sympathetic ganglia that lie close to the side of the vertebral column. The sympathetic ganglia lie in chains that line both the right and left sides of the vertebral column, from the cervical to the sacral region. Portions of the sympathetic preganglionic fibers do not travel to the vertebral ganglionic chains, but travel instead to specialized cervical or abdominal ganglia. Other variations are also possible. For example, preganglionic fibers can synapse directly with cells in the adrenal medulla.

In contrast to the parasympathetic system, the preganglionic fibers of the sympathetic nervous system are usually short, and the sympathetic postganglionic fibers are long fibers that must travel to the target tissue. The sympathetic postganglionic fibers usually travel back to the spinal nerve via unmyelineted or gray rami before continuing to the target effector organs.

With regard to specific target organs and tissues, sympathetic stimulation of the pupil dilates the pupil. The dilation allows more light to enter the eye and acts to increase acuity in depth and peripheral perception.

Sympathetic stimulation acts to increase heart rate and increase the force of atrial and ventricular contractions. Sympathetic stimulation also increases the conduction velocity of cardiac muscle fibers. Sympathetic stimulation also causes a dilation of systemic arterial blood vessels, resulting in greater oxygen delivery.

Sympathetic stimulation of the lungs and smooth muscle surrounding the bronchi results in bronchial muscle relaxation. The relaxation allows the bronchi to expand to their full volumetric capacity and thereby allow greater volumes of air passage during respiration. The increased availability of oxygen and increased venting of carbon dioxide are necessary to sustain vigorous muscular activity. Sympathetic stimulation can also result in increased activity by glands that control bronchial secretions.

Sympathetic stimulation of the liver increases glycogenolysis and lipolysis to make energy more available to metabolic processes. Constriction of gastrointestinal sphincters (smooth muscle valves or constrictions) and a general decrease in gastrointestinal motility assure that blood and oxygen needed for more urgent needs (such as fight or flight) are not wasted on digestive system processes that can be deferred for short periods. The fight or flight response is a physical response; a strong stimulus or emergency causes the release of a chemical called noradrenaline (also called norepinephrine) that alternately stimulates or inhibits the functioning of a myriad of glands

and muscles. Examples include the acceleration of the heartbeat, raising of blood pressure, shrinkage of the pupils of the eyes, and the redirection of blood away from the skin to muscles, brain, and the heart.

Sympathetic stimulation results in renin secretion by the kidneys and causes a relaxation of the bladder. Accompanied by a constriction of the bladder sphincter, sympathetic stimulation tends to decrease urination and promote fluid retention.

Acetylcholine is the neurotransmitter most often found in the sympathetic preganglionic synapse. Although there are exceptions (e.g., sweat glands utilize acetylcholine), epinephrine (noradrenaline) is the most common neurotransmitter found in postganglionic synapses.

The parasympathetic nervous system

Parasympathetic fibers innervate smooth muscle, cardiac muscle, and glandular tissue. In general, stimulation via parasympathetic fibers slows activity and results in a lowering of metabolic rate and a concordant conservation of energy. Accordingly, the parasympathetic nervous subsystem operates to return the body to its normal levels of function following the sudden alteration by the sympathetic nervous subsystem; the so-called "rest and digest" state. Examples include the restoration of resting heartbeat, blood pressure, pupil diameter, and flow of blood to the skin.

The preganglionic fibers of the parasympathetic system derive from the neural cell bodies of the motor nuclei of the occulomotor (cranial nerve: III), facial (VII), glossopharyngeal (IX), and vagal (X) cranial nerves. There are also contributions from cells in the sacral segments of the spinal cord. These cranio-sacral fibers generally travel to a ganglion that is located near or within the target tissue. Because of the proximity of the ganglia to the target tissue or organ, the postganglionic fibers are much shorter.

Parasympathetic stimulation of the pupil from fibers derived from the occulomotor (cranial nerve: III), facial (VII), and glossopharyngeal (IX) nerves constricts or narrows the pupil. This reflexive action is an important safeguard against bright light that could otherwise damage the retina. Parasympathetic stimulation also results in increased lacrimal gland secretions (tears) that protect, moisten, and clean the eye.

The vagus nerve (cranial nerve: X) carries fibers to the heart, lungs, stomach, upper intestine, and ureter. Fibers derived from the sacrum innervate reproductive organs, portions of the colon, bladder, and rectum.

With regard to specific target organs and tissues, parasympathetic stimulation acts to decrease heart rate and decrease the force of contraction. Parasympathetic stimulation also reduces the conduction velocity of cardiac muscle fibers.

Parasympathetic stimulation of the lungs and smooth muscle surrounding the bronchi results in bronchial constriction or tightening. Parasympathetic stimulation can also result in increased activity by glands that control bronchial secretions.

Parasympathetic stimulation usually causes a dilation of arterial blood vessels, increased glycogen synthesis within the liver, a relaxation of gastrointestinal sphincters (smooth muscle valves or constrictions), and a general increase in gastrointestinal motility (the contractions of the intestines that help food move through the system).

Parasympathetic stimulation results in a contracting spasm of the bladder. Accompanied by a relaxation of the sphincter, parasympathetic stimulation tends to promote urination.

The chemical most commonly found in both pre- and postganglionic synapses in the parasympathetic system is the neurotransmitter acetylcholine.

The enteric nervous system

The enteric nervous system is made up of nerve fibers that supply the viscera of the body: the gastrointestinal tract, pancreas, and gallbladder.

Regulation of the autonomic nervous system

The involuntary ANS is controlled in the hypothalamus, while the somatic system is regulated by other regions of the brain (cortex). In contrast, the somatic nervous system may control motor functions by neural pathways that contain only a single axon that innervates an effector (i.e., target) muscle. The ANS is comprised of pathways that must contain at least two axons separated by a ganglia that lies in the path between the axons.

ANS reflex arcs are stimulated by input from sensory or visceral receptors. The signals are processed in the hypothalamus (or regions of the spinal cord) and target effector control is then regulated via myelinated preganglionic neurons (cranial and spinal nerves that also contain somatic nervous system neurons). Ultimately, the preganglionic neurons terminate in a neural ganglion. Direct effector control is then regulated via unmyelinated postganglionic neurons.

The principal **neurotransmitters** in ANS synapses are acetylcholine and norepinephrine.

General PNS disorders

General PNS disorders include loss of sensation or hyperesthesia (abnormal or pathological sensitivity). Sensations such as prickling or tingling without observable stimulus (paresthesia) or burning sensations are also abnormal.

Stabbing or throbbing pains are often due to neuralgia (e.g., **trigeminal neuralgia**, also known as tic douloureux). Neuritis (an inflammation of the nerve) can be caused by a number of factors, including trauma, infection (both bacterial and viral), or chemical injury.

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Peripheral neuropathy

Definition

Peripheral neuropathy is a condition involving the nerves of the peripheral portion of the nervous system. Neurobiologists describe the **peripheral nervous system** as any part of that system found in the arms or legs. The nerves that traverse the arms and legs occur in fibrous groups identified from the vascular system by their whitish color. These nerve tracts, or bundles of similar type nerve cell fibers, exit the brain and spinal cord from the intervertebral spaces in the spinal column to the rest of the body. The majority of the peripheral nerves are responsible for sensations such as touch, **pain**, and temperature. There is a greater concentration of particular types of nerve cells located in both the hands and feet. This concentration is a result of the need for sensory integration with the numerous small muscles and intricacy of movement in these regions of the body.

When certain traumatic conditions exist in the peripheral nerves, some people experience a highly uncomfortable condition in which they describe sensations as burning, tingling, shooting pain, overall persistent pain, and a wide variety of additional discomforting sensations. When this condition this persistent, it is called peripheral neuropathy. Peripheral neuropathy is also known as somatic neuropathy or distal sensory polyneuropathy.

This disorder is primarily recorded in persons with diabetes, compromised immune systems, or those who have suffered some sort of injury to these nerves. The traumas can range from overexposure to certain chemical toxins, penetration injury, fractures, staying in one position too long, severe impact, or even prolonged compression, as in the wearing of inappropriate footwear. Athletes who use their feet in sports such as tennis, basketball, soccer, or any running **exercise** are at moderate-to-severe risk. Among those with diabetes and HIV the risk is highest. As a result of high computer usage, the incidence of **carpal tunnel syndrome**, a type of peripheral neuropathy, is rising.

Many researchers assume the condition itself is caused by the loss of myelin (a waxy type substance) along the axon of the nerve cell. The role of myelin will be discussed later in the description of the nerves themselves. As a result of this loss of myelin, patients describe a variety of symptoms such as those previously described. A variety of initial complaint descriptions like aching, throbbing, the feeling of cold such as frostbite or even heat sensation so severe some patients compare it to "walking on a bed of coals," are the first clues to the possibility of advancing neuropathy.

Because the initial symptoms are similar to many other disorders, doctors are sometimes hesitant to diagnose peripheral neuropathy until the disease has reached a more advanced stage. By that time rehabilitation and treatment may take longer and be less effective.

Description

Many persons with peripheral neuropathy in the legs experience an inability to walk properly. The incidence of injuries from falling increase, and affected persons may eventually develop a shuffling-type gait. In the hands, many people with this disorder must wear a brace or some sort of support. They lack their previous dexterity and fingers become numb. Manual tasks become difficult or almost impossible.

This disease may affect the nerves in several ways. If a single nerve is involved, the condition is called mononeuropathy. This condition is considered rare as it is unusual to find a condition in which only a single nerve maybe involved. Trauma is likely to involve multiple neurons and toxins or diabetes will most likely produce a global reaction.

Another condition likely to exist is one in which two or more nerves in separate areas of the body are affected. This case is described as multiple mononeuropathy. While this is still a less frequent scenario it is more common that the disease will occur in the same areas of either side of the body. This situation is more common when the cause is systemic rather than a physical injury.

Most often many nerves in the same vicinity are simultaneously involved, which is known as polyneuropathy. This is the most common expression of the disorder. Damage to nerve fibers may eventually result in loss of

Key Terms

Diabetic neuropathy A complication of diabetes mellitus in which the peripheral nerves are affected. Diabetic neuropathy is primarily due to metabolic imbalance and secondarily to nerve compression.

Mononeuropathy Neuropathy affecting a single nerve.

Multiple mononeuropathy Neuropathy affecting several individual nerve trunks.

Myelin A covering composed of fatty substances that forms a protective sheath around nerves and speeds the transmission of impulses along nerve cells.

Neuropathy Disease or disorder of the peripheral nerves.

Polyneuropathy Peripheral neuropathy affecting multiple nerves.

Schwann cell The cell that wraps around a nerve fiber to form a protective myelin sheath.

motor function or a reduction in proprioceptive or sensation types of responses. This type of neuropathy causes the greatest distress among patients. Treatment is difficult and often the nerve damage is irreversible. A halt to the advancement of the disease is one of the most promising types of relief a patient can expect.

Demographics

Statistics on the occurrence of this disorder are not always reliable. Because peripheral neuropathy can accompany a great number of other disorders, many cases go undiagnosed. Carpal tunnel syndrome, which is on the increase, is just one form of peripheral neuropathy and affects millions of people worldwide. There is evidence that some forms of this disease are inherited. Those neuropathies that are inherited are called either sensorimotor neuropathies or sensory neuropathies.

Race has not been found as a contributing factor in the onset of peripheral neuropathy. In fact, the only risk factors aside from inheritance are those that result from traumas, reaction to toxic substances, and malnutrition. While malnutrition has been erroneously paired with certain social demographics this does not necessarily mean that those who suffer from inadequate nutritional intake are more susceptible. Trauma and associated diseases, such as diabetes and HIV, are the major factors associated with this neuropathy. The occurrence of peripheral neuropathy is about 2,400 cases per 100,000 population (2.4%). However with continued aging the rates increase to about 8,000 per 100,000 people (8%).

Causes and symptoms

One of the more prevalent and reasonable descriptions of how the disease is caused lies in the declining myelination of the actual nerve cells and fibers. In order to illustrate this condition, a discussion of one of the more common and most often discussed type of nerve cell will aid in the understanding of this type of neuropathy. The motor neuron, which is responsible for the initiation of movement, is a large nerve cell with a body and a long extension called the axon. The cell terminates at the end of the axon into a branched formation from which **neurotransmitters** are released to stimulate other motor neurons. The axon is the region of the cell along which electrical signals are passed. These electrical impulses are generated in the cell body and travel at high speeds to the ends of the neuron. The branched ends, called the synaptic end bulbs release acetylcholine which, in turn, activates the next cell body to produce an electrical signal and on down the fiber of a new nerve cell in the tract.

A waxy lipid is generated inside a specialized cell, the Schwann cell, that wraps around the axon of the nerve cell. Many Schwann cells grow along the axon and act as a kind of insulation for the nerve cell. The Schwann cells assure that the electric charge goes where the **central nervous system** (CNS) intends it to go. In diseases such as **multiple sclerosis**, the degeneration and death of these Schwann cells cause CNS electrical signals to go in random directions, preventing the muscles from responding properly.

It is assumed that in peripheral neuropathy the same sort of condition may occur. Whether due to trauma or a reaction to toxins, the myelin appears to start disappearing in many nerve cells and the otherwise contained electrical signals spread throughout the affected region. In turn, the neighboring neurons receive an overstimulation of random impulses and movement is impaired.

Muscle weakness is one of the first symptoms of peripheral neuropathy and is maximized soon after the beginning of the disease or about three to four weeks after onset. Sensory nerve cells, especially those that transmit pain are overstimulated and can cause severe aching and shooting pains, including the feeling of extreme cold or heat. Misdirected signals can cause cramping in advanced stages.

Diagnosis

Once a physician suspects a patient may be affected with from peripheral neuropathy, the diagnosis can be confirmed by a series of tests. An EMG (a recording of electrical activity in the muscles) allows the physician to see

how much of a small electrical current passing through a suspected nerve region is lost due to damage in the nerves. The difference in electrical charge from its origin to its endpoint provides a measure of potential damage.

Nerve conduction tests are performed by having a machine determine the speed at which a nerve impulse passes through a nerve region. The slower the passage, the greater the neuropathy. This may relate to the loss of myelin around the nerve axons and fibers or actual physical damage. Nerve biopsies are performed in the more serious conditions. The **biopsy** will permit the physician to see the actual condition of the nerve and rule out other causes for the pain the patient experiences.

Finally, a simple blood test can be administered. Toxins that may damage nerves are screened for. Vitamin levels are observed since nutrition may be a causative factor. Vitamin B6 has been demonstrated in some studies to be toxic for some patients with peripheral neuropathy. A diabetic condition is examined for presence or absence or degree of severity.

For persons with HIV, certain drugs such as didanosine (ddI, Videx), zalcitabine (ddC, Hivid), and stavudine (d4T, Zerit) are common culprits in the occurrence of peripheral neuropathy. Not everyone taking these drugs will acquire peripheral neuropathy, but those with the disease appear to have had a damaging response to these chemicals. Additionally, in some cases, alcohol consumption may be a contributing factor.

Treatment team

The family physician and a **neurologist** are the traditional specialists in recognizing and treating peripheral neuropathy. Alternative therapists include nutritionists and acupuncturists, who also have found a place among those seeking treatment for peripheral neuropathy. One thing agreed upon is that peripheral neuropathy is often treatable. Better results occur with those patients who receive an early diagnosis and are younger, although physical therapists working with patients in all stages of the disease have reported improvement over time.

Treatment

A variety of treatments are available to patients with peripheral neuropathy. Some report a significant degree of improvement after taking higher doses of vitamin B12. Physical therapies and exercise influence the nerves to respond to correct stimuli and decrease the loss of myelin. Treatment is aimed at two goals. The first is to try and alleviate or eliminate the cause of the underlying disease. The second is to relieve its symptoms. Painkillers are often prescribed (including morphine) for the most severe cases. Prosthetic devices can be used when muscle weakness has reduced a person's ability to walk.

Managing diabetes is extremely important in those patients who have developed peripheral neuropathy as a symptom of the disease. Good nutrition, exercise, and avoiding alcohol are highly recommended. Those with HIV may experiment with alternate therapies and, again, focus on good nutrition and exercise.

Recovery and rehabilitation

The recovery from peripheral neuropathy varies. Those who are diagnosed early stand a better chance of a full recovery than those who are diagnosed after the disease has progressed over a long period. While not all cases are reversible, many patients have made a full recovery with proper treatment. For many, a halt in the progression of the disease is highly possible and often achieved. No quick cures have been found, however, and those who do improve do so after a great deal of work and commitment to recovery.

One of the aspects of the disease not often discussed is the emotional and psychological impact this disease has on its sufferers. Many find the constant pain an unbearable condition and are left to live a life dependent on pain-killing drugs. Others are distraught at the loss of movement and weakness that accompany the disorder. For these patients, there are support groups and websites devoted to the sharing of ideas and promising new therapies. Relatives and friends can be very supportive in recognizing that this is a real and diagnosable disease with proven treatments. Peripheral neuropathy is not an imaginary condition and it is not only possible to find cessation from advancing symptoms, but a partial if not total recovery.

Clinical trials

Many **clinical trials** are underway to search for treatments and prevention methods for peripheral neuropathy. A clinical trial is a research study designed to test or target a specific aspect of a research topic. They are designed to ask and attempt to answer very specific questions about the causation and new therapies for medical or other research types of questions. Many new vaccines or new ways of using known treatments for a specific pathology have been discovered in clinical trials. They are often the source of new drug therapies or alternate types of treatment. Often, the criteria for entering a clinical trial is very specific, but the results can prove to be enormously helpful.

Some of the current clinical trials for peripheral neuropathy include the following: The University of Chicago is undertaking two separate clinical trials for the study of a particular drug's effectiveness in relieving the pain of diabetic peripheral neuropathy, as well as slowing the rate of progression. Washington University of St. Louis School of

Medicine is sponsoring a trial to study treatments for those with peripheral neuropathy resulting from HIV infection. Information on these studies and other ongoing clinical trials can be found at the National Institutes of Health website for clinical trials at <http://www.clinicaltrials.gov>.

Prognosis

Prognosis varies for persons with peripheral neuropathy. Quick identification and diagnosis is critical to beginning therapies in the early phases of the disease. Age is also a contributing factor, as younger persons fare better than older patients when they follow a multi-disciplinary approach to the disease. However, most patients can find a degree of relief from symptoms and the advancement of the disease.

Special concerns

While there are many cases in which peripheral neuropathy is unavoidable, most podiatrists recommend good foot hygiene. Recommendations include using appropriate and supportive footwear. Support measures such as arch and wrist braces may help in prevention of some types of peripheral neuropathy. If a person finds that one of the conditions of their employment is repetitive motion of the hand, as in typing, newer more ergonomic types of keyboards may reduce pressure on the nerves associated with carpal tunnel syndrome.

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The Neuropathy Association. 60 E. 42nd Street, Suite 942, New York, NY 10165-0999. (212) 692-0662. info@neuropathy.org. <http://www.neuropathy.org>.

Brook Ellen Hall, PhD

Periventricular leukomalacia

Definition

Periventricular leukomalacia is a brain condition affecting fetuses and newborns in which there is softening, dysfunction, and death of the white matter of the brain.

Description

The brain is composed of outer gray matter and inner white matter. The gray matter is responsible for processing information involved in muscle control, sensory perception, emotion, and memory. The white matter is responsible for transmitting information throughout the brain, to the spinal cord, and outside of the brain to the muscles. The ventricles are four cavities within the brain, all of which are interconnected with each other and with the central spinal canal, and through which the cerebrospinal fluid circulates. "Periventricular" refers to the white matter that surrounds the ventricles. "Leukomalacia" means softening of the white tissue. When the white matter softens, the brain tissue begins to die.

Demographics

Periventricular leukomalacia strikes fetuses and newborns, particularly those who have undergone some kind of oxygen deprivation, such as may occur due to complications of prematurity. Some 4–26% of all premature infants in neonatal intensive care units have evidence of periventricular leukomalacia. As many as 76% of premature infants who die of complications of prematurity have evidence of periventricular leukomalacia on autopsy.

The risk of a baby developing periventricular leukomalacia is higher in those babies with smaller birth weights, who are twins, who are born at less than 32 weeks and require mechanical ventilation, and/or who are born of mothers who have abused cocaine. The following conditions also increase a baby's likelihood of developing periventricular leukomalacia:

- low blood pressure
- increased acidity of the blood

Key Terms

Cerebral palsy A group of symptoms, including difficulty with muscle control and coordination and sometimes mental retardation, that occur after oxygen deprivation in the early newborn period.

Cyst A fluid-filled sac.

Intraventricular hemorrhage Bleeding into the brain, specifically into the ventricles.

Ischemia Abnormally low flow of blood to an organ or tissue of the body, resulting in oxygen deprivation of that organ or tissue.

Leukomalacia Softening of the brain's white matter.

Periventricular Located around the brain's ventricles.

Hypoxemia Abnormally low blood oxygen.

Hypoxia Abnormally low oxygen reaching the body's organs and tissues.

Ventricles Four cavities within the brain, all of which are interconnected with each other and with the central spinal canal, and through which the cerebrospinal fluid circulates.

- high blood pressure
- low blood carbon dioxide
- abnormalities of the placenta

Causes and symptoms

Premature babies are at high risk of a variety of complications, including low blood oxygen (hypoxemia), decreased delivery of oxygen to the body's tissues (**hypoxia**), and/or decreased flow of oxygen-rich blood to the body's tissues (ischemia). All of these complications can result in oxygen deprivation of the susceptible newborn brain tissue, and potentially in subsequent brain damage. Without a constant flow of enough oxygen and nutrients, the oxygen-starved brain tissue will begin to soften and die. Additionally, premature infants have a very high risk of bleeding into the brain (intraventricular hemorrhage). When this occurs, the area around the brain hemorrhage is particularly susceptible to periventricular leukomalacia.

Other risk factors for periventricular leukomalacia include early rupture of the amniotic membranes (the birth sac) prior to delivery of the baby, and infections within the mother's uterus during pregnancy and/or labor and delivery of the baby.

Symptoms of periventricular leukomalacia include tight, contracted, spastic leg muscles, delayed motor development, delayed intellectual development, problems with coordination, impaired vision and hearing, and **seizures**. More than 60% of all babies who have periventricular leukomalacia will actually develop **cerebral palsy**, particularly if the periventricular leukomalacia has been accompanied by intraventricular hemorrhage. Cerebral palsy is a constellation of symptoms that occur due to significant oxygen deprivation of the brain tissue, resulting in lifelong difficulties with coordination between the brain and muscles, and sometimes accompanied by **mental retardation**.

Diagnosis

Periventricular leukomalacia can be diagnosed through cranial ultrasound, which allows the brain to be examined using ultrasound techniques through the soft spots, or fontanelles, in the baby's skull. When a baby has periventricular leukomalacia, the ultrasound exam will reveal cysts (fluid-filled compartments) or empty cavities within the brain tissue. **Magnetic resonance imaging (MRI)** scans of the brain may also reveal the characteristic abnormalities of periventricular leukomalacia.

Treatment team

Most premature babies are treated by a perinatologist (a specialist in the care of premature infants). A pediatric **neurologist** may be consulted if a baby is suspected of having periventricular leukomalacia or intraventricular bleeding.

Treatment

There is no cure for periventricular leukomalacia. Efforts, instead, are made to help affected children reach their full potential through a variety of modalities throughout childhood.

Recovery and rehabilitation

The rehabilitation team will depend on the extent of a child's physical and intellectual challenges. Physical therapy, occupational therapy, speech and language therapy, and a specialized educational setting may all be necessary.

Prognosis

The prognosis for babies with periventricular leukomalacia is quite variable, and is dependent on the other complications of prematurity that a baby may face. Deficits may range from mild to devastating disability or even death.

Special concerns

Some studies have suggested that the risk of periventricular leukomalacia is decreased by the administration of steroids to women in premature labor. Other preventive measures include any steps that may decrease the likelihood of intraventricular hemorrhage, such as careful labor management and monitoring, and care in an experienced neonatal intensive care unit.

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Rosalyn Carson-DeWitt, MD

PET scan *see* **Positron emission tomography (PET)**

Phantom limb

Definition

Phantom limb is the term for abnormal sensations perceived from a previously amputated limb. The abnormal sensations may be painful or nonpainful in nature. It is presumed to be due to central and **peripheral nervous system** reorganization as a response to injury. Phantom limb **pain** is often considered to be a form of neuropathic pain, a group of pain syndromes associated with damage to nerves.

Description

Phantom limb syndrome was first described by Ambroise Pare in 1552. Pare, a French surgeon, noticed this phenomenon in soldiers who felt pain in their amputated limbs. Mitchell coined the term "phantom limb" in 1871. Phantom limb syndrome can be subdivided into phantom limb sensation and phantom limb pain. Stump or residual limb pain refers to pain that may persist at the residual site of amputation and may be grouped under phantom limb syndrome as well.

The onset of pain after amputation usually occurs within days to weeks, although it may be delayed months or years. Pain may last for years, and tends to be intermittent rather than constant. Pain may last up to 10–14 hours a day and can vary in severity from mild to debilitating The abnormal "phantom" sensations and pain are usually located in the distal parts of the missing limb. Pain and tingling may be felt in the fingers and hand, and in the lower limbs, in the toes and the feet.

Demographics

The incidence of phantom limb pain is estimated in 50–80% of all amputees. Phantom limb sensation is more frequent and occurs in all amputees at some point. There is no known association with age, gender, or which limb is amputated. Studies have shown a decreased incidence of phantom limb syndrome in those born without limbs versus actual amputees.

Causes and symptoms

The exact etiology of phantom limb pain is unknown. Phantom limb is thought to be secondary to the brain plasticity and reorganization. The human brain has an enormous capacity to alter its connections and function in response to everyday learning or to the setting of injury. These processes of reorganization may occur in retained nerves in the amputated limbs, the spinal cord, or various parts of the brain, including the thalamus and the cerebral cortex. Although phantom pain is presumably a result of a response to amputation injury, phantom limb pain may occur in nonamputees with spinal cord damage causing loss of sensation. This suggests that the phantom limb phenomenon may be a result of damage to pathways responsible for painful sensation in general. Research studies in primates and patients with limb amputation have shown that after amputation, the area of the brain that is responsible for processing the sensations from the missing limb are taken over by areas neighboring the missing limb.

Patients may feel a variety of sensations emanating from the absent limb. The limb may feel completely intact despite its absence. Nonpainful sensations may include changes in temperature, itching, tingling, shock-like sensations, or perceived motion of the phantom limb. The

limb may feel as if it is retracting into the stump in a phenomenon called telescoping. Painful sensations include burning, throbbing, or stabbing in nature. Touching the remaining stump may elicit sensations from the phantom. The quality of the pain may change over time and may not remain constant. Patients may also feel pain from the retained stump itself. Stump pain is often associated with phantom limb sensations and may be related in etiology.

Diagnosis

The diagnosis of phantom limb is a clinical one. A history of previous limb amputation and the subsequent symptoms of abnormal sensations from the missing limb are key to the diagnosis. Spinal cord damage affecting pathways mediating sensation may also be associated with phantom limb. There are no imaging or clinical tests useful in diagnosing phantom limb.

Treatment team

The treatment team for phantom limb pain may involve the participation of neurologists, pain specialists, physical therapists, neurosurgeons, or rehabilitation specialists. Neurologists and pain specialists may help in prescribing medications to treat the phantom limb pain. Physical therapists may help to facilitate and maintain mobility. Neurosurgeons may perform surgery to place electrical nerve stimulators in the spinal cord or lesion procedures to help treat the pain.

Treatment

There are few controlled clinical studies on phantom limb treatment, and therefore no consensus on the best treatment. Treatment is directed towards the management of painful symptoms. Nonpainful symptoms rarely require treatment. Treatment for phantom limb pain involves the use of medications, nonmedical, electrical, and surgical therapy.

Medical treatment of phantom limb pain involves agents typically used for neuropathic pain. Medications such as **anticonvulsants**, muscle relaxants, and antidepressants may be tried. Opiate medications have also been used. Ketamine, an anesthetic agent, or calcitonin has been shown to be effective in some clinical studies.

Various electrical and nonmedical treatments may be tried. Trancutaneous electrical nerve stimulation (TENS) and biofeedback may be used. Massage, ultrasound, and **acupuncture** modalities may be tried as well. Training patients to discriminate sensory signals in the stump appears to be helpful in reducing pain. In research studies, allowing individuals to see a reflection of the normal, intact limb moving in the position of the amputated limb helped alleviate symptoms of phantom limb pain.

Surgical treatments for phantom limb pain are limited in benefit. Lesions of various pain centers in the spinal cord and brain can be performed, and may provide short-term relief on most occasions.

Recovery and rehabilitation

Prospective studies of phantom pain show that in two years, many amputees will experience a reduction of symptoms. Physical and occupational therapists may help in the treatment of phantom limb pain by maintaining range of motion and mobility.

Clinical trials

There are ongoing **clinical trials** conducted by the National Institutes of Neurological Disorders and Stroke (NINDS) studying touch perception in patients with upper limb amputation.

Prognosis

The prognosis for phantom limb varies from individual to individual. Medical treatment shows the most benefit in treating symptoms. Some studies show that in a two-year period, many amputees will experience a reduction or disappearance of their phantom limb pain. The results of the studies are somewhat limited due to the heterogeneity of the populations studied.

Special concerns

Phantom limb may have a chronic course and may lead to feelings of **depression** or anxiety. These feelings may require treatment by a psychiatrist. Patients with phantom limb should continue to be active and participate in community and social activities. There are various support groups for amputees.

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American Pain Foundation. 201 North Charles Street, Suite 710, Baltimore, MD 21201. (410) 783-7292 or (888) 615-7246; Fax: (410) 385-1832. info@painfoundation.org. <http://www.painfoundation.org>.

The Pain Relief Foundation. Clinical Sciences Centre, University Hospital Aintree, Lower Lane, Liverpool, L9 7AL, UK. 0151.529.5820; Fax: 0151.529.5821. pri@liv.ac.uk. <http://www.painrelieffoundation.org.uk/index.html>.

Peter T. Lin, MD

Pharmacotherapy

Definition

Pharmacotherapy is the use of medicine in the treatment of diseases, conditions, and symptoms.

Description

History of pharmacotherapy

Pharmacotherapy is not a contemporary science. The use of drugs to treat illness is a practice that has been accepted for thousands of years. A famous example is Hippocrates, who is generally credited with revolutionizing medicine in ancient Greece by using beneficial drugs to heal illness. Traditionally, plants have been the source of medicinal drugs, but modern day medicine in the United States mostly utilizes synthesized or purified bioactive compounds, rather than an entire sample of plant matter. The advantage to this method of pharmacotherapy is that the dose of medicine rendered is standardized and pure, rather than an unknown drug dosage administered in addition to a wide variety of other chemicals present in the plant. Modern pharmacotherapy is the most common course of treatment for illness in the United States.

Pharmacokinetics and pharmacodynamics

Pharmacokinetics is the study of the concentration of a drug and its metabolites in the body over time. A drug that remains in the body for a longer time period will require lower subsequent doses to maintain a specific concentration. How quickly a drug clears from the body is a function of its absorption, bioavailability, distribution, metabolism, and excretion properties.

The absorption of a drug is the rate at which it leaves its site of administration. The bioavailability of a drug describes the extent to which it is available at the site of action in a bioactive metabolic form. A drug absorbed from the stomach and intestine passes through the liver before reaching the systemic circulation. If the liver biotransforms the drug extensively into an inactive form, its availability in bioactive form would be greatly reduced before it reaches its site of action. This is known as the first pass effect. Sometimes the liver biotransforms an inactive drug into an active form.

Which parts of the body drugs distribute to affects the length of time the drugs remain in the body. Fat-soluble drugs may deposit in fat reservoirs and remain in the body longer than drugs that are not fat-soluble. Drugs are metabolized within cells, often into inactive forms. The rate at which a drug is excreted from the body also affects its pharmacokinetics. Pharmacokinetic information about a drug allows the determination of an optimal dosage regimen and form of administration that will produce a specified drug concentration in the body for a desired period of time.

While pharmacokinetics is the study of drug concentration versus time, pharmacodynamics is the study of drug effect versus concentration, or what effect a drug has on the body. Pharmacodynamics measures a quantifiable drug-induced change in a biochemical or physiological parameter. Pharmacodynamics is the study of the mechanism of action of a drug. Medicinal drugs have targets to reach at the site of action. These targets are usually a specific type of drug receptor. Drug and drug receptor interactions can be measured. Complex pharmacodynamic equations combine with measurable pharmacokinetic values to determine the overall effect of a drug on the body over time.

Pharmacogenetics and pharmacogenomics

Pharmacogenetics is the study of the extent to which genetic differences influence the response of an individual to a medication. This science is still at an early stage in its development, but its importance is well understood. While drug treatment remains the cornerstone of modern medicine, in some cases it has adverse side effects or no effect at all. Adverse drug reactions are a leading cause of disease and death. It has been known for some time that genetic variation often causes these unanticipated situations.

While pharmacogenetics is the term used to describe the relationship between a genetically determined variability and the metabolism of drugs, pharmacogenomics is a separate and much more recent term that expands the concept. Pharmacogenomics includes the identification of

Key Terms

Biotransformation The conversion of a compound from one form to another by the action of enzymes in the body of an organism.

Genome The entire collection of genes of an individual.

Genotype The structure of DNA that determines the expression of a trait. Genotype is the genetic constitution of an organism, as distinguished from its physical appearance or phenotype.

all genetic variations that influence the efficacy and toxicity of drugs, describing the junction of pharmaceutical science with knowledge of genes. Pharmacogenomics is the application of the concept of genetic variation to the whole genome. Pharmacogenomics takes the concept of pharmacogenetics to the level of tailoring drug prescriptions to individual genotypes. There is an emerging trend towards defining both terms as pharmacogenomics.

There are many worrisome issues associated with modern pharmacotherapy that necessitate the study of pharmacogenomics. The optimal dose for many drugs is known to vary among individuals. The daily dose for the drug propranolol varies 40-fold and the dose for warfarin can vary by 20-fold between individuals. Also, the same drug does not always work in every patient. Thirty percent of schizophrenics do not respond to antipsychotic treatment. A major concern is adverse drug reactions. In the United States, adverse effects are a major cause of death. Research has demonstrated that gene polymorphisms influence drug effectiveness and toxicity, leading to these inconsistencies in patient response, affecting all fields of pharmacotherapy. Some drugs are known to produce potentially fatal side reactions at therapeutically effective doses. The current accepted method of addressing this situation involves determining the correct concentration of the drug for the patient so that therapy can be ceased before potentially irreversible damage. At best this is complicated, time-consuming, and expensive. It is also potentially dangerous for the patient.

The goal of pharmacogenomics is to maximize beneficial drug responses while minimizing adverse effects for individuals. In the future, pharmacogenomics may hold the promise of personalized drugs. However, genetic variation is not solely responsible for variable drug response. Other factors such as health, diet, and drug combinations are all very relevant.

Pharmacoepidemiology and pharmacoeconomics

Epidemiology is the study of the distribution and determinants of disease in large populations. Epidemiology has a precise and strict methodology for the study of disease. Pharmacoepidemiology is the application of epidemiology to the study of the effects of drugs in large numbers of people. The discipline of pharmacoepidemiology maintains a close watch on the therapeutic drugs commonly used in society. If the drug monitoring and reviewing process is not implemented, potential adverse effects of drugs and their misuse could have seriously deleterious effects on the population.

Pharmacoepidemiological studies performed on a population seek to address many different issues. Studies are performed to identify and quantify adverse drug effects, including delayed adverse effects. This is where most research in pharmacoepidemiology has focused. Analyses evaluate the efficiency and toxicity of drugs in specific patient groups such as pregnant and lactating women. Studies are performed on unanticipated side effects of drugs, along with anticipated side effects to monitor their severity. Research is done on the expected beneficial effects of drugs to verify their efficacy. Also, unanticipated beneficial effects of some drugs are examined. Factors that may affect drug therapy are studied to draw correlations between them and effects on pharmacotherapy. Such factors include sudden changes in drug regimen, age, sex, diet, patient compliance, other diseases, concurrent recreational drug usage, and genetics.

Pharmacoepidemiology can be used in conjunction with pharmacogenomics to examine how genetic patterns present in a population may affect a society's use of a specific therapeutic, or the need for gene-specific pharmacogenomic studies in a population. Studies are performed to examine a few candidate genes where genetic variability has been shown to have biological consequences. Subsequent research attempts to correlate phenotypic markers with genetic characteristics by association studies, involving the analysis of either a specific drug response as a continuous trait or of separate groups (drug responders versus drug non-responders). These genetic association studies are complex and depend on the frequency of the trait, frequency of the genetic variation within the population, the number of contributing genes, and the relative risk associated with the genetic variation. Reviews of drug utilization are generally done on overuse of drugs or use of costly drugs. Expensive drugs may be reviewed in a cost-benefit analysis involving pharmacoeconomics.

Pharmacoeconomics has a close relationship to the discipline of pharmacoepidemiology. Analysis of cost effectiveness, cost benefit, and cost utility are incorporated in pharmacoepidemiological research. A related topic of

controversy is the validity of using economic analysis of pharmaceuticals as a proxy for prescribing medication, or a reason for prescribing one medication over another. The influence of pharmacoeconomic data on the choice of medication prescribed may be considerable. A general concern is whether a physician has the best interest of the patient in mind or of economics when choosing a medication. While the two concerns are not necessarily in contradiction, they sometimes may be. These topics are also being explored in prescribing research.

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Maria Basile, PhD

Phenobarbital

Definition

Phenobarbital is a barbiturate, a drug that has sedative and hypnotic effects. The drug is classed as a **central nervous system** agent and subclassed as an anticonvulsant (antiseizure).

Purpose

Phenobarbital is used to control the **seizures** that occur in **epilepsy**, and can relieve anxiety. For short-term use, phenobarbital can help those with insomnia fall asleep.

Description

Phenobarbital is available in tablet or capsule form, and as a liquid. All three forms are taken orally one to three times each day with or without food. When taken once a day, the drug is typically taken near bedtime.

Recommended dosage

The dosage is prescribed by a physician. Typically, the total daily dose ranges 30–120 mg. For treatment of seizures, the dosage can be 60–200 mg daily. The daily dosage for children is typically 3–6 mg per 2.2 lb (1 kg) of body weight.

Key Terms

Anticonvulsant drugs Drugs used to prevent convulsions or seizures. They often are prescribed in the treatment of epilepsy.

Hypnotics A class of drugs that are used as a sedatives and sleep aids.

Sedative A medication that has a calming effect and may be used to treat nervousness or restlessness. Sometimes used as a synonym for hypnotic.

Dosages should not be exceeded. It is also important to adhere to the proper timetable for use of the medication. Use of the drug should not be discontinued without consulting a physician.

Precautions

Phenobarbital is potentially habit forming if taken over an extended period of time. When being prescribed to overcome insomnia, the drug should not be used for a period longer than two weeks. Furthermore, phenobarbital should not be taken in a dose that exceeds the prescribed amount. Ingestion of more than the recommended dosage can result in unsteadiness, slurred speech, and confusion. More serious results of overdose include unconsciousness and breathing difficulty.

Long-term use can lead to tolerance, making it necessary to take increased amounts of the drug to achieve the desired effect. This poses a risk of habitual use; however, it should be noted that people with seizure disorders seldom have problems with phenobarbital dependence. Nevertheless, with chemical dependency, symptoms of withdrawal from phenobarbital begin eight to 12 hours after the last dose, and progress in severity. Initial symptoms may include anxiousness, insomnia, and irritability. Twitching and **tremors** in the hands and fingers precludes increasing weakness, **dizziness**, nausea, and vomiting. Symptoms can sometimes become severe or life-threatening, with seizures, **delirium**, or coma.

While there is evidence of risk to a fetus, the benefits of phenobarbital for a pregnant woman can sometimes warrant its use. This must be determined by a physician.

Side effects

Common side effects include drowsiness, **headache**, dizziness, **depression**, stomachache, and vomiting. More severe side effects include nightmares, constipation, and **pain** in muscles and joints. Side effects that require immediate medical attention occur rarely, and include

seizures, profuse nosebleeds, fever, breathing or swallowing difficulties, and a severe skin rash.

Interactions

Phenobarbital can interact with a number of prescription and nonprescription medications including acetaminophen, anticoagulants such as warfarin, chloramphenicol, monoamine oxidase inhibitors (MAOIs), antidepressants, asthma medicine, cold medicine, anti-allergy medicine, sedatives, steroids, tranquilizers, and vitamins. Interactions with these medications can increase the drowsiness caused by phenobarbital. Decreased efficiency of anticoagulants can increase the risk of bleeding. Phenobarbital can also react with oral contraceptives, which can decrease the effectiveness of the birth control medication.

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ORGANIZATIONS

The Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org/>.

Brian Douglas Hoyle, PhD

Phytanic acid storage disease *see* **Refsum disease**

Pick disease

Definition

Pick disease is a rare neurodegenerative disorder that affects pre-senile adults. It is characterized by atrophy of the tissues in the frontal and temporal lobes of the brain and by the presence of aggregated tau protein that accumulates in Pick bodies in the neurons of the affected regions. Named for the German physician who studied patients who with the disease, Pick disease is grouped together with other non-Alzheimer's dementias, under the category of frontotemporal **dementia** (FTD), which is now the preferred term for Pick disease. FTD is classified by the *Diagnostic and Statistical Manual of Mental disorders*, Fourth Edition (DSM-IV) as a Dementia Due to Other General Medical Conditions.

Description

The disease is named after the German physician, Arnold Pick, but it was not named by him. German psychiatrist and pathologist Alois Alzheimer named the illness in 1923 following post-mortem examinations of Pick's patients. One of these patients was a 71-year old man who died following progressive mental deterioration. His autopsy revealed atrophy of the frontal cortex. This feature is seen nearly universally among patients with FTD. The disease is also referred to as frontotemporal lobar degeneration, progressive **aphasia** and semantic dementia.

The disease may be inherited through mutations associated with chromosomes 17, 9 and 3, or develop sporadically.

Demographics

Alzheimer's disease and other non-Alzheimer's dementias are much more common than FTD. The average age of onset is 54 years, and most cases arise between the ages of 40 and 60. Few diagnoses are made in individuals older than 75 years of age, but FTD has been diagnosed in people as young as 20.

At autopsy, 8–10% of all cases of pre-senile dementia meet the diagnostic criteria for FTD disease, although some estimates put the incidence of the disease in the United States at as much as 15% of individuals with dementia. Epidemiological studies have estimated that FTD affects as few as one in 100,000 people. The familial incidence of FTD disease may be higher in Europe; a Dutch study indicated a prevalence of 28 per 100,000 individuals. The incidence increases with age, affecting 10.7 per 100,000 in the 50–60-year age range and 28 per 100,000 in the 60–70-year age range. FTDs account for about 3% of dementias. One-fifth to one-half of individuals diagnosed with FTD has a first-degree relative that has also been diagnosed with dementia.

Discrepancies in neuropathological diagnosis have led some groups to suspect that its incidence is much greater than previously indicated. There is some suggestion that as imaging techniques improve the disease is becoming more frequently recognized in younger patients.

Causes and Symptoms

The molecular cause of Pick disease are a series of mutations linked to chromosomes 17, 9 and 3. One of these mutations is located on the long arm of chromosome 17 (17q35) at the locus known to hold the gene for the tau protein, and accounts for between 9–14% of all FTDs. This gene has also been implicated in Alzheimer's disease. Mutations on chromosomes 9 and 3 have not yet been identified. The gene encodes a scaffold protein that maintains the shape of brain neurons by stabilizing cellular microtubules. Mutations to the tau protein cause it to form clumps and limit its ability to assemble microtubules. The aggregates that form in the neurons of the affected regions of the brain are called Pick bodies. As in Alzheimer's disease, the tau protein is hyperphoshorylated in FTD.

The brain regions most severely affected by the tau mutation are the frontal and temporal lobes. These parts of the brain control reasoning and judgment, behavior and speech. In addition to the accumulation of tau protein, these regions atrophy over the course of the disease.

The clinical features of frontotemporal dementia includes changes in the patient's behavior, and may include additional emotional, neurological and language symptoms. Patients show poor reasoning, judgment and mental flexibility, but memory may not be affected.

Initially, patients become disinhibited and restless, and lose the ability to control their actions or to chose socially acceptable behavior. As the condition progresses, repetitive and ritualistic behaviors, such as hand rubbing or clapping, develop. Hyperoral behaviors are often associated with this phase, and may include overeating, hoarding or fixations on specific foods.

Later, apathy, uncaring and unsympathetic attitudes, and mood changes may develop. The patient may also develop language difficulties, including aphasia and reduced reading and writing comprehension, **dysarthria** and echolalia. Most patients with FTD eventually become mute.

Some patients with FTD will develop ALS, also known as Lou Gehrig's disease, parkinsonian, or psychiatric symptoms.

Diagnosis

Frontotemporal dementia is commonly misdiagnosed as Alzheimer's disease, because of the similarity in their clinical courses. However, FTD should be suspected if Alzheimer's-like symptoms are present in patients of a pre-senile age. Patients show early declines in social conduct, emotional expression and insight. Conversely, perception, spatial skills, memory generally remain intact or well preserved. The following behavioral disorders, altered speech and language, and physical signs also support FTD diagnosis.

The diagnostic criteria for FTD were reviewed and updated at a consensus conference in 1998. The criteria comprising the clinical profile are divided into two groups: core diagnostic features, which must be present, and supportive diagnostic features, which are present in many patients with FTD. Changes to character and altered social conduct are prominent features of the disease and prevalent at all stages.

Core Diagnostic Features

- insidious onset and gradual progression
- early decline in social conduct
- early impaired regulation of personal conduct
- early emotional blunting
- early loss of insight

Supportive Diagnostic Features

- altered behavior: decline in hygiene, mental rigidity, hyperorality and dietary changes, stereotyped behavior
- speech and language: less spontaneous and limited speech, sterotypy, echoalia, mutism
- physical signs: primitive reflexes, incontinence, rigidity and tremor, low blood pressure, frontal or anterior temporal abnormality

Neuropsychological tests reveal a lack of verbal fluency, ability to abstract and limited executive function. Because of the clinical similarities between FTD and Alzheimer's disease, it is difficult not to misdiagnose FTD as Alzheimer's disease. However, one study found that a word fluency test may be the best method of differentiating FTD from Alzheimer's disease.

Neuroimaging studies, such as **CT scans**, will generally show atrophy and reduced blood flow to the frontal and anterior temporal lobes, but will not be conclusive in all cases. Several studies suggest that functional imaging with single photon emission CT or **positron emission tomography** may be better at identifying FTD in its early stages, showing decreased blood flow to the frontal and temporal lobes. Electroencephalograms (EEG) may show non-specific changes in electrical activity, but are usually normal.

Like Alzheimer's disease, a diagnosis of FTD can be confirmed with autopsy. Gross inspection reveals significant atrophy of the cortex and the white matter of the

Key Terms

Alzheimer's disease A progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions such as memory and learning. Formerly called pre-senile dementia.

Analgesics A class of pain-relieving medicines, including aspirin and Tylenol.

Anticholinergic drugs Drugs that block the action of the neurotransmitter acetylcholine. They are used to lessen muscle spasms in the intestines, lungs, bladder, and eye muscles.

Aphasia The loss of the ability to speak, or to understand written or spoken language. A person who cannot speak or understand language is said to be aphasic.

Cytoplasm The substance within a cell including the organelles and the fluid surrounding the nucleus.

Dementia Loss of memory and other higher functions, such as thinking or speech, lasting six months or more.

Dysarthria Slurred speech.

Echolalia Involuntary echoing of the last word, phrase, or sentence spoken by someone else.

Electroencephalogram A record of the tiny electrical impulses produced by the brain's activity picked up by electrodes placed on the scalp. By measuring characteristic wave patterns, the EEG can help diagnose certain conditions of the brain.

Hydrocephalus An abnormal accumulation of cerebrospinal fluid within the brain. This accumulation can be harmful by pressing on brain structures, and damaging them.

Hypothyroidism A disorder in which the thyroid gland produces too little thyroid hormone causing a decrease in the rate of metabolism with associated effects on the reproductive system. Symptoms include fatigue, difficulty swallowing, mood swings, hoarse voice, sensitivity to cold, forgetfulness, and dry/coarse skin and hair.

Microtubules Slender, elongated, anatomical channels.

Parkinson's disease A slowly progressive disease that destroys nerve cells in the basal ganglia and thus causes loss of dopamine, a chemical that aids in transmission of nerve signals (neurotransmitter). Parkinson's is characterized by shaking in resting muscles, a stooping posture, slurred speech, muscular stiffness, and weakness.

frontal and anterior temporal lobes. Neuronal inclusions called "Pick bodies" are characteristic of the disease, but not always present or necessary for diagnosis. Pick bodies are cytoplasmic silver-staining masses made up of 10-to 20-nm filaments. Other investigators have further classified the pathology into three distinct subsets.

- FTD Type A: lobar atrophy with swollen poorly staining neurons and Pick bodies
- FTD Type B: lobar atrophy with swollen poorly staining neurons, but no Pick bodies
- FTD Type C: lobar atrophy, lacking swollen poorly staining neurons and Pick bodies

Differential Diagnosis

FTD is rare and other diseases, such as **hydrocephalus**, tumors, hypothyroidism, vascular dementia, and vitamin B12 deficiency should be ruled out. However, an accurate and rapid diagnosis saves well-intentioned but futile attempts to treat for other conditions such as **depression** or mania.

Treatment

There is no known treatment for frontotemporal dementia and no way to slow the progression of the disease. Treatment focuses on patient care, symptom management, monitoring symptom progression and providing assistance with daily activities and personal care.

During the early stages of the disease speech therapy, occupational therapy, and behavior modification may improve day-to-day functioning and improve autonomy. Disorders that contribute to confusion, such as heart failure, **hypoxia**, thyroid disorders, and infections should be treated appropriately.

Some medications, such as **anticholinergics**, analgesics, cimetidine, **central nervous system** depressants, and lidocaine may heighten confusion and non-essential ones should be discontinued. In addition, it is inadvisable

to prescribe drugs used to treat Alzheimer's disease, as many may increase agitation and aggressivity.

As the disease progresses, a patient's capacity to care for himself will decline and he will become more dependent on caregivers. Around the clock care may be required in the most advanced stages or the disease; family members should consider hiring an in-home caregiver or consider institutional care to meet the patient's needs.

Clinical trials

As of early 2004, two NIH sponsored **clinical trials** were recruiting patients with frontotemporal dementia. Both were operating out of the National Institute of Neurological disorders and Stroke (NINDS) in Bethesda, MD. The Memory and Aging Center at the University of California, San Francisco is also conducting several diagnostic and genetic studies of FTD. Contact information is listed under resources, below.

Prognosis

Patients with frontotemporal dementia have a poor prognosis. The disease is much more aggressive than Alzheimer's disease. Total disability occurs early after diagnosis. Most patients die within two to 10 years after diagnosis, with median survival at three years from diagnosis and six years after symptom inception. Death is usually due to infection or from body system failure.

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ORGANIZATIONS

The National Institute of Neurological Disorders and Stroke (NINDS). 9000 Rockville Pike, Bethesda, MD 20892. (800) 411-1222. prpl@mail.cc.nih.gov.

UCSF Memory and Aging Center. 350 Parnassus Avenue, Suite 706, San Francisco, CA 94143-1207. (415) 476-6880; Fax: (415) 476-4800. <http://memory.ucsf.edu>.

Pick's Disease Support Group. <http://www.pdsg.org.uk/>.

The Association for Frontotemporal Dementias. <http://www.ftd-picks.org>.

Hannah M. Hoag, MSc

Pinched nerve

Definition

A pinched nerve is a general term that describes an injury to a nerve or group of nerves. The damage may include compression, constriction or stretching. Nerves that pass near or through bones or other rigid tissues are most susceptible to pinching. Pinched nerves result in numbness, **pain**, burning and tingling sensations radiating out from the affected area.

Description

Pinched nerves can be grouped into two types depending on where they occur in the body. Pinched nerves can occur within or in the vicinity of the vertebral column. For example, herniation of vertebral discs causes pain along the pathway of the nerve that is affected. Similarly, stenosis, or narrowing, of the vertebral column puts pressure on nerves traveling through the vertebrae. Another group of pinched nerves are referred to as nerve entrapment syndromes and they affect peripheral nerves, most commonly in the arms.

At least 80% of all herniated discs occur in people between the ages of 30 and 50. Between these ages, the tough outer core of the vertebral discs weakens and the soft gel-like inner core, which is under pressure, can more easily squeeze through weakened areas. After age 50, the inner core begins to harden, making herniation of discs less common. The amount of pain and discomfort resulting from a herniated disc varies depending on which disk has herniated and the amount of rupture. One of the most common problems associated with herniated discs is **sciatica**.

Nerve entrapment syndromes refer to a particular type of pinched nerve, in which peripheral nerves are chronically compressed resulting in pain or loss of function in an extremity. The most common nerve entrapment syndromes affect the median, ulnar and radial nerves of the arms. Nerve entrapment syndromes are extremely common, accounting for about 10–20% of all cases seen in neurosurgical practices. The most common entrapment syndrome is **carpal tunnel syndrome**. Cubital tunnel syndrome of the ulnar nerve, which runs down the arm and through the elbow, also occurs frequently.

Causes and symptoms

A nerve can be thought of as a wire encased in insulation that carries electrical information from one part of the body to another part. When the insulation or the wire itself becomes damaged the electrical signal does not move along the nerve efficiently or, in severe cases, the signal is not transmitted at all. The brain interprets this faulty transmission as pain, numbness or burning. Several different types of damage can occur to nerve cells that cause a disruption in the transfer of electrical signal. Compression or pressure on a nerve in one area will result in symptoms such as numbness or tingling in the region from which the nerve should be sending signals. The myelin sheath, which covers the nerve and is analogous to the insulation covering an electrical wire, can be damaged by scarring, in effect causing a short circuit of the nerve. Scar tissue hinders movement of a nerve in its tissue bed as the body moves and compromises the ability of the nerve to function properly, either by stressing the nerve fibers themselves or by impairing the blood supply to the nerve cell. Nerves can also be pulled or stretched, which constricts the nerve fibers. This is called a traction of the nerve and results in a decreased electrical flow through the nerve. The brain interprets the slow electrical signal as numbness, pain, or tingling.

Key Terms

Carpal tunnel syndrome A condition caused by compression of the median nerve in the carpal tunnel of the hand, characterized by pain.

Median nerve A nerve which runs through the wrist and into the hand. It provides sensation and some movement to the hand, the thumb, the index finger, the middle finger, and half of the ring finger.

Myelin A fatty sheath surrounding nerves throughout the body that helps them conduct impulses more quickly.

Nerve Fibers that carry sensory information, movement stimuli, or both from the brain and spinal cord to other parts of the body and back again. Some nerves, including the vagus nerve, innervate distantly separated parts of the body.

Vertebral column The bony structure made up of vertebra and intervertebral disks whose primary function is to protect the spinal cord.

Pinched Nerves in the Spine

Herniated discs are the most common reason for a pinched nerve along the vertebrae. This condition occurs when the gel-like core of a vertebral disc (nucleus puposus) ruptures through the tougher outer section (annulus) of the disc. The extrusion puts pressure on the adjacent nerve root causing it to function improperly. The discs that most often suffer from herniation are those in the cervical spine and the lumbar spine because they are the most flexible.

Lumbar disc herniations usually occur between lumbar segments 4 and 5, which cause pain in the L5 nerve, or between lumbar segment 5 and sacral segment 1, which cause pain on the S1 nerve. Pinching of the L5 nerve causes weakness in the big toe and ankle and pain on the top of the foot that may extend up to the buttocks. Pinching of the S1 nerve causes weakness in the ankle and numbness and pain in the sole and side of the foot. If the sciatic nerve, which runs from lumbar segment 3 down the vertebral column, is pinched by a herniation, the resulting condition is known as sciatica and it can cause pain, burning or tingling in the buttocks and leg. Lumbar disc herniations often heal on their own and conservative treatments are used to provide some relief from symptoms and to aid healing. Such treatments include physical therapy, chiropractic manipulations, non-steroidal anti-inflammatory drugs, oral steroids and, in some cases, an injection of a steroid such as cortisone. In more severe cases, surgery to remove the pressure of the disc from the nerve is warranted. This is most often performed using microsurgical techniques.

Cervical disc herniations occur less frequently than lumbar disc herniations because there is less force in the cervical spine and less disc material between vertebrae. When nerve roots exiting the cervical spine are pinched, they can cause a **radiculopathy**, or a pain in the arm. Rarely, the nerves between the first and second or second and third cervical segments can be pinched. These nerves are sensory nerves and can cause chronic headaches. Usually cervical disc herniations heal on their own and conservative treatments are used to relieve symptoms and pain. These treatments include rest, non-steroidal anti-inflammatory drugs, physical therapy, chiropractic treatments and manual traction. Epidural injections of cortisone may also help relieve pain. Surgical techniques can also be used to remove the herniated disc from impinging on nerves.

Stenosis, or narrowing, of the spinal canal can cause a pinching of the spinal cord. This occurs commonly with age and may cause weakening of muscles or loss of coordination. Often symptoms develop slowly and worsen over a long period of time. Usually treatment for this condition requires surgery to relieve pressure on the spinal canal.

Nerve Entrapment Syndromes

Most nerve entrapment syndromes are caused by injury to the nerve as it travels between a canal consisting of bone or ligament. One side of the canal is able to move so

that the injury is aggravated by repetitive rubbing or slapping against the edges of the canal. Rest and splinting are therefore effective treatments for entrapment syndromes. Symptoms of entrapment syndromes usually proceed from pain and numbness to weakness and muscle atrophy.

The most common nerve entrapment syndrome is **carpal tunnel syndrome** (CTS), with a reported occurrence between 1–10% of the population. Statistics indicate that nearly half of a million surgeries for CTS are performed yearly. It occurs most often in people who perform repetitive motions with their hands, such as bankers, computer operators, secretaries, grocery store workers and bank tellers.

The carpal tunnel is in the wrist of the hand. It is bound on the palm side by the transverse carpal tunnel ligament which attaches to the four carpal tunnel bones that extend around the back of the wrist. The inside of the carpal tunnel houses ten flexor tendons, which are used to bend fingers, as well as the median nerve and the ulnar nerve. The median nerve, which is aggravated in CTS, is between the transverse carpal tunnel ligament and the flexor tendons. When the hand moves, the flexor tendons may glide back and forth through the carpal tunnel up to .75 in (2 cm) in either direction. These tendons are covered in a substance called tenosynovium that allows them to move easily. When the tendons move rapidly, the tenosynovium may heat up and expand, putting pressure on the median nerve. This pressure results in pain and tingling in the thumb, index finger, middle finger and along the thumb side of the fourth finger. Symptoms may also include a dull, aching pain in the wrist, extending up to the elbow. Most people suffering from CTS find that the pain worsens at night and they will awaken with numbness in the middle fingers and thumb. Both bending the wrist and extending the wrist cause increased pain. Given time, CTS may continue to aggravate the median nerve, resulting in scar tissue that only enhances the syndrome.

CTS is usually treated with conservative treatments including rest and splinting of the wrist, especially at night. Using non-steriodal anti-inflammatory medications may relieve some of the swelling in the carpal tunnel. Injections of cortisone into the carpal tunnel are also effective at relieving swelling. Surgery can also be used in severe cases to relieve pressure on the median nerve.

Ulnar nerve entrapment syndrome occurs when the ulnar nerve is injured. The ulnar nerve extends down the arm and into the hand, enervating the ring finger and the little finger. In the elbow, it passes through a tunnel called the cubital tunnel. Most ulnar nerve entrapments occur in the cubital tunnel, although some can occur at the wrist. Most commonly, trauma to the elbow or repetitive bending of the elbow puts pressure on the ulnar nerve that damages the myelin sheath insulating and protecting the nerve. Symptoms include tenderness on the inside of the elbow, numbness in the hand especially the ring and little fingers and decreased coordination and strength in the hand. Conservative treatments for ulnar nerve entrapment include rest and splinting of the elbow and corticosteroids to reduce pain. In severe cases, surgery to move the ulnar nerve from behind the elbow to the front of the elbow relieves the pressure on the nerve.

Suprascapular nerve entrapment is a rare type of entrapment syndrome that most often occurs in athletes. The major symptom is a dull pain near the shoulder blade, which can progress to weakness and muscle atrophy. The pain is not localized, but does not extend to the neck or arm.

Tarsal tunnel syndrome is another uncommon type of nerve entrapment syndrome that causes burning, tingling and pain in the plantar surface of the foot. Bending of the ankle worsens the pain and there is a weakening of muscles in the big toe.

Resources

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ORGANIZATIONS

National Rehabilitation Information Center (NARIC). 4200 Forbes Boulevard Suite 202, Lanham, MD 20706-4829.

Key Terms

Corticosteroids A group of hormones produced naturally by the adrenal gland or manufactured synthetically. They are often used to treat inflammation. Examples include cortisone and prednisone.

Histamine A substance released by immune system cells in response to the presence of an allergen. It stimulates widening of blood vessels and increased porousness of blood vessel walls so that fluid and protein leak out from the blood into the surrounding tissue, causing localized inflammation of the tissue.

Prostaglandins A group of hormonelike molecules that exert local effects on a variety of processes including fluid balance, blood flow, and gastrointestinal function. They may be responsible for the production of some types of pain and inflammation.

Sacroiliac joint The joint between the triangular bone below the spine (sacrum) and the hip bone (ilium).

Serotonin A widely distributed neurotransmitter that is found in blood platelets, the lining of the digestive tract, and the brain, and that works in combination with norepinephrine. It causes very powerful contractions of smooth muscle and is associated with mood, attention, emotions, and sleep. Low levels of serotonin are associated with depression.

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Juli M. Berwald, PhD

Piriformis syndrome

Definition

Piriformis syndrome is a neuromuscular disorder caused by the compression or irritation of the sciatic nerve by the piriformis muscle. It is usually the result of a traumatic injury to the buttocks or hip region. The piriformis muscle is a long, narrow, pyramid-shaped muscle, located deep in the buttocks, that runs from the base of the spine to the top of the femur. Sciatic irritation causes nagging aches, **pain**, tingling and numbness in the area extending from the buttocks to the tibia.

Description

Piriformis syndrome is a frequent cause of low **back pain**. Yoeman first described it in 1928, although the term itself wasn't introduced until 1947, when Robinson correctly identified **sciatica** as a symptom, not a disease. Diagnosis of the condition remains controversial among physicians because its definition and pathophysiology lack consensus.

The condition is caused by the irritation or compression of the proximal sciatic nerve by the piriformis muscle, which at the sacral vertebrae, runs through the sciatic notch and inserts at the greater trochanter of the femur. The piriformis muscle is used to help rotate the leg outwards. It is particularly common among skiers, tennis players, long-distance bikers, and truck drivers. In addition, in as much as 20% of the population, the sciatic nerve passes through the piriformis muscle, contributing to the development of the condition.

Demographics

Due to discrepancies in diagnosis, the incidence of piriformis syndrome ranges from very rare to being responsible for approximately 6% of sciatica cases. Women may be affected more frequently than men, with some reports suggesting a six-fold incidence among females. Some reports find that it is most commonly diagnosed in patients between 30 and 40 years old.

Causes and Symptoms

There is little consensus over the cause of piriformis syndrome. The syndrome is attributed to mechanical or chemical irritation of the sciatic nerve. Approximately 50% of patients have a history of buttocks, lower back or hip injury, although it is frequently diagnosed in people who sit for long periods of time, presumably because the position leads to compression of the sciatic nerve.

The release of chemical mediators, such as serotonin, prostaglandin E, bradykinin, and histamine, into the region surrounding the sciatic nerve during inflammation contributes to irritation.

Piriformis syndrome is characterized by chronic nagging pain, tingling or numbness starting at the buttocks and extending along the length of the thigh, sometimes descending to the calf. It may worsen with sitting, or with lower limb movement.

Diagnosis

Piriformis syndrome is primarily a diagnosis of exclusion, aimed at identifying the piriformis muscle as the primary cause of the pain. Diagnoses should be made through a physical examination, and a complete neurologic examination.

Several maneuvers that contract or stretch the piriformis muscle can be performed. Freiberg's maneuver—an inward rotation of the thigh—stretches the piriformis muscle. In sitting patients, Pace's maneuver will elicit pain with the abduction of the affected leg. In Beatty's maneuver, the patient lies on a table on his non-affected leg, and the knee of the affected leg is bent knee and placed on the table. Raising the knee several inches off the table causes pain in the buttocks, and indicates piriformis syndrome

Imaging studies of the lower spine can exclude disc protrusion or degeneration, or osteoarthritis, hip and joint disease, and other spinal causes. Nerve conduction studies show delayed F waves and H reflexes.

Treatment Team

The structure of the treatment team will vary on the severity of the condition and on the success of initial interventions. Generally the treatment team is composed of a physiotherapist and a massage therapist. In advanced cases that do not respond to mechanical or pharmacological therapy, surgery may be recommended.

Treatment

Treatment for piriformis syndrome includes avoiding activities that aggravate the condition, such as running and bicycling. Patients who experience pain while sitting for long periods of time, should stand frequently, or raise the painful area from the seat.

Physiotherapy aimed at relaxing tight piriformis muscles, hip external rotators and adductors, strengthen hip abductors, or that increase the mobility of the sacroiliac joint can be beneficial. Home stretching routines can also be designed for the patient. Ultrasound has been effective for some patients.

Pharmacotherapy, including non-steroidal anti-inflammatory drugs, analgesics and muscle relaxants may help. An injection of corticosteroid into the piriformis muscle, close to the sciatic nerve, can also ease pain and reduce swelling. In severe cases, surgical resection of the piriformis muscle can be performed.

Prognosis

When piriformis syndrome is diagnosed and treated early, prognosis is good.

Special Concerns

Other causes of sciatica must be ruled out. A rapid and accurate diagnosis of piriformis syndrome can localize the cause of the pain, and can prevent sentencing a patient to long-term chronic pain management.

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National Rehabilitation Information Center (NARIC). 4200 Forbes Boulevard, Suite 202. Lanham, MD 20706-4829. (301) 562-2400 or (800) 346-2472; Fax: (301) 562-2401. naricinfo@heitechservices.com. <http://www.naric.com>.

National Organization of Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD (6673); Fax: (203) 789-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Hannah M. Hoag, MSc

Plexopathies

Definition

Plexopathies are a form of **peripheral neuropathy** (i.e., a form of damage to peripheral nerves).

Common plexopathies include brachial plexopathy affecting the upper thorax (chest and upper back), arm, and shoulder region, cervical plexopathy affecting the neck and head, and lumbosacral plexopathy affecting the lower back and legs.

Description

A branching network of nerves in which individual nerve fibers can pass from one peripheral nerve to another is termed a nerve plexus. Within the **peripheral nervous system**, there are several such plexi (e.g., the cervical plexus, brachial plexus, lumbar plexus, sacral plexus, etc.) that are often associated with neuropathy and **pain**. These neuropathies are termed plexopathies.

Neural plexi

Neural plexi are branching and interwoven connections among peripheral nerves that allow a redistribution of nerve fibers among the peripheral nerves. As nerves are traced through the peripheral nervous system, they divide into branches that then communicate with branches of nearby nerves. Because peripheral nerves are composed of aggregates or collections of individual nerve fibers, individual fibers are able to pass through the branching connections (e.g., the individual nerve fiber that controls a specific muscle in a distant appendage) to then continue their course within a new peripheral nerve. Although the branching between nerves can be complex, in most cases the nerve fibers pass intact without branching and individual fibers remain separate and distinct.

For example, the brachial plexus is a neural plexus (a grouping and branching of nerves) located deep in the neck, shoulder, and maxilla region that is responsible for the proper innervation and control of the muscles of the shoulder, upper chest, and arms (upper limbs). Because of the complexities of branching nerve roots, trunks, and cords of the brachial plexus, injuries to the brachial plexus region often cause loss or impairments of function at distant muscle groups.

Injury to the median nerve of the brachial plexus can cause a loss of flexion of the fingers. This loss of flexion results in a loss of the critical ability to oppose the thumb with individual fingers. Median nerve impairment can also result in a loss of range of motion of the arm. Individuals who sustain median nerve injury causing loss of index finger flexion may develop an index finger that "points" or remains extended. Because the median nerve ultimately passes through the carpal tunnel of the wrist, injuries or inflammation of the wrist (e.g., **carpal tunnel syndrome**) can result in pain and loss of feeling far away from the wrist itself.

Diverse symptoms

Pain, numbness, tingling, and weakness in the area of the affected neural plexus (including the lumbar, sacral, which is also known as the combined lumbsacral plexi, cervical, brachial, etc.), or in the distal appendage or area of the service by nerve fibers traversing through a particular plexus are symptoms of a potential plexopathy. Trauma, disease, or disorder can result in a plexopathy.

Depending on the source of the damage, treatment for plexopathies can include direct surgical correction, medication to relieve pain, and/or physical therapy.

Plexopathies are often initially diagnosed by a careful evaluation of the patient's history and symptoms, but electromyographic examination and nerve conduction studies are often the most accurate means to localize and determine the exact nature and site of the plexopathy.

Key Terms

Peripheral neuropathy (PN) Damage to nerves in the peripheral nervous system (nerves other than the brain or spinal cord).

Symptoms related to plexopathies can be mild or severe, from diffuse irritation to intense and intractable pain as sometime experienced by cancer patients. In cancer patients, the source of pain may be direct damage to the nerves caused by tumor invasion or by damage to adjacent tissue (such as by **radiation** therapy, called a radiation plexopathy).

Damage to the cervical plexus caused by trauma or head and neck tumors often results in pain or a complaint of "aching discomfort" in the neck and head. Cervical plexopathy may be caused by trauma or by head and neck tumors. Brachial plexopathy is commonly related to breast cancer, lung cancer, lymphoma, or metastatic tumor. Similarly, tumors in the pelvis and abdomen may result in plexopathies and pain in the lumar, sacral (lumbosacral) plexi with pain experienced in the abdomen and upper regions of the leg. Specific plexopathy in the sacral region may result in pain in the perineal and perirectal regions.

In many plexopathies, diagnosis can be delayed or made complex by the fact that initial complaints of pain or discomfort may precede (sometimes by weeks, months, or years) the onset of other symptoms of disorder.

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Paul Arthur

Poliomyelitis

Definition

Poliomyelitis is an infectious disease that is caused by a subgroup of viruses. The hallmark of the disease is the rapid development of paralysis. Poliomyelitis is also

commonly called polio. Once a cause of widespread public health measures to control epidemics, polio is now on the brink of eradication.

Description

The term poliomyelitis comes from the Greek words *polio*, meaning gray, and *myelon*, referring to the spinal cord. The term is accurate, as an important consequence of the disease is the involvement of the spinal cord with resulting paralysis.

Poliomyelitis was first described in 1789, although it likely dates back many centuries prior to that time. Outbreaks occurred in Europe and the United States beginning in the early nineteenth century. For the next hundred years, outbreaks became a regular summer and fall event in northern regions. As time passed, the number of cases and people crippled by the infection rose. By 1952, more than 21,000 people in the United States were paralyzed after a bout of poliomyelitis.

The manufacture and widespread use of several vaccines beginning in the 1950s drastically reduced the number of cases of poliomyelitis. In the United States, the last reported case of polio acquired from a wild-type (original form of a naturally occurring) virus was in 1979.

Demographics

Humans are the only known carriers of the polio virus. Poliomyelitis most commonly affects children under the age of five. Several generations ago, the disease was much more common than it is now. Even in the 1950s, poliomyelitis was global in its occurrence. Many children in underdeveloped and developed countries, including the United States, were susceptible. With the successful development of vaccines and the implementation of global vaccination campaigns, the infection has been drastically reduced. As of 2004, only isolated pockets of disease remain. These hot spots include areas in Africa, India, and the eastern Mediterranean.

Males and females are equally susceptible to polio. Irreversible paralysis, usually in the legs, occurs in about one of every 200 polio infections.

Causes and symptoms

Poliomyelitis originates with a viral infection. Poliovirus is a member of a group of viruses designated as enteroviruses. The viruses contain ribonucleic acid (RNA) as their genetic material. More specifically, the various polioviruses belong in a group (or family) called Picornaviridae.

There are three types of poliovirus that are related to each other based on their recognition by the body's immune system. This sort of a relationship is called a serotype. The three poliovirus serotypes are P1, P2, and P3. Even though they are closely related immunologically, developing immunity to one serotype is no guarantee of protection from infection from the other two serotypes. Thus, vaccines are geared towards producing an immune response that will be protective against all three serotypes.

Enteroviruses can be found in the gastrointestinal tract and are not often dissolved by the acidic conditions. Thus, poliovirus can be swallowed and remain intact, capable of causing an infection. As the virus particles lodge at the back of the throat in the pharynx, or are swallowed and end up in the intestinal tract, the viruses can begin to multiply. Like all viruses, the multiplication requires a host cell, in this case, cells lining the throat and intestines.

Shortly after the virus enters a person, viral particles can be recovered from the throat and from feces. About one week later, the virus is not usually detectable in the throat. However, virus can continue to be excreted in the feces for several more weeks. During this time, symptoms of the disease do not develop. Thus, the virus can be unknowingly passed to others via the oral or fecal-to-oral route. This transmission is a common method of transfer of a variety of viral and bacterial infections in settings like daycare centers.

Subsequently, the poliovirus invades lymph tissue. From there, the virus can enter the bloodstream and infect cells of the **central nervous system**. This typically takes from six to 20 days after infection. Multiplication of the virus inside motor neurons in environments like the brain destroys the host cells and causes paralysis. The appearance of paralysis is rapid.

Up to 95% of polio infections do not produce any symptoms or damage. However, these individuals can still excrete the virus in their feces, and so are capable of infecting others. For every 200 people who escape the effects of poliomyelitis, about one person becomes paralyzed.

Approximately 4–8% of polio infections are minor, and consist of fairly nonspecific symptoms, including sore throat and fever, nausea, vomiting, abdominal **pain**, or constipation. Recovery is complete in about a week. Indeed, a person may not know the difference between this brush with polio and the flu. This condition is known as abortive poliomyelitis. There is no involvement of the central nervous system.

In 1–2% of infections, a condition called nonparalytic aseptic meningitis is produced. Nonspecific symptoms characterize this condition, followed several days later by stiffness in the neck, back, and/or legs. The symptoms last from 2–10 days. Recovery is complete.

Less than 1% of those who are infected with the poliovirus develop what is termed flaccid paralysis. Paralysis appears anywhere from one to 10 days after symptoms

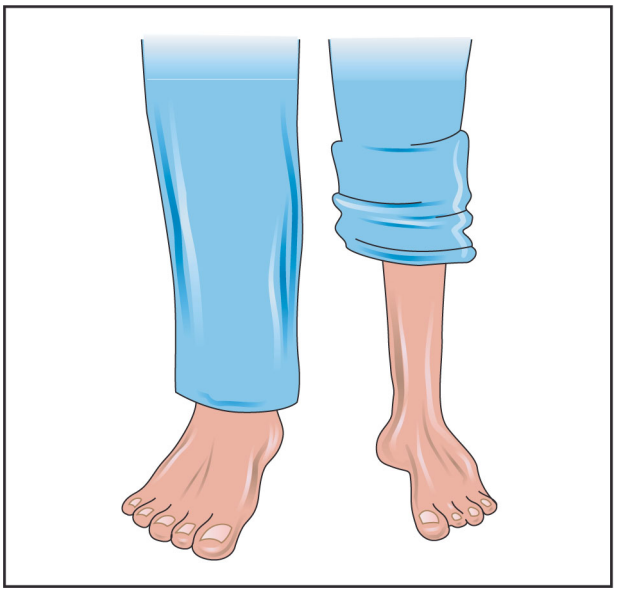

Diagram showing the difference between a healthy leg and foot and those deformed by polio. *(Illustration by Electronic Illustrators Group.)*

that include loss of reflexes, severe muscle aches, and muscle spasms in the arms, legs, or back. In children, the initial symptoms can begin to fade before paralysis appears.

Over the next few days, the paralysis becomes worse. For many people, muscle strength eventually returns. However, for those who still have weak muscles and/or paralysis a year later, the changes are likely permanent.

Types of paralytic poliomyelitis

There are three types of paralysis that can develop in poliomyelitis. The first is called spinal polio. This is the most common form of polio-related paralysis, and accounted for nearly 80% of all polio-related paralysis from 1969 to 1979. This type produces the classical image of a person whose legs have been paralyzed. The second type is known as bulbar polio. This type accounts for about 2% of known cases. Stiffness and paralysis typically occurs in the neck and head. The third type of polio-related paralysis is called bulbospinal polio. A combination of the previous two conditions, it accounts for nearly 20% of paralysis.

Postpolio syndrome

In almost half of those who contract polio in childhood, muscle pain and weakness reappears three or four decades later. Postpolio syndrome does not appear to be caused by a recurrence of the viral infection, as no virus can be detected in the feces. Rather, it may result from motor neurons damaged in the initial bout of polio that fail to operate properly decades later. The reason for the failure is not known.

Diagnosis

The diagnosis of poliomyelitis is based on the recovery of the virus from the throat or feces of a person. It is possible to isolate the virus from the cerebrospinal fluid, but this is uncommon. When the virus is recovered, specialized testing can be done to determine if the virus is wild type (that is, it has been acquired from the environment), or whether it is a vaccine type (polio vaccines utilize intact, but weakened viruses).

Another means of diagnosis relies on the detection of antibodies that have been produced by the virus. Since antibodies are produced as a part of the vaccination process, physicians focus on the increasing levels of antibodies over a short time as evidence that the body is battling an active viral infection.

Still another diagnostic test detects increased number of white blood cells and protein in the cerebrospinal fluid. This is a more general response to infections. Other conditions can present similar symptoms, and need to be ruled out when diagnosing poliomyelitis. These include **Guillain-Barré syndrome**, meningitis, and encephalitis.

Treatment team

The treatment team ideally consists of the family physician, **neurologist**, infectious disease specialist, physical therapists, occupational therapists, specialty nurses, and family members. In field conditions in developing countries, the treatment team may consist of a physician and direct caregivers only. World health agencies rapidly mobilize to provide care and vaccinations in order to contain isolated outbreaks in developing countries.

Treatment

Prevention is the watchword for poliomyelitis, and prevention consists of vaccination. There are two polio vaccines available; inactivated (Salk) poliovirus vaccine, and oral poliovirus vaccine.

The inactivated vaccine was devised by American physician Jonas Salk (1914–1995) in the 1950s. The vaccine contains all three serotypes of the poliovirus. The viruses, which are inactivated and incapable of causing an infection, are grown in a type of monkey kidney cell. When injected, the viruses stimulate an immune response that is protective. Initially, vaccine impurity was the cause of illness and death in some people who received the Salk vaccine. Refinement of the vaccine preparation eliminated these unwanted effects. Still, in the 1990s, a controversy arose regarding the vaccine as a suggested source of acquired immunodeficiency syndrome (**AIDS**), based on the known presence of the AIDS virus in monkey tissue cells. However, scrupulously conducted examinations ruled out this suggestion.

Key Terms

Disease eradication A status whereby no further cases of a diseases occur anywhere, and continued control measures are unnecessary.

Flaccid paralysis Loss of muscle tone resulting from injury or disease of the nerves that innervate the muscles.

Wild-type virus A virus occurring naturally in the environment or a population in its original form.

The oral vaccine was developed by Polish-born American physician Albert Sabin (1906–1993) in the late 1950s and was licensed for use in 1963. This vaccine has largely replaced the injected Salk vaccine. The vaccine also contains live, but weakened (attenuated) poliovirus.

A series of vaccinations given at two, four, six to 18 months, and four to six years produces a lifelong immunity to the three poliovirus serotypes. In regions where poliomyelitis is actively occurring, even a single dose of vaccine can provide adequate protection from infection during the outbreak.

In 2002, a new formulation of polio vaccine was approved for use in the United States. In addition to the polioviruses, the vaccine also bestows immunity to the virus that causes hepatitis B.

Recovery and rehabilitation

There is no cure for poliomyelitis. Some people can partially recover from paralysis, while the condition is irreversible in others. Physical and occupational therapies can be helpful in providing strengthening exercises and assistive devices for walking, but these are seldom available in remote areas of developing countries where polio outbreaks still occur.

Prognosis

Among those who are paralyzed by the viral infection, 5–10% overall die due to the paralysis of muscles used for breathing. For every 100 people who become paralyzed by the viral infection, two to five children and 15–30% of adults will die from polio.

Special concerns

Vaccination can produce reactions ranging from a transient and minor skin irritation and allergic reaction to some components of the oral vaccine to paralysis. The latter, termed vaccine-associated paralytic polio, is very rare. The condition is associated more with the injectable vaccine than with the vaccine given orally. Nonetheless, adults can be affected. From 1980–1998, 152 adults in the United States developed some degree of paralysis from polio vaccination.

The decision by Nigeria to suspend its vaccination program in 2001 contributed to a rise in the number of polio cases in the African country. Nigeria has since reinstated the vaccination program. The Nigerian experience points out that continued vigilance is necessary to keep poliomyelitis under control.

Since the widespread availability of vaccines, the number of cases of poliomyelitis worldwide has decreased by over 99% since 1988. That year, the estimated number of cases was more than 350,000. As of April 2003, the number of cases was reduced to 1,919. The dramatic reduction in the disease is attributed to a multinational worldwide vaccination effort that began in 1988. The program was spearheaded by organizations such as the World Health Organization.

The effort intensified during the first half of 2004, with the urgent distribution of polio vaccine to 250 million children in the world's remaining hotspots. As of April 2004, the number of polio cases worldwide caused by a wild-type virus was reduced to 89. World health officials aim to interrupt the transmission of all wild-type polio virus by the year 2005.

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ORGANIZATIONS

World Health Organization. Avenue Appia 20, Geneva, Switzerland. + 41 22 791 2111; Fax: + 41 22 791 3111. info@who.int. <http://www.who.int>.

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Polymyositis

Definition

Polymyositis (PM) is an inflammatory muscle disease with an unknown cause. The disease has a gradual onset and generally begins in the second decade of life and, thus, it rarely affects persons under the age of 18. It causes muscles to exhibit varying degrees of decreased strength, usually affecting those muscles that are closest to the trunk of the body. Trouble with swallowing (dysphagia) may occur with polymyositis.

Description

In polymyositis, muscles exhibit varying degrees of weakness, evolving gradually over weeks to months. It is known that PM begins when white blood cells, the immune cells of inflammation, spontaneously invade muscles, and is thus termed an autoimmune disease. In PM, muscle fibers are found to be in varying stages of necrosis (tissue death) and regeneration. The muscles affected are typically those closest to the trunk or torso, resulting in weakness that can be severe. Eventually, patients have difficulty rising from a sitting position, climbing stairs, lifting objects, or reaching overhead. In some cases, distal muscles (those not close to the trunk of the body) may also be affected later in the course of the disease. Polymyositis is a chronic illness with periods of increased symptoms, called flares or relapses, and decreased symptoms, known as remissions.

Polymyositis mimics many other muscle disorders and remains a diagnosis of exclusion. It should be viewed as a syndrome of diverse causes that occurs separately or in association with other autoimmune disorders or viral infections. A similar **inflammatory myopathy** is often associated with skin rash and is referred to as **dermatomyositis**.

Demographics

Polymyositis in the United States is most common among African Americans. The disorder is most prevalent in women in a male/female ratio of 1:2. In the United States, its incidence is one per 100,000 persons per year; internationally, a lower incidence among the Japanese has been observed. The age of onset is normally above the second decade of life and it is rare or nonexistent for persons under the age of 20.

Causes and symptoms

To date, no cause of polymyositis has been isolated by scientific researchers. While the initial inciting agent remains unknown, possibilities include infection with certain viruses or muscle trauma. There are many infectious agents that are thought to trigger the disease, mainly Coxsackie virus B1, HIV, human T-lymphotropic virus 1 (HTLV-1), hepatitis B and C, influenza, echovirus, and adenovirus. Certain drugs are also thought to be potential triggers, including D-penicillamine, hydralazine, procainamide, and phenytoin.

There are indicators of heredity (genetic) susceptibility that can be found in some patients, mainly the HLA (human leukocyte antigen) genes, which are responsible for encoding some proteins that can activate the immune system.

The muscle weakness affecting mainly the proximal (closest to the trunk of the body) muscles is the first sign of PM. The onset can be gradual or rapid, but normally progresses over weeks or months. This results in varying degrees of loss of muscle strength and atrophy (tissue degeneration). The loss of strength can be noticed as difficulty getting up from chairs, climbing stairs, or lifting above the shoulders. Trouble with swallowing (dysphagia) and weakness lifting the head from the pillow may occur. Occasionally, the muscles ache at rest or with use, and are tender to the touch (occurs in about 25% patients). Persons with polymyositis can also feel **fatigue**, a general feeling of discomfort, and have weight loss, and/or low-grade fever. Heart and lung involvement can lead to irregular heart rhythm and shortness of breath.

Diagnosis

Persons with polymyositis generally seek initial medical help due to weakness. A physician typically reviews the condition of other body systems, including the skin, heart, lungs, and joints. Blood tests are helpful to reveal abnormal high levels of muscle enzymes in the serum of PM patients, mainly creatinine phosphokinase (CPK) and aldolase. In PM, muscle damage causes the muscular cells to break open and spill their content into the bloodstream. Since most of CPK and aldolase exist in muscles, an increase in the amount of these enzymes in the blood indicates that muscle damage has occurred, or is occurring. Blood tests can also point to active inflammation.

The muscle **biopsy** is one of the best ways to diagnose myositis and other muscle disorders. A muscle biopsy is used to confirm the presence of muscle inflammation typical only of polymyositis. This is a surgical procedure whereby muscle tissue is removed for analysis by a pathologist, a specialist in examining tissue under a microscope. Muscles often used for biopsy include the quadriceps muscle of the front of the thigh, the biceps muscle of the arm, and the deltoid muscle of the shoulder. The results can show conditions such as inflammation, or

Key Terms

Autoimmune disorder A group of disorders characterized by abnormal functioning of the immune system that causes it to produce antibodies against the body's own tissues.

Immunosuppressants Drugs that reduce or eliminate the body's ability to make an immune response.

Myopathy A disorder of the muscles, often involving progressive weakness.

swelling, of the muscle, damage to the muscle, and loss of muscle mass, or atrophy.

Imaging of the muscles using radiology tests such as **magnetic resonance imaging** (**MRI**) can show areas of inflammation of muscle, swelling, or scarring. This sometimes can be used to determine muscle biopsy sites. MRIs show signal intensity abnormalities of muscle due to inflammation.

Another test, an electromyogram (EMG), is used to measure the activity of muscles and to provide clues to the cause of muscle weakness or paralysis, muscle problems such as muscle twitching, numbness, tingling, or **pain**, and nerve damage or injury. EMG is useful in the diagnosis of PM and to exclude other nerve-muscle diseases. Although EMG and MRI imaging are helpful in many cases, the diagnosis of PM is definite when a patient has subacute elevated levels of serum creatine kinase and characteristic findings on muscle biopsy.

Treatment team

A **neurologist** or rheumatologist is the primary consultant for PM, with allied health care areas that include, but are not limited to, physical therapy.

Treatment

In PM, high-dose corticosteroids constitute the first line of treatment, and are effective in more than 70% of patients. Alternatives include immunosuppressant medications, notably azathioprine, methotrexate, and intravenous immunoglobulins (IVIg).

Recovery and rehabilitation

Before the era of corticosteroids, PM was a particularly severe disease with a spontaneous survival rate of less than 40%. Polymyositis in adults now has a relatively favorable prognosis, with a five-year survival rate of around 90%. Only 30–50% of persons with polymyositis achieve complete recovery; the majority of patients have persistent functional problems. However, patients can ultimately do well, especially with early medical treatment of disease and early recognition of disease flares. The disease frequently becomes inactive, and rehabilitation of atrophied (withered) muscles becomes a long-term project.

Clinical trials

The National Institute of Environmental Health Sciences (NIEHS) is recruiting patients for a study entitled "Myositis in Children." The aim of the study is to learn more about the immune system changes and medical problems associated with myositis. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is examining whether infliximab (Remicade[r]) is safe for treatment of PM. Updated information is available at The National Institutes of Health website for **clinical trials** at <http://www.clinicaltrials.gov>.

Prognosis

The prognosis for PM and the response to therapy vary from very good to satisfactory. Most patients respond well to treatment, although residual weakness is common. Osteoporosis, a common complication of chronic corticosteroid therapy, may be significant. For African Americans, older people, females, people with interstitial lung disease and associated malignancies, those who delay treatment, and those with trouble swallowing or heart involvement, the prognosis is much less favorable.

Special concerns

Exercise is generally beneficial, and helps to get the most out of diseased muscles. Falls and injuries, however, can cause substantial disability. People with PM, therefore, have the difficult task of undertaking regular exercise within their capability, but avoiding injury through accident. Because weakened muscles cannot carry an excess load, keeping to an ideal weight is critical. Although this may seem obvious, weight control is more difficult when exercise is limited.

A well-balanced diet is helpful. Patients with severe inflammation of the muscles may need extra protein. Feeding should be avoided prior to bedtime in patients with trouble swallowing.

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Myositis Association of America. 755 Cantrell Ave., Suite C, Harrisonburg, VA 22801. (540) 433-7686; Fax: (540) 432-0206. maa@myositis.org. <http://www.myositis.org>.

Marcos do Carmo Oyama
Iuri Drumond Louro, MD, PhD

Pompe disease

Definition

Pompe disease is a genetically inherited disorder that results in the progressive deterioration of muscle function. The disorder was first described by the Dutch pathologist J.C. Pompe in 1932. Pompe disease is an autosomal recessive disorder, which means that both unaffected parents are carriers and there is a 25% risk of having an affected offspring. Pompe disease is caused by mutations in a gene that encodes an enzyme (a protein that speeds up chemical reactions) called acid alpha-glucosidase. This enzyme is required for breaking down stored sugars in the body.

Description

Pompe disease is also known as glycogen storage disease, type II. Glucose molecules make up sugar, and glucose is stored in the body as glycogen. In this form of the disease, glycogen accumulates in discreet structures in the cell called the lysosomes. Other types of Pompe disease involve the failure to break down glycogen, leading to accumulation in the interior of the cell (not the lysosomal organelles). Glycogen storage diseases collectively, therefore, are all progressive neuromuscular diseases that result from defects in the breakdown or storage of glycogen.

Pompe disease can be categorized into three distinct forms that are determined by the age of onset: the infantile, juvenile, and the adult-onset form. In general, the earlier the onset, the more severe the clinical features of the disease are manifested. Muscle deterioration is the hallmark of Pompe disease. Muscle wasting is progressive, meaning that eventually, patients will lose their ability (or in affected infants, fail to develop an ability) to walk, or perform activities that require sustained motion.

Demographics

In the United States, it is estimated that approximately 1 out of 40,000 individuals is affected with Pompe disease. This estimation is based on population frequencies from a variety of races, but independent of sex or age of onset. Although the frequency has been reported to be less (1 in 50,000) in some Asian populations, including Taiwanese and Southern Chinese, it is felt that most populations share a similar gene frequency found in populations in the United States. As this is an autosomal recessive disorder, males and females are equally affected. Although there are gene mutations that are found in different populations, these gene mutations (otherwise known as an individuals' genotype) do not correlate with the observable clinical feathers (phenotype).

Causes and symptoms

Acid alpha-glucosidase is an enzyme found in discrete organelles within the cell called the lysosomes. Lysosomes are important for storage and release of various molecules that serve as building blocks for the cell or as a source of energy. Lysosomes transport enzymes, like acid alpha-glucosidase, to break down glycogen by breaking down or hydrolyzing specific bonds between sugar molecules. Unlike other types of glycogen storage diseases, Pompe disease patients do not have a condition with low blood sugar (hypoglycemia) or have impairments in energy production. Acid alpha-glucosidase is not the predominant enzyme required to break down glycogen, although it does play a role. Regardless, a deficiency of this enzyme results in an accumulation of glycogen. Toxicity of the accumulated glycogen results in injury to the cells and with enough damage, injury of the entire organ.

Genetic mutations in the acid alpha-glucosidase gene can produce several effects: normal amounts of enzyme can be produced, but with decreased function; or, mutations can also result in a decreased amount of enzyme produced with no defects in function; finally, specific mutations can result in the absence of proper amino acid sequences that are used to produce the acid alpha glucosidase protein.

INFANTILE POMPE DISEASE Infantile Pompe disease typically becomes apparent before the child reaches six months of age. It is particularly progressive, and characterized by rapid muscle deterioration. Failure to reach milestones such as rolling over, sitting up, or standing is typical. Progressive muscular involvement can include tissues that are part of the skeletal system, the cardiac system, and the respiratory system. The cause of death is

Key Terms

Autosomal recessive disorder A genetic disorder that is inherited from parents that are both carriers, but do not have the disorder. Parents with an affected recessive gene have a 25% chance of passing on the disorder to their offspring with each pregnancy.

Glycogen The principle form of carbohydrate energy (glucose) stored within the muscles and liver.

Myopathy Abnormal muscle weakness.

usually due to respiratory and/or heart failure. The heart usually becomes enlarged (cardiomegaly) and becomes dysfunctional, a condition called cardiomyopathy. Cardiomegaly accompanies thickening of the left ventricle of the heart followed by obstruction of blood outflow. Skeletal muscle involvement leads to floppiness and muscle weakness (**myopathy**). Breathing can also become labored due to respiratory muscle injury. This cellular injury will eventually compromise the ability of the respiratory system to function.

JUVENILE POMPE DISEASE Unlike the infant form, children with the juvenile form of Pompe disease usually develop symtomatology after six months of age, but before the age of 20. They may initially complain about muscle weakness and experience failure to progress in terms of motor development, even though intelligence is normal. These patients usually do not have cardiac involvement, and this becomes less likely the older the patient is at the time that clinical manifestations occur. Skeletal and respiratory system failure can eventually lead to death in these patients.

ADULT-ONSET POMPE DISEASE In this form, the course of the disease is less rapid and can develop in persons from 20–60 years old. Patients typically find it difficult to go up a flight of stairs or experience **exercise** intolerance. There is an absence of cardiac abnormality involvement in this type of the disease, and therefore, these patients usually die of complications related to respiratory system dysfunction.

Diagnosis

As there are many disorders that can cause muscle weakness, it is important that laboratory tests, in combination with a physical evaluation, be performed to diagnose Pompe disease. Creatinine kinase, an enzyme involved in muscle function, is also a biomarker for muscle degradation and can be measured in patients' skin cells or other tissues. People with Pompe disease have elevated CK levels, often up to 10 times greater than normal. The test for enzyme activity can also be performed using skin cells or blood cells by a clinical biochemical geneticist. An echocardiogram can help establish the level of heart involvement by testing whether the functions of the heart are normal.

Treatment

There is no cure for Pompe disease. Treatment, therefore, serves only to help minimize the symptoms. The clinical course is typically not affected by drugs that are used to treat the respiratory or cardiac defects. A high protein diet may be helpful and has led to significant improvements in respiratory function in some cases. Ibuprofen has been shown to be effective at relieving muscle aches.

It should be noted that enzyme replacement therapy has been described in Pompe disease recently with some dramatic effects in very small numbers of patients. Although it is still investigational, it may become more available in the future.

Recovery and rehabilitation

As there is no cure for Pompe disease and it is often rapid in its progression, emphasis is placed upon maintaining function for as long as possible, rather than recovery. Occupational therapy can be helpful with positioning devices and strategies for accomplishing daily tasks. Physical therapists can assist with exercises to help maintain maximum possible range of motion and purposeful muscle movement. Speech therapists often provide assistance in feeding strategies for infants affected with Pompe disease.

In the early onset form, it is important and challenging for parents to consider the special needs of babies affected with Pompe disease. This adjustment is often difficult for parents, not only in terms of logistical considerations, but also with the realization that their children will have significant limitations. Parents often utilize community support groups or other counseling to help with these experiences. The late onset form has different emotional and physical issues, as the affected person must cope with progressive lack of mobility and independent function.

Clinical trials

There are several promising ongoing **clinical trials** for the treatment of Pompe disease. In one study, the safety and effectiveness of a recombinant human acid alpha-glucosidase enzyme is being used as a potential enzyme replacement therapy. This recombinant form allows scientist to make a lot of protein, in this case the enzyme that is defective in Pompe disease, and deliver it to patients. Patients diagnosed with infantile-onset Pompe disease who are less

than or equal to six months old (or severely affected) are being studied. (Contact information: Duke University Medical Center, Durham, North Carolina, 27710, Stephanie DeArmey (919) 681-1946, Dearm001@mc.duke.edu; Priya Kishnani, M.D., Principal Investigator.) Other treatment studies are also being invested.

Prognosis

As heart and respiratory muscles quickly weaken, babies affected with Pompe disease usually die within the first year of life. The juvenile form of the disease has a slower progression, with a fatal outcome usually occurring between 20–30 years old. The cause of death is usually respiratory failure. Although the adult form can be fatal, it is likely that these patients will live for several decades following a diagnosis.

Special concerns

Because Pompe disease is a genetic disorder and unaffected carrier parents have a 25% chance of having another affected fetus with each pregnancy, the appropriate genetic counseling is recommended. It should be conveyed to patients and parents that being affected with the disease means that there is a possible risk for other family members to have or pass on the disorder. Prenatal diagnosis is also an option for an expecting mother that wants to know the child's genotype in order to make reproductive decisions.

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Association for Glycogen Storage Disease. P.O. Box 896, Durant, IA 52747. 563-785-6038; Fax: 563-785-6038. maryc@agsdus.org. <http://www.agsdus.org>.

Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718-3208. (520) 529-2000 or (800) 572-1717; Fax: (520) 529-5300. mda@mdausa.org. <http://www.mdausa.org/>.

Bryan Richard Cobb, PhD

Porencephaly

Definition

Porencephaly is a rare condition in which fluid-filled hollows or cavities develop on the surface of the brain. These cavities usually form at sites where damage has been caused by infection, loss of blood flow, or **stroke** during brain development, but may also be genetic in origin. Equivalent terms are cerebral porosis, perencephaly, porencephalia, and (no longer in favor) polyporencephaly. The prefix "por" comes from the Latin *porus,* for hole or cavity.

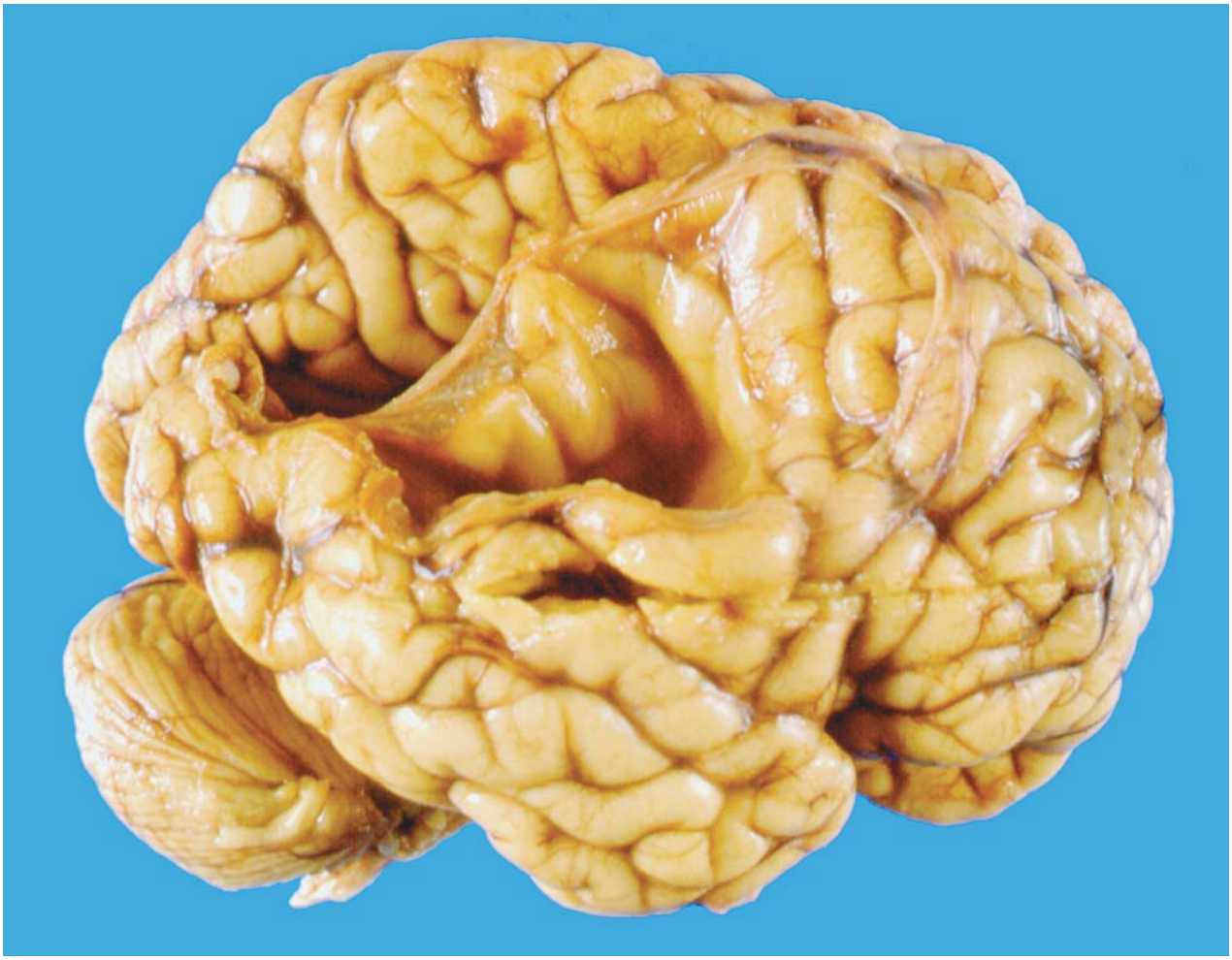
Description

In porencephaly, large dimples, craters, or clefts develop on the surface of the brain. These cavities or cysts are filled with fluid and lined with smooth tissue. They are usually caused by injuries to the fetal or newborn brain before full development of the convolutions or gyri (singular gyrus) on the surface of the cerebrum, especially by infection, ischemia (reduction of blood flow through a vessel), infarction (blockage of blood flow through a vessel), or stroke (bleeding in the brain). The cerebral gyri develop abnormally around a porencephaly cavity, both anatomically and microscopically, and may take on a radiating pattern. Areas of abnormally small gyri (polymicrogyria) may develop on areas of the cerebrum not directly adjacent to a porencephalic cavity.

Porencephaly cavities sometimes develop symmetrically, that is, with a cavity on one side of the brain being matched by a similar cavity on the other side. When a pair of symmetric cavities are very large, they may leave only a thin arch of cerebral cortex running front to back over the top of the brain like a basket handle, a condition termed basket brain. In the most extreme cases, virtually the entire cerebrum may be replaced by fluid, a condition termed **hydranencephaly**.

Demographics

Porencephaly is rare, and its exact incidence is unknown. A 1984 study from the University of Colorado found in a study of 18,000 patients with seizure disorder



Cavities in a hemisphere of a brain affected with porencephaly. *(Custom Medical Stock Photo. All Rights Reserved.)*

or retarded neural development that 11 had porencephaly, a rate of 1:1650 in that abnormal population.

Causes and symptoms

Any agent or event that causes localized tissue death in the brain during development can cause porencephaly. The body walls off the injured area with a barrier of smooth tissue (encysts it), and eventually the dead tissue is cleared away and replaced with cerebrospinal fluid. One infectious agent that can cause porencephaly is cytomegalovirus, which can also cause **microcephaly** (small brain). Ischemic brain necrosis, the death of a portion of the brain due to restriction of blood flow through a specific vessel, most often the middle cerebral artery, can also cause porencephaly. Rarely, porencephaly can be caused by a mechanical injury such as accidental penetration of the skull by an amniocentesis needle.

Because porencephaly usually follows from a disruption during development rather than from a genetic defect, it falls into a class of cerebral defects in between primary malformations (those occurring without any specific injury or trigger, and usually genetic in origin) and secondary malformations (those resulting from injury, infection, or some other external cause). The question of whether a given case of porencephaly is primary (genetic) or secondary is important because geneticists wish to provide accurate counseling to prospective parents with family histories of porencephaly. If a familial case of porencephaly is due to infection or injury, there is probably no increased genetic risk for future generations. If, on the other hand, a familial case of porencephaly is due to heritable genetic abnormalities affecting clotting factors, for instance, there may be increased risk for a fetus affected in future pregnancies. Research by the National Institute of Neurological Disorders and Stroke, an arm of the National Institutes of Health, commenced in 2000 to determine if acquired and/or genetic abnormal coagulation factors in the blood are associated with porencephaly, stroke, and **cerebral palsy**.

The symptoms of porencephaly are varied, and depend on the severity of the defects in each individual case. Persons with porencephaly may suffer early death, **epilepsy**, moderate or severe **mental retardation**, blindness, epilepsy, rigidity, and paralysis.

Diagnosis

Imaging technologies such as ultrasound, x-ray computerized tomography, and **magnetic resonance imaging** (**MRI**) can diagnose porencephaly before or after birth. Ultrasound is preferred for fetal imaging, both because it is cheaper than MRI or computed tomography (**CT**) **scan** and, in most cases, just as informative; and because of lingering concerns that magnetic resonance imaging might, by some unknown mechanism, be capable of disrupting the normal formation of organs. (X rays are not used because fetuses are known to be extremely vulnerable to ionizing radiation.) An initial diagnosis can sometimes be made by shining a light through the newborn's skull.

Treatment team

As with other severe congenital defects of the brain, the membership of a porencephaly patient's treatment team will depend on the severity and exact nature of the damage. A pediatric **neurologist** and physical therapist will probably be involved, at minimum.

Treatment

Treatment is addressed to alleviating symptoms, not to curing the underlying problem, as there is no treatment to induce the brain to grow missing sections of the cerebrum. Treatment includes physical therapy for rigidity, **spasticity**, or movement difficulties; medication to prevent **seizures**; and, if necessary, the installation of a shunt or drain to remove excess cerebrospinal fluid from the inside of the skull.

Clinical trials

As of early 2004, the National Institute of Neurological Disorders and Stroke was sponsoring research entitled "Study of Abnormal Blood Clotting in Children with Stroke." More information can be found by contacting the National Institute of Neurological Disorders and Stroke (NINDS), 9000 Rockville Pike, Bethesda, Maryland, 20892, Patient Recruitment and Public Liaison Office, telephone: (800) 411–1222, email: prpl@mail.cc.nih.gov.

Prognosis

Most persons with porencephaly die before reaching adulthood. Each individual's prognosis will depend on the location and severity of the lesions on their cerebrum.

Key Terms

Amniocentesis Surgical withdrawal of a sample of amniotic fluid from a pregnant female for use in the determination of sex or genetic disorder in the fetus.

Cerebellum Lower back part of the brain responsible for functions such as maintaining balance, and coordinating and controlling voluntary muscle movement.

Cerebrospinal fluid Clear fluid that circulates through the brain and spinal cord.

Cerebrum The main portion of the brain (and the largest part of the central nervous system), occupying the upper portion of the cranial cavity.

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National Organization for Rare Disorders. 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605, USA. (914) 428-7100 or 888-MODIMES (663-4637); Fax: (914) 428-8203. askus@marchofdimes.com. <http://www.marchofdimes.com>.

Larry Gilman, PhD

Positron emission tomography (PET)

Definition

Positron emission tomography (PET) is a noninvasive scanning technique that utilizes small amounts of radioactive positrons (positively charged particles) to visualize body function and metabolism.

Description

PET is the fastest growing nuclear medicine tool in terms of increasing acceptance and applications. It is useful in the diagnosis, staging, and treatment of cancer because it provides information that cannot be obtained by other techniques such as computed tomography (**CT**) and **magnetic resonance imaging (MRI)**.

PET scans are performed at medical centers equipped with a small cyclotron. Smaller cyclotrons and increasing availability of certain radiopharmaceuticals are making PET a more widely used imaging modality.

Physicians first used PET to obtain information about brain function, and to study brain activity in various neurological diseases and disorders including **stroke**, **epilepsy**, **Alzheimer's disease**, **Parkinson's disease**, and Huntington's disease; and in psychiatric disorders such as **schizophrenia**, **depression**, obsessive-compulsive disorder, **attention deficit hyperactivity disorder** (ADHD), and **Tourette syndrome**. PET is now used to evaluate patients for these cancers: head and neck, lymphoma, melanoma, lung, colorectal, breast, and esophageal. PET also is used to evaluate heart muscle function in patients with coronary artery disease or cardiomyopathy.

Procedure

PET involves injecting a patient with a radiopharmaceutical similar to glucose. An hour after injection of this tracer, a PET scan creates an image of a specific metabolic function by measuring the concentration and distribution of the tracer throughout the body.

When it enters the body, the tracer courses through the bloodstream to the target organ, where it emits positrons. The positively charged positrons collide with negatively charged electrons, producing gamma rays. The gamma rays are detected by photomultiplier-scintillator combinations positioned on opposite sides of the patient. These signals are processed by the computer and images are generated.

PET provides an advantage over CT and MRI because it can determine if a lesion is malignant. The two other modalities provide images of anatomical structures, but often cannot provide a determination of malignancy. CT and MRI show structure, while PET shows function. PET has been used in combination with CT and MRI to identify abnormalities with more precision and indicate areas of most active metabolism. This additional information allows for more accurate evaluation of cancer treatment and management.

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Dan Harvey
Lee A. Shratter, MD
Rosalyn Carson-DeWitt, MD

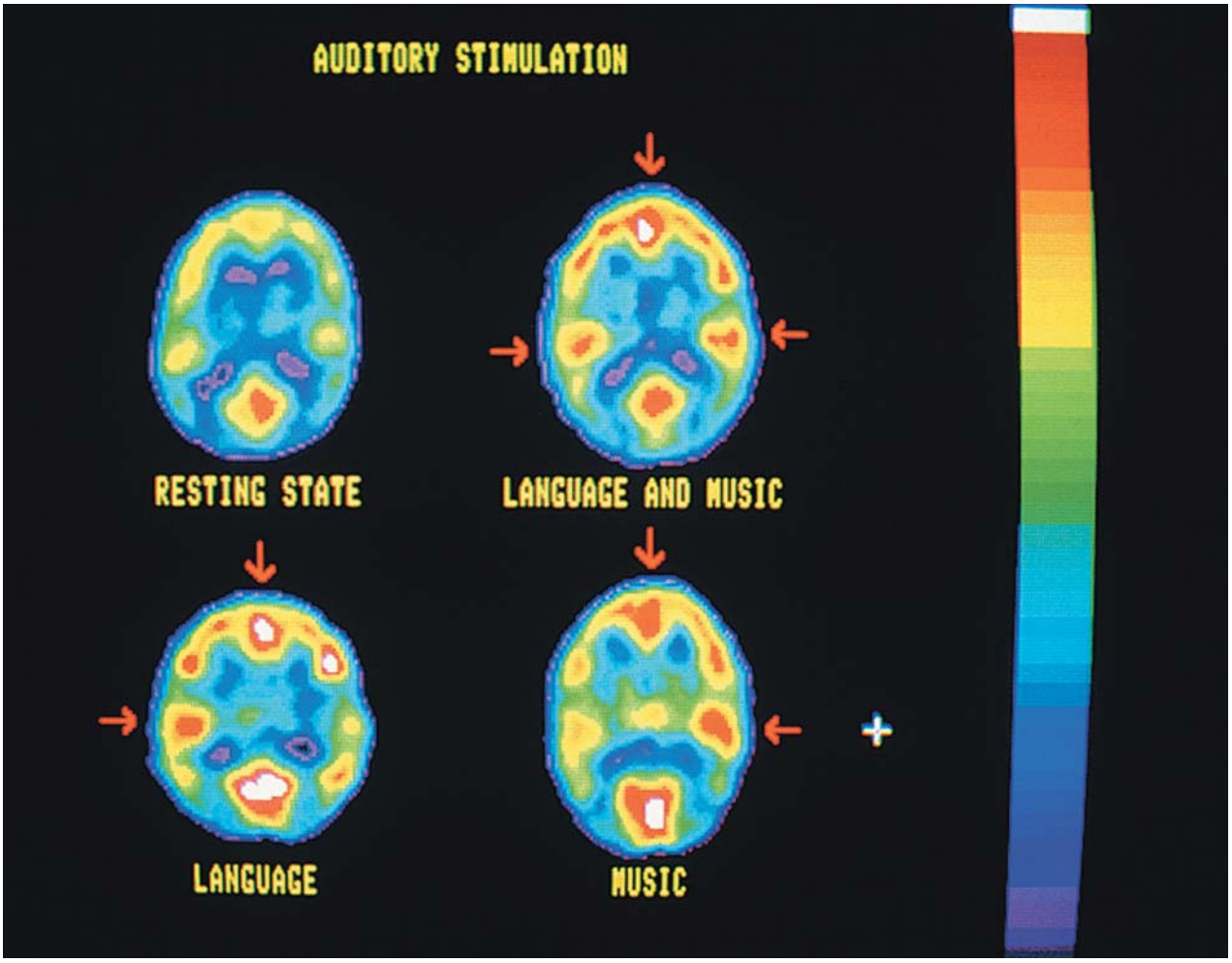
Post-polio syndrome

Definition

Post-polio syndrome is a slowly progressing weakness that affects polio survivors decades after their initial bout with the disease.

Description

In order to understand post-polio syndrome, it's important to understand polio infection in general. Although people of any age can become infected with poliovirus, it tends to infect young children in particular. About 1% of all people who become infected with poliovirus will actually become ill. Initial symptoms include fever, nausea,



Results of a brain stimulation test made with positron emission tomography. *(© Roger Ressmeyer/Corbis. Reproduced by permission.)*

Key Terms

Electron One of the small particles that make up an atom. An electron has the same mass and amount of charge as a positron, but the electron has a negative charge.

Gamma ray A high-energy photon emitted by radioactive substances.

Half-life The time required for half of the atoms in a radioactive substance to disintegrate.

Photon A light particle.

Positron One of the small particles that make up an atom. A positron has the same mass and amount of charge as an electron, but the positron has a positive charge.

and vomiting, followed by several symptom-free days. Some individuals then recover completely. Others go on to develop new symptoms, including severe head, back, and neck **pain**. These symptoms signal that the virus is invading the nervous system, causing inflammation, injury, and destruction of motor nerves (the nerves that are necessary for muscle movement). As motor nerves are destroyed, the muscles cannot receive messages from the brain. Without input from the brain, muscle tone becomes weak and floppy, and paralysis sets in. Over time, the muscle becomes atrophic (shrunken in size). Paralysis is usually asymmetric; that is, it affects only one side of the body. The paralyzed limbs retain their ability to feel. When the muscles of respiration are affected, the patient may need to be put on a mechanical ventilator.

It only takes a few days for the weakness and/or paralysis to progress to its maximum level of severity. Recovery continues for about six months, during which time the

remaining unaffected motor nerves begin sprouting new branches to the muscles, in an attempt to compensate for the nerves that were completely destroyed. During this phase, the patient will regain some degree of functioning. After six months have passed, whatever disability remains will usually be permanent.

Post-polio syndrome occurs some decades after the original infection with polio. Initially, the subtly gradual progressive muscle weakness is barely noticed by the patient, but over time the decrement becomes increasingly obvious. In general, the more severe the original polio infection, the more severe the disability from post-polio syndrome.

Demographics

Only 1% of all people infected with poliovirus actually develop full-fledged polio. About 25-50% of polio survivors will eventually be affected with post-polio syndrome.

Causes and symptoms

Attempts to completely delineate the process by which post-polio syndrome develops have not been totally successful. A number of working theories have been developed.

- The newer nerve sprouts that grew in order to compensate for lost motor units overtax the rest of the nerve, and over time the nerve begins to fail.
- Injured nerves that regained function end up failing after years of overuse attempting to compensate for lost motor units.
- Remaining particles of the poliovirus may precipitate a chemical response in the immune system that accidentally destroys the body's own nerves.
- Spinal cord changes in polio survivors may adversely affect nerves over time.

Symptoms of post-polio syndrome include severe **fatigue**; decreased energy; gradually progressive muscle weakness and muscle atrophy; involuntary muscle twitching (fasciculation); muscle, joint and **back pain**; difficulty breathing and swallowing; and problems with sleep. The most severe muscle problems seem to occur in those muscles that were already affected by the initial bout of polio, although muscles that were not originally affected may also develop some new degree of weakness.

Diagnosis

Diagnosis should be suspected in any polio survivor experiencing new muscle weakness.

Four criteria are required to diagnose post-polio syndrome in a patient with gradually increasing muscle weakness:

- known history of poliovirus infection with residual muscle weakness
- history of recovery of some degree of muscle function, with a period of stability lasting at least 15 years
- at least one limb demonstrating residual muscle atrophy, weakness, lack of normal reflex, and continued normal sensation
- normal function of sphincter muscles (the muscles around the anus and the lower part of the esophagus)

Key Terms

Atrophy Wasting or shrinking of a body part, such as a muscle.

Motor nerve A nerve that is involved in muscle movement.

Polio A disease caused by the poliovirus that can result in muscle weakness and/or paralysis.

Poliovirus The virus responsible for the disease called polio.

Sphincter A band of muscle that encircles an opening in the body, allowing the opening to open and close (anal sphincter, esophageal sphincter).

Treatment team

The treatment team will depend in part on the specific symptoms encountered. In general, once diagnosed, the patient will benefit from work with a physical therapist, occupational therapist, and speech and language therapist. Specialists in arthritis, orthopedics, rehabilitation, and pulmonology may also be helpful.

Treatment

There is no cure for post-polio syndrome. Efforts are primarily directed at retaining mobility and improving patient comfort. Anti-inflammatory medications can help relieve muscle and joint pain by decreasing inflammation. Braces, wheelchairs, or motorized scooters may help very compromised patients retain some independence and mobility. Respiratory and sleep problems may interact with each other to create considerable distress. They may be relieved by the use of supplemental oxygen and/or breathing devices to help keep the airway open while sleeping.

Recovery and rehabilitation

The physical therapist should design a thoughtful **exercise** program to maintain and increase flexibility, although it is important not to overtax already weakened

muscles and nerves. Occupational therapy can help the individual learn methods to compensate for muscle weakness, and still retain independence in the activities of daily living. Speech and language therapists can be helpful for swallowing problems.

Clinical trials

A **clinical trial** through the National Institute of Neurological Disorders and Stroke is studying whether the drug **modafinil** might be helpful in treating the relentless fatigue of post-polio syndrome.

Prognosis

Because the increase in muscle weakness is so gradual, post-polio syndrome is generally thought to have a good prognosis, rarely causing significantly more severe impairment and disability. In a few rare cases, however, progressive weakening of the muscles of respiration can result in death.

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Rosalyn Carson-DeWitt, MD

Postinfectious encephalomyelitis *see* **Acute disseminated encephalomyelitis**

Postural hypotension *see* **Orthostatic hypotension**

Prednisone *see* **Glucocorticoids**

Primary lateral sclerosis

Definition

Primary lateral sclerosis (PLS) is a rare disease that causes progressive weakness in voluntary muscles such as in the legs, hands, and tongue. PLS is one of the diseases, along with **amyotrophic lateral sclerosis** (or Lou Gehrig's disease), that are grouped together as **motor neuron diseases**.

Description

Motor neuron diseases like primary lateral sclerosis develop because the nerve cells that normally control the movement of voluntary muscles degenerate and die. The disease is typically detected in middle age, after age 50. The symptoms of the disorder become progressively worse, with muscles typically affected in the following order: legs and feet, main part of the body (the trunk), arms and hands, and face. PLS is not fatal, and people with the disorder can usually maintain mobility with the use of canes or other assistance.

Demographics

Primary lateral sclerosis predominates in those over 50 years of age, although people in their mid-30s can be affected. PLS is rare in younger people, although one case of a 20-year-old has been reported. It is estimated that only about 500 people in the United States have the disease. Due to its historically rare occurrence, it is not yet possible to know if the disease is more prevalent in males or females. The incidence of PLS is uncertain. ALS is known to affect two to three people per 100,000. Tentative estimates of the occurrence of PLS are on the order of one person in 10 million, which would make it only about 0.5 percent as prevalent as the already rare ALS.

Causes and symptoms

The cause of the disease is the progressive degeneration and death of the nerves (neurons) that control the movement of voluntary muscles. There is no evidence of a genetic basis for the disease. Some other process determines the nerve cell death. PLS affects a part of the neuron called the cell body (or soma). Specifically, it is the cell bodies of upper motor neurons that are affected. Upper motor neurons are located in the brain. Their loss affects the transmission of a signal to other neurons that eventually control the muscle activity. This specificity distinguishes PLS from ALS. ALS, the most common motor neuron disease, affects both the upper neurons and lower motor neurons located in the spinal cord.

PLS is characterized by weakness of voluntary muscles. Typically, the disease is first noticed as a weakening

Key Terms

Gait Manner in which a person walks.

Motor neuron disease A neuromuscular disease, usually progressive, that causes degeneration of motor neuron cells and loss or diminishment of voluntary muscle control.

of the legs, hands, or tongue. Other symptoms include difficulty in maintaining balance and clumsiness, sudden muscle spasms, foot dragging, and difficulty in speaking. The neuron death does not affect regions of the brain that control intellect and behavior.

The muscle weakness becomes progressively worse. For some people, this process can stretch over decades. For others, the progression is much faster. While PLS is related to Lou Gehrig's disease, in PLS there is no degeneration of the spinal motor neurons or the wasting away of muscle mass than occurs in ALS.

Diagnosis

Diagnosis is based on the observance of the muscle weakness and the progressive worsening of the weakness. The diagnosis can be delayed because the disease is mistaken for ALS.

Treatment team

Treatment of PLS involves the family physician, a **neurologist**, and others such as physical therapists. The prolonged nature of the disease means that the energy and commitment of the patient and treatment team must be maintained for a long periods of time, usually decades.

Treatment

The treatment aims to reduce the discomfort and inconvenience of the disease. There is currently no cure for PLS. Medications such as baclofen, **diazepam**, and **gabapentin** have shown effectiveness in reducing muscle spasms in many patients with PLS.

Recovery and rehabilitation

As primary lateral sclerosis is a slowly progressive disorder, emphasis is placed upon maintaining maximum function rather than recovery. Physical therapists can assist with stretching and strengthening exercises to help maintain range of motion and decrease muscle **fatigue** and spasms. Physical therapists are often involved in assessing gait (manner of walking) and balance, and help select the proper type and size of cane or other device to assist with mobility.

Clinical trials

As of April 2004, one clinical trial was recruiting patients in North America. People between the ages of 40 and 75 were sought in the trial, which seeks to relate measurements of voluntary muscle activity to brain activity. The intention is to better understand the areas of the brain that are involved with PLS. Updated information on the trial can be found at the National Institutes for Health website on **clinical trials** at <www.clinicaltrials.gov>. Aside from the clinical trial, research studies are being funded that seek to develop techniques to diagnose, treat, prevent, and hopefully someday to cure motor neuron diseases.

Prognosis

Because PLS can be a slowly progressing disease, the outlook for a normal life span is good. While life can be greatly changed, a person is still usually able to walk, albeit with the assistance of a cane or other device.

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National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

ALS Association (ALSA). 27001 Agoura Road, Suite 150, Calabasas Hills, CA 91301-5104. (818) 880-9007 or (800) 782-4747; Fax: (818) 880-9006. info@alsa-national.org. <http://www.alsa.org>.

Primary Lateral Sclerosis Newsletter. 101 Pinta Court, Los Gatos, CA 95032. (408) 356-8227. 73112.611@compuserve.com.

Brian Douglas Hoyle, PhD

Primidone

Definition

Primidone belongs to the class of medications known as **anticonvulsants**. It is indicated for the control of **seizures** in the treatment of **epilepsy** and other seizure disorders. Primidome may be prescribed alone or as part of a combination of medications for preventing seizures.

Key Terms

Barbiturate A class of drugs including phenobarbital that have sedative properties and depress respiratory rate, blood pressure, and nervous system activity.

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Seizure A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

Purpose

Primidone is thought to decrease abnormal activity within the brain that may trigger seizures. While primidone controls some types of seizures associated with epilepsy (grand mal, psychomotor, and focal seizures) there is no known cure for the disorder. Additionally, primidone has shown promise in alleviating some forms of essential **tremors**, but is not approved in the United States for this use.

Description

In the United States, primidone is also sold under the names Myidone and Mysoline. Although the precise mechanism by which primidone exerts its therapeutic effects is unknown, it is thought to help slow and control nerve impulses in the brain. The active metabolites of primidone are **phenobarbital** and phenylmethylmalonamide (PEMA), both barbiturate-type compounds with anticonvulsant and sedative properties. Primidone is supplied in chewable tablets (in Canada), tablets to be swallowed whole, and in suspension (syrup) forms for oral administration.

Recommended dosage

Primidone is available in 50 milligram (mg) and 250 mg tablets, and is prescribed by physicians in varying dosages. The usual initial dose for adults, teenagers, and children over eight years of age is 100 mg or 125 mg per day. Dosages are gradually increased until arriving at the lowest possible dosage that results in control of seizures. Children under eight years of age typically take an initial daily dose of 50 mg. The maximum daily dose for anyone taking primidone usually is not greater than 2000 mg.

The prescribing physician will schedule a patient's daily dosages, gradually increasing them over the course of several weeks. Primidone may not exert its full therapeutic effect during the initial dose-increasing period.

Primidone should be taken at approximately the same time every night. If a daily dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped. Double doses of primidone should not be taken.

A patient should consult their physician before they stop taking primidone. Suddenly discontinuing this medicine may cause seizures to return or occur more frequently. When ending treatment including primidone, physicians typically direct patients to taper their daily dosages gradually.

Precautions

A physician should be consulted before taking primidone with non-prescription medications. Patients should avoid alcohol and CNS depressants (medicines that can make one drowsy or less alert, such as antihistimines, sleep medications, and some **pain** medications) while taking primidone because it can exacerbate their side effects. Primidone may not be suitable for persons with a history of porphyria, asthma or other chronic lung diseases, liver disease, kidney disease, mental illness, high blood presure, angina (chest pain), irregular heartbeats, or other heart problems. Patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant, or plan to become pregnant.

Anticonvulsant medications, namely phentoyn and phenobarbital, have been shown to cause birth defects. Physicians usually advise women of childbearing age to use effective birth control while taking this medication. Patients who become pregnant while taking primidone should contact their physician immediately.

Side effects

Patients and their physicians should weigh the risks and benefits of primidone before beginning treatment. Most patients tolerate primidone well, but may experience a variety of mild side effects. If any symptoms persist or become too uncomfortable, consult the prescribing physician. The following common side effects usually do not require medical attention and may lessen after taking primidone for several weeks:

- dizziness, unsteadiness, or clumsiness
- nausea or vomiting
- decreased sexual desire or ability
- loss of appetite
- mood or mental changes
- tremors

Other, less common side effects of primidone may be serious. Contact a physician immediately if any of the following symptoms occur:

- rash or bluish patches on the skin

- unusual excitement or restlessness (espeically in children, seniors, or patients taking high dosages)
- double vision
- uncontrolled back-and-forth or rolling eye movements
- speech or language problems
- chest pain
- irregular heartbeat
- faintness or loss of consciousness
- persistent, severe headaches
- persistent fever or pain.

Interactions

Primidone may have negative interactions with adrenocorticoids (cortisone-like medications), antibiotics, antidepressants, anticoagulants, antihistimines, asthma medications, barbituates, and monoamine oxidase inhibitors (MAOIs). Primidone should be used in conjunction with other seizure prevention medications, especially valproic acid, only if advised and closely monitored by a physician. Primidone may decrease the effectiveness of oral contraceptives (birth control pills) that contain estrogen.

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American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. <http://www.aesnet.org>.

Epilepsy Foundation, 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

Adrienne Wilmoth Lerner

Prion diseases

Definition

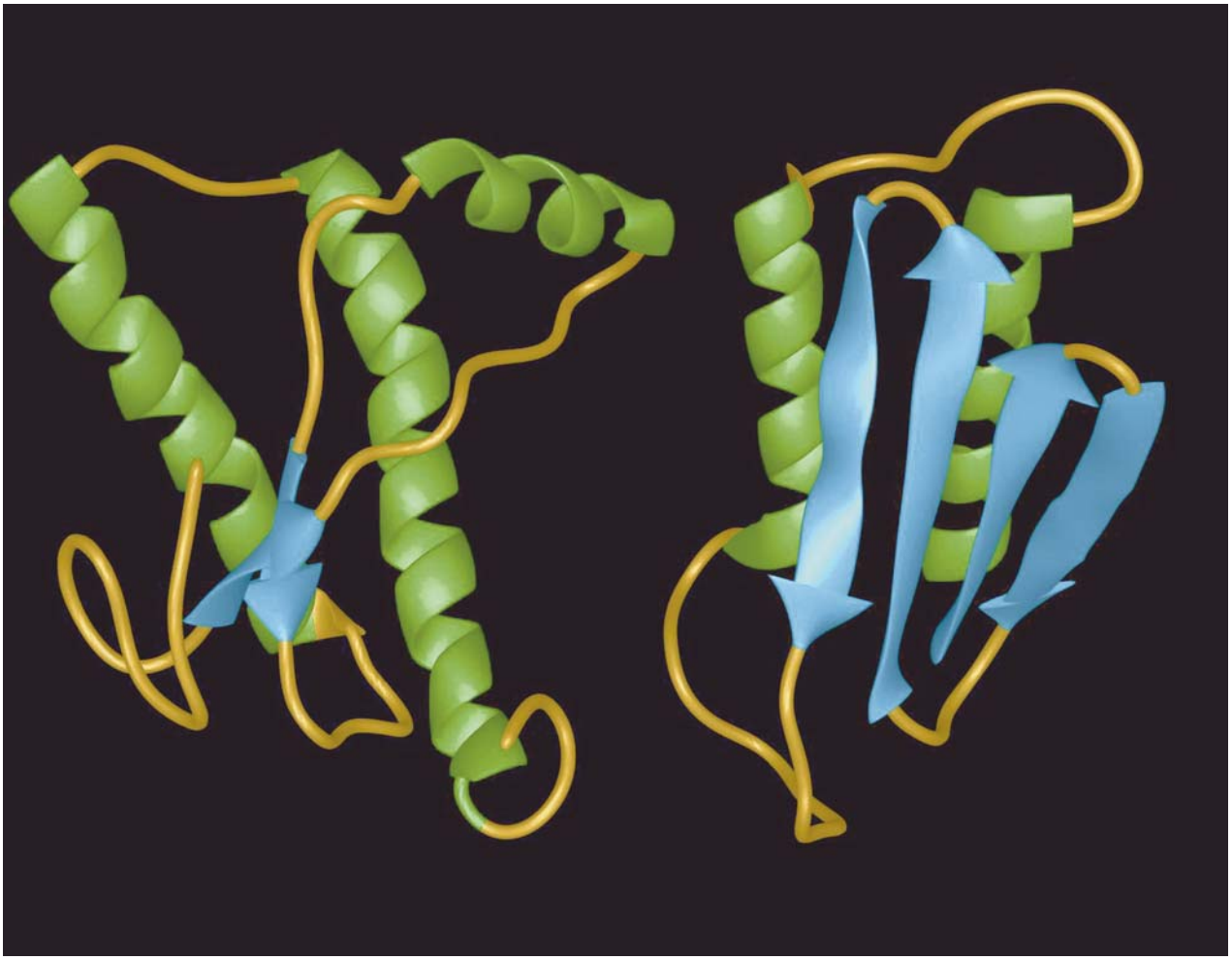
Prion diseases are also called transmissible spongiform encephalopathies (TSEs) because of the sponge-like holes they leave in infected brains. The infectious agents in prion diseases are prions, or proteinaceous infectious particles, that can reproduce themselves. Prions have the ability to transform normal, benign protein molecules into infectious, deadly ones by altering their structure. These deadly proteins initiate a sequence of events in which many benign proteins are transformed into new deadly ones upon contact. Prions are distinct from all other infectious materials in that they do not contain any genetic material. There are multiple prion diseases, including bovine spongiform **encephalopathy** (BSE), or "mad cow disease." Some prion diseases are hereditary, and involve a mutation in the gene that encodes for the prion protein. Prion diseases are transmissible within a species and between compatible species.

Description

Research on prion diseases was founded by Dr. Stanley Prusiner, a **neurologist** at the University of California San Francisco. He spent two decades working on the revolutionary topic of self-reproducing prions. At the time, many other scientists regarded their existence as a preposterous idea. Despite being shunned by the scientific community, Dr. Prusiner was able to prove that prions were truly infectious proteins that could cause brain disease in people and animals. The Nobel Prize for Medicine or Physiology was awarded to Dr. Prusiner in 1997 for discovering this new type of disease-causing agents that contain no DNA.

Prion diseases are transmissible between hosts of a single species and different, compatible species. The term "spongiform" in TSE comes from the spongy appearance of the damaged brain tissue. Some examples of infectious prion diseases include scrapie in sheep and goats, **kuru** in cannibalistic humans of Papua New Guinea, and BSE, or mad cow disease, which is transmitted to humans through infected beef products. Prion diseases can also be transmitted through injections of infected material from a compatible organism. Because of the ability of prions to cross many species barriers, all organisms that carry prion diseases are potential vectors for human infection.

Prion diseases can also be hereditary, as seen in some cases of **Creutzfeldt-Jakob disease** (CJD), fatal familial insomnia (FFI), and **Gerstmann-Straussler-Scheinker disease** (GSS). Hereditary prion diseases occur when the PRNP gene that encodes for the normal human PrP^{C} protein, found on the surface of neurons, is mutated so that the prion PrP^{Sc} protein (Sc for scrapie) is formed. The PrP^{Sc} protein has a different conformational structure than the normal protein and is the infectious agent. PrP^{Sc} proteins can convert similar PrP^{C} proteins upon contact into more infectious agents, thereby reproducing themselves. Prion diseases are inherited when at least one copy of the mutated PRNP gene is present. Nervous tissue from patients with hereditary prion diseases is also infectious.



A computer-generated illustration showing, on the left, a human prion protein in its normal shape at the molecular level, and, on the right, a disease-causing, abnormally shaped prion protein. The blue arrow indicates beta strands, the green spiral shapes are alpha helices, and the yellow strands depict the chain connecting the regions. *(AP/Wide World. Reproduced by permission.)*

A third category of prion disease is sporadic. CJD and FFI sometimes occur in people with no known history of the disease in their family and with no known exposure to infectious materials. The cause of disease in these cases is unknown. Patients with sporadic prion diseases may have a susceptibility polymorphism in their PRNP gene, and may have spontaneous mutations forming prion proteins.

Demographics

Sporadic CJD, with no recognizable pattern of transmission, has an incidence of about one case per million people per year worldwide, making up 85% of total CJD cases, and 80% of all prion disease cases. In the United States, there are approximately 200 sporadic CJD cases per year. Approximately 15% of CJD cases are inherited and associated with a different prion type than that of sporadic CJD. Inherited CJD may show up in geographic clusters. A 60- to 100-fold increase in CJD is seen in Libya- or Slovakia-born Israelis due to a PRNP gene mutation rather than transmission or environmental factors. Other communities genetically at increased risk are found in some areas of Chile. CJD cases caused by accidental transmission routes such as surgical instruments and transplants are extremely rare and make up less than 1% of total cases. In the United States, the CJD cases are almost always in patients older than 30 years of age. In the United States, patients under 30 dying of CJD are less than one case per 100 million people per year, whereas in the United Kingdom, patients dying of a variant CJD (vCJD) in this age group make up over 50% of the CJD cases.

GSS is rarer than CJD, striking one person in every 10 million people. These figures are likely to be underestimated since prion diseases may be misdiagnosed as other neurological disorders. Kuru occurs in approximately 1%

of the indigenous New Guinea population it is associated with. Kuru is found mostly in children older than five years and adult females under 40 years of age.

BSE has been transmitted to humans primarily in the United Kingdom, causing vCJD. An epidemic of mad cow disease began in the United Kingdom in 1985 when cattle feed was contaminated with brain tissue from scrapie-infected sheep. More than 170,000 cattle were infected before the disease was brought under control. Cattle feed containing sheep matter was banned in 1988. In 1989, slaughter techniques that allow nervous tissue to be included in beef intended for human consumption were banned. The mad cow disease epidemic of the United Kingdom reached its peak in 1992, but then declined quickly. More than one million cattle may have been infected with BSE in the United Kingdom. However, as of December 2003, only 143 cases of vCJD have been reported in the United Kingdom, out of 153 cases worldwide. The percentage of BSE cases in cattle reported outside of the United Kingdom is steadily increasing as surveillance increases and disease rates rise. The BSE epidemic in the United Kingdom may have peaked, and may now be in decline. How much of the population has vCJD in the incubation phase is yet to be determined.

To prevent the spread of BSE to the United States, severe restrictions were placed on the importation of ruminants and ruminant products from Europe. In 1997, the U.S. Department of Agriculture (USDA) also implemented a ban on the use of ruminant tissue in ruminant feed. In 2002, the CDC reported a case of vCJD in the United States in a 22-year-old patient who was born and grew up in the United Kingdom. Mad cow disease made its first appearance in cattle of the United States in December 2003, when the USDA announced a possible diagnosis in a cow from Washington State. This diagnosis was confirmed within the month at a laboratory in the United Kingdom. The cow was believed to be imported from Canada in the year 2001 and had been slaughtered for human consumption. The USDA recalled all beef slaughtered at the same slaughter plant on the same date as the infected cow.

Causes and symptoms

Ingested prions are absorbed through Peyer's patches of the small intestine, lumps of lymphoid tissue that readily allow the passage of gut antigens straight through them. Peyer's patches are a part of the mucosal-associated lymphoid tissue that presents microorganisms to the immune system and would normally facilitate a protective immune response. Prions do not activate any immune response. Prions passed through Peyer's patches travel to various sites in the lymph system, such as nodes and the spleen. Because many lymph sites are innervated, prions gain access to the nervous system, make their way to the spinal cord, and eventually the brain.

Prions are not killed by high doses of ultraviolet **radiation** as are bacteria and viruses. Prions are also resistant to high temperatures, strong degradative enzymes, and chemicals. Because of these properties, prions are resistant to many methods of sterilization and to protective, degradative enzymes in the human brain. The plaques formed in the brain by prion proteins are amyloid deposits similar to those seen in **Alzheimer's disease**. Most brain cells contain enzymes that degrade these aggregations. Prions are resistant to these enzymes. The plaques continue to grow and cause damage to the brain, usually along with the formation of large vacuoles that give the brain a spongiform appearance. Brain damage manifests itself in a loss of coordination, paralysis, **dementia**, and wasting, followed by death. Pneumonia also frequently occurs in patients with prion diseases. All prion diseases are inevitably fatal; there are no known cures.

Prion diseases can be inherited in an autosomal dominant matter. This means if one parent carries the mutation on their PRNP gene, each offspring has a 50% chance of inheriting the mutation. In this manner, patients with a prion disease have inherited at least one copy of a mutated PRNP gene on human chromosome 20. There are a variety of mutations in the gene that cause resultant mutated proteins to be expressed, with each type of mutation resulting in a different prion strain, and a different inherited prion disease. Strains show very different and reproducible patterns of brain degeneration. Extracts of autopsied brain tissue from infected patients have been used for research on prion diseases. It has been demonstrated that only animals whose PRNP gene is similar enough to humans can be infected with human prions. Similarly humans can only be infected by prions from animals whose PRNP gene ultimately encodes for a prion protein that is similar to humans. Prions transform their normal cellular counterparts into other prions only between prion-compatible species. Infectious prion diseases are transmitted through consumption of infected materials or through injection of ground-up infected tissues. Prion diseases are not contagious in the traditional sense. Individuals who live with patients with prion diseases are at no increased risk. While casual contact does not transmit the disease, brain tissue and cerebrospinal fluid from patients with prion diseases should be avoided.

Inherited prion diseases

GERSTMANN-STRAUSSLER-SCHEINKER DISEASE Caused by the GSS prion, this disease was first described in 1928. GSS is associated with variations in at least one PRNP gene sequence at positions 102 and 117. It is also highly

associated with a polymorphism on both gene copies at position 129 on the human PRNP gene. GSS typically occurs between the ages of 35 and 55. It is characterized by progressive cerebellar **ataxia** and associated motor complications, following a time course of 2–10 years before death. Dementia with GSS is less common than with CJD, except in very late stages of disease following a long time course. GSS is almost always inherited, but has been known to occur sporadically as well.

CREUTZFELDT-JAKOB DISEASE Caused by the CJD prion, this disease is associated with variations in the PRNP gene at positions 178 and 200, along with an insertion of extra DNA in the familial form. CJD was first described in the 1920s as a progressive dementia, following a course of one year, ending in death. CJD presents with a variety of motor disturbances, including twitching. CJD typically occurs between the ages of 50 and 75. While CJD is an inherited disease, the majority of CJD occurs sporadically. Other CJD cases are due to accidental exposure to infected material.

FATAL FAMILIAL INSOMNIA Caused by the FFI prion, FFI is a rare disorder first described in 1986. It is caused by inherited mutations in the PRNP gene at position 178 and a polymorphism at position 129. FFI typically occurs between the ages of 40 and 60, and is characterized by progressive sleep disturbance classified as untreatable insomnia, ataxia (motor dysfunction), and dysautonomia (sensory dysfunction). The disease course is 7–18 months, followed by death. Postmortem studies associate this prion disease with severe selective atrophy of the thalamus, a brain region controlling sleep and wakefulness. Sporadic FFI has been reported without the characteristic gene mutation.

ALPERS SYNDROME Alpers syndrome is the term used to describe prion diseases in infants.

Infectious prion diseases

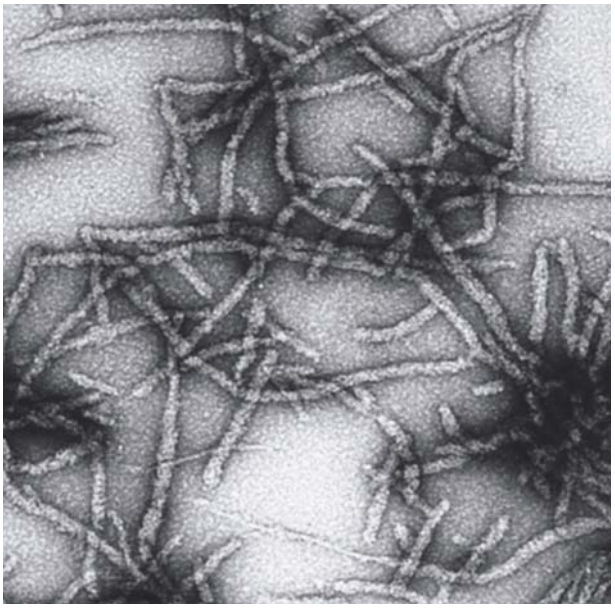
SCRAPIE Caused by the scrapie prion, scrapie is the first prion disease ever studied. Scrapie was first described in sheep and goats more than 200 years ago. It is transmitted through feed contaminated with nervous tissue. It can also be transmitted through pasture infected with placental tissue from infected sheep. The term "scrapie" comes from the behavior of infected sheep that rub up against the fences of their pens to remain upright despite severe ataxia, a loss of muscular coordination due to brain damage. Autopsies of infected animals reveal spongiform encephalopathy. In 1943, scrapie was demonstrated as transmissible when a contaminated vaccine infected healthy sheep.

KURU Decades after scrapie was first discovered, a similar disorder was described in humans called kuru. Kuru was characterized in 1950 as a progressive cerebellar ataxia associated with a shivering tremor, with a disease course of three to nine months, followed by death. The word *kuru* comes from the Fore language and means 'tremor.' Caused by the kuru prion, kuru primarily occurred in the Fore highland people of southern New Guinea, whose cultural practice used to involve ritualistic ingestion of the brain tissue of recently deceased family members. The brain tissue was ground into a pale gray soup, heated, and consumed. Statistically, women of the Fore tribe were more likely than men to develop kuru, due to their greater involvement in the preparation of the brain tissue. Infection in the female population was probably via both ingestion and through minor skin abrasions. Clinically, kuru resembles CJD. Since this practice has stopped, the disease has ceased to occur.

BOVINE SPONGIFORM ENCEPHALOPATHY Humans consuming infected beef are susceptible to the BSE prion strain. Strain typing shows one major strain. BSE is especially insidious in that it is compatible with and transmissible to a wide variety of species. While food items containing blood or nervous tissue are potential vectors for human infection, milk and milk products from cows are not believed to pose any risk for transmitting the BSE prion to humans (see also vCJD).

ACQUIRED CREUTZFELDT-JAKOB DISEASE While CJD is an inherited disease it can also be acquired through iatrogenic transmission, which is accidental exposure to CJD prion-contaminated material through a medical procedure using tainted human matter or surgical instruments. Recipients of corneal transplants and of grafts of dura mater (brain-associated connective tissue) have been infected with CJD. Because prions are resistant to many sterilization procedures and to degradation, surgical instruments used in brain surgery have infected new patients two years after being sterilized. More than 100 people have been infected with CJD through injections of human growth hormones prepared from pools of pituitary glands that included materials from humans with CJD. At present, growth hormones are prepared through recombinant DNA technology and surgical instruments used on potentially infected patients have new sterilization guidelines, so the transmission of CJD via these routes has ceased to occur. The National Center for Infectious Diseases has not found any iatrogenic CJD cases linked to contact with pathogens from surfaces like floors or countertops.

VARIANT CREUTZFELDT-JAKOB DISEASE (VCJD) Variant CJD appeared in 1996 during the mad cow disease epidemic in the United Kingdom. The specific strain found in these patients indicates that they have been infected with prions from contaminated beef, the BSE prion. However, victims of vCJD are homozygous for a polymorphism on the PRNP gene at position 129. Patients with



Close-up of prion structure. Amyloid fibrils form when the protein alters. *(© CNRS/Corbis Sygma. Reproduced by permission.)*

vCJD may develop the disease at an unusually early age with the current median age of 29 years at death. However, the incubation time period before the onset of symptoms may be as long as 40 years. The vCJD affects people between 15 and 60 years of age. The clinical symptoms associated with vCJD differ from those seen with CJD, including psychiatric or sensory symptoms early in the course of the disease, delayed onset of neurological abnormalities that follow a pattern identifiable as but different from CJD, and a duration of illness of at least six months, followed by death. As of January 2004, evidence indicates there has never been a case of vCJD transmitted through direct contact of one person to another.

MISCELLANEOUS INFECTIOUS PRION DISEASES Cats and mink are susceptible to species-specific forms of TSE. In many mid-western states of the United States, some elk and mule deer carry a form of TSE called chronic wasting disease (CWD). CWD prions may possibly be transmissible to humans consuming venison the same way as mad cow disease can be transmitted through contaminated beef.

Diagnosis

There is currently no single diagnostic test for any prion disease. Physicians initially rule out other treatable forms of dementia such as classical encephalitis. Standard diagnostic tests include a spinal tap to exclude other diseases and an electroencephalogram (EEG) to record the patient's brain wave pattern. **CT scans** and **magnetic resonance imaging (MRI)** scans can rule out the possibility of **stroke** and reveal characteristic patterns of brain degeneration associated with various types of prion diseases.

Diagnosis classically relied on clinical symptoms, transmissibility, and postmortem neuropathology. With these diagnosis criteria, many cases of prion diseases may have been misdiagnosed as other neurodegenerative disorders. However, modern diagnosis is also dependent on detection of prion proteins, and identification of mutations in the PRNP gene. A genetic sequence analysis can be performed for a number of different mutations associated with familial CJD. The types of mutations present determine which symptoms will be most prominent. However, the presence of these mutations on the PRNP gene does not necessarily result in CJD. Most CJD patients contain a specific protein in their cerebrospinal fluid and an abnormal EEG brain wave pattern, diagnostic for CJD. However, confirmation requires neuropathological testing of brain tissue obtained through brain **biopsy** or autopsy. Brain biopsies are usually performed only when required to exclude another, treatable condition.

A diagnosis of prion disease is confirmed through examination of the brain tissue. Visible postmortem characteristics of the brain include noninflammatory lesions, vacuoles, amyloid protein deposits forming plaques that follow prion type-specific patterns, and measurable biochemical changes. While dramatic alterations in the brain's appearance are primarily the case, more subtle and noncharacteristic changes have also been reported. Some forms of prion disease with shorter durations only create plaques in a small percentage of patients.

Clinical signs of prion disease in sheep and cattle include cerebellar ataxia (loss of muscle coordination), polydipsia (excessive drinking), and an itching syndrome that, along with the lack of coordination, causes the animals to rub up against fences. However, animals are not diagnosed with prion disease until brain autopsy reveals neuropathology similar to that seen in humans.

Treatment team

Primary-care physicians may notice symptoms of a neurological disorder in a patient and refer them to a neurologist, specialists in brain disorders. They would act as the treatment team for patients with prion diseases.

Oversight of the BSE Action Plan in the United States is done by the Department of Health and Human Services (DHHS). Under this plan, surveillance for human disease is the responsibility of the Centers for Disease Control and Prevention (CDC). Protection against this disease is the responsibility of the Food and Drug Administration (FDA). Research is primarily the responsibility of the National Institutes of Health (NIH).

Treatment

There is no known effective treatment to arrest or cure prion diseases. Treatment focuses on alleviating the patient's symptoms, increasing their comfort, and palliative care. Treatment may include medications to control **pain** and motor disorders, catheters to collect urine, intravenous fluids to maintain hydration, and frequently repositioning the patient to avoid bedsores.

Possible future treatments developed may include chemicals that bind to and stabilize PrP^{C}, agents destabilizing the PrP^{SC} protein, or agents that interfere with the intereaction between PrP^{C} and PrP^{SC}.

Recovery and rehabilitation

There is no recovery or rehabilitation for prion diseases.

Clinical trials

As of January 2004, no **clinical trials** on prion diseases have taken place. In September 2001, the government announced an agenda of the design and implementation of clinical trials on CJD. The trials were originally planned after a vCJD patient received an unproven treatment in California and seemed to be improving. The treatment was with the anti-malaria drug quinacrine, which blocks the formation of prion plaques in mouse cell culture but has undetermined effects in humans with prion diseases. Sadly, the patient died in December 2001. While planned clinical trials will focus on quinacrine, as of January 2004 they are still being designed. Other patients have taken this treatment outside of clinical trials and the results suggest possible limited benefit along with damaging side effects. Another unproven treatment is pentosan polysulphate, which also has dangerous side effects. The first patient to receive this treatment showed some improvement in the condition. As of October 2003, four other patients have been granted permission for its use.

Prognosis

Prions bring about slow degeneration of the **central nervous system**, inevitably leading to death. A very long time period passes between a patient's infection and the initial appearance of clinical symptoms, an incubation process that may take up to 40 years in humans. However, once the symptoms appear, the patient generally dies within a few months with rapid, progressive symptoms. At this time, prion diseases are fatal diseases.

Special concerns

Highly effective public health control procedures have been implemented in Europe to prevent potential BSE-infected tissue from entering the human food chain.

Key Terms

Electroencephalogram A recording of the electrical signals produced by the brain.

Polymorphism A difference in DNA sequence among individuals; genetic variation.

The current risk of becoming infected with vCJD from eating beef and beef products in the United Kingdom is very small, at a rate of one case per 10 billion servings. Other countries have equal or lesser rates of risk. To reduce the risk of being infected with vCJD from food while traveling to geographical areas associated with risk, travelers who do not wish to avoid eating beef entirely may reduce their risk by selecting beef products in solid pieces, as opposed to ground beef tissue.

As of January 2004, there is no evidence that blood or blood products have transmitted TSEs to humans. However, to reduce the theoretical risk of transmission from blood products to humans, those individuals who have lived cumulatively for five or more years in Europe since the year 1980 to the present have been deferred by the FDA from donating blood or blood products. Individuals living specifically in the United Kingdom for three months or more from 1980 to 1996 are also deferred. Variant CJD (vCJD) is more likely to be transmitted through blood than classical CJD.

The CDC has established a National Prion Disease Pathology Surveillance Center (NPDPSC) that provides free, high-tech diagnostic services to physicians in the United States. Relatives of CJD patients who wish to assist research have their physician send brain tissue, blood, cerebrospinal fluid, and urine samples to the center.

Prion research has been done in yeast, a convenient organism easily used in scientific study. Yeast can be infected with prions, begin forming their own prion proteins, and pass the infection on to further generations of yeast. It has been noted that yeast can be "cured" of their prion disease by increasing the activity of chaperone proteins, which help maintain the normal conformational structure of the PrP^{C} protein and keep it from being converted to prion conformation.

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CJD Foundation, Inc. P.O. Box 5313, Akron, OH 44334, (330) 665-5590 or (800) 659-1991; Fax: (330) 668-2474. crjakob@aol.com. <http://www.cjdfoundation.org>.

National Organization for Rare Disorders. 55 Kenosia Avenue, P.O. Box 1968, Danbury, CT 06813. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2211. orphan@rarediseases.org. <http://www.rarediseases.org>.

National Prion Disease Pathology Surveillance Center. Case Western Reserve University 2085 Adelbert Road, Room 418, Cleveland, OH 44106. (216) 368-0587; Fax: (216) 368-4090. cjdsurv@cwru.edu. <http://www.cjdsurv.com>.

National Institutes of Health. 9000 Rockville Pike, Bethesda, MD 20892. (301) 496-4000. nihinfo@od.nih.gov. <http://www.nih.gov>.

Office International des Epizooties. 12, rue de Prony, Paris, France 75017. 33-(0)1 44 15 18 88; Fax: 33-(0)1 42 67 09 87. oie@oie.int. <http://www.oie.int>.

Patient Advocate Foundation. 700 Thimble Shoals Blvd, Suite 200, Newport News, VA 23606. (757) 873-8999 or (800) 532-5274. help@patientadvocate.org. <http://www.patientadvocate.org>.

United States Food and Drug Administration. 5600 Fishers Lane, Rockville, MD 20857. (888) 463-6332. <http://www.fda.org>.

Maria Basile, PhD

Progressive locomotor ataxia *see* **Tabes dorsalis**

Progressive sclerosing poliodystrophy *see* **Alpers' disease**

Progressive multifocal leukoencephalopathy

Definition

Progressive multifocal leukoencephalopathy is a rare, fatal disease of the white matter of the brain that almost solely strikes individuals who already have weakened immune systems.

Description

In progressive multifocal leukoencephalopathy, myelin (the substance that wraps around nerve fibers, providing insulation and speeding nerve transmission) is progressively destroyed. Although the disease is caused by a very prevalent virus (called JC virus), it only develops in individuals who are immunocompromised (have weakened immune systems).

Multiple areas of the brain are affected by the demyelination associated with progressive multifocal leukoencephalopathy. Additionally, other abnormalities and bizarre cells take up residence within the brain, causing destruction of normal brain tissue and impairing normal function.

Demographics

The causative virus in progressive multifocal leukoencephalopathy, JC virus, is extremely common. It is thought to be present in upwards of 85% of all children before the age of nine, and probably is present in an even greater percentage of adults. However, the JC virus does not actually cause any symptoms or disease, except in individuals who have severely compromised immune systems. About 62.2% of all progressive multifocal leukoencephalopathy cases occur in individuals with lymphatic cancers (lymphoproliferative disease, such as Hodgkin's disease and other lymphomas); 6.5% occur in individuals with cancer of bone marrow cells (myeloproliferative disease or leukemias); 2.2% occur in individuals with carcinomatous disease (cancers that affect the lining of tissues or organs of the body); and 10% occur in individuals with any of a number of acquired immunodeficiency states (such as systemic **lupus** erthematosus, sarcoidosis, and organ transplant survivors). Among patients with Acquired Immunodeficiency Syndrome (**AIDS**), about 10% of patients develop progressive multifocal leukoencephalopathy. Only 5.6% of all cases of progressive multifocal leukoencephalopathy occur in individuals with no other underlying source of immunocompromise.

Causes and symptoms

Although much is left to be defined about the mechanism whereby progressive multifocal leukoencephalopathy affects an individual, researchers believe that the JC virus resides in the kidneys of most individuals. In normal, nonimmunocompromised individuals, the virus stays within the kidneys, doing no harm. In immunocompromised individuals, the virus is reactivated, travels through the circulatory system to the brain, and selectively destroys myelinated nerve cells.

Patients with progressive multifocal leukoencephalopathy experience a range of symptoms that grow gradually worse over time, including **headache** and difficulties with speech, thinking, walking, weakness, vision problems (even blindness), memory problems, confusion, slowness of movement, paralysis of half of the body, and **seizures**. Eventually, patients lapse into a coma and die, usually within just months of the onset of their initial symptoms.

Key Terms

Immunocompromise A condition in which the immune system is weak and ineffective.

Myelin An insulating layer of fats around nerve fibers that allows nerve impulses to travel more quickly.

Diagnosis

Diagnosis is usually suggested by a patient's characteristic symptoms of progressive multifocal leukoencephalopathy, in combination with evidence of white matter destruction visualized on **CT** or **MRI** scanning of the brain. Specialized tests on cerebrospinal fluid (called polymerase chain reactions) may demonstrate the presence of JC virus DNA. However, only brain **biopsy** can result in an absolutely definitive diagnosis.

Treatment team

Patients with progressive multifocal leukoencephalopathy are usually seen by neurologists, as well as by hematologist/oncologists for patients with lymphoma or leukemia, infectious disease specialists for patients with AIDS, and a rheumatologist for individuals with specific autoimmune disease.

Treatment

There are no treatments available to cure progressive multifocal leukoencephalopathy. Some degree of slowing of the relentless progression of the disease has been noted in certain patients treated with the AIDS drug AZT.

Prognosis

Progressive multifocal leukoencephalopathy is uniformly fatal, usually within one to four months of the initial symptoms. A few patients have had brief remissions in the disease progression, and have lived for several years beyond diagnosis.

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Progressive supranuclear palsy

Definition

Progressive supranuclear palsy (PSP) is a rare degenerative disorder that causes serious and permanent deficits in movement and cognitive function.

Description

Progressive supranuclear palsy is also known as Steele-Richardson-Olszewski syndrome, reflecting the names of persons who discovered the syndrome. PSP is a neurodegenerative disease (symptoms worsen with time) first described as a distinct disorder in 1964. Characteristics of PSP include slow movement and stiffness, which are also seen similarly in **Parkinson's Disease** (PD). Persons affected by PSP tend to have more postural imbalance with falls than patients with PD. Additionally tremor is usually absent in PSP patients, while those with PD have tremor. PSP is an uncommon disorder and initially it may be difficult to clinically distinguish between PSP and PD. PSP usually begins to produce symptoms in the sixth decade (50–59 years of age) of life and the disorder progressively worsens more quickly than PD. Patients with PSP typically become disabled within five to ten years after diagnosis (PD has a slower progression and typically persons can become disabled 20 years after onset). PSP is the most common Parkinson-like or Parkinson-plus disease.

Demographics

The estimated prevalence (number of existing cases) among persons older than 55 years is approximately seven per 100,000 persons. Studies indicate that there may be a slightly higher male prevalence (1.53), than female prevalence (1.23) per 100,000. In Perth, Australia, the incidence (number of new cases) is estimated at three to four per million cases. The incidence rate for ages 50-99 is 5.3 per 100,000. The peak incidence (the peak age range for new cases) is in the early sixties. PSP is not thought to be genetically transmitted in families, but there are some reported cases of inherited transmission. Survey research (using a questionnaire) in 1996 revealed that patients with PSP were less likely than controls to have completed 12 years of education, which suggests that education level is a marker for direct risk factors which can include chemical exposure or nutritional problems. In 1999 a high prevalence of PSP was found in Guadeloupe (French West Indies) which is related to ingestion of certain teas that are forms of custard apple (called "soursop" and "sweetsop").

Causes and symptoms

The cause of degeneration of nerve cells is unknown. Patients affected with PSP have a gradual and progressive damage to cells in the midbrain, which eventually leads to atrophy (shrinkage and loss of normal cell architecture). Patients have neuronal loss and neurofibrillary tangles in the **diencephalon**, brain stem and basal ganglia. Several theories have been proposed as potential causes. Initially, the main causes of PSP was thought to be due to a virus (possibly related to the influenza virus) or to a slow acting toxin (i.e. "MPTP", a drug of abuse contaminant, herbal Caribbean teas, Cycad nut poisoning in Guam).

However, recent genetic research as of 1999 suggests PSP may be a genetic disorder transmitted with autosomal recessive transmission. The gene implicated with the condition is called the tau gene. Analysis of the tau gene using molecular biology techniques indicate that the tau gene in PSP is different from genes observed in **Alzheimer disease** patients. Studies indicate that the tau gene in PSP is similar to the gene in another disease (Cortico basal degeneration). These genetic studies indicate that some nerve cells may be partially controlled by genetic susceptibility and also related to other environmental stressors/triggers such as viruses and/or toxins.

The symptoms of PSP are insidious and typically there is a prolonged phase of **headaches**, **dizziness**, **fatigue**, arthralgias and **depression**. The most common symptoms include postural instability and falls (seen in 63% of patients) and dyarthria (a symptom expressed in 35% of patients). Other important symptoms include bradykinesia and visual disturbance (diplopia, burning

eyes, blurred vision and sensitivity to light) in 13% of affected PSP patients. The front neck muscles or back neck muscles may be affected. The rigidity of the spine is characterized by a stiff extended spine. PSP patients also exhibit eye movement paralysis. The eye lids may be held wide open with eye movement paralysis resulting in a facial expression that can be described as "staring," "astonished," or "puzzled."

Eye movement difficulties usually begin with difficulty looking up or down. There may be difficulty looking right or left. These eye abnormalities may cause difficulty during driving and reading. There is no treatment for eye movement abnormalities. Patients with PSP do not have eye muscle or eye nerve problems; the problem originates in the brain stem area.

Diagnosis

Lab tests and neuroimaging can be performed to eliminate other possible causes. One specific high resolution neuroimaging study called **PET** (**positron emission tomography**) scan can provide information about blood flow and oxygen supply to the brain. PET scan analysis has revealed a decrease in blood flow and oxygen metabolism in areas of the brain thought to degenerate in PSP patients (i.e. caudate, putamen and thalamus). Sleep patterns in PSP affected patients are often abnormal and demonstrated increased awakenings, diminished total sleep time, and progressive loss of REM sleep. Patients can also develop REM sleep behavior disorder consisting of abnormal motor activity with vivid dreams during REM sleep.

Autopsy results after examination of brain tissue reveals neuronal loss and neurofibrillary tangles and gliosis in the reticular formation and ocular (eye) motor nuclei, as well as neuronal pathology in the midbrain. **MRI** neuroimaging studies can detect abnormal patterns in affected areas within the brain.

Treatment team

As the disease progresses, specialists are required as part of the treatment team. Consultation with rehabilitation medicine specialist may help with walking stability and safety. A speech therapist may modify diet if swallowing is impaired. Consultation with an eye specialist (ophthalmologist) may be indicated for the treatment of eye problems.

Treatment

There is no effective therapy for PSP. Mediation generally has little or short term effects. Treatment is supportive (palliative) until the person dies. Supportive treatment can include speech therapy, walkers, antidepressants, artificial tears (to avoid drying of eyes from excess exposure) and caregiver support. Only few persons demonstrate benefit with medication that increases the **neurotransmitters** dopamine (dopaminergic) or acetylcholine (cholinergic drugs). A well balanced diet is recommended and gastrostomy (a surgical procedure to redirect bowels to pass through an opening in the stomach) is performed when feeding becomes problematic due to dysphagia (difficulty swallowing), or risk of bronchoaspiration (food lodging in the lungs due to abnormal swallowing) is possible.

Key Terms

Basl ganglia Brain structure at the base of the cerebral hemispheres involved in controlling movement.

Bradykinesia Extremely slow movement.

Brain stem The stalk of the brain which connects the two cerebral hemispheres with the spinal cord. It is involved in controlling vital functions, movement, sensation, and nerves supplying the head and neck.

Diencephalon A part of the brain that binds the mesencephalon to the cerebral hemispheres, it includes the thalmus and the hypothalmus.

Diplopia A term used to describe double vision.

Dysarthria Slurred speech.

Neurofibrillary tangles Abnormal structures, composed of twisted masses of protein fibers within nerve cells, found in the brains of persons with Alzheimer's disease.

Recovery and rehabilitation

PSP is a chronic and progressive disorder which means that symptoms worsen with the passing of time. Close follow-up care is advisable, and during visits it is necessary to provide family with direction and education. If the patient opts for experimental treatment protocols, it is mandatory to inform all concerned about potential side effects. Physical therapy involvement can help to maximize safety at home and provide instruction in the use of walking aids (i.e. wheelchair, walker).

Clinical trials

The National Institute of Neurological Disorders and Stroke (NINDS) are currently sponsoring research concerning diagnosis, treatment and causes of PSP. Additionally, studies concerning Parkinson's and Alzheimer's disease are being performed since a better understanding of related diseases may provide valuable information concerning PSP.

Prognosis

In most patients the disease is fatal within six to 10 years. Complications of PSP are related to abnormal balance, immobility (a late feature of PSP) and decreased cognition. Falls may cause patients to injure bones. Late onset immobility can cause infectious complications (pneumonia, urinary tract infection, or sepsis).

Special concerns

A well balanced diet is recommended and physical therapy may help with walking problems and falls which are the two major causes of disability. Educational concerns are important and should be directed to the patient, family members and caregivers. Education includes an understanding of the natural history of PSP and should include information concerning prognosis, complications, supportive therapy. Patients and families may benefit from PSP support group involvement.

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ORGANIZATIONS

Society for Progressive Supranuclear Palsy, Woodholme Medical Building. 1838 Greene Tree Road, #515, Baltimore, MD 21208. (410) 486-3330 or 800-457-4777; Fax: (410) 486-4383. spsp@psp.org. <http://www.psp.org>.

The PSP Association, The Old Rectory, Wappenham, Towcester, Northants NN12 8SQ, United Kingdom. 011-44-1327-860299; Fax: 011-44-1327-861007. psp.eur@virgin.net. <http://www.pspeur.org>.

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Pseudobulbar palsy

Definition

Pseudobulbar palsy refers to a group of symptoms—including difficulty with chewing, swallowing, and speech, as well as inappropriate emotional outbursts—that accompany a variety of nervous system disorders.

Description

Pseudobulbar palsy refers to a cluster of symptoms that can affect individuals suffering from a number of nervous system conditions, such as **amyotrophic lateral sclerosis**, **Parkinson's disease**, **stroke**, **multiple sclerosis**, or brain damage due to overly rapid correction of low blood sodium levels.

Causes and symptoms

Pseudobulbar palsy occurs when nervous system conditions cause degeneration of certain motor nuclei (nerve clusters responsible for movement) that exit the brain stem.

Patients with pseudobulbar palsy have progressive difficulty with activities that require the use of muscles in the head and neck that are controlled by particular cranial nerves. The first noticeable symptom is often slurred speech. Over time, speech, chewing, and swallowing become progressively more difficult, eventually becoming impossible. Sudden emotional outbursts, in which the patient spontaneously and without cause begins to laugh or cry, are also a characteristic of pseudobulbar palsy.

Diagnosis

Diagnosis is usually made by noting the symptom cluster characteristic of pseudobulbar palsy. Diagnostic tests will be run to determine what underlying neurological disorder has led to the development of pseudobulbar palsy. In particular, neuroimaging (**CT** and **MRI** scans) can be used to diagnose many of the conditions that prompt the development of pseudobulbar palsy.

Treatment team

Neurologists usually care for patients with the kinds of conditions that include the symptoms of pseudobulbar palsy.

Treatment

There are no cures for pseudobulbar palsy; the symptoms usually progress over the course of several years, leading to complete disability. Some medications may improve the emotional symptoms associated with pseudobulbar palsy; these include levodopa, **amantadine**, amitriptyline, and fluoxetine.

Prognosis

The prognosis for pseudobulbar palsy is quite poor. When the symptoms progress to disability, there is a high risk of choking and aspiration (breathing food or liquids into the lungs), which can lead to severe pneumonia and death. The conditions with which pseudobulbar palsy is associated also have a high risk of progression to death.

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Pseudotumor cerebri

Definition

Pseudotumor cerebri is a chronic elevation of intracranial pressure that causes papilloedema and possibly blindness, which occurs in the absence of a mass lesion in the brain.

Description

Pseudotumor cerebri primarily affects obese women of childbearing age, and its cause is not known. The disorder is possibly the result of an abnormality in venous blood outflow from the brain, or from an abnormality in cerebrospinal fluid (CSF) flow. The increase in intracranial pressure can result in **headache**, visual impairment, **pain**, and hearing problems.

Demographics

Three significant studies concerning pseudotumor cerebri have been conducted in Iowa and Louisiana, the Mayo Clinic in Rochester, Minnesota, and Benghazi, Libya. The incidence of pseudotumor cerebri increases in women between 14 and 44 years of age, who are obese. In the Iowa and Louisiana study, the incidence was 19.3 per 100,000 in women who were 20% over ideal weight. In the Mayo Clinic study, the annual incidence number of new cases between 1976 and 1990 was found to be approximately eight per 100,000 for obese women 15–44 years old. In the Benghazi study (from 1982–1989), the annual incidence was 21 per 100,000 obese women 15–44 years old. No evidence of any racial or ethnic predilection exists.

Key Terms

Cerebrospinal fluid A colorless and clear fluid that contains glucose and proteins that bathe and nourish the brain and spinal cord.

Recombinant human growth hormone A synthetic form of growth hormone that can be given to a patient to help skeletal growth.

Papilloedema Edema or swelling in the optic disk (a portion of the optic nerve that collects nerves from the light sensitive layer of the eye, also called the retina).

Intraocular Inside the eye.

Causes and symptoms

The cause of pseudotumor cerebri is unknown, but it is thought to result from a faulty mechanism in CSF or venous flow from the brain. Certain risk factors have been associated with the disorder that include female gender, menstrual irregularity, obesity, recent weight gain, endocrine (hormone) disorders such as hypothyroidism (underactive thyroid disorder), or medication taken such as cimetidine (anti-ulcer), corticosteroids, lithium (used to treat bipolar disorder), tetracycline, sulfa antibiotics, recombinant human growth hormone, oral contraceptives, and vitamin A intake in infants.

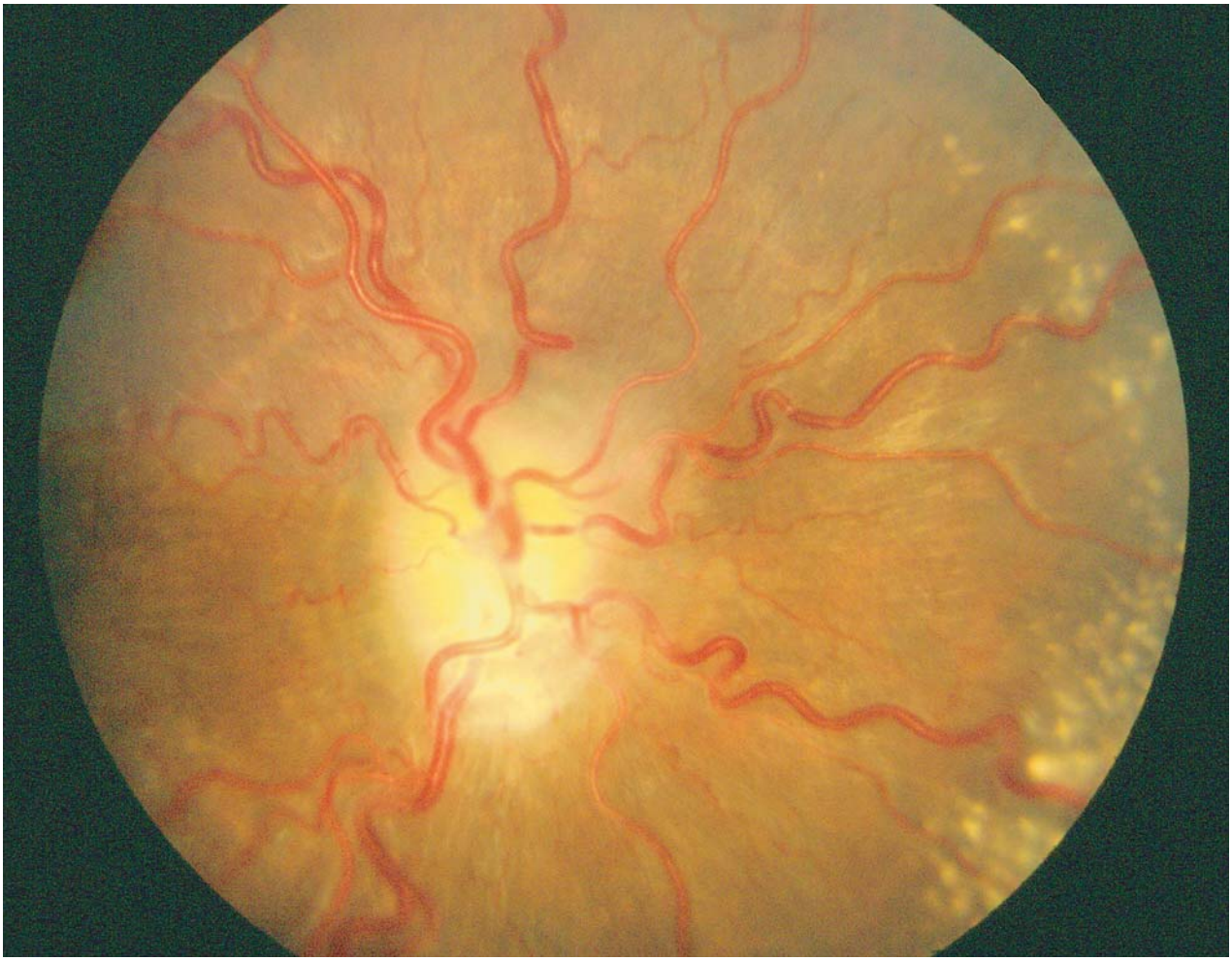
Patients can have symptoms such as headache, ringing sounds in the ears, double vision (diplopia), or pain in the arms. Additionally, patients may have **back pain**, neck pain, or stiffness and arthralgias in the shoulder, knee, and wrist. Patients usually develop papilloedema, which can causes visual obscurations (dimming), progressive loss of peripheral vision, blurring, and sudden visual loss (resulting from intraocular hemorrhage).

Diagnosis

Neuroimaging studies are the best diagnostic tools, especially brain **magnetic resonance imaging (MRI)** scans. **MRI** scans provide good images that can reveal other possible disease states that cause increased intracranial pressure. General and special blood tests are typically ordered. CSF studies are also indicated and are usually done by inserting a needle into the lumbar region of the spine to withdraw a fluid sample. CSF studies are done to detect an infection within the **central nervous system**; the sample is used for tumor tests.

Treatment team

Management of pseudotumor cerebri requires a lumbar puncture that is performed by a **neurologist** or



Retinal photograph showing the effects of a pseudotumor cerebri. *(Phototake, Inc. All rights reserved.)*

internist. Visual problems may be monitored by a neuro-ophthalmologist. Neurosurgical consultations are necessary if treatment does not arrest or reverse the condition quickly, within hours to days.

Treatment

Patients who do not develop visual loss are often treated with a drug called **acetazolamide** (a carbonic anhydrase inhibitor) that lowers intracranial pressure. In persons who present with more severe symptoms such as early loss of vision, a short treatment course with high-dose corticosteroids (prednisone) is recommended. Tapering down from the initial corticosteroid dose is individualized and based on the improvement of symptoms. If new visual loss is noted despite treatment, emergency surgical intervention may be indicated. A procedure called a lumboperitoneal shunt is the method of choice utilized for prompt reduction of intracranial hypertension; this is a surgical redirection of fluid flow in the brain, which creates an outflow of fluid from the brain that decreases intracranial pressure.

Recovery and rehabilitation

A formal weight loss and **exercise** program is required once the diagnosis is established. Admission to the hospital is uncommon, but some patients may be admitted for a short stay for intravenous fluid hydration and pain management in cases of intractable headache. Admission to the hospital is also indicated if the patient is a surgical candidate due to severe visual loss. Patients require education concerning blindness and weight reduction. Programs designed to lose weight should include an exercise program and psychological consultations. Many patients do not successfully lose enough weight and may require drastic treatment approaches such as gastric resection or stapling.

Clinical trials

The National Institute of Health is conducting a trial concerning the role of thrombosis inside blood vessels and the development of pseudotumor cerebri.

Prognosis

Typically, persons affected with pseudotumor cerebri can develop blindness, which is the only severe and permanent complication of this disorder. The blindness, which progressively worsens, is due to papilloedema.

Special concerns

Diligent treatment is required since eye deficits in one or both eyes can have a very quick onset and can be disabling. The disorder is not statistically correlated with weight gain during pregnancy; however, both pregnancy and pseudotumor cerebri are linked to weight gain and female gender (within childbearing age).

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ORGANIZATIONS

Pseudotumor Cerebri Support Network. 8247 Riverside Drive, Powell, OH 43065. (614) 895-8814. <http://www.pseudotumorcerebri.com>.

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Pyridostigmine *see* **Cholinergic stimulants**

R

Radiation

Definition

Radiation and radioisotopes are extensively used medications to allow physicians to image internal structures and processes *in vivo* (in the living body) with a minimum of invasion to the patient. Higher doses of radiation are also used as means to kill cancerous cells.

Radiation is actually a term that includes a variety of different physical phenomena. However, in essence, all these phenomena can be divided into two classes: phenomena connected with nuclear radioactive processes are one class, the so-called radioactive radiation (RR); electromagnetic radiation (EMR) may be considered as the second class.

Both classes of radiation are used in diagnoses and treatment of neurological disorders.

Description

There are three kinds of radiation useful to medical personnel: alpha, beta, and gamma radiation. Alpha radiation is a flow of alpha particles, beta radiation is a flow of electrons, and gamma radiation is electromagnetic radiation.

Radioisotopes, containing unstable combinations of protons and neutrons, are created by neutron activation. This involves the capture of a neutron by the nucleus of an atom, resulting in an excess of neutrons (neutron rich). Proton-rich radioisotopes are manufactured in cyclotrons. During radioactive decay, the nucleus of a radioisotope seeks energetic stability by emitting particles (alpha, beta, or positron) and photons (including gamma rays).

Radiation—produced by radioisotopes—allows accurate imaging of internal organs and structures. Radioactive tracers are formed from the bonding of short-lived radioisotopes with chemical compounds that, when in the body, allow the targeting of specific body regions or physiologic processes. Emitted gamma rays (photons) can be detected by gamma cameras and computer enhancement of the resulting images and allows quick and relatively noninvasive (compared to surgery) assessments of trauma or physiological impairments.

Because the density of tissues is unequal, x rays (a high frequency and energetic form of electromagnetic radiation) pass through tissues in an unequal manner. The beam passed through the body layer is recorded on special film to produce an image of internal structures. However, conventional x rays produce only a two-dimensional picture of the body structure under investigation.

Tomography (from the Greek *tomos*, meaning "to slice") is a method developed to allow the detailed construction of images of the target object. Initially using the x rays to scan layers of the area in question, with computer assisted tomography a computer then analyzes data of all layers to construct a 3D image of the object.

Computed tomography (also known as CT, **CT scan**) and computerized axial tomography (CAT) scans use x rays to produce images of anatomical structures.

Single proton (or photon) emission computed tomography (SPECT) produces three-dimensional images of an organ or body system. SPECT detects the presence and course of a radioactive substance that is injected, ingested, or inhaled. In neurology, a SPECT scan can allow physicians to examine and observe the **cerebral circulation**. SPECT produces images of the target region by detecting the presence and location of a radioactive isotope. The photon emissions of the radioactive compound containing the isotope can be detected in a manner that is similar to the detection of x rays in computed tomography (CT). At the end of the SPECT scan, the stored information can be integrated to produce a computer-generated composite image.

Positron emission tomography (PET) scans utilize isotopes produced in a cyclotron. Positron-emitting radionuclides are injected and allowed to accumulate in the target tissue or organ. As the radionuclide decays, it emits a positron that collides with nearby electrons to result in the emission of two identifiable gamma photons. **PET**

Key Terms

Radioisotopes An unstable isotope that emits radiation when it decays or returns to a stable state.

Radiotherapy The use of x rays or other radioactive substances to treat disease.

scans use rings of detectors that surround the patient to track the movements and concentrations of radioactive tracers. PET scans have attracted the interest of physicians because of their potential use in research into metabolic changes associated with mental diseases such as **schizophrenia** and **depression**. PET scans are used in the diagnosis and characterizations of certain cancers and heart disease, as well as clinical studies of the brain. PET uses radio-labeled tracers, including deoxyglucose, which is chemically similar to glucose and is used to assess metabolic rate in tissues and to image tumors, and dopa, within the brain.

Electromagnetic radiation

In contrast to imaging produced through the emission and collection of nuclear radiation (e.g., x rays, CT scans), **magnetic resonance imaging (MRI)** scanners rely on the emission and detection of electromagnetic radiation.

Electromagnetic radiation results from oscillations of components of electric and magnetic fields. In the simplest cases, these oscillations occur with definite frequency (the unit of frequency measurement is 1 Hertz (Hz), which is one oscillation per second). Arising in some point (under the action of the radiation source), electromagnetic radiation travels with the velocity that is equal to the velocity of the light, and this velocity is equal for all frequencies. Another quantity, wavelength, is often used for the description of electromagnetic radiation (this quantity is similar to the distance between two neighbor crests of waves spreading on a water surface, which appear after dropping a stone on the surface). Because the product of the wavelength and frequency must equal the velocity of light, the greater the wave frequency, the less its wavelength.

MRI scanners rely on the principles of atomic nuclear-spin resonance. Using strong magnetic fields and radio waves, MRIs collect and correlate deflections caused by atoms into images. MRIs allow physicians to see internal structures with great detail and also allow earlier and more accurate diagnosis of disorders.

MRI technology was developed from nuclear magnetic resonance (NMR) technology. Groups of nuclei brought into resonance, that is, nuclei absorbing and emitting photons of similar electromagnetic radiation such as radio waves, make subtle yet distinguishable changes when the resonance is forced to change by altering the energy of impacting photons. The speed and extent of the resonance changes permit a non-destructive (because of the use of low-energy photons) determination of anatomical structures.

MRI images do not utilize potentially harmful ionizing radiation generated by three-dimensional x-ray CT scans, but rely on the atomic properties (nuclear resonance) of protons in tissues when they are scanned with radio frequency radiation. The protons in the tissues, which resonate at slightly different frequencies, produce a signal that a computer uses to tell one tissue from another. MRI provides detailed three-dimensional soft tissue images.

These methods are used successfully for brain investigations.

Radiation therapy (radiotherapy)

Radiotherapy requires the use of radioisotopes and higher doses of radiation that are used diagnostically to treat some cancers (including brain cancer) and other medical conditions that require destruction of harmful cells.

Radiation therapy is delivered via external radiation or via internal radiation therapy (the implantation/injection of radioactive substances).

Cancer, tumors, and other rapidly dividing cells are usually sensitive to damage by radiation. The goal of radiation therapy is to deliver the minimally sufficient dosage to kill cancerous cells or to keep them from dividing. Cancer cells divide and grow at rates more rapid than normal cells and so are particularly susceptible to radiation. Accordingly, some cancerous growths can be restricted or eliminated by radioisotope irradiation. The most common forms of external radiation therapy use gamma and x rays. During the last half of the twentieth century, the radioisotope cobalt-60 was the frequently used source of radiation used in such treatments. More modern methods of irradiation include the production of x rays from linear accelerators.

Iodine-131, phosphorus-32 are commonly used in radiotherapy. More radical uses of radioisotopes include the use of boron-10 to specifically attack tumor cells. Boron-10 concentrates in tumor cells and is then subjected to neutron beams that result in highly energetic alpha particles that are lethal to the tumor tissue.

Precautions

Radiation therapy is not without risk to healthy tissue and to persons on the health care team, and precautions (shielding and limiting exposure) are taken to minimize exposure to other areas of the patient's body and to personnel on the treatment team.

Therapeutic radiologists, radiation oncologists, and a number of technical specialists use radiation and other methods to treat patients who have cancer or other tumors.

Care is taken in the selection of the appropriate radioactive isotope. Ideally, the radioactive compound loses its radioactive potency rapidly (this is expressed as the half-life of a compound). For example, gamma-emitting compounds used in SPECT scans can have a half-life of just a few hours. This is beneficial for the patients, as it limits the contact time with the potentially damaging radioisotope.

The selection of radioisotopes for medical use is governed by several important considerations involving dosage and half-life. Radioisotopes must be administered in sufficient dosages so that emitted radiation is present in sufficient quantity to be measured. Ideally the radioisotope has a short enough half-life that, at the delivered dosage, there is insignificant residual radiation following the desired length of exposure.

New areas of radiation therapy that may prove more effective in treating brain tumors (and other forms of cancers) include three-dimensional conformal radiation therapy (a process where multiple beans are shaped to match the contour of the tumor) and stereotactic radiosurgery (used to irradiate certain brain tumors and obstructions of the cerebral circulation). Gamma knives use focused beams (with the patient often wearing a special helmet to help focus the beams), while cyberknifes use hundreds of precise pinpoint beams emanating from a source of irradiation that moves around the patient's head.

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Alexander Ioffe

Radiculopathy

Definition

Radiculopathy refers to disease of the spinal nerve roots (from the Latin *radix* for root). Radiculopathy produces **pain**, numbness, or weakness radiating from the spine.

Description

At the joints between the vertebrae, sensory nerves (nerves conducting sensory information toward the **central nervous system**) and motor nerves (nerves conducting commands to muscles away from the central nervous system) connect to the spinal cord. Each spinal nerve divides or fans out just before merging with the spinal cord. These smaller, separate nerve bundles are termed the roots of the nerve because they are reminiscent of the way the roots of a plant divide in the ground.

Damage to the spinal nerve roots can lead to pain, numbness, weakness, and paresthesia (abnormal sensations in the absence of stimuli) in the limbs or trunk. Pain may be felt in a region corresponding to a dermatome, an area of skin innervated by the sensory fibers of a given spinal nerve or a dynatome, an area in which pain is felt when a given spinal nerve is irritated. Dynatomes and dermatomes may overlap, but do not necessarily coincide.

Radiculopathies are categorized according to which part of the spinal cord is affected. Thus, there are cervical (neck), thoracic (middle back), and lumbar (lower back) radiculopathies. Lumbar radiculopathy is also known a **sciatica**. Radiculopathies may be further categorized by what vertebrae they are associated with. For example, radiculopathy of the nerve roots at the level of the seventh cervical vertebra is termed C7 radiculopathy; at the level of the fifth cervical vertebra, C5 radiculopathy; at the level of the first thoracic vertebra, T1 radiculopathy; and so on.

Radiculopathy is to be distinguished from myelopathy, which involves pathological changes in or functional problems with the spinal cord itself rather than the nerve roots. Sometimes, radiculopathy is also distinguished from radiculitis, the latter being defined as irritation (hence the "itis" suffix) of a nerve root that causes pain in the dermatome or dynatome corresponding to that nerve. Radiculopathy, on the other hand, denotes spinal nerve dysfunction (not just irritation) presenting with pain, altered reflex, weakness, and nerve-conduction abnormalities. Pain may not be present with radiculopathy, but is always present with radiculitis.

Demographics

Millions of persons experience some form of radiculopathy at some point in their lives. Because many of the causes of radiculopathy are long-term diseases (e.g., ankylosing spondylosis, diabetes) or diseases that tend to affect the elderly (e.g., arthritis), radiculopathy occurs more often in the middle-aged and elderly than in the young. However, injuries due to sports, heavy lifting, or bad posture affect the young as well. Cervical **disc herniation** with radiculopathy (mostly involving the C4 to C5 levels) affects 5.5 per 100,000 adults every year, with the highest risk being for adults 35 to 55 years year old.

Key Terms

Dermatome An area of skin that receive sensations through a single nerve root.

Dynatome An area in which pain is felt when a given spinal nerve is irritated.

Motor nerves Nerves conducting commands to muscles away from the central nervous system.

Sensory nerves Nerves conducting sensory information toward the central nervous system.

Causes and symptoms

Radiculopathy can be caused by any disease or injury process that compresses or otherwise injures the spinal nerve roots. Violent blows or falls, cancer, some infections such as flu and **Lyme disease**, diseases that lead to degeneration of the vertebrae and/or intervertrebral discs (osteoarthritis), slipped or herniated discs, scoliosis, and other factors can cause radiculopathy. For example, extreme backward bending of the neck can trigger cervical radiculopathy. This has given rise to a recently-recognized category of radiculopathy termed "salon sink radiculopathy," so-called because salon patrons are asked to tip their heads sharply backward into sinks for shampooing. Spondylosis (immobilization and growing-together of one or more vertebral joints, often due to osteoarthritis) can deform the structures of bone, cartilage, and ligament through which spinal nerves must pass, leading to cervical and lumbar radiculopathy. Thoracic and lumbar radiculopathies are a common result of diabetes, which can impair blood flow to the spinal nerve roots.

Diagnosis

Radiculopathy is a possible diagnosis when numbness, pain, weakness, or paresthesia of the extremities or torso are reported by a patient, especially in a dermatomal pattern. However, these symptoms can also be caused by **nerve compression** remote from the spine, and the physician must rule out this possibility before ruling in favor of radiculopathy. Electrodiagnostic studies can help distinguish radiculopathy from other diagnoses. These techniques include current perception threshold testing, which tests patient ability to sense alternating electric currents at several frequencies; electromyographic nerve conduction tests; and testing of sensory evoked potentials (changes in brain waves in response to sensory stimuli).

When radiculopathy is diagnosed, the location of the affected nerve roots and, ultimately, the cause of their dysfunction must be determined. Diagnosticians look at the precise features of radicular symptoms in order to determine the spinal level of the affected root or roots. For example, radiculopathy at the C7 level (the nerve root most often affected by herniated cervical disc) is characterized by weak triceps and wrist extensor muscles and a numb middle finger. Radiculopathy at the L3 (third lumbar disc) level is characterized by decreased patellar (kneecap) reflex, loss of sensation and/or pain in the anterior (forward) part of the thigh, and weakness in quadriceps muscle; and so on.

X ray or **MRI** may be used to confirm the diagnosis. A herniated disc, for example, will be revealed by imaging. A herniated disc is one that has partly popped or bulged out from between the vertebra above and below it. This may place pressure on the nerve roots and on the spinal cord itself.

In persons with spinal cancer or other progressive disorders, the appearance of radiculopathy may be an important sign that pressure is beginning to be exerted by the tumor or some other changing structure. This may signal that it is time for surgical intervention.

Treatment team

Diagnosis of radiculopathy will usually involve a **neurologist**. An orthopedist will usually be involved as well. Other specialists will be required depending on the cause of the radiculopathy (e.g., oncologist, if cancer is present). Treatment will usually call for a physical therapist. An orthopedic surgeon would perform any necessary surgery.

Treatment

Treatment for radiculopathy varies with the nature and severity of the disease process or injury that has caused the disorder. Conservative (non-surgical) treatment is often attempted first. This consists primarily of rest, **exercise**, and medication. Patient-specific exercises are prescribed by a physical therapist for the targeted strengthening of muscles and other supporting tissues to relieve pressure on affected spinal nerve roots. Weight loss may be advised to decrease stress on the spine. Medications may include oral opioids (e.g., morphine) or other analgesic (anti-pain) medications. In severe cases, injection of an opioid by an external or implanted pump directly into the affected area may be prescribed. Epidural corticosteroid injections, selective nerve root block, and epidural lysis (destruction) of adhesions are also used to treat radiculopathy. A soft neck collar may be prescribed for persons with cervical radiculopathy.

When conservative treatment fails, surgery may be necessary. The primary purpose of surgery is to take pressure off of affected nerve roots or the blood vessels that serve them and to stabilize spinal structure, but surgery

may also sever nerves in order to relieve severe pain. Fusion of vertebrae (i.e., removal of the flexible intervertebral disc and joining of the adjacent vertebrae so that they grow into a single bone) was for many decades a common treatment for intractable radiculopathy, but as of 2003, a novel implant, the Bryan disc, was under study by the US Food and Drug Administration. The Bryan disc is a flexible disc or ring of titanium and Teflon that is used to replace the intervertebral disc in patients with degenerative disc disease. Two versions of the disc, one cervical (for the neck) and the other lumbar (for the lower back) were under development. Early reports from surgeons were positive. The advantage of such an implant over fusion is that the patient does not lose flexibility in that part of their spine.

Recovery and rehabilitation

Exercise is key to the treatment of both conservative and surgical treatment of radiculopathy. It may even be curative in some cases. It is also an important aspect of recovery from surgery. Exercise is done as directed by a physical therapist.

Clinical trials

As of mid-2004, a clinical trial sponsored by the National Institute of Dental and Craniofacial Research was recruiting participants. The goal of this clinical trial was to evaluate the effectiveness of two drugs (i.e., nortriptyline and MS Contin, a type of morphine) in treating lumbar radiculopathy, also known as sciatica. This was a phase II clinical trial, meaning that it involved a medium-size group (100–300 participants) to evaluate effectiveness and side effects of the treatment. Persons interested in participating should contact the Patient Recruitment and Public Liaison Office at telephone (800) 411-1222, or e-mail at: prpl@mail.cc.nih.gov.

Prognosis

Prognosis varies with the underlying process causing the radiculopathy. For sports injuries, at one extreme, the prognosis is excellent; for degenerative disc disorders, even surgery may not completely or permanently resolve the problem. However, new surgical techniques are improving this picture.

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National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

Larry Gilman, PhD

Ramsay-Hunt syndrome type II

Definition

Ramsay-Hunt syndrome type II is a very rare, progressive neurological disorder that causes **epilepsy**, tremor, mental impairment, and eventually death.

Description

Ramsay-Hunt syndrome type II begins in adulthood. It is a relentlessly progressive degenerative disease that culminates in death, characterized by Parkinson-like **tremors**, and muscle jerks (**myoclonus**).

Demographics

The average age of onset is about 30 years of age.

Causes and symptoms

Some cases seem to be caused by abnormalities of the mitochondria within the cell. Mitochondria are the cells' power stations. They are organelles within each cell that are responsible for producing energy.

Some cases of Ramsay-Hunt syndrome type II appear to be inherited in an autosomal dominant fashion, meaning that a child who has one parent with the abnormal gene has a 50:50 chance of inheriting the disorder. Other cases appear to be inherited in an autosomal recessive fashion, meaning that individuals who develop the disease have inherited defective genes from both parents.

Key Terms

Mitochondria The organelles within each cell that are responsible for the production of energy.

Myoclonus Involuntary jerking or twitching of muscles.

Ramsay-Hunt syndrome type II begins as an intention tremor in the limbs, particularly the arms. An intention tremor is an involuntary shaking or trembling that occurs when an individual is attempting a purposeful movement; the tremor is not manifested when the individual is at rest. The intention tremor generally occurs in just one limb. Over time, the entire muscular system is affected. In addition to the tremor, individuals with Ramsay-Hunt syndrome type II experience sudden twitching or contraction of muscle groups, called myoclonus. Some individuals experience progressive hearing impairment. As the disease progresses, the individual experiences decreased muscle tone, increasing weakness, disturbances of fine motor control, difficulty walking, epilepsy, and (in some cases) mental deterioration. The disease usually progresses over the course of about 10 years, ultimately resulting in the death of the patient.

Diagnosis

An electroencephalogram (EEG) may reveal certain abnormalities of the electrical patterns in the brain. Muscle **biopsy** may or may not reveal mitochondrial abnormalities.

Treatment team

Ramsay-Hunt syndrome type II is usually diagnosed and treated by a **neurologist**. In an effort to maintain functioning as long as possible, other treatment members may include physical therapists, occupational therapists, and speech and language therapists.

Treatment

There is no cure for Ramsay-Hunt syndrome type II. **Seizures** may respond to antiseizure medications such as **phenobarbital**, clonazepam, or valproic acid. The involuntary muscle jerking (myoclonus) may decrease with such medication as valproic acid; **benzodiazepines** such as clonazepam; L-tryptophan; 5-hydroxytryptophan with carbidopa; or piracetam.

Prognosis

Ramsay-Hunt syndrome type II generally progresses to death within about 10 years of the onset of symptoms.

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National Ataxia Foundation. 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447-4752. (763) 553-0020; Fax: (763) 553-0167. naf@ataxia.org. <http://www.ataxia.org>.

WE MOVE. 204 West 84th Street, New York, NY 10024. (212) 875-8389 or (800) 437-MOV2. wemove@wemove.org. <http://www.wemove.org>.

Rosalyn Carson-DeWitt, MD

Rasmussen's encephalitis

Definition

Rasmussen's encephalitis, also termed Rasmussen's syndrome, is a rare degenerative brain disease that initially affects only one side of the brain. It first manifests in childhood with the onset of epileptic **seizures**. Later, it progresses to paralysis of one side of the body (hemiparesis), blindness in one eye (**hemianopsia**), and loss of mental function. The seizures in Rasmussen's encephalitis usually resist therapy with anticonvulsant drugs, but respond well to hemispherectomy, the surgical removal of the entire affected side of the brain.

Description

Rasmussen's encephalitis usually appears in children, but may also strike in adulthood. It initially affects only one side (hemisphere) of the brain. The disease causes uncontrollable seizures and other symptoms that become progressively worse. The affected hemisphere shows changes characteristic of chronic inflammation, including long-term atrophy or shrinkage, hence, the term encephalitis (inflammation of the brain). Unless the affected

hemisphere is removed, the disorder eventually spreads to the brain's other hemisphere.

Demographics

Rasmussen's encephalitis is very rare; between 1958, when the syndrome was first identified, and 2000, barely 100 cases were identified. The medical literature does not describe a higher incidence of this disease in either gender or in any particular racial group or geographical area.

Causes and symptoms

For many years, the cause of Rasmussen's encephalitis was a mystery. It seemed to resemble a viral infection, but despite much research, no organism could be consistently found in the brains of those who had suffered from the disorder. Finally, in the early 1990s, it was discovered that Rasmussen's encephalitis is an autoimmune disease, that is, a disorder in which the body is attacked by its own immune system.

Specifically, the body responds to one of the glutamate receptors, GluR3, as if it were an invading organism. Glutamate is a neurotransmitter, or one of the chemicals that neurons use to signal to each other. A receptor is a complex molecule embedded in the cell membrane of a neuron that detects the presence of a specific neurotransmitter and responds by causing some change in the neuron itself, such as admitting a flow of sodium, potassium, or calcium ions into the cell. There are at least 20 distinct receptors for glutamate in the brain, one of which is denoted GluR3. In Rasmussen's encephalitis, the body (for reasons still unknown) produces anti-GluR3 antibodies. Attracted by these antibodies, groupings of special immune system proteins, termed complement, gather on neurons in the affected parts of the brain, eventually forming "membrane attack complexes" that damage the neurons. It is not known why this autoimmune response attacks only one side of the brain at first, but it was hypothesized that a breach in the blood-brain barrier in one part of the brain might allow initial access of antibodies to neurons. The arrival of lymphocytes in the affected area, with consequent swelling of tissues, may then cause further damage to the blood-brain barrier and allow more anti-GluR3 antibodies access to the neurons. Finally, it remains possible that infection by cytomegalovirus may play a role in triggering the autoimmune processes of Rasmussen's encephalitis. Cytomegalovirus DNA has been detected in the brains of some patients.

The first symptom of Rasmussen's encephalitis is seizures, usually beginning suddenly before the age of 10. Loss of control over voluntary movements, loss of speech ability (**aphasia**), hemiparesis (weakness on one side of the body), **dementia**, **mental retardation**, and eventually, death, will follow if untreated.

Key Terms

Aphasia Total or partial loss of the ability to use or understand language; usually caused by stroke, brain disease, or injury.

Autoimmune disorder Disorders in which the body mounts a destructive immune response against its own tissues.

Blood-brain barrier The protective membrane that separates circulating blood from brain cells, allowing some substances to enter while others, such as certain drugs, are prevented from entering brain tissue.

Cytomegalovirus A herpes type of virus that may be transmitted through blood or body fluids and can be fatal in people with weakened immune systems.

Encephalitis Inflammation of the brain.

Hemiparesis Muscle weakness on one side of the body.

Neurotransmitter A chemical that is released during a nerve impulse that transmits information from one nerve cell to another.

Diagnosis

Rasmussen's encephalitis is diagnosed by the sudden onset of epileptic seizures in childhood, gradual worsening of seizures, gradual intellectual deterioration, the onset of hemiparesis and other one-sided symptoms, and the elimination of other possible causes for these symptoms.

Treatment

Early in the progress of Rasmussen's encephalitis, anticonvulsant drugs may help control seizures. Use of the anti-cytomegalovirus drug ganciclovir early in the syndrome produces improvement in some patients. Also, some patients have shown dramatic positive response to removal of anti-GluR3 antibodies from the blood by a process known as plasmapheresis. Currently, researchers are studying the hypothesis that drugs to prevent the formation of membrane-attack complexes might slow or halt the progression of Rasmussen's encephalitis as well as of other neurodegenerative diseases. However, the treatment of choice remained hemispherectomy, surgical removal of the affected half of the brain.

Remarkably, children may show little or no change in personality and no loss of intelligence or memory after having half their brain removed. Some children are irritable, withdrawn, or depressed immediately after surgery,

but these symptoms are not permanent. So flexible is brain development that a child with a hemispherectomy may become fluent in one or more languages even if the left side of the brain, where the speech centers are usually located, is removed. Blindness or vision loss in one eye usually results from hemispherectomy, but normal hearing in both ears may be recovered. The older the patient is when the surgery is performed, however, the more likely they are to suffer permanent sensory, speech, and motor losses.

Recovery and rehabilitation

Rehabilitation begins immediately after hemispherectomy with passive range-of-motion exercises. Physical, occupational, and speech therapists are required. For children of school age, **neuropsychological testing** can help determine what academic setting or grade level is best. Children with hemispherectomies are often able to participate in school at the level appropriate for their age.

Prognosis

The prognosis for children below the age of 10 who are treated early in the course of the syndrome is good. This group can often achieve normal psychosocial and intellectual functioning. Without hemispherectomy, however, persons with Rasmussen's encephalitis eventually suffer near-continuous seizures, mental retardation, and death.

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Larry Gilman, PhD

Reflex sympathetic dystrophy

Definition

Reflex sympathetic dystrophy is the feeling of **pain** associated with evidence of minor nerve injury.

Description

Historically reflex sympathetic dystrophy (RSD) was noticed during the Civil War in patients who suffered **pain** following gunshot **wounds** that affected the median nerve (a major nerve in the arm). In 1867 the condition was called causalgia from the Greek term meaning "burning pain." Causalgia refers to pain associated with major nerve injury. The exact causes of RSD are still unclear. Patients usually develop a triad of phases. In the first phase, pain and sympathetic activity is increased. Patients will typically present with swelling (**edema**), stiffness, pain, increased vascularity (increasing warmth), hyperhydrosis, and x-ray changes demonstrating loss of **minerals** in bone (demineralization). The second phase develops three to nine months later, It is characterized by increased stiffness and changes in the extremity that include a decrease in warmth and atrophy of the skin and muscles. The late phase commencing several months to years later presents with a pale, cold, painful, and atrophic extremity. Patients at this stage will also have **osteoporosis**.

It has been thought that each phase relates to a specific nerve defect that involves nerve tracts from the periphery spinal cord to the brain. Both sexes are affected, but the number of new cases is higher in women, adolescents, and young adults. RDS has been associated with other terms such as Sudeck's atrophy, post-traumatic osteoporosis, causalgia, shoulder-hand syndrome, and reflex neuromuscular dystrophy.

Causes and symptoms

The exact causes of RSD at present is not clearly understood. There are several theories such as sympathetic overflow (overactivity), abnormal circuitry in nerve impulses through the sympathetic system, and as a post-operative complication for both elective and traumatic

Key Terms

Atrophy Abnormal changes in a cell that lead to loss of cell structure and function.

Osteoporosis Reduction in the quantity of bone.

surgical procedures. Patients typically develop pain, swelling, temperature, color changes, and skin and muscle wasting.

Diagnosis

The diagnosis is simple and confirmed by a local anesthetic block along sympathetic nerve paths in the hand or foot, depending on whether an arm or leg is affected. A test called the **erythrocyte sedimentation rate** (ESR) can be performed to rule out diseases with similar presentation and arising from other causes.

Treatment

The preferred method to treat RSD includes sympathetic block and physical therapy. Pain is improved in motion of the affected limb improves. Patients may also require tranquilizers and mild **analgesics**. Patients who received repeated blocks should consider surgical symathectomy (removal of the nerves causing pain).

Prognosis

The prognosis for treatment during phase one is favorable. As the disease progresses undetected into phase two or three the prognosis for recovery is poor.

Resources

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Laith Farid Gulli, MD
Robert Ramirez, BS

Refsum disease

Definition

Refsum disease is one of several inherited disorders that are collectively called leukodystrophies. Refsum disease results from defects in the formation of the myelin sheath, a fat covering that protects the nerves in the brain and spinal cord.

Description

Refsum disease has also been called Refsum-Thiébaut disease and Refsum-Thiébaut-Klenk-Kahlke disease since Drs. W. Kahlke, E. Klenk, M.F. Thiébaut, and Sigvald Bernhard Refsum all contributed to the identification and clinical characterization of the disorder. The Norwegian **neurologist**, Sigvald Refsum first described the disorder in 1946.

Refsum disease is a rare genetic disorder that affects the ability of the body to breakdown fats, a process called fatty acid oxidation. As a result, a metabolite called phytanic acid accumulates in the blood as well as other tissues. Phytanic acid is not produced by the human body but is obtained from meat, dairy, and fish products. Phytanic acid is a branched chain fatty acid. The accumulation of this compound in the blood was detected by the German scientist Klenk and Kahlke around 1963. Phytanic acid can also be produced through the breakdown of a substance that is found in green leafy vegetables called phytol.

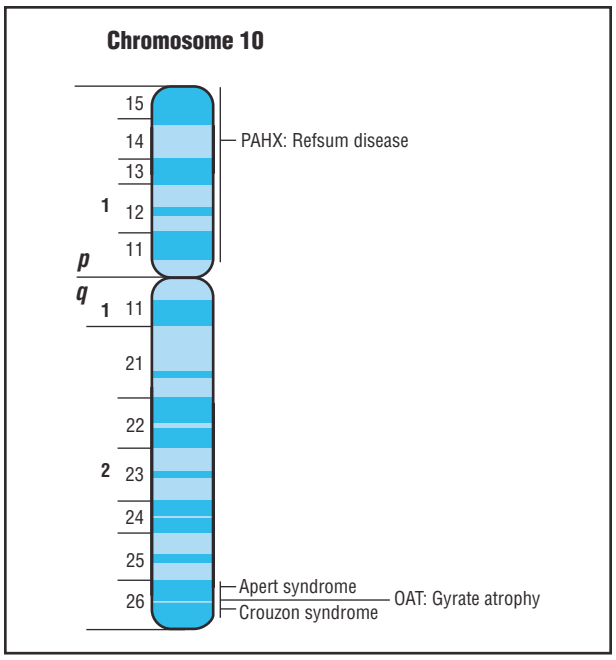
Refsum disease is inherited as an autosomal recessive disorder, which means that two unaffected carrier parents have a 25% chance of having an affected child in every pregnancy. Other less commonly used synonyms for Refsum syndrome include: **ataxia** hereditaria hemeralopia polyneuritiformis, hemeralopia heredotaxia polyneuritiformis, hereditary motor sensory neuropathy type IV, heredopathia atactica poluneuritiformis, and phytanic acid storage syndrome.

Demographics

Refsum disease is an extremely rare disorder that affects males and females with equal frequency. It has been observed in Norwegian populations as well as others.

Causes and symptoms

One of the earliest symptoms in Refsum disease that the patients develop is night blindness. The age of onset of all clinical manifestations tends to occur during childhood and usually develop before 50 years of age. It is a progressive disorder characterized by periods of subtle worsening and often appears to be in remission.



Refsum disease, on chromosome 10. *(Gale Group.)*

Key Terms

Autosomal recessive disorder A genetic disorder that is inherited from parents that are both carriers, but do not have the disorder. Parents with an affected recessive gene have a 25% chance of passing on the disorder to their offspring with each pregnancy.

Leukodystrophy A genetically determined progressive disorder that affects the brain, spinal cord, and peripheral nerves.

Myelin A fat-like substance that forms a protective sheath around nerve fibers.

People with Refsum disease typically experience progressive hearing loss due to nerve damage that occurs early during development. They can develop a progressive degeneration of the eye leading to blindness due to an atypical form of retinitis pigmentosa, a degenerative condition associated with night blindness and pigment changes in the retina. The visual loss involves progressive constriction of the visual fields and these patients can develop nystagmus (an involuntary oscillation of the eyeball) as well as cataracts.

Cerebellar ataxia (brain-damage-related loss of motor coordination) can also occur with Refsum disease, leading to an unsteady gait. They can have syndactyly of the fingers, where two fingers appear fused due to a failure to separate during embryo formation. The neurological damage appears to be localized toward the head and trunk of the body (rather than the limbs). A fetus with Refsum disease often develops heart disease and can also be born with skeletal abnormalities in bone formation. It is also common for people with Refsum disease to lose their sense of smell. Finally, changes in the skin can also occur with Refsum disease.

Refsum was the first genetic disorder identified to be caused by defects in lipid (fat) metabolism. It is currently felt to be caused by mutations in a gene (PAHX) that encodes a protein called phyanoly-CoA hydroxylase and is important for metabolizing phytanic acid.

Diagnosis

The diagnosis for Refsum disease is made based on the development of clinical manifestations and biochemical analysis detecting elevated phytanic acid in the blood.

Treatment team

There are several specialists that are helpful in the diagnosis, treatment, and long-term care of patients with Refsum disease. A neurologist is helpful initially in diagnosing the disorder, as well as providing the appropriate follow-up studies and treatment regimen. A genetic counselor is helpful in explaining the recurrence risks to the family, especially if they are considering reproductive implications.

Treatment

Dietary treatment involving the restriction of foods that contain phytanic acid began in Norway in 1966 by Professor Lorentz Eldjarn, the Head of the Central Laboratory and Institute for Clinical Biochemistry at the Oslo University Hospital, Rikshospitalet. This treatment continues today. Additionally, plasmapheresis or the removing of plasma from the patient's blood may also be helpful and necessary.

Recovery and rehabilitation

Recovery with treatment is often possible for many of the symptoms, although treating patients with Refsum disease cannot reverse damage to the eyesight and hearing.

Clinical trials

The National Institute for Neurological Diseases and Stroke and the National Institutes of Health supports research to help increase understanding and awareness or Refsum disease, as well as to find new prevention, treatments, or a cure for this disorder. One study, which is

aimed at determining the effectiveness of an oral bile acid therapy regimen is currently recruiting patients with the infantile form of Refsum disease. (Contact information: Kenneth Setchell, Study Chair, Children's Hospital Medical Center, Cincinnati OH; (513) 636-4548).

Prognosis

The prognosis for Refsum disease is highly variable. Without treatment, the prognosis is poor. In patients who are treated appropriately, many neurological symptoms and ichthyosis (scaly, dry skin) generally disappear.

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National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD (6673); Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

National Tay-Sachs and Allied Diseases Association. 2001 Beacon Street Suite 204, Brighton, MA 02135. (617) 277-4463 or (800) 90-NTSAD (906-8723; Fax: (617) 277-0134. info@ntsad.org. <http://www.ntsad.org>.

Bryan Richard Cobb, PhD

Repetitive stress injuries *see* **Repetitive motion disorders**

Repetitive motion disorders

Definition

Repetitive motion disorders are a group of syndromes caused by injuries to muscles, tendons, nerves, or blood vessels from repeated or sustained exertions of different body parts. Most of these disorders involve the hands, arms, or neck and shoulder area. Other names for repetitive motion disorders include repetitive trauma disorders, repetitive strain injuries (RSIs), overuse syndrome, work-related disorders, and regional musculoskeletal disorders.

Description

Repetitive motion disorders are characterized by **pain**, loss of strength and coordination, numbness or tingling, and sometimes redness or swelling in the affected area. The symptoms come on gradually, and are usually relieved temporarily by resting or avoiding the use of the affected body part. Repetitive motion disorders are commonly thought of as work related, but they can occur as a result of academic, leisure-time, or household activities as well.

Demographics

The demographics of repetitive motion disorders vary according to the specific syndrome. As of 2004, about 50% of all industrial injuries in the United States and Canada are attributed to overuse disorders. Professional athletes, dancers, and musicians experience one of these disorders at a much higher percentage at some point in their careers. The Institute of Medicine's 2001 study, Musculoskeletal Disorders and the Workplace, reported that nearly a million American workers were treated in 1999 for work-related pain or impaired function in the arms, hands, or back. Other experts estimate that overuse injuries cost the United States economy between $27 million and $45 million every year.

Race is not known to be a factor in repetitive motion disorders. Gender has a significant effect on the demographics of some disorders, but it is not clear whether the higher incidence of some disorders in women reflects different occupational choices for men and women, or whether it reflects biological differences. For example, de Quervain's syndrome is a common overuse disorder in women involved with childcare, because repeated lifting and carrying of small children places severe strains on the wrist joint. On the other hand, some researchers think that the greater frequency of this disorder in women is related to the effects of female sex hormones on connective tissue, as women's ligaments are slightly looser during pregnancy and at certain points in the menstrual cycle.

Some repetitive motion disorders appear to be age related. **Carpal tunnel syndrome** is more common in middle-aged than in younger women, and trigger finger is most common in people aged 55–60. It is not yet known whether the widespread use of computers in the workplace will change the age distribution of repetitive motion disorders as present workers grow older.

The Industrial Revolution led to increased job specialization, which meant that more and more workers were employed doing one task repeatedly rather than many different tasks. Office work is a case in point. *(© Photo Reasearchers. Reproduced by permission.)*

Causes and symptoms

SOFT TISSUE DAMAGE Repetitive motion disorders are the end result of a combination of factors. One basic cause of repetitive motion disorders, however, is microtraumas, which are tiny damages to or tears in soft tissue that occur from routine stresses on the body or repeated use of specific muscles and joints. When microtraumas are not healed during sleep or daily rest periods, they accumulate over time, causing tissue damage, inflammation, and the activation of pain receptors in peripheral nerves.

NERVE COMPRESSION Some repetitive motion disorders are associated with entrapment neuropathies, which are functional disorders of the **peripheral nervous system**. In an entrapment neuropathy, a nerve is damaged by compression as it passes through a bony or fibrous tunnel. Carpal tunnel syndrome, de Quervain's syndrome, ulnar nerve syndrome, and **thoracic outlet syndrome** are examples of entrapment neuropathies.

Compression damages peripheral nerves by limiting their blood supply. Even slight pressures on a nerve can limit the flow of blood through the smaller blood vessels surrounding the nerve. As the pressure increases, transmission of nerve impulses is affected and the patient's sensation and coordination are affected, with further increases in **nerve compression** producing greater distortion of sensation and range of motion.

TECHNOLOGICAL AND SOCIAL FACTORS Economic and social factors that have affected people's occupations and leisure-time activities over the past two centuries have contributed to the increase in repetitive motion disorders. The Industrial Revolution led to increased job specialization, which meant that more and more workers were employed doing one task repeatedly rather than many different tasks. In addition, industrialization brought about the invention of complex tools and machinery that affect the tissues and organs of the human body in many ways.

The high levels of psychological and emotional tension in modern life also contribute to repetitive stress injuries by increasing the physical stresses on muscles and joints.

INDIVIDUAL RISK FACTORS Risk factors that are associated with repetitive stress injuries include the following:

- Awkward or incorrect body postures. Each joint in the body has a position within its range of motion in which it is least likely to become injured. This position is called the neutral position. Any deviation from the neutral position puts increased strain on body tissues. Inadequate work space, using athletic or job-related equipment that is not proportioned to one's height, or improper technique are common reasons for RSIs related to body posture.
- Use of excessive force to perform a task. Pounding on piano keys or hammering harder than is necessary to drive nails are examples of this risk factor.
- Extended periods of static work. This type of work requires muscular effort, but no movement takes place. Instead, the muscles contract, preventing blood from reaching tissues to nourish the cells and carry away waste products. Over time, the muscle tissue loses its ability to repair microtraumas. Examples of static work include sitting at a desk for hours on end or holding the arms over the head while painting a ceiling.
- Activities that require repetitive movements. Assembly-line work and word processing are examples of job-related repetitive motion. In addition, such leisure-time activities as knitting, embroidery, gardening, model construction, golf or tennis, etc. can have the same long-term effects on the body as work-related activities.
- Mechanical injury. Tools with poorly designed handles that cut into the skin or concentrate pressure on a small area of the hand often contribute to overuse disorders.
- Vibration. There are two types of vibration that can cause damage to the body. One type is segmental vibration, which occurs when the source of the vibration affects only the part of the body in direct contact with it. An example of segmental vibration is a dentist's use of a high-speed drill. Overexposure of the hands to segmental vibration can eventually damage the fingers, leading to Raynaud's phenomenon. The second type is whole-body vibration, which occurs when the vibrations are transmitted throughout the body. Long-distance truckers and jackhammer operators often develop back injuries as the result of long-term whole-body vibration.
- Temperature extremes. Cold temperatures decrease blood flow in the extremities, while high temperatures lead to dehydration and rapid **fatigue**. In both cases, blood circulation is either decreased or redirected, thus slowing down the process of normal tissue recovery.
- Psychological stress. People who are worried, afraid, or angry often carry their tension in their neck, back, or shoulder muscles. This tension reduces blood circulation in the affected tissues, thus interfering with tissue recovery. In addition, emotional stress has been shown to influence people's perception of physical pain; workers who are unhappy in their jobs, for example, are more likely to seek treatment for work-related disorders.
- Structural abnormalities. These abnormalities include congenital deformities in bones and muscles, changes in the shape of a bone from healed breaks or fractures, bone spurs, and tumors. Overdevelopment of certain muscle groups from athletic workouts may result in entrapment neuropathies in the shoulder area.
- Other systemic conditions or diseases. People with such disorders as rheumatoid arthritis (RA), joint infections, hypothyroidism, or diabetes are at increased risk of developing repetitive motion disorders. Pregnancy is a risk factor for overuse disorders affecting the hands because of the increased amount of fluid in the joints of the wrists and fingers.

Symptoms

The symptoms of repetitive motion disorders include the following:

- Pain. The pain of an RSI is typically felt as an aching sensation that gets worse if the affected joint(s) or limb is moved or used. The pain may be severe enough to wake the patient at night.
- Paresthesias. Paresthesia refers to an abnormal sensation of pricking, tingling, burning, or "insects crawling beneath the skin" in the absence of an external stimulus.
- Numbness, coldness, or loss of sensation occur in the affected area.
- Clumsiness, weakness, or loss of coordination result.
- Impaired range of motion or locking of a joint occur.
- Popping, clicking, or crackling sounds in a joint are experienced.
- Swelling or redness in the affected area are observed.

Diagnosis

History and physical examination

The diagnosis of a repetitive motion disorder begins with taking the patient's history, including occupational history. The doctor will ask about the specific symptoms in the affected part, particularly if the patient suffers from rheumatoid arthritis, diabetes, or other general conditions as well as overuse of the joint or limb.

The next step is physical examination of the affected area. The doctor will typically palpate (feel) or press on

Key Terms

Alexander technique A form of movement therapy that emphasizes correct posture and the proper positioning of the head with regard to the spine.

de Quervain's syndrome Inflammation of the tendons contained within the wrist, associated with aching pain in the wrist and thumb. Named for the Swiss surgeon who first described it in 1895, the syndrome is sometimes called washerwoman's sprain because it is commonly caused by overuse of the wrist.

Entrapment neuropathy A disorder of the peripheral nervous system in which a nerve is damaged by compression as it passes through a bony or fibrous passage or canal. Many repetitive motion disorders are associated with entrapment neuropathies.

Ergonomics The branch of science that deals with human work and the efficient use of energy, including anatomical, physiological, biomechanical, and psychosocial factors.

Median nerve The nerve that supplies the forearm, wrist area, and many of the joints of the hand.

Neuropathy Any diseased condition of the nervous system.

Paresthesia The medical term for an abnormal touch sensation, usually tingling, burning, or prickling, that develops in the absence of an external stimulus. Paresthesias are a common symptom of repetitive motion disorders.

Peripheral nervous system The part of the human nervous system outside the brain and spinal cord.

Raynaud's phenomenon A disorder characterized by episodic attacks of loss of circulation in the fingers or toes. Most cases of Raynaud's are not work-related; however, the disorder occasionally develops in workers who operate vibrating tools as part of their job, and is sometimes called vibration-induced white finger.

Transcutaneous electrical nerve stimulation (TENS) A form of treatment for chronic pain that involves the use of a patient-controlled device for transmitting mild electrical impulses through the skin over the injured area.

Trigger finger An overuse disorder of the hand in which one or more fingers tend to lock or "trigger" when the patient tries to extend the finger.

Ulnar nerve The nerve that supplies some of the forearm muscles, the elbow joint, and many of the short muscles of the hand.

the sore area to determine whether there is swelling as well as pain. He or she will then perform a series of maneuvers to evaluate the range of motion in the affected joint(s), listen for crackles or other sounds when the joint is moved, and test for weakness or instability in the limb or joint. There are simple physical tests for specific repetitive motion disorders. For example, the Finkelstein test is used to evaluate a patient for de Quervain's syndrome. The patient is asked to fold the thumb across the palm of the affected hand and then bend the fingers over the thumb. A person with de Quervain's will experience sharp pain when the doctor moves the hand sideways in the direction of the elbow. Tinel's test is used to diagnose carpal tunnel syndrome. The doctor gently taps with a rubber hammer along the inside of the wrist above the median nerve to see whether the patient experiences paresthesias.

Laboratory tests

Laboratory tests of blood or tissue fluid are not ordinarily ordered unless the doctor suspects an infection or wishes to rule out diabetes, anemia, or thyroid imbalance.

Imaging studies

Imaging studies may be ordered to rule out other conditions that may be causing the patient's symptoms or to identify areas of nerve compression. When surgery is being planned, x rays may be helpful in identifying stress fractures, damage to cartilage, or other abnormalities in bones and joints. **Magnetic resonance imaging (MRI)** can be used to identify injuries to tendons, ligaments, and muscles as well as areas of nerve entrapment.

Electrodiagnostic studies

The most common electrodiagnostic tests used to evaluate repetitive motion disorders are **electromyography** (EMG) and nerve conduction studies (NCS). In EMG, the doctor inserts thin needles in specific muscles and observes the electrical signals that are displayed on a screen. This test helps to pinpoint which muscles and nerves are affected by pain. Nerve conduction studies are done to determine whether specific nerves have been damaged. The doctor positions two sets of electrodes on the patient's skin over the muscles in the affected area. One set of electrodes

stimulates the nerves supplying that muscle by delivering a mild electrical shock; the other set records the nerve's electrical signals on a machine.

Treatment team

A mild repetitive motion disorder may be treated by a primary care physician. If conservative treatment is ineffective, the patient may be referred to an orthopedic surgeon or neurosurgeon for further evaluation and surgical treatment. Patients whose disorders are related to job dissatisfaction, or who have had to give up their occupation or favorite activity because of their disorder, may benefit from psychotherapy.

Physical therapists and occupational therapists are an important part of the treatment team, advising patients about proper use of the injured body part and developing a home **exercise** program. Some patients benefit from having their workplace and equipment evaluated by the occupational therapist or an ergonomics expert. Professional athletes, dancers, or musicians usually consult an expert in their specific field for evaluation of faulty posture or technique.

Treatment

Conservative treatment

Conservative treatment for overuse injuries typically includes:

- Resting the affected part. Complete rest should last no longer than two to three days, however. What is known as "relative rest" is better for the patient because it maintains range of motion in the affected part, prevents loss of muscle strength, and lowers the risk of "sick behavior." Sick behavior refers to using an injury or illness to gain attention or care and concern from others.
- Applying ice packs or gentle heat.
- Oral medications. These may include mild pain relievers (usually NSAIDs); amitriptyline or another tricyclic antidepressant; or vitamin B6.
- Injections. Corticosteroids may be injected into joints to lower inflammation and swelling. In some cases, local anesthetics may also be given by injection.
- Splinting. Splints are most commonly used to treat overuse injuries of the hand or wrist; they can be custom-molded by an occupational therapist.
- Ergonomic corrections in the home or workplace. These may include changing the height of chairs or computer keyboards; scheduling frequent breaks from computer work or musical practice; correcting one's posture; and similar measures.
- Transcutaneous electrical nerve stimulation (TENS). TENS involves the use of a patient-controlled portable device that sends mild electrical impulses through injured tissues via electrodes placed over the skin. It is reported to relieve pain in 75–80% of patients treated for repetitive motion disorders.

Surgery

Repetitive motion disorders are treated with surgery only when conservative measures fail to relieve the patient's pain after a trial of six to 12 weeks. The most common surgical procedures performed for these disorders include nerve decompression, tendon release, and repair of loose or torn ligaments.

Complementary and alternative (CAM) treatments

CAM treatments that have been shown to be effective in treating repetitive motion disorders include:

- **Acupuncture**. Studies funded by the National Center for Complementary and Alternative Medicine (NCCAM) since 1998 have found that acupuncture is an effective treatment for pain related to repetitive motion disorders.
- Sports massage, Swedish massage, and shiatsu.
- Yoga and tai chi. The gentle stretching in these forms of exercise helps to improve blood circulation and maintain range of motion without tissue damage.
- Alexander technique. The Alexander technique is an approach to body movement that emphasizes correct posture, particularly the proper position of the head with respect to the spine. It is often recommended for dancers, musicians, and computer users.
- Hydrotherapy. Warm whirlpool baths improve circulation and relieve pain in injured joints and soft tissue.

Recovery and rehabilitation

Recovery from a repeated motion disorder may take only a few days of rest or modified activity, or it may take several months when surgery is required.

Rehabilitation is tailored to the individual patient and the specific disorder involved. Rehabilitation programs for repetitive motion disorders focus on recovering strength in the injured body part, maintaining or improving range of motion, and learning ways to lower the risk of re-injuring the affected part. Professional musicians, dancers, and athletes require highly specialized rehabilitation programs.

Clinical trials

As of early 2004, there were four **clinical trials** related to repetitive motion disorders sponsored by the National Institutes of Health (NIH) that are recruiting

subjects. One is a comparison of amitriptyline (an antidepressant medication) and acupuncture as treatments for CTS. A second study will evaluate the effectiveness of a protective brace in preventing overuse disorders associated with hand-held power tools. The third study will evaluate the effects of fast-paced assembly-line work on the health of rural women. The fourth study is a comparison of surgical and nonsurgical treatments for CTS.

Prognosis

The prognosis for recovery from repetitive motion disorders depends on the specific disorder, the degree of damage to the nerves and other structures involved, and the patient's compliance with exercise or rehabilitation programs. Most patients experience adequate pain relief from either conservative measures or surgery. Some, however, will not recover full use of the affected body part and must change occupations or give up the activity that produced the disorder.

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American Academy of Orthopaedic Surgeons (AAOS). 6300 North River Road, Rosemont, IL 60018-4262. (847) 823-7186 or (800) 346-AAOS; Fax: (847) 823-8125. <http://www.aaos.org>.

American Society for Surgery of the Hand (ASSH). 6300 North River Road, Suite 800, Rosemont, IL 60018. (847) 384-8300; Fax: (847) 384-1435. info@hand-surg.org. <http://www.hand-surg.org>.

National Institute for Occupational Safety and Health (NIOSH). Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333. (404) 639-3534 or (800) 311-3435. <http://www.cdc.gov/niosh/homepage.html>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Information Clearinghouse, National

Institutes of Health. 1 AMS Circle, Bethesda, MD 20892-3675. (301) 495-4844 or (877) 22-NIAMS; Fax: (301) 718-6366. NIAMSinfo@mail.nih.gov. <http://www.niams.nih.gov>.

National Institute of Neurological Disorders and Stroke (NINDS). 9000 Rockville Pike, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

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Respite

Definition

Respite literally means a period of rest or relief. Respite care provides a caregiver temporary relief from the responsibilities of caring for individuals with chronic physical or mental disabilities. Respite care is often referred to as a gift of time.

Description

Respite was developed in response to the deinstitutionalization movement of the 1960s and 1970s. Maintaining individuals in their natural homes rather than placing them in long-term care facilities was viewed as beneficial to the individual, the involved family, and society (in terms of lowered health care costs). The primary purpose of respite care is to relieve caregiver stress, thereby enabling them to continue caring for the individual with a disability.

Respite care is typically provided for individuals with disorders related to aging (**dementia**, frail health), terminal illnesses, chronic health issues, or developmental disabilities. More recently, children with behavior disorders have also been eligible for respite care. Respite care is usually recreational and does not include therapy or treatment for the individual with the disability.

Caregivers frequently experience stress in the forms of physical **fatigue**, psychological distress (resentment, frustration, anxiety, guilt, **depression**), and disruption in relations with other family members. The emotional aspects of caring for a family member are often more taxing than the physical demands. Increased caregiver stress may result in health problems such as ulcers, high blood pressure, difficulty sleeping, weight loss or gain, or breathing difficulties.

Types of respite

Length of respite care can be anywhere from a few hours to several weeks. Services may be used frequently or infrequently, such as for emergencies, vacations, one day per week or month, weekends, or everyday.

A variety of facilities provide respite care services. The type of service available is often closely related to the characteristics of the facility, including:

- In-home respite services consist of a worker who comes to the family home while the caregiver is away. These services are usually provided by agencies that recruit, screen, and train workers. This type of respite is usually less disruptive to the individual with the disability, provided there is a good match between the worker and the individual. However, issues of reliability and trustworthiness of the worker can be an additional source of stress for the caregiver.
- Respite centers are residential facilities specifically designed for respite care. Adult day care programs and respite camps also fall into this category. This type of respite offers more peace of mind to the caregiver, and may provide a stimulating environment for the individual with the disability. However, centers usually restrict length of stay and may exclude individuals based on severity of disability.
- Institutional settings sometimes reserve spaces to be used for respite purposes. These include skilled nursing facilities, intermediate care facilities, group homes, senior housing, regular day care or after-school programs for children, and hospitals. Some of these facilities provide higher levels of care, but are less home-like. The individual with the disability may oppose staying in an institutional setting or may fear abandonment.
- Licensed foster care providers can also provide respite services in their homes.

Funding

Costs of respite care present a financial burden to many families. Community mental health centers often fund respite services if the individual meets certain criteria, including eligibility for Medicaid. Wraparound programs (also accessed through community mental health centers) for children with emotional or behavioral disorders also pay for respite services. Veteran's Administration hospitals provide respite care at little or no charge if the individual receiving the care is a veteran (but not if the caregiver is a veteran). Private insurance companies rarely pay for respite, and many respite providers do not accept this form of payment. Some respite facilities have sliding-scale fees. Other facilities operate as a co-op, where caregivers work at the facility in exchange for respite services.

In addition, respite agencies may have difficulty recruiting and retaining qualified employees, because limited funding prevents agencies from offering desirable salaries. The high turnover and unavailability of employees may result in delays in service delivery or family dissatisfaction with services.

Key Terms

Behavior disorders Disorders characterized by disruptive behaviors such as conduct disorder, oppositional defiant disorder, and attention-deficit/hyperactivity disorder.

Community mental health centers Organizations that manage and deliver a comprehensive range of mental health services, education, and outreach to residents of a given community.

Deinstitutionalization The process of moving people out of mental hospitals into treatment programs or halfway houses in local communities. With this movement, the responsibility for care shifted from large (often governmental) agencies to families and community organizations.

Developmental disabilities Disabilities that are present from birth and delay or prevent normal development, such as mental retardation or autism.

Intermediate care facility An inpatient facility that provides periodic nursing care.

Medicaid A program jointly funded by state and federal governments that reimburses hospitals and physicians for the care of individuals who cannot pay for their own medical expenses. These individuals may be in low-income households or may have chronic disabilities.

Skilled nursing facility An inpatient facility that provides 24-hour nursing services to individuals in need of extended care.

Veteran's Administration hospitals Medical facilities operated by the federal government explicitly for veterans of the United States military.

Wraparound A relatively new form of mental health service delivery that strives to accommodate all family members based on self-defined needs, flexibly incorporating both formal and informal community services.

Barriers to using respite services

Recent research suggests that families who use respite tend to have higher levels of perceived stress, lower levels of support from others, and fewer resources. In many of these families, the individuals in need of care have more severe disabilities, problem behaviors such as aggression or self-injury, and communication difficulties; are school-aged; and are more dependent for basic needs such as eating, toileting, and dressing.

It has been well documented that many families eligible for respite care never utilize these services. Research regarding the use, availability, and effectiveness of respite care is still in the preliminary stages. Various reasons for non-utilization of respite include:

- Unfamiliarity: Some families are unaware that such services exist, or may be uncertain about how to access services. This implies a need for improved referral services.
- Funding: Limited funding may prevent some families from receiving services.
- Caregiver qualities: Some caregivers experience guilt or anxiety over allowing someone else to care for their loved one. Being able to maintain one's family independently may be tied to gender roles or cultural customs. Relatives and friends may assist in caregiving, making formal respite unnecessary.
- Care recipient qualities: Occasionally the individual with the disability is opposed to respite care. He or she may not trust strangers or may refuse to leave home. In other instances, the individual may have behaviors, or require physical care, that is too challenging for the respite provider.
- Program qualities: Many researchers believe that respite programs are not adequately meeting the needs of families. In some cases, times that services are offered are inconvenient. Individuals with severe disabilities who pose the most need for services are sometimes excluded.

Many caregivers obtain respite in informal ways not offered by respite services. Some researchers have suggested that respite care should be just one form of service available to caregivers. Other services that may alleviate caregiver stress could include home-delivered meals, transportation assistance, recreational resources, or care skills training.

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The Arc National Headquarters, P.O. Box 1047, Arlington, TX 76004. (817) 261-6003; (817) 277-0553 TDD. thearc@metronet.com.<http://www.thearc.org>.

ARCH National Respite Network and Resource Center. Chapel Hill Training-Outreach Project, 800 Eastowne Drive, Suite 105, Chapel Hill, NC 27514. (888) 671-2594; (919) 490-5577. <http://www.chtop.com>.

National Aging Information Center. Administration on Aging, 330 Independence Avenue, SW, Room 4656, Washington, DC 20201. (202) 619-7501. <http://www.aoa.gov/naic>.

National Information Center for Children and Youth with Disabilities. P.O. Box 1492, Washington, DC 20013. (800)-695-0285. <http://www.nichcy.org>.

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Restless legs syndrome

Definition

Restless legs syndrome (RLS) is a neurological disorder characterized by uncomfortable sensations in the legs and, less commonly, the arms. These sensations are exacerbated (heightened) when the person with RLS is at rest. The sensations are described as crawly, tingly, prickly and occasionally painful. They result in a nearly insuppressible urge to move around. Symptoms are often associated with sleep disturbances.

Description

Restless legs syndrome is a sensory-motor disorder that causes uncomfortable feelings in the legs, especially during periods of inactivity. Some people also report sensations in the arms, but this occurs much more rarely. The sensations occur deep in the legs and are usually described with terms that imply movement such as prickly, creepy-crawly, boring, itching, achy, pulling, tugging and painful. The symptoms result in an irrepressible urge to move the leg and are relieved when the person suffering from RLS voluntarily moves. Symptoms tend to be worse in the evening or at night.

Restless legs syndrome is associated with another disorder called periodic limb movements in sleep (PLMS). It is estimated that four out of five patients with RLS also suffer from PLMS. PLMS is characterized by jerking leg movements while sleeping that may occur as frequently as every 20 seconds. These jerks disrupt sleep by causing continual arousals throughout the night.

People with both RLS and PLMS are prone to abnormal levels of exhaustion during the day because they are unable to sleep properly at night. They may have trouble concentrating at work, at school or during social activities. They may also have mood swings and difficulty with interpersonal relationships. **Depression** and anxiety may also result from the lack of sleep. RLS affects people who want to travel or attend events that require sitting for long periods of time.

Demographics

As much as 10% of the population of the United States and Europe may suffer from some degree of restless legs syndrome. Fewer cases are indicated in India, Japan and Singapore, suggesting racial or ethnic factors play a role in the disorder. Although the demographics can vary greatly, the majority of people suffering from RLS are female. The age of onset also varies greatly, but the number of people suffering from RLS increases with age. However, many people with RLS report that they had symptoms of the disorder in their childhood. These symptoms were often disregarded as growing pains or hyperactivity.

Causes and symptoms

Restless legs syndrome is categorized in two ways. Primary RLS occurs in the absence of other medical symptoms, while secondary RLS is usually associated with some other medical disorder. Although the cause of primary RLS is currently unknown, a large amount of research into the cause of RLS is taking place. Researchers at Johns Hopkins University published a study in July 2003 suggesting that iron deficiencies may be related to the disorder. They dissected brains from cadavers of people who suffered from RLS and found that the cells in the midbrain were not receiving enough iron. Other researchers suggest that RLS may be related to a chemical imbalance of the neurotransmitter dopamine in the brain. There is also evidence that RLS has a genetic component. RLS occurs three to five times more frequently in an immediate family member of someone who has RLS than in the general population. A site on a chromosome that may

Key Terms

Anemia A condition in which there is an abnormally low number of red blood cells in the bloodstream. It may be due to loss of blood, an increase in red blood cell destruction, or a decrease in red blood cell production. Major symptoms are paleness, shortness of breath, unusually fast or strong heart beats, and tiredness.

Anticonvulsant drugs Drugs used to prevent convulsions or seizures. They often are prescribed in the treatment of epilepsy.

Benzodiazepine drugs One of a class of drugs that have a hypnotic and sedative action, used mainly as tranquilizers to control symptoms of anxiety. Diazepam (Valium), alprazolam (Xanax), and chlordiazepoxide (Librium) are all benzodiazepines.

Dopamine-receptor agonists (DAs) The older class of antipsychotic medications, also called neuroleptics. These drugs primarily block the site on nerve cells that normally receives the brain chemical dopamine.

Opioid Any natural or synthetic substance that produces the same effects as an opiate, such as pain relief, sedation, constipation and respiratory depression. Some opioids are produced by the human body (e.g., endorphins), while others are produced in the laboratory (e.g., methadone).

Periodic Limb Movements in Sleep (PLMS) Random movements of the arms or legs that occur at regular intervals of time during sleep.

contain a gene for RLS has been identified by molecular biologists.

In many people, other medical conditions play a role in RLS and the disorder is therefore termed secondary RLS. People with peripheral neuropathies (injury to nerves in the arms and legs) may experience RLS. Such neuropathies may result from diabetes or alcoholism. Other chronic diseases such as kidney disorders and rheumatoid arthritis may result in RLS. Iron deficiencies and blood anemias are often associated with RLS and symptoms of the disease usually decrease once blood iron levels have been corrected. Attention deficit/hyperactivity disorder has also been implicated in RLS. Pregnant women often suffer from RLS, especially in the third trimester. Some people find that high levels of caffeine intake may result in RLS.

The symptoms of RLS are all associated with unpleasant feelings in the limbs. The words used to describe these feelings are various, but include such adjectives as deep-seated crawling, jittery, tingling, burning, aching, pulling, painful, itchy or prickly. They are usually not described as a muscle cramp or numbness. Most often the sensations occur during periods of inactivity. They are characterized by an urge to get up and move. Such movements include stretching, walking, jogging or simply jiggling the legs. The feelings worsen in the evening.

A variety of symptoms are associated with RLS, but may not be characteristic of every case. Some people with RLS report involuntary arm and leg movements during the night. Others have difficulty falling asleep and are sleepy or fatigued during the day. Many people with RLS have leg discomfort that is not explained by routine medical exams.

Diagnosis

Restless legs syndrome cannot currently be diagnosed using any laboratory tests or via a routine physical examination. Diagnosis is based on information given to a doctor by the patient regarding his or her symptoms. Usually the doctor takes a complete medical history as well as a family history. The International Restless Legs Syndrome Study group has proposed a set of criteria that can be used while taking a medical history in order to diagnose RLS:

- a compelling urge to move the arms and legs
- restlessness that manifests itself in pacing, tossing and turning and/or rubbing the legs
- symptoms that worsen when the patient is resting and are relieved when the patient is active
- symptoms that worsen at the end of the day

In addition, a physical examination will be made to identify if there are any other medical conditions, such as neurological disorders or blood disorders that may be causing secondary RLS. A doctor who suspects a patient has RLS may suggest that the person spend the night in a sleep clinic to determine whether the patient also suffers from PLMS.

Treatment

Treatment for restless legs syndrome is generally two-pronged, consisting of making lifestyle changes and using medications to relieve some of the symptoms. Lifestyle

changes involve making changes to the diet, exercising and performing other self-directed activities, and practicing good sleep hygiene. Although the United States Food and Drug Administration has not yet approved any drugs for treating RLS, four classes of pharmaceuticals have been found effective for treating RLS: dopaminergic agents, **benzodiazepines**, opioids and **anticonvulsants**.

Lifestyle changes

Simple changes to the diet have proven effective for some people suffering from RLS. Vitamin deficiencies are a common problem in RLA patients. In patients with RLS, most physicians will check the levels of blood serum ferritin, which can indicate low iron storage. If these levels are below 50 mcg/L, then supplemental iron should be added to the diet. Other physicians have found that supplements of vitamin E, folic acid and B vitamins, and magnesium provide relief to symptoms or RLS. Reducing or eliminating caffeine and alcohol consumption has been effective in other patients.

Many who suffer from RLS find that **exercise** and massage help reduce symptoms. Walking or stretching before bed, taking a hot bath and using massage or acupressure help improve sleep. Practicing relaxation techniques such as mediation, yoga and biofeedback have also been found to be useful.

Good sleep hygiene includes having a restful, cool sleep environment and sleeping during consistent hours every night. Often people who suffer from RLS find that going to sleep later at night and sleeping later into the morning result in a better sleep.

Pharmaceuticals

Dopaminergic agents are the first type of drug prescribed in the treatment of RLS. Most commonly doctors prescribe dopamine-receptor agonists that are used to treat **Parkinson's disease** such as Mirapex (pramipexole), Permax (pergolide) and Requip (ropinirole). Sinemet (carbidopa/levodopa), which is a drug that adds dopamine to the nervous system, is also commonly prescribed. Sinemet has been used the more frequently than other drugs in treating RLS, but recently a problem known as augmentation has been associated with its use. When augmentation develops, symptoms of RLS will return earlier in the day and increasing the dose will not improve the symptoms.

Benzodiazepines are drugs that sedate and are typically taken before bedtime so that a patient with RLS can sleep more soundly. The most commonly prescribed sedative in RLS is Klonopin (clonazepam).

Opioids are synthetic narcotics that relieve **pain** and cause drowsiness. They are usually taken in the evening. The most commonly used opioids prescribed for RLS include Darvon or Darvocet (propoxyphene), Dolophine (methadone), Percocet (oxycodone), Ultram (Tramadol) and Vicodin (hydrocodone). One danger associated with opioids is that they can be addicting.

Anticonvulsants are drugs that were developed to prevent **seizures** in patients with **epilepsy** and **stroke**. Some RLS patients who report pain in their limbs have reported that these drugs, particularly **Gabapentin** (neurontin), are useful for relieving symptoms.

A few drugs have been found to worsen symptoms of RLS and they should be avoided by patients exhibiting RLS symptoms. These include anti-nausea drugs such as Antivert, Atarax, Compazine and Phenergan. Calcium channel blockers that are often used to treat heart conditions should be avoided. In addition, most anti-depressants tend to exacerbate symptoms of RLS. Finally, antihistamines such as Benadryl have been found to aggravate RLS symptoms in some people.

Clinical trials

A broad spectrum of **clinical trials** are currently underway to study RLS. The Restless Legs Syndrome Foundation maintains a website that lists a variety of studies throughout the United States that are currently recruiting volunteers. The studies test the effects of a variety of treatments including intravenous iron supplements, exercise and sleeping aids on RLS. More information can be found at <http://www.rls.org/frames/home_frame.htm>.

The National Institutes of Health support three clinical trials to gain information about RLS. The first study investigates the effects of the drug Ropinirole, a dopamine-receptor agonist, on spinal cord reflexes and on symptoms of restless legs syndrome. A second study is testing whether or not sensorimotor gating (the brain's ability to filter multiple stimuli) is deficient in patients who suffer from RLS. The goal of the third study is to improve understanding of neurological conditions associated with RLS by taking careful histories and following the treatment provided by primary car physicians. Information on all three trials can be found at <http://clinicaltrials.gov/search/term=Restless%20Legs%20Syndrome> or by calling the Patient Recruitment and Public Liaison Office at 1-800-411-1222 or sending an electronic message to prpl@mail.cc.nih.gov.

Prognosis

RLS is usually compatible with an active, healthy life when symptoms are controlled and nutritional deficits are corrected.

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ORGANIZATIONS

RLS Foundation, Inc. 819 Second Street SW, Rochester, MN 55902. (507) 287-6465; Fax: (507) 287-6312. rlsfoundation@rls.org. <http://www.rls.org>.

National Center on Sleep Disorders Research (NCSDR). Two Rockledge Center, Suite 7024, 6701 Rockledge Drive, MSC 7920, Bethesda, MD 20892. (301) 435-0199; Fax: (301) 480-3451.

Juli M. Berwald, PhD

Retrovirus-associated myelopathy *see* **Tropical spastic paraparesis**

Rett syndrome

Definition

Rett syndrome (RS) is a neurological disease of children that is also referred to as Rett's disorder or by the compound name of **autism**, **dementia**, **ataxia**, and loss of purposeful hand use. Named for the Austrian pediatrician who first described it, RS is sometimes grouped together with other childhood neurological disorders under the category of pervasive developmental disorders (PDDs) or autistic spectrum disorders. RS is classified by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), as a developmental disorder of childhood. More recently, Rett syndrome has been categorized along with Rubinstein-Taybi syndrome (RSTS), Coffin-Lowry syndrome (CLS), and several other rare disorders as a chromatin disease. Chromatin is the easily stained part of a cell nucleus that contains the cell's DNA, RNA, and several proteins that maintain its structure.

Description

RS was first described by an Austrian pediatrician, Andreas Rett, in 1966. His article attracted little attention, however, because it appeared in a German-language medical journal that was not widely read outside Europe. In 1983, a Swedish researcher named Bengt Hagberg published a follow-up study in the English-language *Annals of Neurology*, which led to worldwide recognition of RS as an identifiable neurological disorder.

RS has a distinctive onset and course. The affected child—almost always a girl—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 her first five months. After 30 months, the child frequently develops repetitive hand-washing or hand-wringing gestures; 50–80% of children with the disorder will eventually have **seizures**. RS is also associated with varying degrees of **mental retardation**.

The doctors who first studied RS attributed it to the breakdown or destruction of brain tissue. Later research indicated, however, that it is caused by the failure of the infant's brain to develop normally. This developmental failure is in turn associated with a genetic mutation affecting production of a key protein that organizes the structure of chromatin. Changes in chromatin structure lead to inappropriate activation of the genes that regulate brain development. About 80% of patients who meet the updated 2002 criteria for "classic" RS have this mutation on one of their two X chromosomes.

Demographics

According to the National Institute of Neurological Disorders and Stroke (NINDS), RS affects between one in 10,000 and one in 15,000 female infants. It is thought to occur in all races and ethnic groups with equal frequency. Although Rett syndrome is associated with a genetic mutation, less than 0.5% of reported cases are recurrences within families. Almost all cases represent sporadic (new) mutations of the gene responsible for the syndrome. The risk that the parents of a daughter with RS will have a second child with the disorder is less than 1%.

The reason that almost all patients with RS are female is that the mutation that causes the disorder is located on the X chromosome. While boys have an X and a Y chromosome, girls have two X chromosomes, only one of which is active in any given body cell. The other X chromosome is turned off in a process known as X inactivation, which helps to explain why the symptoms of RS vary from patient to patient. According to mathematical probability, the X chromosome with the mutation will be active in about half the girl's cells, with the healthy X chromosome

active in the other half. If by chance a majority of the girl's cells have an active healthy X chromosome, she will have only mild symptoms of RS. On the other hand, if the X chromosome with the mutation is active in a majority of the girl's cells, she will have more severe symptoms. Since boys have only one X chromosome, they have no "backup" healthy X chromosome to compensate for one that contains the mutation. As a result, boys affected by the mutation usually die shortly before or after birth. The few cases of boys surviving with RS involve another genetic disorder known as Klinefelter's syndrome, in which the boy is born with three or more sex chromosomes, two or more Xs and a Y. If one of the X chromosomes contains the RS mutation, the boy may develop RS.

Causes and symptoms

RS is the first neurological disorder in humans to be traced to defects in a protein that controls the expression of other genes. The molecular cause of Rett's disorder is a genetic mutation on the long arm of the X chromosome (Xq28) at a locus known as MECP2. Dr. Huda Zoghbi at Baylor College of Medicine and her collaborator, Dr. Uta Francke at Stanford University, discovered the gene in 1999. The gene contains instructions for the formation of a protein known as methyl cytosine-binding protein 2 or MeCP2, which is crucial to the normal development of the human brain. The mutation associated with RS results in insufficient production of MeCP2. When this key protein is lacking, other genes are "turned on" or remain active at inappropriate points in the brain's development. These activated genes interfere with the normal pattern of brain maturation. The discovery of the MECP2 gene showed that RS should be understood as a genetic interference with normal brain development rather than the result of tissue loss or destruction.

The areas of the brain that are most severely affected by the lack of MeCP2 are the frontal, motor, and temporal portions of the brain cortex; the brain stem; the base of the forebrain; and the basal ganglia. These parts of the brain control such basic functions as movement, breathing, and speech. In addition, the disruption of the normal pattern of brain development in RS affects the child's emotions and ability to learn. RS is now known to be one of the most common causes of mental retardation in girls.

The symptoms of RS are usually described in terms of four stages in the child's development.

STAGE 1, EARLY ONSET (SIX TO 18 MONTHS OF AGE) The early symptoms of RS are not always noticeable in stage 1. The infant may not make eye contact with family members and may not show much interest in toys. She may be considered a "good baby" because she is so calm and quiet. She may also be able to use single words or word combinations before she loses the ability to speak in stage 2. On the other hand, there may also be noticeable hand-wringing and slowing of head growth in this early stage.

STAGE 2, RAPID DETERIORATION (ONE TO FOUR YEARS) The second stage may be either rapid or gradual in onset. The child loses her ability to speak and to make purposeful hand movements—a condition known as **apraxia**. Hand-to-mouth movements may appear, as well as hand-wringing or hand-clapping gestures. These movements may be nearly constant while the child is awake, but disappear during sleep. There may be noticeable episodes of breath holding, air swallowing, and hyperventilating (rapid shallow breathing). The child may have trouble sleeping, and may become irritable or agitated. If she is able to walk, she will start to look unsteady on her feet (ataxia) and may have periods of trembling or shaking. Some girls completely lose the ability to walk in stage 2 and move by crawling or "bottom scooting." Slowed growth of the child's head is usually most noticeable during this stage.

STAGE 3, PLATEAU (TWO TO 10 YEARS) Motor problems and seizures often appear during this stage. The child's behavior, however, often shows some improvement, with less irritability and crying. She may show greater interest in her surroundings, and her attention span and communication skills often improve.

STAGE 4, LATE DETERIORATION OF MOTOR SKILLS (USUALLY AFTER 10 YEARS OF AGE) In stage 4, patients with RS gradually lose their mobility; some stop walking, while others have never learned to walk. There is, however, no loss of cognitive or communication skills, and the repetitive hand movements may decrease. Seizures and breathing problems typically lessen in severity by late adolescence. The spine, however, begins to develop an abnormal sideways curvature (scoliosis), which is usually more severe in girls that have never learned to walk. The patient may also develop muscle rigidity, or **spasticity**. Puberty begins at the same age as in most girls.

Other symptoms associated with RS include a greater risk of bone fractures due to low bone density in spite of adequate calcium in the diet; constipation, which results from poor muscle tone in the digestive tract, scoliosis, and the side effects of anticonvulsant medications; excessive salivation and drooling; gastroesophageal reflux disease (GERD), which results from poor muscle tone in the esophagus; and crying or emotional agitation, which is thought to result from frustration with the inability to communicate.

Diagnosis

The diagnosis of RS is clinical, which means that it is based on external observation of the patient's symptoms rather than on the results of laboratory tests or imaging

Key Terms

Apraxia Inability to carry out ordinary purposeful movements in the absence of paralysis.

Ataxia Loss or failure of muscular coordination, particularly of the arms or legs.

Autism A severe developmental disorder of childhood with onset before three years of age. RS is sometimes categorized as an autistic spectrum disorder because it shares some features with autism, including communication problems, difficulties with social interaction, and abnormal muscle tone.

Basal ganglia Groups of nerve cell bodies located deep within the brain that govern movement as well as emotion and certain aspects of cognition (thinking).

Brain stem The stalk-like portion of the brain that connects the cerebral hemispheres and the spinal cord. The brain stem receives sensory information and controls such vital functions as blood pressure and respiration.

Bruxism Involuntary clenching or grinding of teeth, usually during sleep. Bruxism is considered a supportive criterion of RS.

Cerebral cortex The thin layer of gray matter that covers the surface of the cerebral hemispheres of the brain. It controls movement, perception, behavioral responses, the higher mental functions, and the integration of these activities.

Chromatin The readily stainable portion of a cell nucleus, consisting of DNA, RNA, and various proteins. It coils and folds itself to form chromosomes during the process of cell division. RS is sometimes described as a chromatin disease.

Dementia An overall decline in a person's intellectual function, including difficulties with language, simple calculations, judgment, organizational abilities, and abstract thinking skills as well as loss of memory.

Hyperventilation A pattern of rapid but shallow breathing that is frequently found in patients with Rett syndrome.

Hypotonia Reduced muscle tone. It is one of the earliest symptoms of Rett syndrome.

Klinefelter's syndrome A genetic disorder in males characterized by the presence of two or more X chromosomes instead of the normal XY pattern. The few male patients diagnosed with Rett syndrome who have lived past infancy also have Klinefelter's syndrome.

Kyphosis An abnormal convex (outward) curvature of the upper portion of the spinal column, sometimes called a humpback or hunchback.

Mutation A spontaneous change in the sequence of nucleotides in a chromosome or gene. Mutations may affect the number and structure of chromosomes or cause deletions of part of a chromosome. Rett syndrome is caused by a mutation on the long arm of the X chromosome.

Pervasive developmental disorders (PDDs) A category of childhood disorders that includes Rett syndrome. The PDDs are sometimes referred to collectively as autistic spectrum disorders.

Psychomotor Referring to skills that involve physical movement as well as a mental component.

Scoliosis An abnormal lateral (sidewise) curvature of the spine. Many patients with RS develop scoliosis after puberty.

Spasticity A condition in which the muscles become hypertonic or stiff and the patient's movements awkward or clumsy. Many patients with RS develop spasticity in adult life.

Storage diseases Diseases in which too much of a substance (usually fats, glycogen, or certain enzymes) builds up in specific cells of the body and causes metabolic or tissue disorders.

Vasomotor Referring to the regulation of the diameter of blood vessels.

X inactivation The process in which each cell in a girl's body selects at random and turns off one of its two X chromosomes. X inactivation is one reason why some patients with RS have more severe symptoms than others.

studies. In some cases, however, the child's doctor may order blood or urine tests or an electroencephalogram (EEG) to rule out **epilepsy** or other disorders. The doctor will observe the affected child—usually over a period of several hours or days at various intervals—and interview the parents. In most cases, the diagnosis cannot be made with certainty until the child is three to five years old. A diagnosis of RS can be made by a pediatrician or primary care physician, but should be confirmed by a pediatric **neurologist** (specialist in disorders of the nervous system

in children) or developmental pediatrician. In addition to ordering genetic testing, a specialist who is evaluating a child for RS will use several different types of criteria.

Diagnostic criteria

The diagnostic criteria for RS, which were first established in 1985, were revised by an international committee in 2001–2002 in order to improve the consistency of diagnosis as well as take recent genetic discoveries into account. The criteria are divided into three groups: necessary criteria, which must be present for the doctor to make the diagnosis; supportive criteria, which are present in many patients with RS; and exclusion criteria, which rule out a diagnosis of RS.

Necessary criteria include the following:

- child is apparently normal before and around the time of birth
- psychomotor development (development of skills that involve the brain's regulation of motor activity) is either normal for the first six months or is slightly delayed from birth
- circumference of child's head at birth is normal
- head growth slows down after birth
- child loses purposeful hand motions between six and 30 months
- child makes repeated gestures, most commonly hand wringing or squeezing, clapping or tapping, and washing or rubbing motions
- child withdraws socially, loses ability to communicate in words, and loses cognitive skills
- ability to walk is impaired or lost

Supportive criteria include the following:

- disturbed breathing (hyperventilation, air swallowing, breath holding) when awake
- bruxism (grinding the teeth during sleep)
- disturbed sleeping pattern from early infancy
- muscle wasting and loss of muscle tone
- scoliosis or kyphosis
- retarded growth
- hands and feet that are very small compared to the rest of the child's body
- vasomotor disturbances

Exclusion criteria include the following:

- enlargement of the internal organs or other signs of storage diseases
- cataract formation or damage to the retina of the eye
- evidence of brain damage before or shortly after birth
- identification of a metabolic or other progressive neurological disorder
- damage to the nervous system resulting from an infectious disease or head trauma

About 15% of children who are evaluated for RS have RS-like symptoms, or have the MECP2 mutation without fulfilling all the diagnostic criteria. These children are said to have "variant" or "atypical" RS. Children below the age of three years who show some of the signs of RS but do not yet meet the full criteria are said to have "provisional" RS.

Genetic testing

It is important to understand that even though RS is associated with mutations in the MECP2 gene, the syndrome sometimes occurs without the mutation. Conversely, the mutation can occur without producing the symptoms of RS. Genetic testing can identify about 80% of RS cases but is not sufficient to use alone to make the diagnosis. Researchers think that the remaining 20% of cases may be caused either by mutations in other parts of the gene or by genes that have not yet been identified.

Treatment team

Treatment for patients with RS is highly individualized because the severity of specific symptoms varies from patient to patient; for example, some may never have seizures. In almost all cases, however, the treatment team for a child with RS will include a neurologist, an orthopedic surgeon, a physical therapist, an occupational therapist, a dietitian, and a speech-language therapist in addition to a pediatrician and a dentist. In some cases, the treatment team may include a psychiatrist who specializes in childhood and adolescent psychiatry. Most patients will also have a case manager to coordinate treatments.

When the patient reaches puberty, she should be seen by a developmental pediatrician and an orthodontist. **Respite** and in-home caregivers may also be added to the treatment team for adults with RS.

Treatment

There is no cure for RS; treatment is intended to ease the symptoms and to keep the patient mobile as long as possible. It will include most or all of the following:

- Medications. A patient with RS may be given drugs for breathing problems and difficulties with muscle control. One medication that is useful is baclofen (Lioresal), a muscle relaxant. Patients with seizures are given anticonvulsant (anti-seizure) medications.
- Special diets. Many patients with RS have a poor appetite and problems swallowing. The patient may need an assessment by a dietitian to plan meals that are appealing as well as nutritionally sound. Patients with

seizures that cannot be controlled by medications may benefit from a special high-fat, low-carbohydrate diet known as a ketogenic diet.

- Physical therapy. Physical therapy of patients with RS is focused on maintaining or improving the patient's balance and ability to walk; maintaining full range of motion whenever possible; and preventing the muscle contractures that lead to deformities in adult life.
- Splints and braces. Hand or elbow splints may be used to reduce repetitive hand movements and increase the child's purposeful use of her dominant hand. Patients who develop kyphosis (humpback) or scoliosis may be fitted for spinal braces.
- Occupational therapy.
- Speech therapy. Some patients with RS are taught to communicate with body language; others use eye blinking, communication boards, or electronic devices.
- Complementary and alternative therapies. Music therapy has been successfully used in patients with RS, as well as hydrotherapy, equine therapy (horseback riding), and acupuncture.

Clinical trials

As of late summer 2003, there are no open **clinical trials** for RS at the National Institutes of Health (NIH). There are, however, two medical centers funded by the NIH that evaluate patients for RS and conduct research on the disorder; contact information for the Blue Bird Circle Rett Center and the Kennedy Krieger Institute is listed under Resources.

Prognosis

It is difficult to predict the severity or the course of RS in any specific individual. Although the symptoms of RS are disabling, most patients survive into the 40s and 50s. Little is known about patients' long-term prognosis after age 40 because the disorder has been studied intensively only since the mid-1980s.

What is known about the short-term prognosis of middle-aged adults with RS is encouraging, however. Their mental state stabilizes and they are often able to continue to learn as well as improve the use of their hands. They make better eye contact with others. In addition, patients are usually less irritable, sleep better, and have fewer seizures and breathing problems. The chief additional problem for adults with RS is decreased mobility. After the early adult years, the patient's muscles may become rigid or spastic, causing joint deformities and increased difficulty in walking.

Special concerns

Educational and social needs

Most patients with RS can benefit from special educational programs. Education in the public schools is available in most areas until the patient is 21. After that age, the patient may be able to attend sheltered workshops or day centers, depending on where she lives. In the last few years, some young women with milder forms of RS have been able to attend classes at local community colleges or find employment with the help of a job coach.

It is important for patients with RS to participate in community activities and social events precisely because they have a fairly long life expectancy. Personal accounts of adults with RS indicate that they enjoy travel, church or synagogue activities, volunteer work, swimming, camping, music, sports events, and similar outings.

Legal issues

The most pressing long-term concern for patients with RS is working out a life plan for ongoing care, since many are likely to outlive their parents. The parents of a girl diagnosed with RS should consult an estate planner, an attorney, and a certified public accountant (CPA) in order to draft a life plan and letter of intent. A letter of intent is not a legally binding document, but it gives the patient's siblings and other relatives or caregivers necessary information on providing for her in the future. The attorney can help the parents decide about such matters as guardianship as well as guide them through the legal process of appointing a guardian, which varies from state to state.

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Rebecca J. Frey, PhD

Reye syndrome

Definition

Reye syndrome is a serious, potentially fatal condition that strikes children and adolescents who have just recovered from a viral infection, especially when that illness has been treated with aspirin or aspirin-containing products. Reye syndrome causes damage to the liver and brain.

Description

Reye syndrome is a relatively rare disease. Since the late 1980s, when concern regarding aspirin use in children became more widely publicized, fewer than 20 cases of

Reye syndrome have been reported annually. This is down from a peak of over 600 cases in 1980. Although researchers have not been able to state this definitively, the decreased incidence of Reye syndrome has been commonly attributed to a greatly decreased use of aspirin-containing products in children.

When Reye syndrome strikes, it can be a devastating illness. The death rate from the disease used to be as high as 50–60%. Better, faster methods of diagnosis have allowed earlier identification of the disorder, allowing the death rate to drop to 30–35%. Younger children seem to have a higher risk of death. Even those children who recover may be faced with lifelong disability, depending on the degree of brain damage suffered. Long-term problems may include behavior problems, attention disorders, **mental retardation**, blindness, **seizures**, varying degrees of paralysis, and learning difficulties.

Key Terms

Aflatoxin A toxin produced by a fungus that infests grains, peanuts, soybeans, and corn that have been stored in warm, moist conditions.

Decerebrate posture Stiff, rigid posture indicative of severe damage to brain stem.

Decorticate posture A stiff, rigid posture indicative of damage to nerve tracts that run between spinal cord and brain.

Electroencephalogram (EEG) A test in which electrodes applied to the scalp allow the electrical activity of the brain to be recorded.

Mitochondria Small, energy-producing structures within the body's cells.

Demographics

Reye syndrome primarily strikes children and adolescents who have recently recovered from a viral infection, particularly chicken pox or influenza. Because the frequency of most viral infections peaks in the winter months, Reye syndrome is most common in January, February, and March. In the United States, the most common age for Reye syndrome is six to eight years. Reye syndrome is extremely rare in individuals over the age of 18.

Causes and symptoms

Scientists do not feel convinced that the true cause of Reye syndrome has been defined. Although there is a clear-cut association between recent viral infection and the disease, and between use of aspirin-containing products and the disease, the actual mechanism of the condition has not been fully delineated. There may also be an association between the development of Reye syndrome and exposure to pesticides and/or aflatoxin (a toxin produced by a fungus that infests grains, peanuts, soybeans, and corn that have been stored in warm, moist conditions).

The underlying problem in Reye syndrome seems to be dysfunction of the small, energy-producing structures within the body's cells (the mitochondria). The blood becomes more acidic, ammonia levels increase, and sugar levels drop. Large quantities of fat are deposited throughout many organs of the body, most significantly, the liver. The fatty deposits in the liver interfere with normal liver functioning. Swelling and increased pressure in the brain puts pressure on the delicate brain tissues, resulting in damage.

Reye syndrome begins within about a week of recovery from a viral illness. Vomiting and listlessness are some of the earliest symptoms, although they are not necessarily universal in every patient. Children tend to become sleepy, disoriented, confused, and even combative. Reye syndrome can progress very quickly. Within hours, symptoms can become more severe, with loss of consciousness, seizures, stupor, and coma, all signaling critical illness.

Reye syndrome is graded I through V at the time of diagnosis, in order to determine a level of severity. Grades I through III are considered mild to moderate, while grades IV and V are considered critically ill. Criteria for this grading is as follows:

- Grade I: Child is quiet, sleepy, vomiting, and there is some blood evidence of a drop in liver functioning.
- Grade II: Child is confused, delirious, combative, with overly-active reflexes, breathing quickly.
- Grade III: Child is in a light coma, may have seizures, pupils still responsive to light, is in decorticate posture (stiff, rigid posture indicative of damage to nerve tracts that run between spinal cord and brain).
- Grade IV: Child is in a deepening coma, experiencing seizures, pupils nonresponsive to light, has abnormal reflexes, is in decerebrate posture (stiff, rigid posture indicative of severe damage to brain stem).
- Grade V: Child is in a deep coma, pupils are fixed and dilated (abnormally enlarged, do not constrict when exposed to light), no normal reflexes, alternates between decerebrate posture and completely limp, flaccid muscles, cannot breathe independently, EEG reading lacks normal waves.

Diagnosis

There is no specific test to diagnose Reye syndrome. Diagnosis is suggested by a number of different abnormalities, including:

- extremely elevated liver enzymes (20–30 times normal)
- increases in blood ammonia (three times normal)
- low blood sugar
- high blood acidity
- blood clotting abnormalities
- abnormal electroencephalogram (EEG, a test in which electrodes applied to the scalp allow the electrical activity of the brain to be recorded)
- abnormal liver **biopsy**, revealing large quantities of fat deposited within the liver

Treatment team

Children with Reye syndrome are usually cared for in a hospital, with more severely ill children requiring care in an intensive care unit. Health care providers may include pediatric intensivists, neurologists, and gastroenterologists (to closely monitor liver function).

Treatment

There is no cure for Reye syndrome. Treatment is considered supportive, meaning that treatment is given to address the specific complications, in order to try to prevent progression of the liver and brain damage and permanent effects.

Medications such as steroids and/or diuretics may be given to try to relieve brain swelling; at the same time, fluid intake should be restricted to prevent further swelling. Glucose is given to increase blood sugar levels. Vitamin K, platelet transfusions, and frozen plasma may be given to improve a bleeding disorder. Seriously ill patients will probably need to be on a ventilator.

Recovery and rehabilitation

Even children who seem to have made a complete recovery may actually demonstrate significant neuropsychological deficits with specific testing. Depending on the actual deficits, physical therapy, occupational therapy, speech and language therapy, and educational interventions may be necessary.

Prognosis

Prognosis depends on the severity of the brain swelling. The liver functioning is usually fully recovered, but brain damage will leave permanent deficits. When Reye syndrome is diagnosed earlier in its course, aggressive treatment can be started to slow the progress of damaging brain swelling, improving the patient's chance of complete recovery. There is a higher risk of death or of permanent damage when there is a delay in diagnosis and therefore in treatment. When Reye syndrome is not diagnosed and treated quickly, death can occur within only days of the syndrome's onset. Death rates from Reye syndrome are currently about 30–35%.

Special concerns

Reye syndrome can be almost completely prevented by parental awareness of the dangers of administering any aspirin-containing substances to their children. This includes aspirin itself, as well as various cold and flu preparations that may contain salicylates or salicylic acid (the chemical names for aspirin). Many common over-the-counter medications for upset stomach also contain salicylates. Parents should carefully read the list of active ingredients and/or consult a physician or pharmacist before giving their children over-the-counter medicines. Making sure that children are immunized yearly against the flu (influenza vaccine) and considering giving children the chicken pox vaccine may also help decrease the risk of Reye syndrome.

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Rosalyn Carson-DeWitt, MD

Rivastigmine *see* **Cholinesterase inhibitors**

S

Sacral nerve root cysts *see* **Perineural cysts**

Sacral radiculopathy *see* **Radiculopathy**

Saint Vitus Dance *see* **Sydenham's chorea**

Salivary gland disease *see* **Cytomegalic inclusion body disease**

Sandhoff disease

Definition

Sandhoff disease is a relatively rare, genetically inherited disease that results in the progressive deterioration of the **central nervous system**. In Sandhoff disease, abnormal lipid (fat) accumulation due to a storage defect causes damage to the brain as well as other organs of the body.

Description

Sandhoff disease is an autosomal recessive disorder, meaning that having an affected offspring requires both unaffected parents to be carriers. Parents who carry the disorder will have a 25% risk of having an affected offspring in subsequent pregnancies. This disease is similar to a related disorder known as Tay-Sachs disease, although Sandhoff disease is more severe.

Demographics

As Sandhoff disease is a recessive disorder, males and females are affected with equal frequency. This disorder is more common in people with non-Jewish descent, unlike Tay-Sachs disease, which is prevalent mainly in individuals with Jewish ancestry.

Causes and symptoms

Sandhoff disease is caused by mutations in two different genes that encode subunits that make up a protein called hexosaminidase. Hexosaminidase is an enzyme that breaks down certain fats in the brain. This enzyme is either composed of an alpha and a beta subunit (HexA) or two beta subunits (HexB). Sandhoff disease is caused by a mutation in a gene that is distinct from the gene that causes Tay-Sachs disease. In Tay-Sachs disease, a mutation that affects the alpha subunit of the enzyme causes a deficiency in HexA. Sandhoff disease is caused by mutations that affect the beta subunit, rendering both the HexA and HexB enzymes deficient. A deficiency of this enzyme leads to the accumulation of GM2 ganglioside, a fatty material found in the brain.

The beta subunit is encoded by a gene localized to chromosome 5, while the alpha subunit is encoded by a gene on chromosome 13. There is also another gene on chromosome 5 that encodes an activator that is required for either enzyme to be functional. Similar symptoms are observed in diseases arising from mutations that affect any of these three genes. Only biochemical genetic analysis of enzyme activity can pinpoint the cause and specify the disorder. However, Sandhoff disease can be distinguished from Tay-Sachs disease clinically by virtue of skeletal system or abdominal organ involvement (if present) in the later disease.

At birth, infants tend to be without symptoms and usually do not develop them until approximately six months of age. The symptoms begin with motor deficits (lack of normal movement) and a characteristic startle reaction to various sounds. Babies with Sandhoff disease progressively deteriorate in terms of motor function, and they often have **seizures** and **myoclonus**. Myoclonus is abnormal, exaggerated muscle contractions. Blindness can also be part of the symptoms. The loss of motor function includes the ability to swallow, and the affected infant has an increased risk for inhaling feedings into the lungs, frequently leading to pneumonia.

Key Terms

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

Lipids Organic compounds not soluble in water, but soluble in fat solvents such as alcohol. Lipids are stored in the body as energy reserves and are also important components of cell membranes. Commonly known as fats.

Myoclonus Involuntary contractions of a muscle or an interrelated group of muscles. Also known as myoclonic seizures.

A typical physical feature of Sandhoff disease is the presence of cherry-red spots in the back of the eyes. Additionally, affected children have an abnormally enlarged head and appear to have a doll-like appearance.

Diagnosis

Because Sandhoff disease and Tay-Sachs disease have similar clinical symptoms, distinguishing them requires biochemical analysis. This involves a test to measure enzyme activity of the two hexosaminidase enzymes. If the enzyme activity results indicate that there is no hexosaminidase activity, it means that the patient has Sandhoff disease. If, however, there is still B subunit activity, then this indicates that the patient might have Tay-Sachs disease.

Treatment

There is no cure for Sandhoff disease, and treatment is based on lessening the symptoms once they begin. Medication is usually given to reduce seizures, for example, and a feeding tube may be inserted to prevent aspiration of feedings into the lungs.

Recovery and rehabilitation

Emphasis is placed on comfort rather than recovery, due to the progressive nature of Sandhoff disease. Because of the nature of the disorder, rehabilitation is not usually applicable to help with improving the motor deficits that develop. Physical therapy may be helpful to maintain muscle tone and skeletal alignment for as long as possible, while positional strategies and devices provided by an occupational therapist may increase comfort as symptoms progress.

Clinical trials

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is sponsoring, as of February 2004, a study to evaluate children with glycosphingolipid (GSL) storage disorders (such as Sandhoff disease) to investigate changes that occur in the brain that are responsible for nervous system degeneration. In this study, patients will receive medical treatment for their disorder. Contact the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), located at 9000 Rockville Pike, Bethesda, Maryland, 20892, Recruiting: Patient Recruitment and Public Liaison Office, (800) 411-1222 or prpl@mail.cc.nih.gov.

Prognosis

The prognosis for Sandhoff disease is poor. Affected babies usually do not survive past the age of three and typically, death occurs due to complications associated with respiratory infections.

Special concerns

Children who are affected with Sandhoff disease will require full time supervision and caretaking responsibilities. Psychological counseling for family members is often helpful. Genetic counseling for reproductive risks is recommended. There are also several support groups operated and comprised of other families nationwide with Sandhoff disease.

Resources

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National Tay-Sachs and Allied Diseases Association. 2001 Beacon Street Suite 204, Brighton, MA 02135. (617) 277-4463. (617) 277-0134. (800) 90-NTSAD (906-8723). info@ntsad.org. <http://www.ntsad.org>.

National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744-0100. (203) 798-2291. (800) 999-NORD (6673). orphan@rarediseases.org. <http://www.rarediseases.org>.

Bryan Richard Cobb, PhD

Schilder's disease

Definition

Schilder's disease is a form of **multiple sclerosis** that strikes in childhood.

Description

Schilder's disease is a very rare progressive degenerative disease that affects children. It resembles multiple sclerosis both in its symptoms (difficulties with movement and speech) and its pathology (widespread demyelination of the brain). Demyelination refers to the destruction of the myelin that normally encases nerve fibers. Myelin is the fatty white substance that wraps around nerve fibers, providing insulation and allowing nerve signals to move quickly. Without myelin, nervous transmission is significantly slowed. As the disease progresses, larger and larger patches of demyelination occur, interfering with motor movement, speech, personality, hearing and vision. Ultimately, the vital functions (respiration, heart rate, blood pressure) are affected, leading to the individual's death.

Demographics

Schilder's disease is exceedingly rare. Because there are no specific criteria for the diagnosis, there continues to be debate among researchers and clinicians regarding the most appropriate way to definitively diagnose the disease and collect data on its frequency and incidence. Some sources suggest that there have only been nine cases of definitively diagnosed Schilder's disease since it was originally described in the German medical literature in 1912.

Most patients with Schilder's disease are diagnosed between the ages of seven and twelve years of age.

Causes and symptoms

The underlying cause of Schilder's disease is unknown. Symptoms of the disease are caused by widespread patches of demyelination throughout the brain and spinal cord, resulting in slowed, faulty nervous transmission.

Symptoms of Schilder's disease include weakness of one side of the body (hemiparesis), slowness of movement (psychomotor retardation), paralysis of all four extremities (quadraparesis), **seizures**, difficulty with speech (**dysarthria**), visual and hearing impairment, irritability, memory problems, personality changes, and gradual loss of awareness and responsiveness. Over time, patients become unable to maintain their nutritional status and become increasingly thin and malnourished. Bowel and bladder function are often lost as the disease progresses.

Some children have a relentlessly progressive course of the disease, culminating in death. Other children have remissions and exacerbations, with each subsequent exacerbation more severe and each remission less complete, until death supervenes.

Diagnosis

Because researchers and clinicians have not been able to delineate a clear-cut list of criteria for the diagnosis of Schilder's disease, definitive diagnosis is difficult. EEG studies may show some abnormalities. **MRI** studies will certainly reveal demyelination. Other lab studies (blood tests, test on cerebrospinal fluid obtain via lumbar puncture, brain **biopsy**) are usually performed in an effort to rule out some other cause for the patient's symptoms, such as an infectious, malignant, or metabolic condition; in Schilder's disease, these will all come back normal.

Treatment team

The treatment team for a child with Schilder's disease usually consists of neurologists, specialists in multiple sclerosis, and rheumatologists. Support from physical therapists, occupational therapists, and speech and language therapists can help a child maintain as much functioning as possible.

Treatment

There is no cure for Schilder's disease. Treatments are aimed at slowing the inexorable course of the disease, and are similar to treatments used for multiple sclerosis, such as high dose steroids, beta interferon, and immunosuppressants.

Key Terms

Demyelination Destruction of the myelin that should normally wrap around nerve fibers.

Dysarthria Disturbances of speech and communication.

Hemiparesis Weakness of one side of the body.

Myelin The fatty white substance that wraps around nerve fibers, providing insulation and allowing for speedier nervous transmission.

Psychomotor retardation Slowing of movement and speech.

Quadriparesis Weakness of all four limbs.

Prognosis

Schilder's disease is uniformly fatal.

Resources

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ORGANIZATIONS

Multiple Sclerosis Association of America. 706 Haddonfield Road, Cherry Hill, NJ 08002. 856-488-4500 or 800-532-7667; Fax: 856-661-9797. msaa@msaa.com. <http://www.msaa.com>.

Multiple Sclerosis Foundation. 6350 North Andrews Avenue, Ft. Lauderdale, FL 33309-2130. 954-776-6805 or 888-MSFocus (673-6287); Fax: 954-351-0630.

National Multiple Sclerosis Society. 733 Third Avenue, 6th Floor, New York, NY 10017-3288. 212-986-3240 or 800-344-4867 (FIGHTMS); Fax: 212-986-7981. nat@nmss.org. <http://www.nationalmssociety.org>.

Rosalyn Carson-DeWitt, MD

Schizencephaly

Definition

Schizencephaly, or "split brain," is a neurological disease caused by abnormal development of the brain, leading to the characteristic appearance of abnormal clefts in either one or both cerebral hemispheres. The exact etiology is unknown, although it is classified as a type of neuronal migration disorder and thought to be due to a defect in development that occurs during the period of one to seven months of fetal gestation.

Description

Schizencephaly may have different forms. The appearance of the abnormal schizencephalic brain varies depending on the size and extent of the clefts. Clefts may be unilateral or bilateral and usually extend from the surface of the brain to the fluid-filled ventricles. Clefts are usually located next to the Sylvian fissure, but may be located in any part of the hemispheres. Separation of the walls of the cleft is referred to as open-lip schizencephaly, whereas apposed walls are referred to as closed-lip schizencephaly.

Schizencephaly differs from **porencephaly**, another developmental disorder that is due to early injuries to the developing fetal brain. Porencephaly results from injured brain tissue that subsequently dissolves and leaves a fluid-filled area known as a porencephalic cyst. This cyst can resemble the cleft seen in schizencephaly. Whereas schizencephaly is thought to be a primary disorder of development or neuronal migration, porencephaly is thought to be due to secondary brain damage, although the distinction is not entirely clear. Some theories of schizencephaly also propose early brain injury as contributory, but at an earlier stage of development than in porencephaly. Differentiation between the two often requires brain imaging such as **magnetic resonance imaging (MRI)** to identify the nature of the brain tissue lining the cleft. In porencephaly, scar tissue and white matter is often present, whereas in schizencephaly, gray matter lines the cleft.

Demographics

Schizencephaly is a rare disorder and the incidence is unknown. It usually is noticed in infancy or childhood, although it may be diagnosed in adulthood with the onset of **seizures**.

Causes and symptoms

The cause of schizencephaly is unknown, although environmental and genetic factors have been proposed. Various theories exist as to the timing and nature of the defect in development. Early injury to the brain during the

second trimester of pregnancy has been proposed to cause the characteristic clefts. These insults may be due to infection, poor blood flow causing **stroke**, or genetic abnormalities. The earlier onset of injury leading to absence of scar tissue around the defect presumably differentiates schizencephaly from porencephaly. A mutation in the EMX2 gene has been associated with schizencephaly in some familial cases, providing evidence for genetic causes. EMX2 is a transcription factor on human chromosome 10 that is important in early brain formation in mice and flies. The clefts in schizencephaly are often lined by normal brain tissue, but may often be surrounded by abnormal brain tissue that has an unusually high density of folding (polymicrogyria). Schizencephaly may also be associated with abnormal nerve clusters called heterotopias in different parts of the brain. Polymicrogyria and heterotopias are thought to be due to defective neuronal migration, and their association with schizencephaly suggests a common underlying mechanism.

Symptoms

Symptoms can vary widely depending on the extent and the size of the cleft. Patients may show developmental delay that can range from mild to severe. Bilateral and open-lip clefts are associated with more severe delay. Affected individuals may have small heads (**microcephaly**) or increased pressure due to fluid accumulation inside the brain, known as **hydrocephalus**. Paralysis of the limbs may be present. The paralysis may be on one or both sides of the body depending on the location of the clefts. Abnormal muscle tone, including decreased tone (**hypotonia**) and increased tone (**spasticity**), can be seen. Some patients may have only seizures. Seizures usually present before three years of age, but patients may present with seizures in later life as their only symptom and then be diagnosed with schizencephaly by brain imaging.

Diagnosis

Diagnosis is made by imaging of the brain. A computed tomography scan (**CT**) or **MRI** demonstrates the abnormal clefts, which may be bilateral or unilateral, open or closed lip. The clefts may appear symmetric or asymmetric. MRI may show evidence of polymicrogyria lining the clefts. There is no genetic testing available at this time for schizencephaly.

Treatment team

Treatment for patients with schizencephaly differs among patients due to the wide variety of clinical manifestations and symptoms. The team responsible for medical care may include a pediatrician and pediatric **neurologist**. A pediatric neurosurgeon may be involved in performing a shunt procedure for hydrocephalus. An orthopedic surgeon may perform surgeries to improve the mobility of spastic limbs. Physical and occupational therapists can help with improving mobility. A case manager may help in coordinating care and treatments.

Treatment

There is no cure for schizencephaly at this time. The treatment of schizencephaly is directed towards the symptoms caused by the abnormally formed brain. Seizures may require anticonvulsant drug therapy. Seizures that cannot be controlled with medications may be treated by surgical removal of the abnormal tissue surrounding the cleft. With complications of hydrocephalus, a surgical shunt procedure may be necessary to relieve fluid accumulation and pressure.

Recovery and rehabilitation

Due to the congenital nature of schizencephaly, symptoms tend to be unchanging and there is little recovery. Physical therapy may be useful in relieving symptoms of spasticity or paralysis and in improving mobility and ambulation. Occupational therapists may help maintain hand function in those with impaired ability.

Clinical trials

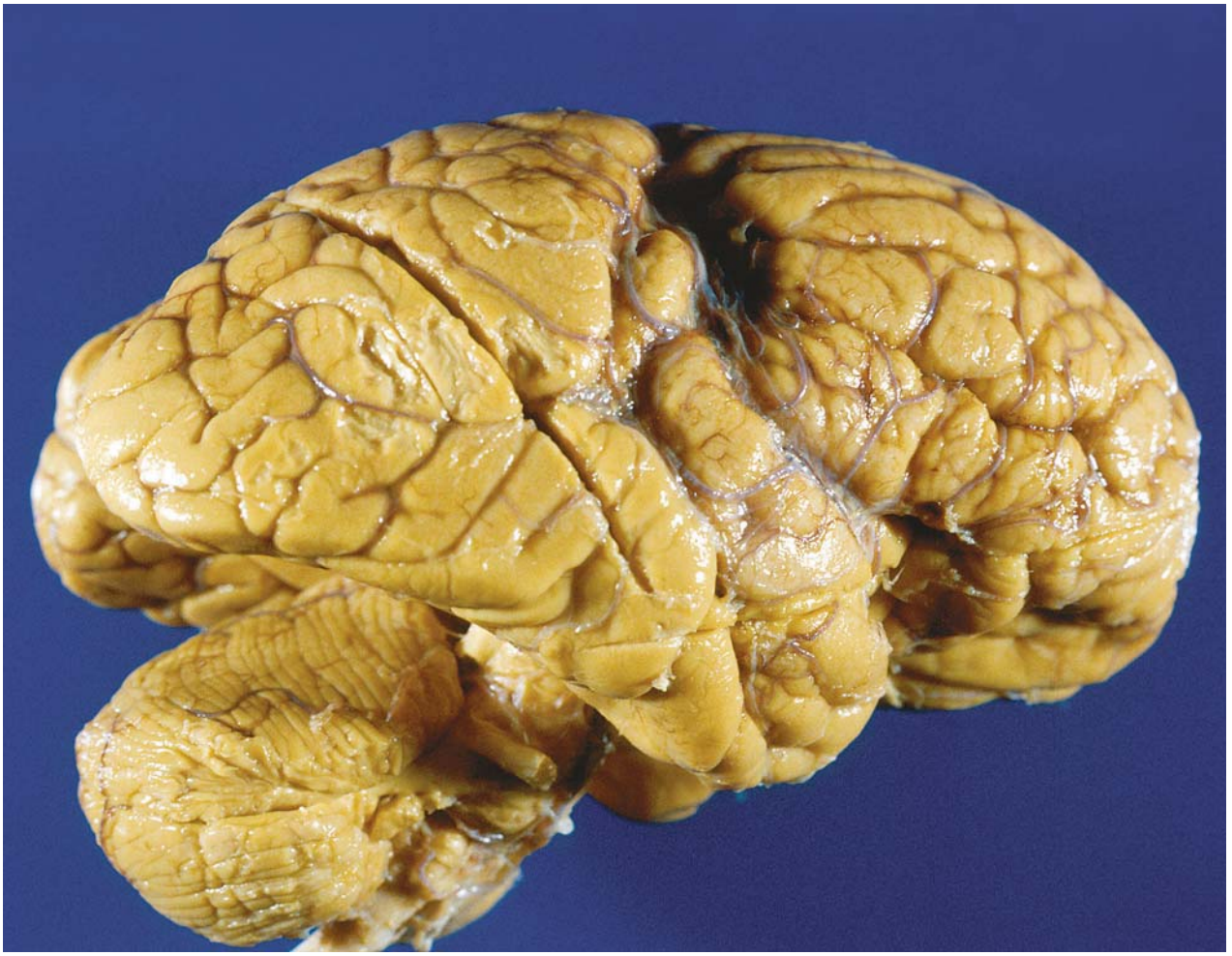
A clinical trial funded by the National Institutes of Health is underway to identify the genes responsible for schizencephaly and other developmental brain disorders associated with **epilepsy**. Contact information for the Walsh laboratory is listed under Resources.

Prognosis

The prognosis for individuals with schizencephaly depends on the amount of neurologic deficiency associated with the malformation. Some patients with unilateral clefts may only have seizures and no other cognitive or motor abnormalities. Seizures may respond to medications or require surgery if unmanageable. Patients with severe **mental retardation** and paralysis will often require lifelong dependent care and may have a shortened lifespan as a result of infections such as pneumonias. Bilateral clefts are associated with earlier onset of seizures and seizures that are more difficult to treat.

Special Concerns

Due to developmental disability, individuals with schizencephaly may benefit from special education programs. Various state and federal programs are available to help individuals and their families with meeting these needs.



A gray-matter lined cleft in a schizencephalic brain. *(Custom Medical Stock Photo. All Rights Reserved.)*

Key Terms

Neuronal migration A step of early brain development in which nerve cells travel over large distances to different parts of the brain.

Sylvian fissure The lateral fold separating the brain hemisphere into the frontal and temporal lobes.

Transcription factor A protein that acts to regulate the expression of genes.

Ventricle The spaces in the cerebral hemispheres containing cerebrospinal fluid, a nutrient-rich fluid that bathes the brain.

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March of Dimes Birth Defects Foundation. 1275 Mamaroneck Avenue, White Plains, NY 10605. (914) 428-7100 or (888) MODIMES; Fax: (914) 428-8203. askus@marchofdimes.com. <http://www.marchofdimes.com>.
National Information Center for Children and Youth with Disabilities. P.O. Box 1492, Washington, DC 20013-1492. (202) 884-8200 or (800) 695-0285; Fax: (202) 884-8441. nichcy@aed.org. <http://www.nichcy.org>.
National Institute of Child Health and Human Development (NICHD). Bldg. 31, Rm. 2A32, Bethesda, MD 20892-2425. (301) 496-5133 or (800) 370-2943. NICHDClearinghouse@mail.nih.gov. <http://www.nichd.nih.gov>.
Walsh Lab Web Site. 4 Blackfan Circle, Boston, MA 02115. (617) 667-0813; Fax: (617) 667-0815. cwalsh@bidmc.harvard.edu. <http://walshlab.bidmc.harvard.edu/>.

Peter T. Lin, MD

Schizophrenia

Definition

Schizophrenia is a collection of related psychiatric disorders of unknown etiology that follow a specific pattern of behavior. Typical behavior seen in schizophrenia includes psychotic episodes in which there is a severe mental disturbance and perceptions of reality are distorted. Psychotic episodes may also involve hallucinations. Schizophrenics often have delusions about personal identity, immediate surroundings or society, and paranoia. Schizophrenia has a component of heredity, but many factors other than genetics are involved. Schizophrenia is treated with antipsychotic medication.

Description

Schizophrenia involves a specific type of disordered thinking and behavior. It could be described as the splitting of the mind's cognitive functions pertaining to thought, perception, and reasoning from the appropriate emotional responses. Family history of schizophrenia increases an individual's chance of having the disorder, but the exact mode of inheritance is unknown. Only some schizophrenic patients have detectable anatomical brain abnormalities. The cause of schizophrenia has not been determined, yet drugs effective in its treatment have been identified. Schizophrenia is treated with antipsychotic drugs that primarily act on receptors in the brain for the **neurotransmitters** dopamine and serotonin. These neurotransmitters are chemicals that the brain uses to communicate normal functioning behavior. Receptors for neurotransmitters are sites on the surface of neurons that bind to the neurotransmitters and allow the communication. In schizophrenia, some of the communication mediated by the neurotransmitters dopamine and serotonin and their receptors is abnormal. By inhibiting the activity of these receptors, antipsychotics are effective at decreasing some of the bizarre behavior patterns associated with schizophrenia. Unfortunately, the medication necessary for schizophrenic patients also has severe and pronounced adverse side effects, mostly affecting the control of movement. Schizotypal personality disorder is a milder form of the disease.

Demographics

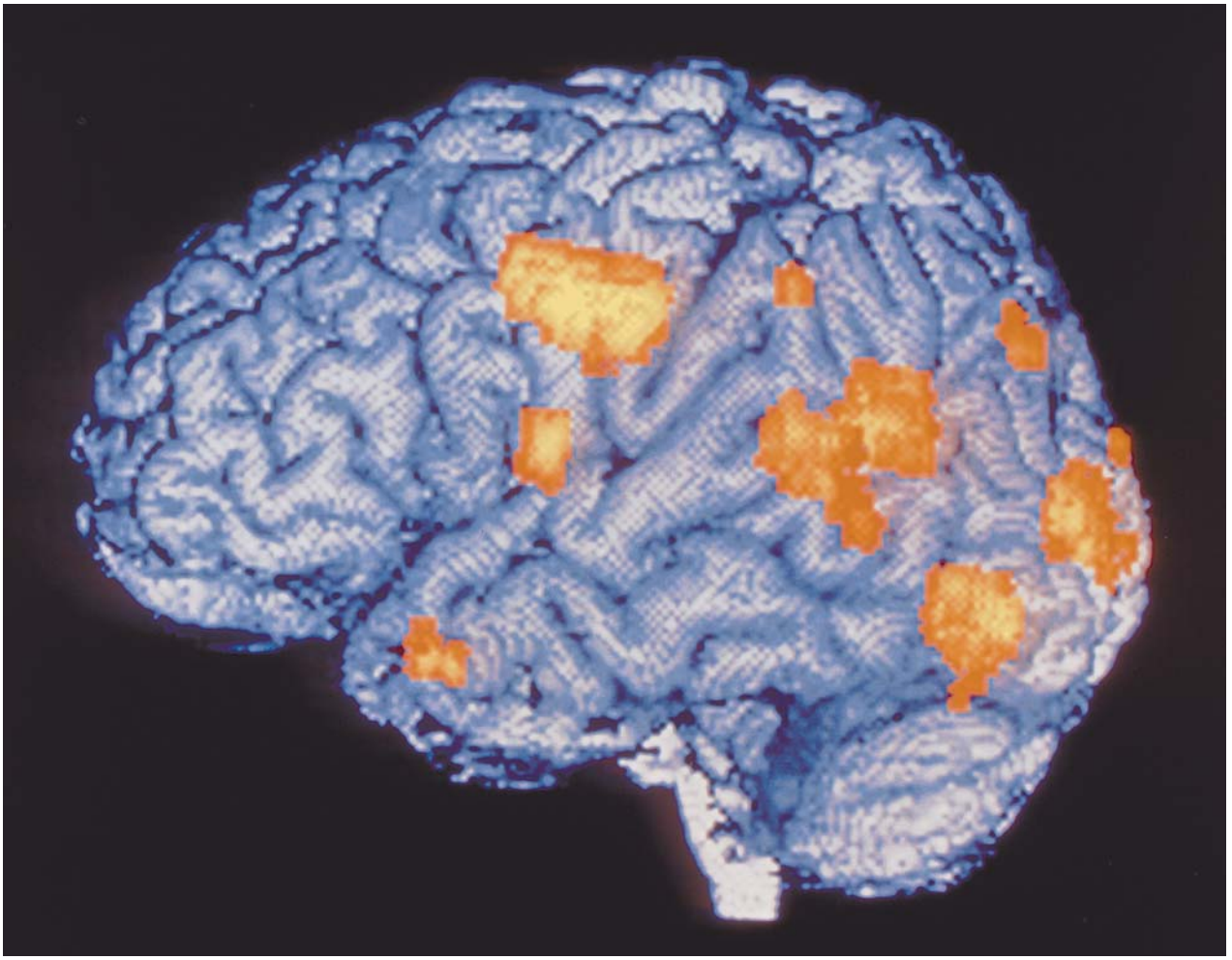
Schizophrenia is estimated to afflict 1% of the world's population, whereas schizotypal personality disorder afflicts 2–3%. Approximately 2.7 million people have schizophrenia in the United States. The incidence of schizophrenia among parents, children, and siblings of patients with the disease is 15%. The rate of adopted children with schizophrenic parents is also 15%. However, the disease is not caused entirely by genetic factors, as identical twins have only a 30–50% tendency to have the same schizophrenic illness. Schizophrenia occurs equally in males and females. The disease may be seen at any age, but the average age for the initiation of treatment is from 28–34 years. Schizophrenia is associated with low economic status, probably due to a lack of proper health care during fetal development.

Causes and symptoms

The cause of schizophrenia is unknown. Some patients display specific physical abnormalities in the brain that are associated with the disease. These include atrophy or degeneration in some brain areas and enlargement of fluid-filled cavities called ventricles. Schizophrenics also have abnormalities in chemical neurotransmitters the brain normally uses to communicate information, specifically the neurotransmitters dopamine and serotonin and their receptors. The imbalance in the activity of these communication components is complex, with overactivity in some parts of the brain and decreased activity in others responsible for different symptoms. The symptoms of schizophrenia are divided into three types: the positive, negative, and disorganized symptoms.

Positive symptoms

Positive symptoms reflect the presence of distinctive behaviors. There are many different positive symptoms of schizophrenia. Schizophrenic patients may experience



A colored PET scan of the left side of a schizophrenic male patient during a hallucination. The visual and auditory regions of the brain (at the right and the upper center, respectively) are active, confirming that he both saw and heard colored talking heads during the hallucination. *(Wellcome Department of Cognitive Neurology/SPL/Photo Researchers, Inc. Reproduced by permission.)*

strange or paranoid delusions that are out of touch with reality such as the belief that others are persecuting them, or that others are controlling their minds. Schizophrenic patients may have disturbing or frightening hallucinations. The most common hallucinations are auditory, but may also be visual. Other positive symptoms include sensitivity and fearful reaction to ordinary sights, sounds, or smells, along with agitation, tension, and the inability to sleep (insomnia).

Negative symptoms

Negative symptoms reflect the absence of normal social and interpersonal behaviors. Negative symptoms of schizophrenia are varied. Schizophrenic patients often have a reduction in their ability to experience appropriate emotions, or express their emotions. This reduced expressiveness often leads to periods of withdrawal from others. Patients may also experience a lack of motivation, energy, and ability to experience pleasure. Schizophrenic patients often have poverty of speech, and will not speak readily with others.

Disorganized symptoms

Schizophrenic patients may have confused thinking and speech, which makes it difficult for them to communicate effectively with others. Disorganized behaviors such as unnecessary, repetitive movements are also common.

Diagnosis

Schizophrenics often initially display prodromal signs, which are signs preceding a psychotic episode. Schizophrenic prodromal signs may include social isolation, odd behavior, lack of personal hygiene, and blunted emotions. The prodromal phase is followed by one or more separate

psychotic episodes, which are characterized by severe mental disturbances and distorted perceptions of reality. Physicians examining this set of behaviors first attempt to exclude disorders of mood that respond to antidepressants, such as manic **depression**. Sometimes schizophrenia is diagnosed through the patient's response to different therapeutic regimens. Schizophrenic symptoms are not affected by antidepressants, but rather are alleviated by antipsychotics.

Once other disorders have been excluded, the criteria for a diagnosis of schizophrenia is that a patient be continuously ill for at least six months, and that there be one psychotic phase followed by one residual phase of odd behavior. During the psychotic phase, one or more of three groups of psychotic symptoms must be present. The three groups are bizarre delusions, hallucinations, and a disordered or incoherent thought pattern.

Treatment team

Schizophrenic patients are diagnosed and treated by psychiatrists. A licensed therapist performs rehabilitation therapy. Treatment teams from supportive agencies may help with everyday living.

Treatment

Schizophrenia is treated with antipsychotic drugs used in the lowest effective doses. The antipsychotic drugs work mainly to antagonize (inhibit) dopamine and serotonin receptors in specific areas of the brain that are in dysfunction. Classical antipsychotics function primarily on dopamine receptors and have more side effects than modern, atypical antipsychotics that also work on serotonin receptors. The newer, atypical antipsychotics are the treatment of choice because of their comparative lack of side effects, but classical antipsychotics may still be used if a patient is already doing well on the drug. The positive, psychotic symptoms of schizophrenia respond better to antipsychotic treatment than the negative symptoms.

Recovery and rehabilitation

Although antipsychotic drug treatment is necessary for schizophrenic patients, it is not enough for rehabilitation alone. Rehabilitation also requires supportive psychotherapy. Various psychosocial treatments are available for varying stages in the disease, and each patient requires a unique treatment regimen. Doctor and therapist appointments for medication management and psychological healing are necessary in all stages of recovery, even when symptoms are under control. Peer support groups are also very important for rehabilitation. Assertive community treatment (ACT) programs are available for patients who have a severe and unstable course of illness. These programs provide intensive services within a patient's home on a day-to-day basis. ACT teams can follow a patient through all courses of illness and assist them in normal living activities. Patients who are in the later stages of recovery and have few lingering symptoms may get involved with programs designed to help them achieve personal goals pertaining to work, education, and social interactions.

Key Terms

Etiology The cause or origin of disease.

Neurotransmitter Chemicals that act as messengers between cells of the nervous system. Neurotransmitters are released from the axon of one neuron and bind to a specific site such as a receptor in the dendrite of an adjacent neuron, triggering a nerve impulse.

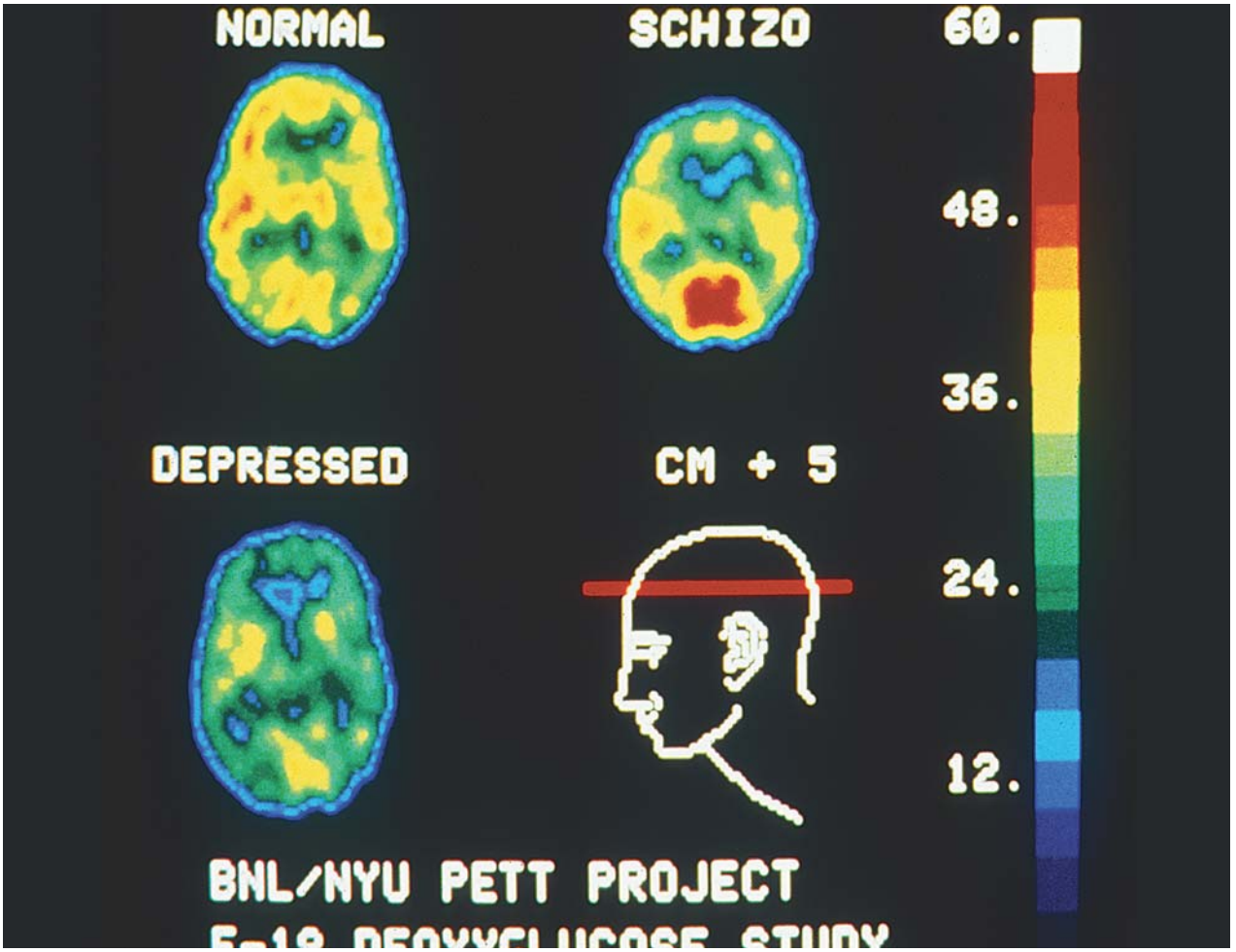
Prodromal Symptomatic of the approaching onset of an attack or a disease.

Clinical trials

Most **clinical trials** performed by the National Institute of Mental Health (NIMH) as of January 2004 are centered around three new atypical antipsychotics: olanzapine, risperidone, and aripiprazole. Many clinical trials are being conducted in the United States in different phases. Some studies of schizophrenic patients examine the causes of and potential treatments for negative symptoms as a group, specific symptoms such as cognitive dysfunction, schizophrenia in different age groups such as childhood-onset psychosis, and schizophrenia in different phases of disease course such as first-episode psychosis. Conventional antipsychotics that have excellent initial effects on first episodes also have severe side effects, and hence are associated with eventual patient noncompliance and relapses. The newer antipsychotics may alleviate this problem. Because of this, an NIMH clinical study scheduled to end in June 2004 is examining the role of new atypical antipsychotics in treatment of first psychotic schizophrenic episodes. Clinical trials also examine the ability of specific areas of the brain to function after cognitive stimulation in schizophrenic patients, or analyze DNA samples from families of patients with schizophrenia.

Prognosis

The prognosis for schizophrenia is varied. A diagnosis of schizophrenia does not necessarily mean that the patient will experience a life-long illness. Over a time period of 25–30 years, approximately one-third of schizophrenic patients experience remission or even recovery. Recovery may be in the form of a lack of symptoms or learning to



PET scans of normal, schizophrenic, and depressed human brains. *(© NIH/Science Source/Photo Researchers, Inc. Reproduced by permission.)*

live acceptably with some minor symptoms. For this reason, an early negative prognosis should be avoided. However, schizophrenia can be a severe and even dangerous disorder. A wide range of outcomes has been reported, including opposite extremes of full recovery to severe incapacity. A significant proportion of schizophrenic patients have resultant negative outcomes, including an increased mortality rate mostly associated with suicide. Suicide, accidents, and disease are common among patients with schizophrenia, along with an approximate 10-year decrease in lifespan.

Special concerns

A special concern for patients with schizophrenia is the importance of patient compliance even when symptoms have lessened or ceased. It is extremely important for patients to remain in close contact with their treatment team, take all medications consistently, and keep all appointments associated with therapy in order to prevent relapse.

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National Alliance for the Mentally Ill. Colonial Place Three, 2107 Wilson Blvd., Suite 300, Arlington, VA 22201. (703) 524-7600 or (800) 950-6264; Fax: (703) 524-9094. info@nami.org. <http://www.nami.org>.

National Hopeline Network Crisis Center. 201 N. 23rd Street, Suite 100, Purcellville, VA 20132. (540) 338-5756 or (800) 784-2433. Reese@hopeline.com. <http://www.hopeline.com>.

National Institutes of Mental Health. 6001 Executive Blvd., Room 8184, MSC 9663, Bethesda, MD 20892. (301) 443-4513 or (866) 615-6464; (301) 443-4279. nimhinfo@od.nih.gov. <http://www.nimh.nih.gov>.

National Mental Health Association. 2001 N. Beauregard Street, 12th Floor, Alexandria, VA 22311. (703) 684-7722 or (800) 969-6642; (703) 684-5968. <http://nmha.org>.

National Mental Health Consumer Self Help Clearinghouse. 1211 Chestnut Street, Suite 1207, Philadelphia, PA 19107. (215) 751-1810 or (800) 553-4539; Fax: (215) 636-6312. info@mhselfhelp.org. <http://www.mhselfhelp.org>.

Maria Basile, PhD

Sciatica

Definition

Sciatica is **pain** in the lower back that can radiate down the buttocks and leg and occasionally into the foot. The pain is a result of inflammation of the sciatic nerve, usually from a herniated vertebral disk, although other causes are common. Sciatica is one of the frequently reported causes of lower **back pain**.

Description

Sciatica, also known as lumbago or lumbar **radiculopathy**, causes pain as a result of pressure on the sciatic nerve. The sciatic nerve is formed from lumbar roots that emerge from the spinal column. It rises into the pelvis, and travels down the buttocks, the leg, and into the foot. Occurring on both the left and right side of the body, these nerves are the largest in the body, with a diameter as great as a finger; they branch at several points along their path. Sciatica occurs when these nerves become irritated, most often because of a herniated vertebral disk that puts pressure on the sciatic nerve as it emerges from the spinal column.

Sciatica causes pain that may be constant or intermittent and it may include numbness, burning, or tingling. Coughing, sneezing, bending over, or lifting heavy objects may increase the pain. In some cases, there is weakening of muscles in the buttocks, legs, and/or feet.

Key Terms

Herniated disk A condition in which part or all of the soft, central portion of an intervertebral disk is forced through a weakened part of the disk, resulting in back pain and leg pain caused by nerve root irritation.

Sciatic nerve The nerve controlling the muscles of the back of the knee and lower leg, and providing sensation to the back of the thigh, part of the lower leg, and the sole of the foot.

Demographics

Sciatica is one of the most common forms of back pain. It occurs in about 5% of people who visit their doctor for back pain and in 1–3% of the general adult population. It is most common in people who are between 30 and 50 years of age, as those are the ages most prone to herniating vertebral disks. After age 30, the tough exterior of the vertebral disks undergoes a natural thinning, making it easier for the gel-like inner core to rupture it. After the age of 50, the interior of the vertebral disk becomes slightly hardened, making it less likely to protrude out.

Causes and symptoms

Pressure on the sciatic nerve can result from poor posture, muscle strain, pregnancy, wearing high heels, or being overweight. A herniated disk in the lumbar spine is the most common cause of sciatica. Herniated disks occur when the gel-like inner core of a vertebral disk (*nucleus puposus*) ruptures through the tougher outer section (*annulus*) of the disk. This extrusion puts pressure on the nerve root, causing it to function improperly. Another common cause of sciatica is lumbar spinal stenosis, or narrowing of the spinal canal, which puts pressure on the roots making up the sciatic nerve. Degenerative disk disease causes sciatica when the disk weakens enough to allow excessive movement of the vertebrae near the sciatic nerve. In addition, the degenerated disk may leak irritating proteins in the vicinity of the nerve. Although isthmic spondylolisthesis is relatively common in adults, it only occasionally causes sciatica. This occurs when a vertebra develops a stress fracture and slips, slightly impinging on the sciatic nerve as it exits the spine. **Piriformis syndrome** causes sciatica when the sciatic muscle is irritated as it runs under the piriformis muscle in the buttocks. Finally,

sacroiliac joint dysfunction can put pressure on the sciatic nerve, leading to sciatica.

Diagnosis

A physician will perform a physical exam on a patient complaining of sciatica in order to try to identify the part of the nerve that is irritated. This exam may include squatting, walking, standing on toes, and leg raising tests. Most commonly, lifting the leg to a 45° angle while holding it straight helps localize the pain. Other tests that may be performed include x ray to look for stress fractures in bones and **magnetic resonance imaging (MRI)** or computerized tomography (**CT**) to look at softer tissues and ligaments. A nerve conduction velocity test and **electromyography** may also aid in diagnosis.

Treatment

In most cases, conservative treatments are effective for sciatica. A short period of rest, coupled with the application of cold packs and heat packs to the affected area, reduces inflammation of the nerve. Non-steroidal anti-inflammatory medicines can also be taken to decrease inflammation. Injection of corticosteriods may also be recommended to decrease swelling of the nerve. Physical therapy and short walks are also recommended.

If after three or more months, sciatica continues and become progressively worse, surgical techniques can be used to relieve the pressure on the sciatic nerve. Surgery is often very effective in relieving pain, although results can vary depending upon the cause of the sciatica. Overall, about 90% of patients undergoing surgery for sciatica pain receive some relief.

Recovery and rehabilitation

Usually, sciatica improves within a few weeks. In cases of severe injury to the nerve, such as laceration or other trauma, recovery may be not possible or may be limited. The extent of disability may vary from partial to complete loss of movement or sensation in the affected leg. Nerve pain may also persist.

Clinical trials

A recent drug trial found that the drug Remicade (infliximab), which is used to treat arthritis, is often effective for treating sciatica. The drug reduces the level of a chemical called tumor necrosis factor alpha, which plays an important role in the inflammatory response of the body. It is thought that this factor is also critical to sciatica.

The National Institutes of Health (NIH) are conducting three ongoing studies on the treatment of sciatica. One study investigates the effects of the antidepressants desipramine and benztropine on sciatica. A second looks at the effects of magnets on sciatica. A third investigates the role of two drugs, nortriptyline and MS Contin (a type of morphine), as treatment for sciatica. Contact information for these studies is the National Institute for Dental and Craniofacial Research (NIDCR), 9000 Rockville Pike, Bethesda, MD 20892; the toll-free number is (800) 411-1222.

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ORGANIZATIONS

American Academy of Orthopaedic Surgeons. 6300 North River Road, Rosemont, IL 60018-4262. (847) 823-7186 or (800) 346-AAOS; Fax: (847) 823-8125. <http://www.aaos.org>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases. Office of Communications and Public Liaison, National Institute of Health, Bldg. 31, Room 4C02 31 Center Dr. MSC 2350. Bethesda, MD 20892-2350. (301) 496-8190; Fax: (301) 480-2814. <http://www.niams.nih.gov/>.

Juli M. Berwald, PhD

Sciatic neuropathy

Definition

Sciatica is a term given to any painful condition of the leg that originates in the lower back and descends down the leg. Because it tends to involve a single nerve tract it is designated as mononeuropathy (localized nerve disorder).

The cause of this **pain** is the neuropathy defined by the inflammation and swelling of the large sciatic nerve that originates from the exit of an intervertebral nerve plexus between one of the large lumbar vertebral discs. A portion of the sciatic nerve also originates from the sacrum. The name for the region from which this nerve emanates is the sacral plexus. It encompasses the lumbar vertebra L 4– 5 through the sacral vertebra S 1–3. The intervertebral nerves join to form one of the larger nerve tracts in the body, the sciatic nerve. This nerve tract winds over the pelvic bones and down the proximal posterior side of the femurs (either right or left). From there it branches into the tibial and common peroneal nerve. Further branching produces the deep peroneal nerve.

An inflammation or irritation of this nerve can produce pain that ranges anywhere from mild discomfort to extreme distress. Many sufferers describe a constant pain that does not ease with change in body position or conventional medications. The pain can originate from a small area of the lower back to running along the hip, and down the leg past the ankle to the foot.

Additional symptoms of sciatic neuropathy that distinguish it from **peripheral neuropathy** include sensation changes. These occur on the soles of the foot and up the leg. They may include numbness and tingling and even a burning sensation. Difficulty in walking is common and, in serious conditions, there may be an inability to move the foot or knee.

Description

The most common source of inflammation of the sciatic nerve and its branches is injury to an intervertebral disc. This neuritis (nerve inflammation) may occur when pressure on the disc forces it to rupture, squeezing some of the softer more gelatinous interior against the nerve. In turn, this constant pressure begins to irritate the sciatic nerve until eventual swelling from inflammation occurs. The irritation is transmitted to the brain and the patient experiences constant or intermittent pain of varying degrees.

Depending on the degree of herniation to the disc, the pain may eventually go away or the patient may consider lower back surgery. Surgery is the most extreme form of treatment for this condition, as most cases will be relieved with **exercise** and anti-inflammatory medications. Healing may be slow and take up to six weeks.

A common source of sciatic neuropathy is wounding of the sciatic nerve. This condition presents itself when a person has been forced to lie down for extended lengths of time. The resulting pressure on the nerve and lack of movement produces neuropathy. This condition is often confused with tibial nerve dysfunction or common nerve dysfunction.

Key Terms

Herniated disk A blisterlike bulging or protrusion of the contents of the disk out through the fibers that normally hold them in place. It is also called a ruptured disk, slipped disk, or displaced disk.

Wounds to the sciatic nerve may result from fractures of the pelvis, gunshots, or blunt objects such as a bat or stick. Car injuries may often produce damage to the sciatic nerve. Physiological damage can also result from diabetes or an abscess.

Another possible cause of pressure on the sciatic nerve is that imposed by a tumor. Again, surgery may be considered to treat this form of sciatica. The physician may offer alternative therapies to treat the tumor, but therapies are case dependent and vary widely. In cases where tumors are present, the primary cause of the sciatica usually requires treatment that is are not aimed specifically at resolving the sciatica.

Direct trauma to the sciatic nerve may also produce inflammation. A fall or a puncture from an injection could produce insult to the nerve tissues and result in sciatica. In these cases, the treatment is simple and effective. Movement and anti-inflammatory medications usually improve the situation until it eventually resolves.

Demographics

While there varying demographics regarding sciatica, there are conditions that may alert a physician to look for underlying cause of the condition. People under 20 or over 55 are often examined for additional symptoms of other disorders. Associated pain in the back of the chest is a concern along with recent major injury as the type sustained from a traffic injury.

Included in the groups of patients who receive additional examination when they complain of sciatica are those who have lost weight recently, have had cancer, are on steroids, have worsening pain, and those who have developed other nervous system disorders in the past.

Causes and symptoms

As previously noted, the most common cause of sciatica is a “slipped” or herniated disk, also called a prolapsed intervertebral disk (PID) or a herniated nucleus pulposus. Any trauma or injury to the nerve will result in swelling and inflammation. While this healing condition persists, the nerve will respond with pain, which in turn, will often reduce normal movement.

Rarely, sciatic neuropathy has been reported after surgical procedures that required the patient to be immobilized in the operating room for long periods of time or in positions that may have irritated the sciatic nerve.

Diagnosis

Sciatica is in itself a symptom of some other condition which must be diagnosed by a physician. The root causes of the disorder may vary. Only a professional who is trained in recognizing the information provided by the patient and laboratory results can determine if or whether the condition is an isolated symptom or a symptom of a more general or serious disorder of the patient.

Although the diagnosis is based primarily upon symptoms of pain, the physician will usually test for muscle strength, reflexes and flexibility while considering a diagnosis of sciatic neuropathy. Areas of spinal problems that may cause sciatic nerve irritation or compression are usually visible on **MRI** or **CT** images. Occasionally, further nerve function tests may be necessary.

Treatment team

Physicians are the first contact to be made in a treatment team. It is the physician who must first make the diagnosis. A radiologist or laboratory technician may take x rays of the area to look for bone spurs of disk protrusions. Once the diagnosis is made the pharmacist may be called to provide appropriate medication for treatment. In more severe cases, a physical therapist may be used to keep the patient active and performing physical tasks that help reduce the pain. With intractable pain, a neurosurgeon may be consulted for surgery.

Treatment

The immediate treatment of most cases of sciatica is to recommend medications specific to the inflammation. Staying active is also highly recommended, while avoiding activities that put pressure on the back. Studies have found that a simple combination of anti-inflammatory medication such as ibuprofen and mild exercise, such as walking, are effective treatment for most cases of common sciatica. Sometimes an epidural injection (an injection to the epidural space of the spine) may provide pain relief. Surgery for a herniated disk is an aggressive alternative, and includes more risk.

Recovery and rehabilitation

The majority of patients suffering with sciatica recover in a few weeks to six or seven weeks. While the pain may be intense for some sufferers, it is usually temporary. With treatment, person has an excellent chance for reduction or resolution of the neuropathy pain of sciatica.

Clinical trials

A large clinical trial testing the effectiveness of new drug therapies is being conducted by the National Institute of Dental and Craniofacial Research (NIDCR). This may seem like an unlikely group to sponsor such a trial, but any study that examines the effectiveness of medication on nerves may be of great aid to patients suffering from sciatica. Information on additional **clinical trials** can be found at the United States government website for clinical trials: <http://www.clinicaltrials.gov>.

Prognosis

The prognosis for the pain relief of most cases of sciatica is excellent. With a combined use of anti-inflammatory drugs and mild exercise, such as walking, sciatica can be reduced and even eliminated. If the underlying cause is more serious, the prognosis varies with the degree of severity and type of condition.

Special concerns

One of the myths associated with sciatica is the need to rest in bed. In fact, mild exercise is one of the best treatments for the pain. Prolonged sitting is a primary cause of many cases of sciatica. If a job requires extended periods of sitting, it is wise to take short walks or perform mild stretches to keep compression of the lower lumbar vertebrae from occurring.

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National Institute of Arthritis and Musculoskeletal and Skin Dieseases (NIAMS). National Institutes of Health, Bldg. 31, Rm. 4C05, Bethesda, MD 20892. (301) 496-8188; Fax: (540) 862-9485. ncpoa@cfw.com. <http://www.niams.nih.gov/index.htm>.

Brook Ellen Hall, PhD

Seizure disorder *see* **Epilepsy**

Seizures

Definition

A seizure is a sudden change in behavior characterized by changes in sensory perception (sense of feeling) or motor activity (movement) due to an abnormal firing of nerve cells in the brain. **Epilepsy** is a condition characterized by recurrent seizures that may include repetitive muscle jerking called convulsions.

Description

Seizure disorders and their classification date back to the earliest medical literature accounts in history. In 1964, the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) devised the first official classification of seizures, which was revised again in 1981. This classification is accepted worldwide and is based on electroencephalographic (EEG) studies. Based on this system, seizures can be classified as either focal or generalized. Each of these categories can also be further subdivided.

Focal seizures

A focal (partial) seizure develops when a limited, confined population of nerve cells fire their impulses abnormally on one hemisphere of the brain. (The brain has two portions or cerebral hemispheres—the right and left hemispheres.) Focal seizures are divided into simple or complex based on the level of consciousness (wakefulness) during an attack. Simple partial seizures occur in patients who are conscious, whereas complex partial seizures demonstrate impaired levels of consciousness.

Generalized seizures

A generalized seizure results from initial abnormal firing of brain nerve cells throughout both left and right hemispheres. Generalized seizures can be classified as follows:

- Tonic-clonic seizures: This is the most common type among all age groups and is categorized into several phases beginning with vague symptoms hours or days before an attack. These seizures are sometimes called grand mal seizures.
- Tonic seizures: These are typically characterized by a sustained nonvibratory contraction of muscles in the legs and arms. Consciousness is also impaired during these episodes.
- Atonic seizures (also called "drop attacks"): These are characterized by sudden, limp posture and a brief period of unconsciousness and last for one to two seconds.
- Clonic seizures: These are characterized by a rapid loss of consciousness with loss of muscle tone, tonic spasm, and jerks. The muscles become rigid for about 30 seconds during the tonic phase of the seizure and alternately contract and relax during the clonic phase, which lasts 30–60 seconds.
- Absence seizures: These are subdivided into typical and atypical forms based on duration of attack and level of consciousness. Absence (petit mal) seizures generally begin at about the age of four and stop by the time the child becomes an adolescent. They usually begin with a brief loss of consciousness and last between one and 10 seconds. People having a petit mal seizure become very quiet and may blink, stare blankly, roll their eyes, or move their lips. A petit mal seizure lasts 15–20 seconds. When it ends, the individual resumes whatever he or she was doing before the seizure began, will not remember the seizure, and may not realize that anything unusual happened. Untreated, petit mal seizures can recur as many as 100 times a day and may progress to grand mal seizures.
- Myoclonic seizures: These are characterized by rapid muscular contractions accompanied with jerks in facial and pelvic muscles.

Subcategories are commonly diagnosed based on EEG results. Terminology for classification in infants and newborns is still controversial.

Causes and symptoms

Simple partial seizures can be caused by congenital abnormalities (abnormalities present at birth), tumor growths, head trauma, **stroke**, and infections in the brain or nearby structures. Generalized tonic-clonic seizures are associated with drug and alcohol abuse, and low levels of blood glucose (blood sugar) and sodium. Certain psychiatric medications, antihistamines, and even antibiotics can precipitate tonic-clonic seizures. Absence seizures are implicated with an abnormal imbalance of certain chemicals in the brain that modulate nerve cell activity (one of these **neurotransmitters** is called GABA, which functions as an inhibitor). Myoclonic seizures are commonly diagnosed in newborns and children.

Symptoms for the different types of seizures are specific.

Partial seizures

SIMPLE PARTIAL SEIZURES Multiple signs and symptoms may be present during a single simple partial seizure. These symptoms include specific muscles tensing and then alternately contracting and relaxing, speech arrest, vocalizations, and involuntary turning of the eyes or head. There could be changes in vision, hearing, balance, taste, and smell. Additionally, patients with simple partial seizures may have a sensation in the abdomen, sweating,

Key Terms

Electroencephalograph (EEG) An instrument that measures the electrical activity of the brain. The EEG traces the electrical activity in the form of wave pattens onto recording paper. Wave patterns that have sudden spikes or sharp waves strongly suggest seizures. An EEG with a seizure-type wave pattern is called an epileptiform EEG.

Hallucination False sensory perceptions. A person experiencing a hallucination may "hear" sounds or "see" people or objects that are not really present. Hallucinations can also affect the senses of smell, touch, and taste.

Illusion A misperception or misinterpretation in the presence of a real external stimulus.

paleness, flushing, hair follicles standing up (piloerection), and dilated pupils (the dark center in the eye enlarges). Seizures with psychological symptoms include thinking disturbances and **hallucinations**, or illusions of memory, sound, sight, time, and self-image.

COMPLEX PARTIAL SEIZURES Complex partial seizures often begin with a motionless stare or arrest of activity; this is followed by a series of involuntary movements, speech disturbances, and eye movements.

Generalized seizures

Generalized seizures have a more complex set of signs and symptoms.

TONIC-CLONIC SEIZURES Tonic-clonic seizures usually have vague prodromal (pre-attack) symptoms that can start hours or days before a seizure. These symptoms include anxiety, mood changes, irritability, weakness, **dizziness**, lightheadedness, and changes in appetite. The tonic phases may be preceded with brief (lasting only a few seconds in duration) muscle contractions on both sides of affected muscle groups. The tonic phase typically begins with a brief flexing of trunk muscles, upward movement of the eyes, and pupil dilation. Patients usually emit a characteristic vocalization. This sound is caused by contraction of trunk muscles that forces air from the lungs across spasmodic (abnormally tensed) throat muscles. This is followed by a very short period (10–15 seconds) of general muscle relaxation. The clonic phase consists of muscular contractions with alternating periods of no movements (muscle atonia) of gradually increasing duration until abnormal muscular contractions stop. Tonic-clonic seizures end in a final generalized spasm. The affected person can lose consciousness during tonic and clonic phases of seizure.

Tonic-clonic seizures can also produce chemical changes in the body. Patients commonly experience lowered carbon dioxide (hypocarbia) due to breathing alterations, increased blood glucose (blood sugar), and elevated level of a hormone called prolactin. Once the affected person regains consciousness, he or she is usually weak, and has a **headache** and muscle **pain**. Tonic-clonic seizures can cause serious medical problems such as trauma to the head and mouth, fractures in the spinal column, pulmonary edema (water in the lungs), aspiration pneumonia (a pneumonia caused by a foreign body being lodged in the lungs), and sudden death. Attacks are generally one minute in duration.

TONIC SEIZURES Tonic and atonic seizures have distinct differences but are often present in the same patient. Tonic seizures are characterized by nonvibratory muscle contractions, usually involving flexing of arms and relaxing or flexing of legs. The seizure usually lasts less than 10 seconds but may be as long as one minute. Tonic seizures are usually abrupt and patients lose consciousness. Tonic seizures commonly occur during non-rapid eye movement (non-REM) sleep and drowsiness. Tonic seizures that occur during wakeful states commonly produce physical injuries due to abrupt, unexpected falls.

ATONIC SEIZURES Atonic seizures, also called "drop attacks," are abrupt, with loss of muscle tone lasting one to two seconds, but with rapid recovery. Consciousness is usually impaired. The rapid loss of muscular tone could be limited to head and neck muscles, resulting in head drop, or it may be more extensive, involving muscles for balance and causing unexpected falls with physical injury.

CLONIC SEIZURES Generalized clonic seizures are rare and seen typically in children with elevated fever. These seizures are characterized by a rapid loss of consciousness, decreased muscle tone, and generalized spasm that is followed by jerky movements.

ABSENCE SEIZURES Absence seizures are classified as either typical or atypical. The typical absence seizure is characterized by unresponsiveness and behavioral arrest, abnormal muscular movements of the face and eyelids, and lasts less than 10 seconds. In atypical absence seizures, the affected person is generally more conscious, the seizures begin and end more gradually, and do not exceed 10 seconds in duration.

MYOCLONIC SEIZURES Myoclonic seizures commonly exhibit rapid muscular contractions. Myoclonic seizures are seen in newborns and children who have either symptomatic or idiopathic (cause is unknown) epilepsy.

Demographics

Approximately 1.5 million persons in the United States suffer from a type of seizure disorder. The annual incidence (number of new cases) for all types of seizures

is 1.2 per 1,000 and, for recurrent seizures, is 0.54 per 1,000. Isolated seizures may occur in up to 10% of the general population. Approximately 10–20% of all patients have intractable epilepsy (epilepsy that is difficult to manage or treat). It is estimated that 45 million people in the world are affected by seizures. Seizures affect males and females equally and can occur among all age groups. There seems to be a strong genetic correlation, since seizures are three times more prevalent among close relatives than they are in the general population.

Children delivered in the breech position have increased prevalence (3.8%) of seizures when compared to infants delivered in the normal delivery position (2.2%). Seizures caused by fever have a recurrence rate of 51% if the attack occurred in the first year of life, whereas recurrence rate is decreased to 25% if the seizure took place during the second year. Approximately 88% of children who experience seizures caused by fever in the first two years experience recurrence.

Approximately 45 million people worldwide are affected by epilepsy. The incidence is highest among young children and the elderly. High-risk groups include persons with a previous history of brain injury or lesions.

Diagnosis

Patients seeking help for seizures should first undergo an EEG that records brain-wave patterns emitted between nerve cells. Electrodes are placed on the head, sometimes for 24 hours, to monitor brain-wave activity and detect both normal and abnormal impulses. Imaging studies such as **magnetic resonance imaging** (**MRI**) and computed axial tomography (**CT**)—that take still "pictures"—are useful in detecting abnormalities in the temporal lobes (parts of the brain associated with hearing) or for helping diagnose tonic-clonic seizures. A complete blood count (CBC) can be helpful in determining whether a seizure is caused by a neurological infection, which is typically accompanied by high fever. If drugs or toxins in the blood are suspected to be the cause of the seizure(s), blood and urine screening tests for these compounds may be necessary.

Antiseizure medication can be altered by many commonly used medications such as sulfa drugs, erythromycin, warfarin, and cimetidine. Pregnancy may also decrease serum concentration of antiseizure medications; therefore, frequent monitoring and dose adjustments are vital to maintain appropriate blood concentrations of the antiseizure medication—known as the therapeutic blood concentration. Diagnosis requires a detailed and accurate history, and a physical examination is important since this may help identify neurological or systemic causes. In cases in which a **central nervous system** (CNS) infection (i.e., meningitis or encephalitis) is suspected, a lumbar puncture (or spinal tap) can help detect an increase in immune cells (white blood cells) that develop to fight the specific infection.

Treatments

Treatment is targeted primarily to:

- assist the patient in adjusting psychologically to the diagnosis and in maintaining as normal a lifestyle as possible
- reduce or eliminate seizure occurrence
- avoid side effects of long-term drug treatment

Simple and complex partial seizures respond to drugs such as **carbamazepine**, **valproic acid** (valproate), phenytoin, **gabapentin**, **tiagabine**, **lamotrigine**, and **topiramate**. Tonic-clonic seizures tend to respond to valproate, carbamazepine, phenytoin, and lamotrigine. Absence seizures seem to be sensitive to ethosuximide, valproate, and lamotrigine. Myoclonic seizures can be treated with valproate and clonazepam. Tonic seizures seem to respond favorably to valproate, **felbamate**, and clonazepam.

People treated with a class of medications called barbiturates (Mysoline, Mebral, **phenobarbital**) have adverse cognitive (thinking) effects. These cognitive effects can include decreased general intelligence, attention, memory, problem solving, motor speed, and visual motor functions. The drug phenytoin (Dilantin) can adversely affect speed of response, memory, and attention. Other medications used for treatment of seizures do not have substantial cognitive impairment.

Surgical treatment may be considered when medications fail. Advances in medical sciences and techniques have improved methods of identifying the parts of the brain that generate abnormal discharge of nerve impulses. Surgical treatment now accounts for about 5,000 procedures annually. The most common type of surgery is the focal cortical resection. In this procedure, a small part of the brain responsible for causing the seizures is removed. Surgical **intervention** may be considered a feasible treatment option if:

- the site of seizures is identifiable and localized
- surgery can remove the seizure-generating (epileptogenic) area
- surgical procedure will not cause damage to nearby areas

Prognosis

About 30% of patients with severe seizures (starting in early childhood), continue to have attacks and usually never achieve a remission state. In the United States, the prevalence of treatment-resistant seizures is about one to

two per 1,000 persons. About 60–70% of persons achieve a five-year remission within 10 years of initial diagnosis. Approximately half of these patients become seizure-free. Usually the prognosis is better if seizures can be controlled by one medication, the frequency of seizures decreases, and there is a normal EEG and neurological examination prior to medication cessation.

People affected by seizure have increased death rates compared with the general population. Patients who have seizures of unknown cause have an increased chance of dying due to accidents (primarily drowning). Other causes of seizure-associated death include abnormal heart rhythms, water in the lungs, or heart attack.

Prevention

There are no gold standard recommendations for prevention, since seizures can be caused by genetic factors, blood abnormalities, many medications, illicit drugs, infection, neurologic conditions, and other systemic diseases. If a person has had a previous attack or has a genetic propensity, care is advised when receiving medical treatment or if diagnosed with an illness correlated with possible seizure development.

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Septo-optic dysplasia

Definition

Septo-optic dysplasia (SOD) is a rare, congenital disorder. Findings include optic nerve hypoplasia with a thin or absent septum pellucidum and/or corpus callosum and pituitary dysfunction. Optic nerve hypoplasia is mandatory for the diagnosis of SOD.

Description

SOD also known as DeMorsier's syndrome is a combination of optic nerve underdevelopment (hypoplasia) with abnormalities of a part of the brain called the septum pellucidum and/or corpus callosum. Endocrine disorders such as dwarfism, decreased thyroid gland function (hypothyroidism), dehydration, delayed or precocious puberty and reduced blood sugar may occur from dysfunction of the pituitary gland of the brain. SOD has also been associated with congenital architectural brain anomalies.

Causes and symptoms

The cause of SOD is thought to be related to intrauterine viral infections or diabetes during pregnancy. Antiseizure medications, alcohol and illicit drugs have also been linked to SOD. In addition vascular abnormalities and uncommonly genetics are thought to play a role.

Patients afflicted with SOD can present at any age depending on the severity of the symptoms. Signs and symptoms such as failure to thrive, prolonged jaundice, body temperature dysregulation, decreased blood sugar, small genitalia or muscular flaccidity can herald the diagnosis of SOD in newborns.

Older children may complain of visual difficulties and be found to have strabismus (crossed eyes), nystagmus (involuntary, jerky eye movements) or inability to fixate on an object. In addition pupillary and color vision abnormalities may be noted. The optic nerves will appear small and grey or pale in color and can be surrounded by a yellowed halo signifying hypoplasia or atrophy.

A large percentage of SOD patients will have endocrine disorders. By far growth hormone deficiencies are the most common in patients with optic nerve hypoplasia. Growth hormone deficiency can lead to reduced blood sugar, while abnormal levels of reproductive hormones can result unusual pubertal development. Reduced levels of thyroid-stimulating hormone will cause suboptimal thyroid gland functioning (hypothyroidism). Other endocrine problems include increased urination, dehydration and death.

In some instances patients will have behavioral and cognitive problems resulting from brain maldevelopment or endocrinologic disorders.

Diagnosis

Suspicion for the diagnosis of SOD is based on clinical findings described above. In addition **magnetic resonance imaging (MRI)** of the brain focusing on the visual

Key Terms

Corpus callosum The largest commissure connecting the right and left hemispheres of the brain.

Septum pellucidum Two-layered thin wall separating the right and the left anterior horn of lateral ventricle.

pathways, hypothalamus-pituitary region and other midline structures and septum pellucidum is invaluable for solidifying the diagnosis.

Treatment team

Pediatricians, endocrinologists, optometrists, ophthalmologists, neuro-ophthalmologists and neurologists can all contribute to patient care.

Treatment

SOD is treated symptomatically. Hormone deficiencies are managed with hormone replacement therapy while the best possible visual acuity is achieved with corrective spectacle lenses.

Recovery and rehabilitation

Patients with extremely poor vision may benefit from a low vision specialist. He or she may be able to prescribe a visual apparatus to maximally improve visual function.

Special concerns

Patients with severe visual **depression** may have difficulty obtaining a driver's license or gainful employment.

Resources

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National Organization for Rare Disorders. PO Box 1968, Danbury, CT 06813-1968. 202-744-1000 or 800-999-NORD; Fax: 203-798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

National Eye Institute. National Institute of Health, Bldg. 31, Rm. 6A32, Bethesda, MD 20892-2510. 301-496-5248. 2020@b31.nei.nih.gov. <http://www.nei.nih.gov>.

Adam J. Cohen, MD

Shaken baby syndrome

Definition

Shaken baby syndrome is a severe form of head injury caused by the forcible shaking of a child. The force is sufficient to cause the brain to bounce against the baby's skull, causing injury or damage to the brain.

Description

Shaking an infant forcibly transfers a great deal of energy to the infant. When the shaking occurs as the infant is being held, much of the force is transferred to the neck and the head. The force can be so great that the brain can move within the skull, rebounding back and forth from one side of the skull to the other. The bashing can be very destructive to the brain, causing bruising, swelling, or bleeding. Bleeding of the brain is also called intracerebral hemorrhage. The force of shaking can also damage the neck.

As its name implies, shaken baby syndrome can often be a result of deliberate abuse. The brain damage can also be the result of an accident. The force and length of the force necessary to cause shaken baby syndrome is debatable. What is clear is that not much time is needed, since most shaking events likely tend to last only 20 seconds or less. It is the explosive violence of the shaking that exacts the damage.

Demographics

Reliable statistics on the prevalence of shaken baby syndrome do not exist. Estimates in the United States approach 50,000 cases each year. Nearly 25% of infants with shaken baby syndrome die from the brain injuries sustained. The victims of this syndrome range in age from just a few days to five years, with an average age of six to eight months. Statistics point to men as the usual perpetrators, typically young men (i.e., early 20s). Females who shake babies tend to be caregivers. As reliable statistics emerge, it would not be unexpected to find the actual number of cases greatly exceeds these crude estimates. Abuse of children is a hidden event, so many cases of abuse, including shaken baby syndrome, are not reported or are presented in some other form (such as a fall or an accident).

Key Terms

Increased intracranial pressure Increased overall pressure inside the skull.

Subdural hematoma A collection of blood or a clot trapped under the dura matter, the outermost membrane surrounding the brain and spinal cord, often causing neurological damage due to pressure on the brain.

Causes and symptoms

The cause of the brain, neck, and spine damage that can result from shaken baby syndrome is brute force. The violent shaking of a baby by a much stronger adult conveys a tremendous amount of energy to the infant. Part of the reason for the damage is because an infant's head is much larger than the rest of the body, in relation to an older child or an adult. This, combined with neck muscles that are still developing and are incapable of adequately supporting the head, can make shaking an explosively destructive event. The amount of brain damage depends on how hard the shaking is and how long an infant is shaken. If accidental, the force and length of the head trauma similarly determines the extent of injury.

The normal tossing and light "horse play" that can occur between an adult and an infant is not sufficient to cause shaken baby syndrome.

The damage to the brain can have dire consequences that include permanent and severe brain damage or death. Other symptoms that can develop include behavioral changes, lack of energy or motivation, irritable behavior, loss of consciousness, paling of the skin color or development of a bluish tinge to the skin, vomiting, and convulsions. These symptoms are the result of the destruction of brain cells that occurs directly due to the trauma of the blow against the skull, and secondarily as a result of oxygen deprivation and swelling of the brain. The banging of the brain against the sides of the skull causes the inflammation and swelling as well as internal bleeding. Increased intracranial pressure can be damaging to the structure and function of the brain.

Additionally, because the neck and head can absorb a tremendous amount of energy due to the shaking force of the adult, bones in the neck and spine can be broken and muscles can be torn or pulled. The eyes can also be damaged by the explosive energy of shaking. Retinal damage occur in 50–80% of cases. The damage can be so severe as to permanently blind an infant.

Shaken baby syndrome is also known as abusive head trauma, shaken brain trauma, pediatric **traumatic brain injury**, **whiplash** shaken infant syndrome, and shaken impact syndrome.

Diagnosis

Diagnosis depends on the detection of a blood clot below the inner layer of the dura (a membrane that surrounds the brain), but external to the brain. The clot is also known as a **subdural hematoma**. Two other critical features of shaken baby syndrome that are used in diagnosis are brain swelling and hemorrhaging in the eyes.

An infant may also have external bruising on parts of the body that were used to grip him or her during shaking. Bone or rib fractures can also be apparent. However, these external features may not always be present. Diagnosis can also involve the nondestructive imaging of the brain using the techniques of computed tomography (**CT**), skull x ray, or **magnetic resonance imaging (MRI)**. Typically, these procedures are done after an infant has been stabilized and survival is assured.

Treatment team

Treatment in an emergency setting typically involves nurses and emergency room physicians. A neurosurgeon is usually consulted when shaken baby syndrome is suspected. Depending on the extent of injury, neurosurgeons can become involved if surgery for brain repair is needed.

Police officers and **social workers** also become involved in cases of shaken baby syndrome, who work to ensure that the child is placed in a safe environment.

Treatment

Initially, treatment is provided on an emergency basis. Life-saving measures can include stopping internal bleeding in the brain and relieving pressure that can build up in the brain because of bleeding and swelling of the brain.

Recovery and rehabilitation

If the infant survives the initial injury from shaken baby syndrome, rehabilitation focuses on recovering as much function as possible. Physical and occupational therapies can offer exercises for caregivers to provide the child, as well as any supportive or positional devices required. The full effects of the brain injury sustained in infants who survive shaken baby syndrome may not become apparent until delays in developmental milestones such as sitting alone, walking, or acquiring speech are noticed.

Clinical trials

As of May 2004, there are no **clinical trials** on shaken baby syndrome underway or recruiting participants in the United States. However, agencies such as the National Institute of Neurological Disorders and Stroke fund

studies that seek to better understand the basis of the damage. Other agencies attempt to lessen the occurrence of the syndrome through counseling, anger management, and interventions in abusive situations.

Prognosis

The prognosis for children with shaken baby syndrome is usually poor. Twenty percent of cases result in death within the first few days. If an infant survives, he or she will most often be left with intellectual and developmental disabilities such as **mental retardation** or **cerebral palsy**. Damage to the eyes can cause partial or total loss of vision. A survivor will likely require specialized care for the remainder of his or her life.

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National Institute for Neurological Diseases and Stroke. P.O. Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424. <http://www.ninds/nih.gov>.

The National Center on Shaken Baby Syndrome. 2955 Harrison Blvd., #102, Ogden, UT 84403. (801) 627-3399 or (888) 273-0071; Fax: (801) 627-3321. dontshake@mindspring.com. <http://www.dontshake.com>.

National Institute of Child Health and Human Development. 31 Center Drive, Rm. 2A32 MSC 2425, Bethesda, MD 20892-2425. (301) 496-5133; Fax: (301) 496-7101. <http://www.nichd.nih.gov>.

The Arc of the United States. 1010 Wayne Avenue, Suite 650, Silver Spring, MD 20910. (301) 565-3842; Fax: (301) 565-3843. info@thearc.org. <http://www.thearc.org>.

Think First Foundation [National Injury Prevention Program]. 5550 Meadowbrook Drive, Suite 110, Rolling Meadows, IL 60008. (847) 290-8600 or (800) 844-6556; Fax: (847) 290-9005. thinkfirst@thinkfirst.org. <http://www.thinkfirst.org>.

Brian Douglas Hoyle, PhD

Shingles

Definition

Shingles is infection by the varicella-zoster virus of the dorsal root ganglia of the spine. Equivalent terms for shingles are herpes zoster, zoster, zona, or acute posterior ganglionitis.

Description

Shingles is an infection of the **central nervous system**, in particular, the dorsal root ganglia of the spine, which migrates through sensory nerves to the skin. There it manifests (usually on the upper trunk) as painful, bumpy, fluid-filled eruptions or vesicles. Shingles may also cause nerve **pain** (neuralgia). The affected areas of skin are those supplied by sensory nerves radiating from the infected dorsal root ganglia. Sensory nerves from these ganglia serve non-overlapping, sharply bounded strips or areas of the skin called dermatomes. Because the left and right sides of the body are divided into separate sets of dermatomes, shingles lesions do not cross the midline of the body.

Demographics

The virus that causes shingles is usually contracted in childhood. It is the same virus that causes chicken pox, which is primarily a disease of childhood because it is highly contagious; that is, few individuals live to adulthood without contracting chicken pox. (This statement applies to the temperate zones of the world. For unknown reasons, chicken pox and shingles are less prevalent in tropical regions.) The virus that causes both chicken pox and shingles can, however, be contracted by an individual for the first time in adulthood. First infection, at whatever age it occurs, is called primary infection. Primary infection does not cause shingles; shingles arises from reactivation of virus introduced to the body by an earlier, primary infection.

Shingles arises in individuals who have already had chicken pox, and especially in people with weakened immune systems, such as the elderly or people receiving chemotherapy or bone marrow transplantation. Persons with **AIDS** are also vulnerable to shingles. Shingles incidence increases steadily with age. Among 10–19 year olds, the rate per 1,000 persons per year is only 1.38. In the 30–49 age range, it rises to 2.29 cases of shingles per 1,000 persons per year. By age 60–79, almost seven cases occur per 1,000 people per year, and this increases to 10 in the 80–89 age group.

Causes and symptoms

Shingles is caused by the varicella-zoster virus (VZV), also known as HHV-3. VZV is genetically similar to the herpes simplex viruses, the type of viruses that

Key Terms

Ganglion A mass of nerve cells usually found outside the central nervous system, from which axons arrive from the periphery and proceed to the spinal cord or brain; plural form: ganglia .

Herpes simplex An infection caused by the herpes simples virus, affecting the skin and nervous system and producing small, temporary, often-painful blisters on the skin and mucous membranes.

Hemiparesis Muscle weakness of one side of the body.

Neuralgia Pain along a nerve pathway.

Vesicle A small, raised lesion filled with clear fluid.

causes cold sores and genital herpes. Herpes simplex virus also takes up permanent residence in sensory nerve ganglia, but not in the dorsal root ganglia of the spine, as does VZV. In chicken pox, the virus is inhaled and begins replicating in the upper respiratory tract before spreading to the liver and other body systems.

Following primary infection, VZV remains as a symptomless infection in the dorsal root ganglia of the spinal cord. It may or may not become active again, that is, begin reproducing, later in life. Reactivation occurs more often in older people, probably as a result of decreased immune response with age. Reactivation may be symptomless, but usually causes shingles. Repeat episodes of shingles are rare (occurring in less than 4% of patients) because the immune system's response to VZV is boosted by a first shingles episode.

Chills, fever, malaise, gastrointestinal problems, and pain in the affected skin areas may precede appearance of skin eruptions by several days. Viral particles travel away from the spinal cord along the sensory nerves toward the skin, causing inflammation of those nerves, which may be painful. On the fourth or fifth day, skin vesicles begin to appear. The affected area is usually hypersensitive, and disabling pain (described as sharp, stabbing, or burning) may occur in the affected area. About the fifth day after appearing, the vesicles begin to crust or scab and the disease resolves within the next two weeks. There may be no visible aftereffects, although slight scarring from the vesicles may occur.

Especially in elderly patients, pain may persist for months or years after shingles has otherwise resolved. This pain, postherpetic neuralgia, is caused by damage to the dorsal root ganglia that renders them either spontaneously active (perceived as chronic pain) or hypersensitive to slight stimuli such as light touch.

VZV can become active in the cranial nerves as well as in the spinal ganglia. Involvement of branches of the trigeminal nerve (fifth cranial nerve) is most common. When the ophthalmic branch of the trigeminal nerve is involved, this condition is called herpes zoster ophthalmicus. It can cause swelling of the eyelid, pain, and other complications involving the eye. Herpes zoster ophthalmicus can also lead to weakness or partial paralysis (hemiparesis) on the opposite side of the body from the nerve affected, possibly by inducing irritation of the blood vessels in the brain. Infection of cranial nerves by reactivated VZV can also affect the hearing. When this occurs, it is usually associated with facial palsy and is known as Ramsay-Hunt syndrome.

Large amounts of free virus (i.e., virus not held inside cells) is present in the fluid-filled vesicles or bumps that erupt on the skin during shingles. Thus, people who are not resistant to VZV are easily infected by contact with persons having an outbreak of shingles. A particular strain of VZV can remain latent for decades and then reappear as a new epidemic.

Diagnosis

Diagnosis is based on history and symptoms. The person must have initially had chicken pox in order to have shingles. Definite diagnosis is difficult before eruption of the characteristic vesicles or bumps on the skin. Often persons with early shingles mistake the reddened, painful area as an accidental burn. Once vesicles appear, however, they are hard to mistake because of their dermatome-bounded distribution on the body. In children, shingles (VZV reactivation) must be differentiated from chicken pox (primary VZV infection). This is normally not difficult, as chicken pox vesicles occur widespread on the body and shingles lesions are usually limited to one area on the person's midsection. Herpes simplex virus can also produce vesicle eruptions similar to those of shingles. If there is doubt about which virus is present, virus from the patient can be cultured.

Treatment team

Unless there are complications such as in a person with AIDS, or a child with leukemia, a primary physician can usually treat shingles.

Treatment

Treatment for shingles is primarily with **antiviral drugs**, traditionally acyclovir but, more recently, famcyclovir and valacyclovir. Additionally, a live attenuated-virus vaccine for chicken pox has been licensed since

1995. The vaccine was developed to immunize children undergoing cancer treatment because chicken pox can cause severe complications in such children.

The pain associated with shingles, and with the postherpetic neuralgia that may linger (especially in older patients, after the condition has otherwise resolved), is best treated using combination therapy based on antivirals, antidepressants, corticosteroids, opioids (morphine), and topical agents (applied directly to the skin). The inexpensive amino acid lysine has also been reported to ease the symptoms of both herpes simplex infections and shingles.

Recovery and rehabilitation

Recovery from shingles for the otherwise healthy patient is straightforward and generally requires no special rehabilitation aid or therapy.

Clinical trials

As of mid 2004, several **clinical trials** related to shingles are recruiting patients. One is sponsored by the National Center for Research Resources, University of Texas, and titled "Randomized Study of Two Doses of Oral Valacyclovir in Immunocompromised Patients with Uncomplicated Herpes Zoster." The study seeks to investigate the efficacy of higher-than-standard doses of valacyclovir by assessing quality of life, pain level, and utilization of medical resources of patients treated with a higher-than-standard dose of valacylovir as compared to a control group treated with the standard dose. Contact information is University of Texas Medical Branch, Galveston, Texas, 77555-0209; Stephen K. Tyring is the recruiter, telephone: (281) 333-2288.

Another trial recruiting patients as of 2004 is sponsored by the Baylor College of Medicine, Texas Children's Hospital, and titled "Valacyclovir in Immunocompromised Children." The study seeks to learn how the body handles valacyclovir, its efficacy in treating immunocompromised children with shingles, and the side effects of such treatment. The recruiting inquiries in Pennsylvania is Children's Hospital of Philadelphia, Pennsylvania, 19104; Donna Sylvester, RN, phone: (215) 590-3284. The recruiting inquiries in Texas is Texas Children's Hospital, Houston, Texas, 77030; Susan Blaney, MD, phone: (832) 822-4215, e-mail: sblaney@bcm.tmc.edu , or Lisa R Bomgaars, MD, phone: (832) 824-4688, e-mail: lbomgaars@bcm.tmc.edu.

A third study ongoing in 2004 is sponsored by the drug maker NeurogesX and titled "Controlled Study of NGX-4010 for the Treatment of Postherpetic Neuralgia." NGX-4010 consists of a capsaicin dermal (skin) patch. Capsaicin is the active substance in chili peppers, and is used, paradoxically, both as an irritant and for pain relief. The purpose of this clinical trial is to evaluate the efficacy of a capsaicin patch for relief of postherpetic neuralgia. Contact information varies by state but can viewed at the National Institutes of Health Web site at <http://www.clinicaltrials.gov/ct/show/NCT00068081?order=3>.

Prognosis

Generally, the prognosis for persons with shingles is good. Shingles is almost never a life-threatening disease in otherwise healthy patients, and usually resolves without treatment in a few weeks. However, postherpetic neuralgia, which occurs more often in elderly patients, can be disabling and difficult to treat.

Persons who have an impaired immune system , such as those deficient in cytotoxic T lymphocytes, persons undergoing immune suppression (e.g., for organ transplant), and persons who have AIDS or leukemia may suffer more serious effects from shingles, as the reactivated virus sometimes disseminates from the dorsal root ganglia to other parts of the body. In these cases, complications can resemble those for primary infection of adults with VZV, namely, viral pneumonia, male sterility, acute liver failure, and (in pregnant women) birth defects.

Resources

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Larry Gilman, PhD

Shy-Drager syndrome *see* **Multiple system atrophy**

Single Proton Emission Computed Tomography

Definition

Single proton (or photon) emission computed tomography (SPECT) allows a physician to see three-dimensional images of a person's particular organ or body system. SPECT detects the course of a radioactive substance that is injected, ingested, or inhaled. In neurology, a SPECT scan is often used to visualize the brain's cerebral blood flow and thereby, indicate metabolic activity patterns in the brain.

Purpose

SPECT can locate the site of origin of a seizure, can confirm the type of seizure that has occurred, and can provide information that is useful in the determination of therapy. Other uses for SPECT include locating tumors, monitoring the metabolism of oxygen and glucose, and determining the concentration of neurologically relevant compounds such as dopamine.

Currently, a clinical trial is underway in the United States to evaluate the potential of SPECT to study brain receptors for the neurotransmitter acetylcholine. The study will help to determine the usefulness of the technique in charting the progress of the brain deterioration associated with **Parkinson's disease**.

Precautions

The exposure to **radiation**, particularly to the thyroid gland, is minimized as described below in the sections on preparation and aftercare.

Description

Since its development in the 1970s, single proton emission computed tomography has become a critical and routine facet of a clinician's diagnostic routine. A SPECT scan is now a typical part of the diagnosis of coronary artery disease, cancer, **stroke**, liver disease, bone and spinal abnormalities, and lung maladies.

SPECT produces two-dimensional and three-dimensional images of a target region in the body by detecting the presence and location of a radioactive compound given prior to the test. The photon emissions of the radioactive compound can be detected in a manner that is similar to the detection of x rays in computed tomography (**CT**). The image produced is a compilation of data collected over time following introduction of the tracer.

Key Terms

Half-life The time required for half of the atoms in a radioactive substance to decay.

Radioisotope One of two or more atoms with the same number of protons but a different number of neutrons with a nuclear composition. In nuclear scanning, radioactive isotopes are used as a diagnostic agent.

Seizure A sudden attack, spasm, or convulsion.

The radioactive compound that is introduced typically loses its radioactive potency rapidly (this is expressed as the half-life of a compound). For example, gamma-emitting compounds can have a half-life of just a few hours. This is beneficial for the patients, as it limits the contact time with the potentially damaging radioisotope.

The emitted radiation is collected by a gamma-camera through thousands of round or hexagonal channels that are arranged in parallel in a part of the machine called the collimator. Only gamma rays can pass through the channels. At the other end of the channel, the radiation contacts a crystal of sodium iodide. The interaction produces a photon of light (hence, the name of the technique). The light is subsequently detected and the time and body location of the light-producing radiation is stored computationally. At the end of the SPECT scan, the stored information can be integrated to produce a composite image.

Typically, a patient is stationary. The SPECT scanner can move completely around the patient. Usually the patient will lie on a bed with their head restrained in a holder. Scans are taken for periods up to six hours following the injection of the tracer.

Monitoring of the heartbeat (electrocardiogram), respiration, and blood pressure are accomplished just prior to the start of the scan, five minutes after the introduction of the tracer, and 30–60 minutes after injection. Blood and urine samples are often collected towards the end of the scan.

Preparation

On the night before a scan, the patient takes an oral dose of potassium iodide. This protects the thyroid gland from the radioactive tracer. If a patient is allergic to potassium iodide, potassium perchlorate can be taken instead. Just prior to a scan, small radioisotope markers that contain the element 99Tc are attached with adhesive to the patient's

head. Two intravenous catheters are usually placed in veins, through which the radioactive tracer is injected, and so that blood samples can be withdrawn during the scan.

Aftercare

Oral doses of potassium iodide or potassium perchlorate are taken daily for four days following a scan. Patients are asked to urinate every two hours for the first 12 hours following the scan to eliminate the tracer from their body as quickly as possible.

Risks

The use of radiation poses a risk of cellular or tissue damage. However, the injection of the radioactive tracer results in the swift movement of the tracer through the body, and its rapid elimination.

Normal results

The image of the target region of the body is compared to an image of the healthy target region. Analysis of the images by a qualified physician determines the result.

Resources

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Brian Douglas Hoyle, PhD

Sixth nerve palsy

Definition

Cranial nerve six supplies the lateral rectus muscle allowing for outward (abduction) eye movement. A sixth nerve palsy, also known as abducens nerve palsy, is a neurological defect resulting from an impaired sixth nerve or the nucleus that controls it. This may result in horizontal double vision (diplopia) with in turning of the eye and decreased lateral movement.

Description

Isolated sixth nerve palsies usually manifest as a horizontal diplopia worse when looking towards the affected eye, with a decreased ability to abduct. Since the sixth nerve only innervates the lateral rectus muscle, isolated palsies will only manifest in this fashion.

Demographics

Sixth nerve palsies have no predilection for males or females and can occur at any age.

Causes and symptoms

For all intensive purposes causes of abducens nerve palsy can be classified as congenital or acquired. Isolated congenital sixth nerve palsy is quite uncommon. If congenital the usual presentation is accompanied by other cranial nerve deficits as seen with Duane's retraction or **Moebius syndromes**. Strabismus, commonly known as "lazy eye," may mimic the appearance of abducens nerve palsy and may go undetected until adulthood because of compensatory mechanisms allowing for alignment of the eyes when focusing. Abduction deficits may also result from **myasthenia gravis**, thyroid eye disease, inflammation and orbital fractures which imitate sixth nerve palsies.

A myriad of causes resulting in abducens nerve palsies have been reported. In order to better differentiate these one must take into account the patient's age and underlying illnesses. In children trauma and tumors were reported as the most common causes. Therefore if no trauma has occurred one must consider a tumor of the **central nervous system** in the pediatric population. Other causes include idiopathic intracranial hypertension, inflammation following viral illness or immunization, **multiple sclerosis**, fulminant ear infections, Arnold-Chiari malformations and meningitis.

New onset palsies in adults can stem from myasthenia gravis, diabetes, meningitis, microvascular disease (atherosclerotic vascular disease) or giant cell arteritis (arterial inflammation). Other causes include **Lyme disease**, syphilis, cancers, autoimmune disorders, central nervous system tumors, and vitamin deficiencies.

Children may be found to have head tilt or in-turning of the affected eye, with reduction of outward gaze. They will very rarely complain of double vision, while adults may describe two images, side by side (horizontal diplopia), which are furthest apart when looking towards the affected eye. Covering of one eye, no matter which one is covered, and gazing away from the affected eye will resolve their diplopia. Patients may also note muscle weakness, possibly heralding myasthenia gravis, or **headache** and jaw **pain**, raising the possibility of giant cell arteritis.

Optic nerve swelling or jumpy eye movements (nystagmus) may occur at any age and warrants immediate work-up for a central nervous system tumor.

Key Terms

Multiple sclerosis A slowly progressive CNS disease characterized by disseminated patches of demyelination in the brain and spinal cord, resulting in multiple and varied neurologic symptoms and signs, usually with remissions and exacerbations.

Myasthenia gravis A disease characterized by episodic muscle weakness caused by loss or dysfunction of acetylcholine receptors.

Strabismus Deviation of one eye from parallelism with the other.

Diagnosis

Diagnosis of sixth nerve palsy is based on history and clinical findings. Once the diagnosis has been established the work-up should be tailored based on the patient's age and medical history.

Pediatric patients with no apparent trauma should undergo **magnetic resonance imaging** of the brain with contrast enhancement to rule out a central nervous system structural lesion (tumor or aneurysm). If the imaging is without abnormal findings a lumbar puncture (spinal tap) should be done to exclude increased intracranial pressure or infection. If this is normal, consideration of a post-viral or post-immunization palsy may be safely entertained.

Isolated abducens palsies in the adult population should be approached in a more conservative manner. If a patient is known to have diabetes, high blood pressure, or atherosclerotic vascular disease, a small **stroke** is likely. If diplopia worsens or no improvement occurs at eight weeks time, a more extensive work-up including magnetic resonance imaging of the brain with contrast and blood work to exclude infections, autoimmune disorders, vitamin deficiencies, or inflammation is warranted. A potentially devastating, blinding disorder known as cranial arteritis may occur in patients usually over 50 years of age. Headache, jaw pain worsened with chewing, night sweats, fevers, weight loss, or muscle aches necessitate blood work to rule out this inflammatory disorder.

Treatment team

Ophthalmologists, neuro-ophthalmologists, optometrists, neurologists, and pediatricians are medical specialists who can evaluate and diagnose a patient with a sixth nerve palsy. Usually an optometrist or ophthalmologist will initially see a patient complaining of diplopia or displaying findings of sixth nerve palsy. A referral will then likely be made to a **neurologist** or neuro-ophthalmologist for evaluation and work-up.

Treatment

Treatment of sixth nerve palsies is dictated by the underlying causes. Older patients who are thought to have had a mini-stroke are observed for several months, because of likely spontaneous resolution. Causes related to masses of the central nervous system or systemic disease should be managed and treated promptly by the appropriate specialist.

Children who are at risk for amblyopia can be treated with patching to reduce the risk of permanent visual loss. Older patients may elect to use a prism incorporated into a spectacle to reduce or eliminate their double vision. Prisms or fogging of one eye are excellent options for the older patient being observed for spontaneous resolution of their palsy.

If diplopia persists for greater than six months and prisms cannot realign the images surgical intervention is an option. Depending on the amount of lateral rectus muscle function one or two surgical options are used. If muscle function remains, weakening of the medial rectus muscle and tightening of the affected lateral rectus muscle may resolve the patient's complaint. If no function exists then a muscle transposition surgery can help restore some abduction ability.

Botulinum toxin may also be used to weaken the medial rectus muscle of the affected eye. This weakening effect is short-lived and repeat injections are necessary.

Clinical trials

As of November, 2003, no **clinical trials** regarding abducens nerve palsies were underway.

Prognosis

Isolated abducens nerve palsies in the older population are usually related to a small stroke and resolve within several months. Palsies related to trauma or brain masses have a guarded prognosis and recovery, if any, may take up to one year. Treatment of systemic disorders, such as myasthenia gravis, have an excellent prognosis, while inflammation related to multiple sclerosis is likely to improve as well. Unfortunately there are no hard and fast rules regarding recovery of any sixth nerve palsy.

Special concerns

Patients afflicted with a sixth nerve palsy should refrain from driving unless an eye patch is used. In addition certain types of employment may warrant a medical leave or temporary change of duties.

Resources

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Adam J. Cohen, MD

Key Terms

Ichthyosis Dry, thickened, rough, coarse skin, sometimes with evident scaling.

Myelin The coating on nerves that helps speed the electrical transmission along them.

Spasticity Stiff, rigid, dysfunctional muscles.

Sjogren-Larsson syndrome

Definition

Sjogren-Larsson syndrome is an inherited condition resulting in thickened, dry, rough skin (ichthyosis), **mental retardation**, and stiff, rigid muscles (**spasticity**). Although not all the manifestations of the disease may be immediately evident at birth, the disease is not considered to be progressive.

Description

Originally identified in Swedish patients, Sjogren-Larsson is a rare genetic disorder. The condition is more common in places where intermarriage within families is traditional, such as among the Haliwa Native Americans of Halifax and Warren counties in North Carolina, and in Vasterbotten and Norrbotten Counties in Sweden.

Demographics

The frequency of Sjogren-Larsson syndrome in the United States is unknown. In Sweden, 0.4 of every 100,000 babies is born with the condition. There is no increased association with a particular race or sex.

Causes and symptoms

Sjogren-Larsson syndrome is inherited in an autosomal recessive fashion, meaning that an affected child has received a faulty gene from both the mother and the father. The disorder has been traced to a variety of defects on chromosome 17, resulting in a defective or deficient enzyme called fatty aldehyde dehydrogenase and an inability to appropriately metabolize compounds called fatty alcohols. Fatty alcohols and fatty aldehydes accumulate and cause water loss from the skin, leading to the severely dry, thickened skin characteristic of the disease.

Most babies with Sjogren-Larsson syndrome are born prematurely. They often have noticeably reddened skin at birth (erythema), with fine scales evident. Over the course of the first year, the skin becomes increasingly dry, rough, scaly, and thickened. The skin is often itchy. Neurological signs become obvious when the child is late or completely misses reaching various developmental milestones (sitting, crawling, pulling to a stand, vocalizing). The muscles are stiff and rigid, prohibiting normal motor development. Some children are able to walk with braces, but others must rely on a wheelchair throughout life. Mild to moderate mental retardation also becomes evident over time. Language is usually quite delayed. About 40% of children with Sjogren-Larsson syndrome suffer from **seizures**. Other characteristics of people with Sjogren-Larsson syndrome include short stature, poor eyesight, sensitivity to light resulting in squinting, defective tooth enamel, coarse and brittle hair, curved spine (hunchback), and unusually widely-spaced eyes.

Diagnosis

Sjogren-Larsson syndrome can be diagnosed by demonstrating greatly decreased activity of the deficient enzyme, or by identifying one of the genetic defects known to cause Sjogren-Larsson syndrome. **MRI** of the brain will reveal problems with myelin, the whitish material that normally forms a sheath around nerves, allowing for quick conduction of nerve messages. Skin biopsies will reveal a variety of abnormalities characteristic of Sjogren-Larsson syndrome. An EEG (electroencephalogram) will reveal disordered electrical patterns throughout the brain.

Treatment team

A child with Sjogren-Larsson syndrome will usually require diagnostic and treatment help from a team of professionals, including a **neurologist**, orthopedic surgeon, dermatologist, and ophthalmologist. Most children with Sjogren-Larsson syndrome need to be placed in a special educational setting.

Treatment

There are no treatments that can cure Sjogren-Larsson syndrome. A number of lotion or cream preparations (including mineral oil, urea, and vitamin D-3) may help improve itching and flaking, decrease the speed of skin turnover, and soften the skin. Sauna treatments and frequent showering and bathing may improve moisture levels in the skin.

Spasticity is sometimes improved through various surgical procedures. Braces may help increase mobility.

Recovery and rehabilitation

Most children with Sjogren-Larsson syndrome will benefit from services by a physical therapist (to help improve mobility), occupational therapist (to help improve ability to attend to activities of daily living), and speech and language therapist (to help develop both receptive and expressive language).

Prognosis

People with Sjogren-Larsson syndrome will not be able to live independently. They will require care throughout their lives. They may live to an adult age. The disease is not progressive, so the level of disability identified will remain constant.

Special concerns

In families who have an increased risk of Sjogren-Larsson disease, prenatal diagnosis can be accomplished through amniocentesis, chorionic villi sampling, or fetal skin **biopsy**.

Resources

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ORGANIZATIONS

Foundation for Ichthyosis & Related Skin Types, Inc. (F.I.R.S.T.). 650 N. Cannon Avenue, Suite 17, Lansdale, PA 19446. 215-631-1411; Fax: 215-631-1413. info@scalyskin.org. <http://www.scalyskin.org/>.

Rosalyn Carson-DeWitt, MD

Sleeping sickness *see* **Encephalitis lethargica**

Sleep apnea

Definition

Sleep apnea, or sleep-disordered breathing, is a condition in which breathing is briefly interrupted or even stops episodically during sleep. Because repeated arousal or even full awakening when breathing stops disturbs sleep, individuals suffering from sleep apnea are often drowsy during the day. Complications from an insufficient amount of oxygen reaching the brain are serious and even potentially life threatening. Sleep apnea appears to be far more common than was initially realized when it was first described in 1965.

Description

The syndrome of sleep apnea is subdivided into two types: central and obstructive. Central sleep apnea, in which the brain does not properly signal respiratory muscles to begin breathing, is much less common than obstructive sleep apnea. In the latter condition, there are repeated episodes of upper airway obstruction during sleep, typically reducing blood oxygen saturation.

A distinctive form of obstructive sleep apnea is known as the Pickwickian syndrome, named after the protagonist in Charles Dickens' *Pickwick Papers*. Like that character, individuals with the Pickwickian syndrome are overweight, with large necks, fat buildup around the soft tissues of the neck, and loss of muscle tone with aging. When the neck muscles relax during sleep, these characteristics allow the windpipe to collapse during breathing, which usually causes loud snoring.

When the individual with obstructive sleep apnea attempts to inhale, this causes suction that collapses the windpipe and blocks air flow for 10–60 seconds. The resulting fall in blood oxygen level signals the brain to awaken the person enough to tighten the upper airway muscles and reopen the windpipe, resulting in a snort or gasp before snoring resumes. The entire cycle may occur repeatedly, as often as hundreds of times each night.

Demographics

Approximately 6–7% of the population of the United States, or 18 million Americans, are thought to have sleep apnea, but only 10 million have symptoms, and only 0.6 million have yet been diagnosed. In Americans aged 30–60 years, obstructive sleep apnea affects nearly one in four men and one in 10 women; men are twice as likely as

Key Terms

Central sleep apnea A less-common form of sleep apnea in which the brain does not properly signal respiratory muscles to begin breathing.

Continuous positive airway pressure (CPAP) A device that keeps the airway open during sleep by delivering pressurized air through a mask over the nose or over both the nose and mouth.

Obstructive sleep apnea The most common form of sleep apnea characterized by repeated episodes of upper airway obstruction during sleep.

Pickwickian syndrome A distinctive form of obstructive sleep apnea associated with being overweight, having a large neck, fat buildup around the soft tissues of the neck, and loss of muscle tone with aging.

Polysomnography (PSG) A test done at a specialized sleep center in which breathing, brain waves, heartbeat, muscle tension, and eye movement are monitored during sleep through wires attached to the skin; additional testing may include oxygen levels and audio and/or video recordings.

Sleep apnea (sleep-disordered breathing) A condition in which breathing is briefly interrupted or even stops episodically during sleep.

Tracheostomy A surgical procedure that makes an opening in the windpipe to bypass the obstructed airway.

Uvulopalatopharyngoplasty (UPPP) A surgical procedure to remove excess tissue at the back of the throat and relieve airway obstruction.

women to have sleep apnea. As sleep apnea seldom occurs in premenopausal females, it is suggested that hormones may play some role in the disorder.

Other predisposing factors include age, as nearly 20–60% percent of the elderly may be affected; overweight status or obesity; or use of alcohol or sedatives. Based on a 1995 study, elderly African Americans are more than twice as likely as elderly whites to suffer from sleep apnea. Some families appear to have increased incidence of sleep apnea.

Causes and symptoms

Causes of central sleep apnea include various severe and life-threatening lesions of the lower brainstem, which controls breathing. Examples include bulbar **poliomyelitis**, a form of polio affecting the brainstem; degenerative diseases; **radiation** treatment to the neck, damaging the lower brainstem; and severe arthritis of the cervical spine and/or base of the skull, putting pressure on the lower brainstem.

Symptoms of central sleep apnea include cessation of breathing during sleep, often causing frequent awakenings and complaints of insomnia. In central sleep apnea, breathing patterns may also be disrupted during wakefulness. Other symptoms may relate to the underlying neurological condition affecting the brainstem, and may include difficulty swallowing, change in voice, or limb weakness and numbness.

Normally, muscles in the upper throat keep this part of the airway open, allowing air to enter the lungs. Although these muscles relax somewhat during sleep, they retain enough tone to keep the passage open. If the passage is narrow, relaxation of throat muscles during sleep can obstruct, or block, the passage and hinder or prevent air from flowing into the lungs.

Individuals with obstructive sleep apnea may have airway obstruction because of excessive relaxation of throat muscles or because of an already narrowed passage.

Because many patients with obstructive sleep apnea have no major structural defects in the airway and are not obese, other factors such as disordered control of ventilation and changes in lung volume during sleep may play a role in causing the condition.

Soon after falling asleep, the patient with obstructive sleep apnea typically begins snoring heavily. The snoring continues for some time and may become louder before the apnea, during which breathing stops for 10–60 seconds. A loud snort or gasp ends the apnea, followed by more snoring in a recurrent pattern. Decreased oxygen level in the blood during the apneas may cause decreased alertness and other symptoms, while disturbance of the sleep pattern at night may cause daytime drowsiness.

Those with the Pickwickian syndrome have a large neck or collar size, nasal obstruction, a large tongue, a narrow airway, or certain shapes of the palate and jaw.

While patients with sleep apnea may not be aware of the problem, their spouse may seek medical assistance because they are frequently awakened by their partner's snoring, which may be described as loud, squeaky, or raspy. In other cases, the patient may seek help for **fatigue**, difficulty staying awake during the day, or falling asleep at inappropriate times.

Because of restless sleep and decreased oxygen supply to the brain, patients with sleep apnea may complain of impaired mental function, slowed reaction times, problems concentrating, memory loss, poor judgment, personality changes such as irritability or **depression**, morning headaches, and decreased interest in sex.

Additional symptoms may include excessive sweating during sleep, bedwetting, nightmares, dry mouth when awakening caused by sleeping with the mouth open, development of high blood pressure, and frequent upper respiratory infections. Young children with sleep apnea may have visible inward movement of the chest during sleep, learning problems, growth or developmental problems, and hyperactive behavior.

Drinking alcohol before bedtime or taking sleeping pills may increase the risk of apneic episodes, as may breathing through the mouth rather than the nose during sleep.

Severe obstructive sleep apnea may cause pulmonary hypertension, or increased pressure in lung arteries, eventually leading to heart failure. Other complications may include increased risk of cardiovascular disease, **stroke**, heart arrhythmias or irregular heartbeats, and disorders of immune function.

Diagnosis

Although sleep apnea has been more widely diagnosed in the past decade, experts estimate that at least 90–95% of cases remain undiagnosed. Reasons for this include vague, slowly developing symptoms that largely occur when the patient is sleeping; limited knowledge of the disease by physicians; and expensive, specialized testing needed for definitive diagnosis.

Talking to the patient and the spouse or parent is an important first step, but it may not be sufficient. Similarly, the physical examination often fails to reveal distinctive abnormalities. Helpful diagnostic aids may include a questionnaire asking about typical symptoms and sleep habits, and a detailed inspection of the mouth, neck, and throat. Arterial blood gases may reveal low oxygen or high carbon dioxide levels in the blood.

More recently, it has been recognized that obstructive sleep apnea can occur even in individuals of normal weight who lack the other distinctive features of the Pickwickian syndrome. Up to 40% of people with obstructive sleep apnea are not obese.

When sleep apnea is suspected from characteristic symptoms and physical appearance, in many other cases, an overnight polysomnography (PSG) testing at a specialized sleep center may be suggested. During this test, breathing, brain waves, heartbeat, muscle tension, and eye movement are monitored through wires attached to the skin while the patient sleeps. Oxygen levels can be monitored through a device applied to a fingertip, and audio and/or video recordings may provide additional diagnostic information.

After the test, a physician trained in PSG testing analyzes the recordings to determine if sleep apnea or other conditions are present. In some cases, PSG can also be done at home after a sleep technologist attaches the wires and instructs the parent or other responsible adult on how to record sleep activity. Although portable PSG tests are less expensive and more convenient, they are subject to lost or inadequate recording, technical problems, and slightly lower diagnostic accuracy. Patients with inconclusive results on home studies and those with negative studies but persistent symptoms should have standard PSG testing in a sleep center.

Treatment team

The internist or family practitioner is often the first physician consulted because the earliest symptoms of sleep apnea are typically vague. If sleep apnea is suspected, the patient is usually referred to a **neurologist** or specialist in sleep disorders. Ear, nose, and throat specialists can help determine if there are characteristic abnormalities of the jaw or palate contributing to the problem, and in some cases they may perform corrective surgery if indicated. Lung specialists should manage severe cases of sleep apnea that result in pulmonary hypertension. Technicians involved in the diagnosis and treatment of sleep apnea may include PSG technicians and respiratory therapists.

Treatment

For mild cases of sleep apnea, simple measures may suffice, such as losing weight through a diet and **exercise** program, or preventing the person from sleeping on their back. More severe cases may need assisted breathing devices to wear at night or surgery to correct airway obstruction. Individuals with sleep apnea should avoid sedatives, sleeping pills, narcotics, and alcohol, especially at bedtime, as these **central nervous system** depressants can prevent them from awakening enough to keep breathing.

General suggestions to promote better sleep include good sleep habits, going to bed at a regular time each night, and arising at the same time each morning rather than sleeping late on weekends. Keeping the bedroom at a comfortable temperature is conducive to better sleep. Exercising 20–30 minutes each day, at least five to six hours before bedtime, may be helpful both for sleeping better and for weight loss.

Caffeine and related stimulants found in coffee, tea, chocolate, and some diet drugs and **pain** relievers should be avoided. Smoking disrupts sleep by causing early

morning awakening in response to nicotine withdrawal. Alcohol reduces the amount of time spent in deep sleep and rapid eye movement (REM) sleep and proportionately increases time spent in the lighter stages of sleep, which are less refreshing.

To relax before bedtime, taking a warm bath, reading, or other restful bedtime ritual may be helpful. Sleeping until the sun rises helps the body's internal biological clock reset itself, as does daily exposure to an hour of morning sunlight. When unable to sleep despite these measures, it is better to read, watch television, or listen to soothing music rather than lying in bed awake, which can cause anxiety and worsen insomnia.

To keep the airway open during sleep, some individuals with obstructive sleep apnea need a device called nasal CPAP, or continuous positive airway pressure, which delivers air through a mask over the nose or over both the nose and mouth. This is considered to be the most effective and widely used therapy.

Complications of CPAP may include nasal congestion or dryness, discomfort related to wearing the mask, and feelings of claustrophobia. To relieve these problems, heated humidifiers to moisturize and warm the air, better fitting and more comfortable masks, or applying steroids within the nasal passages may be helpful. In patients who find it difficult to exhale against the increased pressure of CPAP, bilevel positive-pressure therapy may be equally effective.

Some investigators are studying mechanical devices inserted into the mouth during sleep to open the airway by moving the jaw forward. Although these oral appliances appear to prevent daytime sleepiness and sleep disordered breathing, they do not seem to be as effective as nasal CPAP. However, they may be a reasonable option for patients who are unwilling or unable to use nasal CPAP.

Obstructive sleep apnea in children may be caused by enlarged tonsils and adenoids and can be corrected by tonsillectomy. In adults, surgery to remove airway obstruction may be needed, depending on the anatomical structure. Excess tissue at the back of the throat may be removed in a procedure called an uvulopalatopharyngoplasty, or UPPP. Some cases may require repairing a deviated nasal septum, or other surgery to remove blockage of the nose or upper throat. Surgery to correct obstructive sleep apnea seems to be most effective when it is tailored to the individual's specific anatomical obstruction.

As a last resort, a tracheostomy can be performed, making an opening in the windpipe to bypass the obstructed airway during sleep. During the day, a valve over the opening is closed so the person can speak, and at night, the valve is opened to bypass the obstruction.

If brainstem injury or disease impairs respiratory drive, causing central sleep apnea, mechanical ventilation on a respirator may be needed to ensure continued breathing.

Medications being tested in sleep apnea include Provigil, a nonaddictive drug that improves daytime alertness. Side effects may include nausea and headaches. Decongestants may reduce airway obstruction related to nasal congestion. Results of a controlled trial published in November 2003 suggest that the cholinesterase inhibitor physostigmine may reduce apnea episodes.

Clinical trials

The National Institutes of Neurological Disorder and Stroke, the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute on Aging all support sleep apnea research.

The National Institute of Child Health and Human Development (NICHD) is recruiting children and adolescents with obstructive sleep apnea or other obesity-related diseases for a trial of orlistat (Xenical, Hoffmann LaRoche). By preventing the action of digestive enzymes, this drug interferes with the absorption of approximately one-third of dietary fat. Study subjects may receive active medication or placebo, but all will be enrolled in a weight loss program, including nutrition education, behavioral self-monitoring strategies, and promotion of physical activity.

The APPLES study (apnea positive pressure long-term efficacy study), sponsored by the NHLBI, is recruiting patients with obstructive sleep apnea to determine the effectiveness of nasal CPAP therapy as compared with a similar-appearing control device that does not administer air delivered under positive pressure. Outcomes studied in this trial include mental function, mood, daytime sleepiness, and quality of life. Contact information is the office of study chair William C. Dement, MD, PhD, (650) 723-8131, or <http://apples.stanford.edu>.

The NHLBI is also planning a study of the outcomes of sleep disorders in men aged 65 years and older. It will look at whether sleep disorders such as obstructive sleep apnea are associated with increased risk of cardiovascular disease, falls, decreased physical function, impaired mental function, decreased bone density, fractures, and death.

Prognosis

Treating sleep apnea by eliminating the obstruction usually prevents and reverses complications such as pulmonary hypertension, high blood pressure, and heart disease. Individuals with obstructive sleep apnea who are unable or unwilling to tolerate CPAP may suffer from abnormal heart rhythms, reduced alertness, and sleep deprivation.

Left untreated, sleep apnea can profoundly reduce daytime functioning, work performance, social relationships, and quality of life. If patients fall asleep while driving or engaging in another potentially hazardous activity during the day, sleep apnea may be fatal. Severe, untreated sleep apnea doubles or even triples the risk of automobile accidents compared with the general population. These individuals are also at risk of sudden death from respiratory arrest during sleep.

Children with unrecognized obstructive sleep apnea may experience problems with learning, development, and behavior, as well as failure to grow, heart problems, and high blood pressure. Daytime sleepiness may cause personality changes, poor school performance, and difficulties with interpersonal relationships. Lagging development may lead to frustration and even depression.

Until additional research is carried out, it remains unclear if there is a "safe" number of apnea episodes, or how sleep apnea interacts with other causes of lung or heart failure. It appears that most patients with sleep apnea and heart or lung failure also have underlying diseases such as obstructive lung disease caused by smoking or asthma, severe obesity, or coronary artery disease.

Central sleep apnea usually has a poor prognosis related to the underlying injury or disease affecting the brainstem. Most patients with central sleep apnea require prolonged mechanical ventilation, which can also lead to many serious complications.

Special concerns

Sleep apnea is difficult to diagnose without expensive testing, can aggravate or cause heart and lung problems, often reduces function and quality of life, and may require invasive surgical procedures or long-term use of nasal CPAP. For all these reasons, prevention of obstructive sleep apnea is a worthwhile goal.

Weight reduction in overweight individuals and decreasing intake of alcohol and sedatives have independent health benefits as well as reducing risk of developing obstructive sleep apnea. In children with enlargement of the tonsils and adenoids, corrective surgery may reduce upper respiratory infections while preventing sleep apnea.

In experiments in rats, intermittent decreases in blood oxygen levels during sleep, similar to those seen with obstructive sleep apnea, cause degenerative changes in the hippocampus, a brain region involved in memory and learning. These degenerative changes in the brain are associated with deficits in maze learning. If similar changes occur in obstructive sleep apnea, this might explain decreased mental function observed with this disorder. Brain degeneration related to episodic decreases in oxygen levels would be another important reason to ensure that obstructive sleep apnea is diagnosed and effectively treated.

Although it is well recognized that sleep apnea is more common in men than in women, a study in October 2003 also suggested that men are far more likely than women to seek treatment at a specialized sleep clinic. Research is ongoing to determine the cause of gender differences in sleep apnea and to increase referrals of women to sleep centers where they may obtain appropriate care.

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Laurie Barclay

Social workers

Definition

A social worker is a helping professional who is distinguished from other human service professionals by a focus on both the individual and his or her environment. Generally, social workers have at least a bachelor's degree from an accredited education program and in most states they must be licensed, certified, or registered. A Master's in Social Work is required for those who provide psychotherapy or work in specific settings such as hospitals or nursing homes.

Description

Social workers comprise a profession that had its beginnings in 1889 when Jane Addams founded Hull House and the American settlement house movement in Chicago's West Side. The ethics and values that informed her work became the basis for the social work profession. They include respect for the dignity of human beings, especially those who are vulnerable, an understanding that people are influenced by their environment, and a desire to work for social change that rectifies gross or unjust differences.

The social work profession is broader than most disciplines with regard to the range and types of problems addressed, the settings in which the work takes place, the levels of practice, interventions used, and populations served. It has been observed that social work is defined in its own place in the larger social environment, continuously evolving to respond to and address a changing world. Although several definitions of social work have been provided throughout its history, common to all definitions is the focus on both the individual and the environment, distinguishing it from other helping professions.

Social workers may be engaged in a variety of occupations ranging from hospitals, schools, clinics, police departments, public agencies, and court systems to private practices or businesses. They provide the majority of mental health care to persons of all ages in this country, and in rural areas they are often the sole providers of services. In general, they assist people to obtain tangible services, help communities or groups provide or improve social and health services, provide counseling and psychotherapy with individuals, families, and groups, and participate in policy change through legislative processes. The practice of social work requires knowledge of human development and behavior, of social, economic and cultural institutions, and of the interaction of all these factors.

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Sodium oxybate

Definition

Sodium oxybate is primarily used to treat cataplexy attacks (episodes of weak or paralyzed muscles) in patients with **narcolepsy**, a condition that causes excessive sleepiness.

Purpose

There is no known cure for narcolepsy. Sodium oxybate is specifically indicated only for the treatment of cataplexy; it does not promote wakefulness or relieve excessive sleepiness, the main symptom of narcolepsy.

Description

Sodium oxybate is also sold in the United States under the name Xyrem. It is a Schedule III, federally controlled substance. Sodium oxybate has a high potential for abuse and is commonly known by its non-medical name, GHB. Patients who are prescribed sodium oxybate should use care when storing and disposing of the medication and its containers.

Recommended dosage

Sodium oxybate is taken as an oral solution, mixed with water. Physicians prescribe it in varying dosages. Sodium oxybate is usually taken in two divided doses, the first administered at bedtime and the second 2.5–4 hours later. As the medication induces sleep quickly, an alarm clock is sometimes needed to wake the person for the second dose. Typical adult daily dosages range from .17–.31 oz (5–9 g). If the first half of a daily divided dose is missed, it should be taken as soon as possible. If the second half of a daily divided dose is missed, that dose should be skipped and no more sodium oxybate should be taken until the following day. Two doses of sodium oxybate should never be taken at the same time.

Sodium oxybate works quickly, relaxing muscles and inducing sleep. As food will decrease the amount of sodium oxybate absorbed into the body, patients should not take the medication with meals.

Precautions

Sodium oxybate may be habit forming and has a high potential for non-medical abuse. When taking the medication, it is important to follow physician instructions precisely.

Sodium oxybate is sleep inducing and takes effect quickly. It should, therefore, be taken only at bedtime and while in bed. It may also cause clumsiness and impair clarity of thinking. It can exacerbate the side effects of alcohol and other medications. A physician should be consulted before taking sodium oxybate with certain non-prescription medications. Patients should avoid alcohol and **central nervous system** (CNS) depressants (medications that can make one drowsy or less alert, such as antihistimines, sleep medications, and some **pain** medications) while taking sodium oxybate because they can exacerbate the side effects.

Sodium oxybate may not be suitable for persons with a history of hypopnea (abnormally slow breathing), **sleep apnea**, liver or kidney disease, **depression**, metabolic disorders, high blood pressure, angina (chest pain), or irregular heartbeats and other heart problems.

Before beginning treatment with sodium oxybate, patients should notify their physician if they have a history of consuming a large amount of alcohol or a history of drug use. In these cases, dependence on sodium oxybate may be more likely to develop.

Patients who become pregnant while taking sodium oxybate should contact their physician immediately. Taking sodium oxybate while pregnant may cause fetal harm.

Side effects

Research indicates that sodium oxybate, when used under a physician's direction, is generally well tolerated. However, sodium oxybate may case a variety of usually mild side effects. These side effects usually do not require medical attention, and may diminish with continued use of the medication. They include:

- flu-like feeling
- abdominal pain
- difficulty sleeping
- nightmares
- nervousness or anxiety
- depression
- diarrhea
- dry mouth
- runny nose
- neck pain or stiffness

Key Terms

Cataplexy A sudden and dramatic loss of muscular strength without loss of consciousness; one symptom of narcolepsy.

Narcolepsy A serious sleep disorder characterized by excessive daytime sleepiness, sudden uncontrollable attacks of REM sleep, and attacks of cataplexy.

- **back pain**
- nausea or vomiting
- **headache**

Other, uncommon side effects of sodium oxybate can be potentially serious. A patient taking soduim oxybate who experiences any of the following symptoms should immediately contact their physician:

- sleepwalking
- change in vision
- ringing or pounding in the ears
- problems with memory
- numbness or tingling feelings on the skin
- disorientation, **fainting**, or loss of consciousness
- irregular heartbeat
- shortness of breath
- hives, rashes, or bluish patches on the lips and skin
- chest pain
- severe headache

Interactions

Sodium oxybate may have negative interactions with some anticoagulants (blood thinners), antidepressants, antifungals, antibiotics, asthma medications, barbiturates, and monoamine oxidase inhibitors (MAOIs). Seizure prevention medications **diazepam** (Valium), **phenobarbital** (Luminal, Solfoton), phenytoin (Dilantin), propranolol (Inderal), and rifampin (Rifadin, Rimactane) may also adversely react with sodium oxybate.

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Center for Narcolepsy. 701B Welch Road; Room 146, Palo Alto, CA 94304-5742. (650) 725-6517; Fax: (650) 725-4913. <http://www-med.stanford.edu/school/Psychiatry/narcolepsy/>.

Adrienne Wilmoth Lerner

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), a distinctive appearing face, and 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 others. The rate of growth 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

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).

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, 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 had 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 clinical 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 clear cut 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 facial appearance, with special attention paid to the shape of the head, width of the face at the level of the eyes, and the 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.

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 excessive growth is not treated. Regular eye and dental examinations are also recommended. 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.

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Sotos Syndrome Support Association Quarterly Newsletter.

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

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Spasticity

Definition

Spasticity is a form of muscle overactivity. A spastic muscle is one in which a muscle resists being stretched out, and the resistance to stretch is greater the faster the muscle is moved. Spasticity is often used as an umbrella

term for other forms of muscle overactivity that often occur at the same time in the same patient.

Description

Spasticity occurs following damage to the neurons, or nerve cells, that send signals from the brain to the muscles to cause movement. These neurons, which run from the brain through the spinal cord, are called upper motor neurons, and damage to them produces an upper motor neuron syndrome. The upper motor neuron syndrome may be caused by **stroke**, **traumatic brain injury**, **spinal cord injury**, **multiple sclerosis**, or numerous other less common causes of damage to the motor neurons. Damage to the brain occurring prior to or shortly after birth is called **cerebral palsy** (CP), which is the most common cause of an upper motor neuron syndrome in children.

The other forms of muscle overactivity common in the upper motor neuron syndrome are:

- Clonus, a relatively slow rhythmic contraction and relaxation of a muscle, typically occurring after a stimulus such as movement or while attempting to hold the muscle still. Clonus can be mild or severe in intensity.
- Spasms, strong and sustained contractions of muscles, which are often painful.
- Increased reflexes, in which the normal reflexes (such as knee extension in response to tapping) are greatly exaggerated.

Together, all these forms of muscle overactivity can cause significant disability in a patient, interfering with dressing, bathing, feeding, mobility, and other activities of daily living. The upper motor neuron syndrome also involves weakness and loss of dexterity, which may be even more disabling to the patient, and may be much less amenable to treatment.

Clinical patterns and problems

Spasticity may affect any muscle or group of muscles, but common patterns are often seen. Each causes its own set of impairments. For instance, the forearm may be drawn up and in toward the chest, making it difficult to put on or take off a shirt. The thighs may be pulled close together, not only making dressing difficult, but narrowing the base of support for standing and walking. The fingers may be clenched tight, driving the nails into the palm and preventing access for cleaning, resulting in infections and skin breakdown. One of the most common patterns is termed equinus, in which the calf muscles tighten, preventing the ankle from flexing completely and leading to walking on the toes.

When the muscle that is overactive is also very strong, it can lead to more severe complications, including partial dislocation. Hip dislocation is a common complication of spasticity in cerebral palsy. A constant imbalance in the forces across a joint due to spasticity can cause the bone to form new tissue in response, leading to bony deformities.

Inactivity brought on by disability can lead to a host of other problems, including pressure sores, osteoporosis, respiratory infections, and social isolation.

Key Terms

Equinus Excess contraction of the calf, causing toe walking.

Contracture

The resistance to stretch that characterizes spasticity may be mild and infrequent, or it may be severe and quite frequent. In the latter case, the patient can rarely attain a fully stretched position for the muscle, and the muscle spends more time than normal in a partially shortened position. When this occurs, a muscle can develop contracture. A contracture is the loss of full range of motion of a joint due to changes in the soft tissues (muscles and tendons) surrounding that joint. In contracture, the muscle fibers remodel themselves to accommodate this shorter length, thus shortening the muscle overall. In addition, the muscle may develop more fibrous tissue that cannot stretch as much, further increasing its resistance to stretch.

A muscle that develops contracture becomes almost impossible to stretch out to its full length, further worsening the clinical problems of the person with spasticity.

Treatments

Spasticity or other forms of muscle overactivity should be treated if they interfere with function, comfort, or care, or have the potential to lead to deformity that will later require treatment. Treatments available include physical therapy, oral medications, chemical denervation, intrathecal baclofen, neurosurgery, and orthopedic surgery.

Physical therapy

Physical therapy includes daily stretching exercises to maintain the full range of motion for the affected muscles. In mild spasticity, this may be the only treatment needed, while in severe spasticity, it is a part of the full therapy plan. Physical therapy also includes instructions in how to perform activities that are energy-efficient and do not worsen spasticity, including ways to transfer in and out of bed, sitting positions, and hygiene activities.

Bracing may be used to support a weak muscle, or to prevent excess contraction of a spastic muscle. A knee-ankle-foot brace is common to help correct equinus, for instance. Serial casting may be used to stretch out a contractured muscle, with a series of casts at increasing joint angles applied over time. The physical therapist also provides advice on assistive equipment such as wheelchairs and walkers.

Oral medications

Four main medications are used to treat spasticity and other forms of muscle overactivity. Each causes sedation, and thus their uses are limited in patients for whom excess sedation is a significant problem. Oral medications are typically most useful in patients with mild, widespread spasticity, or those for whom sedation is not a problem. They may also be useful at night, to improve comfort during sleep.

Benzodiazepines include **diazepam** and clonazepam. They are most commonly used in spinal cord injury and multiple sclerosis, and may be especially effective against painful spasms. They also reduce anxiety, which may be useful in some patients. Typical side effects include weakness, sedation, and confusion.

Oral baclofen is primarily used for patients with spinal cord injury or multiple sclerosis (MS). A special caution with baclofen is that sudden withdrawal may cause **seizures** and hallucinations. Tizanidine is also used widely in those with spinal cord injury or MS, and is also used in other patients. It is less likely to cause weakness than some other oral medications.

Dantrolene sodium is used for patients with stroke, cerebral palsy, MS, and spinal cord injury. It is somewhat less likely to cause confusion and sedation than other medications, and may be more effective against clonus than some of the other medications. Diarrhea is a side effect in some patients, and monitoring for liver damage is required.

Chemodenervation

Chemodenervation refers to use of a chemical to prevent a nerve from stimulating its target muscle. This reduces spasticity. Chemodenervation is performed with phenol, ethyl alcohol, or **botulinum toxin**. Chemodenervation is most appropriate in patients with localized spasticity in one or two large muscles or several small muscles.

Phenol and ethyl alcohol are injected directly onto the nerve, causing the nerve fiber to degenerate so that it cannot send messages to the muscle. Benefits may last from a month to six months or more, when the nerve regrows. Advantages of the procedure are that the chemicals are inexpensive and can be used repeatedly. Disadvantages are that the injection requires a high degree of skill, may cause **pain** due to damage to nerves carrying sensory information, and has a somewhat unpredictable duration of action.

Botulinum toxin is injected into the overactive muscle. It prevents the nerve endings from releasing the chemical they use to stimulate the muscle. The effect lasts approximately three months. Benefits include a simpler and easier injection procedure, with more predictable and reproducible results, with no risk of pain. Disadvantages include high cost and the potential to develop antibodies against the toxin after repeat injections, rendering it ineffective.

Intrathecal baclofen

Intrathecal baclofen (ITB) delivers baclofen directly to the spinal cord, via a tube from an implanted pump. It is most commonly used in patients with widespread spasticity, especially children with cerebral palsy. The pump is implanted in the wall of the abdomen, and the tube is inserted between the vertebrae in the lower or mid-back, releasing the drug into the space surrounding the spinal cord. This allows a much smaller amount of baclofen to be used than if delivered orally, reducing side effects. The baclofen is contained in a reservoir within the pump, and is refilled approximately every three months. The dose can be adjusted to match activities, for instance, increasing at night to aid sleep and decreasing in the morning to increase stiffness slightly to aid getting out of bed. Risks include pump failure and sudden withdrawal from baclofen, which can be dangerous or even fatal, as well as surgery and anesthesia risks. Benefits include reduced spasticity without excess sedation.

Neurosurgery

Selective dorsal rhizotomy (SDR) is used to treat spasticity in cerebral palsy. During SDR, certain overactive nerves entering the spinal cord are cut, reducing the activity that leads to spasticity. Children receiving SDR tend to be able to walk more normally, assuming they have good underlying strength before the operation. SDR is a major surgery requiring general anesthesia. Long-term results indicate children receiving SDR require slightly fewer orthopedic surgeries later in life.

Orthopedic surgery

This type of surgery is performed on muscle or bone, in order to correct deformity, including contracture. The most common surgery is tendon lengthening to treat equinus. In this procedure, the Achilles tendon is cut and the leg is placed in a cast in a more normal position. The tendon regrows to a longer length, reducing the equinus. Other tendon lengthening procedures are performed at the hips and knees. An osteotomy may also be performed to remove abnormal bone growth.

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ORGANIZATIONS

WE MOVE. 204 West 84th Street, New York, NY 10024. (212) 875-8389 or (800) 437-MOV2. wemove@wemove.org. <http://www.wemove.org>.

Richard Robinson

SPECT scan *see* **Single proton emission computed tomography**

Speech synthesizer

Definition

A speech synthesizer is a computerized device that accepts input, interprets data, and produces audible language.

It is capable of translating any text, predefined input, or controlled nonverbal body movement into audible speech. Such inputs may include text from a computer document, coordinated action such as keystrokes on a computer keyboard, simple action such as directional interpretation of a joystick, or basic functions such as eye, head, or foot movement.

Purpose

According to a study by the American Speech and Hearing Association, approximately 1.5 million people in the United States are unable to communicate through vocal language; this number does not include hearing impaired. A speech synthesizer can provide an electronic means of verbal communication for individuals who are unable to speak or have visual impairments. Since spoken language is the primary means of communication in most societies, it is often essential for people who are unable to speak on their own to capture that ability.

Individuals with motor neuron disease (MND) often lose their ability to speak due to weakened vocal cords. MND is a classification for disorders that cause muscle weakness and wasting such as **amyotrophic lateral sclerosis** (ALS), progressive bulbar palsy (PBP), **primary lateral sclerosis** (PLS), and progressive muscular atrophy (PMA). In patients with **cerebral palsy**, the area of the brain controlling vocal muscles is damaged resulting in speech loss.

Speech synthesizers can also be useful for people who are visually impaired. Although they may be able to produce oral speech, they are unable to read or produce written text in a non-Braille format. In the example of a student who is visually impaired, the ability to take notes during a lecture and to then review those notes later is not possible. However, with a speech synthesizer, the student can type lecture notes into a laptop and have a text-to-speech software program read them back for review and revision. Without this technology, the more time-consuming method of transcribing audio-recorded lectures into Braille is used.

Precautions

There are many considerations involved in selecting a method for speech synthesis. Key factors are the type of technology used, costs, and equipment. Technology can be overpriced or can quickly become obsolete. When considering the purchase of a speech synthesizer, it is important to determine the reliability of the manufacturer as well as policies regarding maintenance and upgrades of equipment or software. The most cost-effective tools are a laptop computer equipped with appropriate software and hardware. Unfortunately, many insurance companies will not cover the purchase of speech synthesizers or related assistive communication devices.

Description

There are many technologies involved in the production of speech with speech synthesizers. The two most definitive segments are how the user inputs information to be spoken and how the sounds for the words are actually interpreted and produced.

The first step to produce the speech is the composition of text to be spoken. In some cases, it is as simple as loading a computer text file into a software program. In other cases, a more complicated input system is required.

There are many different input devices, but the most prevalent is a keyboard or other similar typing board (such as a touchscreen). Patients with severe mobility restrictions may instead use a joystick device. Special input devices are created that act as switches. These switches are programmed to accept and decipher the motions of the user, even blinking of the eyes. Essentially any muscular movement can be interpreted as a switch and programmed to produce language.

The second step is deciphering the input and producing the desired audio speech. Data is gathered or assembled through the input device until the user indicates that the information is complete. The computer then interprets and speaks the words, phrases, or sentences. Complicated logic is involved when translating written text into spoken

Key Terms

Speech synthesizer A computerized device that accepts input, interprets data, and produces audible language.

language. For example, there are many words that are spelled the same, but pronounced differently in different contexts. The software must make that determination.

Depending on the device, multiple shortcuts may be available to the user. Examples include:

- storing phrases or sentences to reuse at a later time
- translation of abbreviations such as ASAP, which can also be programmed to speak the full phrase, i.e., "as soon as possible"
- software programs that "guess" what the user wants to say and predicts the output as input is gathered; if correct, the user can acknowledge the completion, thereby speeding up the entry of data

Preparation

Even with the advanced technology available for speech synthesizers, a bottleneck of information often occurs with the input. A typical spoken conversation takes place at a rate of 150–200 words per minute. While some individuals can become proficient at touch-typing, allowing for greater success with interactive conversations, many individuals are challenged to produce even 15 words per minute with communication devices.

The typical setup for individuals who use a computer or touchscreen includes a computer, keyboard, monitor, and speakers. In many cases, this equipment can be attached to a wheelchair or bed frame, allowing the user access to "speech" at any time. Other users may simply carry a laptop, batteries, and the necessary connection cables.

For those users unable to manipulate a computer or keyboard-style input device, there is a period of learning and acclimation required to become accustomed to the switch-style inputs. The user must learn how to complete the step-by-step process of composing thoughts into text for output.

A major challenge for individuals who are visually impaired is the presence of graphics in text. Because graphics typically lack a textual equivalent, they are not recognized and spoken by the synthesizer. This may cause the user to miss some information on the screen.

Aftercare

Once an individual has selected a speech synthesis device, there is little follow-up necessary. Hardware and software updates frequently evolve and so there is potential to upgrade devices periodically. Depending on the underlying cause of speech loss, some patients may need to change devices as they lose or regain the ability to speak or move.

Normal results

Through a speech synthesizer, non-vocal users can communicate with spoken words and people who are visually impaired can hear written text. The challenge of becoming proficient with these devices may be greater for some individuals based on physical restrictions.

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American Speech-Language-Hearing Association. 10801 Rockville Pike, Bethesda, MD 20852. (800) 638-8255. actioncenter@asha.org. <http://www.asha.org>.

Motor Neuron Disease Association. P.O. Box 246, Northampton NN1 2PR, United Kingdom. 01604 250505; Fax: 01604

638289/624726. enquiries@mndassociation.org. <http://www.mndassociation.org>.

Stacey L. Chamberlin

Spinal cord tumors *see* **Brain and spinal tumors**

Spinal surgery *see* **Laminectomy**

Spinal cord infarction

Definition

Spinal cord infarction (sometimes called spinal **stroke**) refers to injury to the spinal cord due to oxygen deprivation.

Description

Spinal cord infarction occurs when one of the three major arteries that supply blood (and therefore oxygen) to the spinal cord is blocked. As a result of such an occlusion, the spinal cord is deprived of oxygen, resulting in injury and destruction of the very vulnerable nerve fibers. The resulting disability will depend on what level of the spinal cord suffers the injury; everything below the area of the occlusion will be affected.

Demographics

Spinal cord infarction is a relatively rare condition, affecting about 12 in 100,000 people in the population.

Causes and symptoms

A variety of conditions can result in occlusion of the spinal arteries and spinal cord infarction, including:

- atherosclerosis of the aorta
- a dissecting aortic aneurysm (as well as surgical accidents that occur when clipping aortic aneurysms)
- a tumor or abscess impinging on an artery
- blockages in smaller blood vessels due to diabetes, polyarteritis nodosa, systemic **lupus** erythematosus, neurosyphilis, tuberculous meningitis, pneumococcal meningitis
- severe low blood pressure
- blood clots
- vasculitis

Rare cases of spinal cord infarction have resulted from conditions that exert pressure on the spine (pregnancy, back injury, **exercise**), resulting in the core of a spinal disc (nucleus pulposus) extruding out of the disc and entering into a spinal artery, resulting in a blockage of blood flow.

Depending on the mechanism underlying the spinal cord infarction, the symptoms may begin abruptly and acutely or slowly and gradually. Specific symptoms depend on where in the spinal cord the infarction occurs. Symptoms can include **pain**; paraplegia; quadriplegia; initially limp, floppy muscles that become tightly contracted (spastic) over the next several days; initial loss of reflexes, which become overactive (hyperreflexia) over the next several days; loss of the sense of pain and temperature; and loss of bladder and bowel control.

Diagnosis

Diagnosis is often made by excluding other conditions that might account for the patient's symptoms. Although many tests will not actually reveal spinal cord infarction as the reason for a patient's loss of function, it is important that a variety of tests are performed in order to search for potentially reversible causes of disability. **MRI** scanning may be helpful in this effort; it may not actually reveal images indicative of spinal cord infarction, however.

Treatment team

Individuals with spinal cord infarction are usually cared for by neurologists, physiatrists, physical therapists, and occupational therapists. Complications of spinal cord infarction may require consultation with urologists and pulmonologists.

Treatment

Once an individual has suffered a spinal cord infarction, there are no treatments that will reverse the damage. Some degree of functioning may return as the acute inflammation decreases. Underlying conditions that may have predisposed the individual to spinal cord infarction should certainly be addressed and treated.

Recovery and rehabilitation

Rehabilitation will involve teaching the individual new ways of being as independent as possible, based on the new limitations rendered by the disabilities of spinal cord infarction. The efforts of physical and occupational therapists will be crucial in this endeavor.

Prognosis

The prognosis of spinal cord infarction tends to be very poor. There is a high risk of death, either during the acute phase of infarction or over the long term, particularly

Key Terms

Aneurysm A weakness and ballooning of the wall of an artery, which can burst with potentially catastrophic ramifications.

Aorta The major artery that carries oxygenated blood from the heart to be delivered by arteries throughout the body.

Atherosclerosis A disease in which fatty deposits line the blood vessel walls, eventually threatening to block blood flow.

Infarction Tissue injury and death due to blocked blood flow and oxygen delivery.

Occlusion Blockage.

Vasculitis A condition in which inflammation of the blood vessels sometimes interferes with normal blood flow to various organs and tissues.

due to blood clots in the lungs (pulmonary emboli) or infection of bladder, lungs, or skin ulcerations secondary to inactivity and debilitation. Disability is significant, with a risk of paraplegia or quadriplegia.

Special concerns

The sudden loss of normal functioning and independence that can occur due to spinal cord infarction can prompt severe **depression**. Supportive psychotherapy can be an important adjunctive aid to optimal recovery.

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ORGANIZATIONS

Christopher Reeve Paralysis Foundation / Paralysis Resource Center. 500 Morris Avenue, Springfield, NJ 07081. 973-379-2690 or 800-225-0292; Fax: 973-912-9433. info@crpf.org; research@crpf.org. <http://www.christopherreeve.org>.

National Spinal Cord Injury Association. 6701 Democracy Blvd. #300-9, Bethesda, MD 20817. 301-214-4006 or 800-962-9629; Fax: 301-881-9817. info@spinalcord.org. <http://www.spinalcord.org>.

Rosalyn Carson-DeWitt, MD

Spinal cord injury

Definition

Spinal cord injury is damage to the spinal cord that causes loss of sensation and motor control.

Description

Approximately 10,000 new spinal cord injuries (SCIs) occur each year in the United States. About 250,000 people are currently affected. Spinal cord injuries can happen to anyone at any time of life. The typical patient, however, is a man between the ages of 19 and 26, injured in a motor vehicle accident (about 50% of all SCIs), a fall (20%), an act of violence (15%), or a sporting accident (14%). Most SCI patients are white, but the nonwhite fraction of SCI patients is larger than the nonwhite fraction of the general population. Alcohol or other drug abuse plays an important role in a large percentage of all spinal cord injuries. Six percent of people who receive injuries to the lower spine die within a year, and 40% of people who receive the more frequent higher injuries die within a year.

Short-term costs for hospitalization, equipment, and home modifications are approximately $140,000 for an SCI patient capable of independent living. Lifetime costs may exceed one million dollars. Costs may be three to four times higher for the SCI patient who needs long-term institutional care. Overall costs to the American economy in direct payments and lost productivity are more than $10 billion per year.

Causes and symptoms

The spinal cord is about as big around as the index finger. It descends from the brain down the back through hollow channels of the backbone. The spinal cord is made of nerve cells (neurons). The nerve cells carry sensory data from the areas outside the spinal cord (periphery) to the brain, and they carry motor commands from brain to periphery. Peripheral neurons are bundled together to make

up the 31 pairs of peripheral nerve roots. The peripheral nerve roots enter and exit the spinal cord by passing through the spaces between the stacked vertebrae. Each pair of nerves is named for the vertebra from which it exits. These are known as:

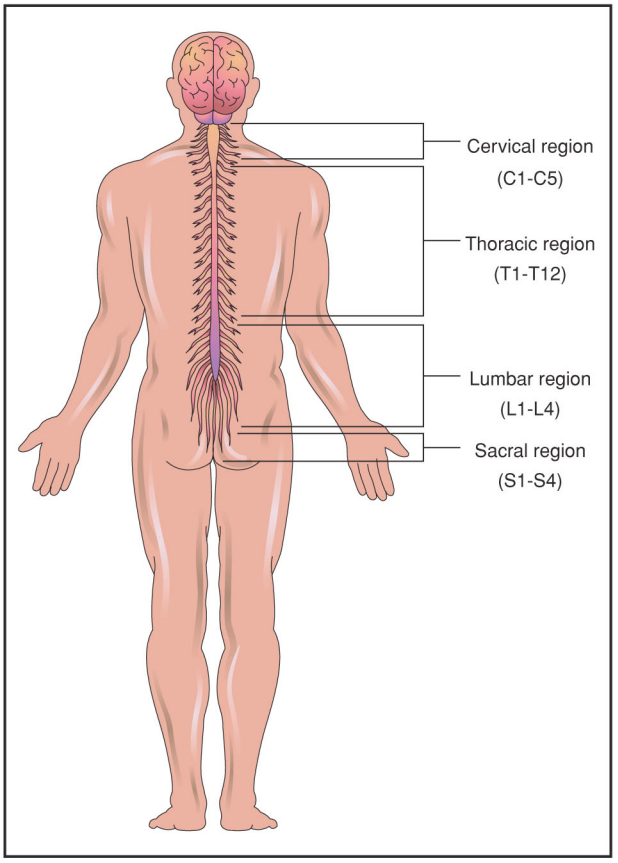
- C1-8. These nerves enter from the eight cervical or neck vertebrae.
- T1-12. These nerves enter from the thoracic or chest vertebrae.
- L1-5. These nerves enter from the lumbar vertebrae of the lower back.
- S1-5. These nerves enter through the sacral or pelvic vertebrae.
- Coccygeal. These nerves enter through the **coccyx** or tailbone.

Peripheral nerves carry motor commands to the muscles and internal organs, and they carry sensations from these areas and from the body's surface. (Sensory data from the head, including sight, sound, smell, and taste, do not pass through the spinal cord and are not affected by most SCIs.) Damage to the spinal cord interrupts these signals. The interruption damages motor functions that allow the muscles to move, sensory functions such as feeling heat and cold, and autonomic functions such as urination, sexual function, sweating, and blood pressure.

Spinal cord injuries most often occur where the spine is most flexible, in the regions of C5-C7 of the neck, and T10-L2 at the base of the rib cage. Several physically distinct types of damage are recognized. Sudden and violent jolts to nearby tissues can jar the cord. This jarring causes a temporary spinal concussion. Concussion symptoms usually disappear completely within several hours. A spinal contusion or bruise is bleeding within the spinal column. The pressure from the excess fluid may kill spinal cord neurons. Spinal compression is caused by some object, such as a tumor, pressing on the cord. Lacerations or tears cause direct damage to cord neurons. Lacerations can be caused by bone fragments or missiles such as bullets. Spinal transection describes the complete severing of the cord. Most spinal cord injuries involve two or more of these types of damage.

PARALYSIS AND LOSS OF SENSATION The extent to which movement and sensation are damaged depends on the level of the spinal cord injury. Nerves leaving the spinal cord at different levels control sensation and movement in different parts of the body. The distribution is roughly as follows:

- C1-C4: head and neck
- C3-C5: diaphragm (chest and breathing)
- C5-T1: shoulders, arms and hands



The extent of sensory and motor loss resulting from a spinal cord injury depends on the level of the injury because nerves at different levels control sensation and movement in different parts of the body. The distribution is as follows: C1-C4: head and neck; C3-C5: diaphragm; C5-T1: shoulders, arms, and hands; T2-T12: chest and abdomen (excluding internal organs); L1-L4: abdomen (excluding internal organs), buttocks, genitals, upper legs; L4-S3: legs; S2-S4: genitals, muscles of the perineum. *(Illustration by Electronic Illustrators Group.)*

- T2-T12: chest and abdomen (excluding internal organs)
- L1-L4: abdomen (excluding internal organs), buttocks, genitals, and upper legs
- L4-S1: legs
- S2-S4: genitals and muscles of the perineum

Damage below T1, which lies at the base of the rib cage, causes **paralysis** and loss of sensation in the legs and trunk below the injury. Injury at this level usually does no damage to the arms and hands. Paralysis of the legs is called paraplegia. Damage above T1 involves the arms as well as the legs. Paralysis of all four limbs is called quadriplegia or tetraplegia. Cervical or neck injuries not only cause quadriplegia but also may cause difficulty in breathing. Damage in the lower part of the neck may leave enough diaphragm control to allow unassisted breathing.

Patients with damage at C3 or above, just below the base of the skull, require mechanical assistance to breathe.

Symptoms also depend on the extent of spinal cord injury. A completely severed cord causes paralysis and loss of sensation below the wound. If the cord is only partially severed, some function will remain below the injury. Damage limited to the front portion of the cord causes paralysis and loss of sensations of **pain** and temperature. Other sensation may be preserved. Damage to the center of the cord may spare the legs but paralyze the arms. Damage to the right or left half causes loss of position sense, paralysis on the side of the injury, and loss of **pain** and temperature sensation on the opposite side.

DEEP VENOUS THROMBOSIS Blood does not flow normally to a paralyzed limb that is inactive for long periods. The blood pools in the deep veins and forms clots, a condition known as **deep vein thrombosis**. A clot or thrombus can break free and lodge in smaller arteries in the brain, causing a **stroke**, or in the lungs, causing **pulmonary embolism**.

PRESSURE ULCERS Inability to move also leads to pressure ulcers or bed sores. Pressure ulcers form where skin remains in contact with a bed or chair for a long time. The most common sites of pressure ulcers are the buttocks, hips, and heels.

SPASTICITY AND CONTRACTURE A paralyzed limb is incapable of active movement, but the muscle still has tone, a constant low level of contraction. Normal muscle tone requires communication between the muscle and the brain. Spinal cord injury prevents the brain from telling the muscle to relax. The result is prolonged muscle contraction or **spasticity**. Because the muscles that extend and those that bend a joint are not usually equal in strength, the involved joint is bent, often severely. This constant pressure causes deformity. As the muscle remains in the shortened position over several weeks or months, the tendons remodel and cause permanent muscle shortening or contracture. When muscles have permanently shortened, the inner surfaces of joints, such as armpits or palms, cannot be cleaned and the skin breaks down in that area.

HETEROTOPIC OSSIFICATION Heterotopic ossification is an abnormal deposit of bone in muscles and tendons that may occur after injury. It is most common in the hips and knees. Initially heterotopic ossification causes localized swelling, warmth, redness, and stiffness of the muscle. It usually begins one to four months after the injury and is rare after one year.

AUTONOMIC DYSREFLEXIA Body organs that regulate themselves, such as the heart, gastrointestinal tract, and glands, are controlled by groups of nerves called autonomic nerves. Autonomic nerves emerge from three different places: above the spinal column, in the lower back from vertebrae T1-L4, and from the lowest regions of the sacrum at the base of the spine. In general, these three groups of autonomic nerves operate in balance. Spinal cord injury can disrupt this balance, a condition called autonomic dysreflexia or autonomic hyperreflexia. Patients with injuries at T6 or above are at greatest risk.

In autonomic dysreflexia, irritation of the skin, bowel, or bladder causes a highly exaggerated response from autonomic nerves. This response is caused by the uncontrolled release of norepinephrine, a hormone similar to adrenaline. Uncontrolled release of norepinephrine causes a rapid rise in blood pressure and a slowing of the heart rate. These symptoms are accompanied by throbbing **headache**, nausea, **anxiety**, sweating, and goose bumps below the level of the injury. The elevated blood pressure can rapidly cause loss of consciousness, **seizures**, cerebral hemorrhage, and **death**. Autonomic dysreflexia is most often caused by an over-full bladder or bladder infection, impaction or hard impassable fecal mass in the bowel, or skin irritation from tight clothing, **sunburn**, or other irritant. Inability to sense these irritants before the autonomic reaction begins is a major cause of dysreflexia.

LOSS OF BLADDER AND BOWEL CONTROL Bladder and bowel control require both motor nerves and the autonomic nervous system. Both of these systems may be damaged by SCI. When the autonomic nervous system triggers an urge to urinate or defecate, continence is maintained by contracting the anal or urethral sphincters. A sphincter is a ring of muscle that contracts to close off a passage or opening in the body. When the neural connections to these muscles are severed, conscious control is lost. In addition, loss of feeling may prevent sensations of fullness from reaching the brain. To compensate, the patient may help empty the bowel or bladder by using physical maneuvers that stimulate autonomic contractions before they would otherwise begin. However, the patient may not be able to relax the sphincters. If the sphincters cannot be relaxed, the patient will retain urine or feces.

Retention of urine may cause muscular changes in the bladder and urethral sphincter that make the problem worse. Urinary tract infection is common. Retention of feces can cause impaction. Symptoms of impaction include loss of appetite and nausea. Untreated impaction may cause perforation of the large intestine and rapid overwhelming infection.

SEXUAL DYSFUNCTION Men who have sustained SCI may be unable to achieve an erection or ejaculate. Sperm formation may be abnormal too, reducing fertility. Fertility and the ability to achieve orgasm are less impaired for women. Women may still be able to become pregnant and deliver vaginally with proper medical care.

Key Terms

Autonomic nervous system The part of the nervous system that controls involuntary functions such as sweating and blood pressure.

Botulinum toxin Any of a group of potent bacterial toxins or poisons produced by different strains of the bacterium *Clostridium botulinum*.

Computed tomography (CT) An imaging technique in which cross-sectional x rays of the body are compiled to create a three-dimensional image of the body's internal structures.

Magnetic resonance imaging (MRI) An imaging technique that uses a large circular magnet and radio waves to generate signals from atoms in the body. These signals are used to construct images of internal structures.

Motor Of or pertaining to motion, the body apparatus involved in movement, or the brain functions that direct purposeful activity.

Motor nerve Motor or efferent nerve cells carry impulses from the brain to muscle or organ tissue.

Peripheral nervous system The part of the nervous system that is outside the brain and spinal cord. Sensory, motor, and autonomic nerves are included.

Postural drainage The use of positioning to drain secretions from the bronchial tubes and lungs into the trachea or windpipe.

Range of motion (ROM) The range of motion of a joint from full extension to full flexion (bending) measured in degrees like a circle.

Sensory nerves Sensory or afferent nerves carry impulses of sensation from the periphery or outward parts of the body to the brain. Sensations include feelings, impressions, and awareness of the state of the body.

Voluntary An action or thought undertaken or controlled by a person's free will or choice.

Diagnosis

The location and extent of spinal cord injury is determined with **computed tomography scans** (CT scans), **magnetic resonance imaging** (**MRI**) scans, and x rays. X rays may be enhanced with an injected contrast dye.

Treatment

A person who may have a spinal cord injury should not be moved. Treatment of SCI begins with **immobilization**. This strategy prevents partial injuries of the cord from severing it completely. Use of splints to completely immobilize suspected SCI at the scene of the injury has helped reduce the severity of spinal cord injuries in the last two decades. Intravenous methylprednisone, a steroidal anti-inflammatory drug, is given during the first 24 hours to reduce inflammation and tissue destruction.

Rehabilitation after spinal cord injury seeks to prevent complications, promote recovery, and make the most of remaining function. Rehabilitation is a complex and long-term process. It requires a team of professionals, including a **neurologist**, physiatrist or rehabilitation specialist, physical therapist, and occupational therapist. Other specialists who may be needed include a respiratory therapist, vocational rehabilitation counselor, social worker, speech-language pathologist, nutritionist, special education teacher, recreation therapist, and clinical psychologist. Support groups provide a critical source of information, advice, and support for SCI patients.

Paralysis and loss of sensation

Some limited mobility and sensation may be recovered, but the extent and speed of this recovery cannot be predicted. Experimental electrical stimulation has been shown to allow some control of muscle contraction in paraplegia. This experimental technique offers the possibility of unaided walking. Further development of current control systems will be needed before useful movement is possible outside the laboratory.

The physical therapist focuses on mobility, to maintain range of motion of affected limbs and reduce contracture and deformity. Physical therapy helps compensate for lost skills by using those muscles that are still functional. It also helps to increase any residual strength and control in affected muscles. A physical therapist suggests adaptive equipment such as braces, canes, or wheelchairs.

An occupational therapist works to restore ability to perform the activities of daily living, such as eating and grooming, with tools and new techniques. The occupational therapist also designs modifications of the home and workplace to match the individual impairment.

A pulmonologist or respiratory therapist promotes airway hygiene through instruction in assisted coughing techniques and postural drainage. The respiratory professional also prescribes and provides instruction in the use of ventilators, facial or nasal masks, and tracheostomy equipment where necessary.

Pressure ulcers

Pressure ulcers are prevented by turning in bed at least every two hours. The patient should be turned more frequently when redness begins to develop in sensitive areas. Special mattresses and chair cushions can distribute weight more evenly to reduce pressure. Electrical stimulation is sometimes used to promote muscle movement to prevent pressure ulcers.

Spasticity and contracture

Range of motion (ROM) exercises help to prevent contracture. Chemicals can be used to prevent **contractures** from becoming fixed when ROM **exercise** is inadequate. Phenol or alcohol can be injected onto the nerve or **botulinum toxin** directly into the muscle. Botulinum toxin is associated with fewer complications, but it is more expensive than phenol and alcohol. Contractures can be released by cutting the shortened tendon or transferring it surgically to a different site on the bone where its pull will not cause as much deformity. Such tendon transfers may also be used to increase strength in partially functional extremities.

Heterotopic ossification

Etidronate disodium (Didronel), a drug that regulates the body's use of calcium, is used to prevent heterotopic ossification. Treatment begins three weeks after the injury and continues for 12 weeks. Surgical removal of ossified tissue is possible.

Autonomic dysreflexia

Autonomic dysreflexia is prevented by bowel and bladder care and attention to potential irritants. It is treated by prompt removal of the irritant. Drugs to lower blood pressure are used when necessary. People with SCI should educate friends and family members about the symptoms and treatment of dysreflexia, because immediate attention is necessary.

Loss of bladder and bowel control

Normal bowel function is promoted through adequate fluid intake and a diet rich in fiber. Evacuation is stimulated by deliberately increasing the abdominal pressure, either voluntarily or by using an abdominal binder.

Bladder care involves continual or intermittent catheterization. The full bladder may be detected by feeling its bulge against the abdominal wall. Urinary tract infection is a significant complication of catheterization and requires frequent monitoring.

Sexual dysfunction

Counseling can help in adjusting to changes in sexual function after spinal cord injury. Erection may be enhanced through the same means used to treat erectile dysfunction in the general population.

Prognosis

The prognosis of SCI depends on the location and extent of injury. Injuries of the neck above C4 with significant involvement of the diaphragm hold the gravest prognosis. Respiratory infection is one of the leading causes of death in long-term SCI. Overall, 85% of SCI patients who survive the first 24 hours are alive 10 years after their injuries. Recovery of function is impossible to predict. Partial recovery is more likely after an incomplete wound than after the spinal cord has been completely severed.

Prevention

Risk of spinal cord injury can be reduced through prevention of the accidents that lead to it. Chances of injury from automobile accidents, the major cause of SCIs, can be significantly reduced by driving at safe speeds, avoiding alcohol while driving, and using seat belts.

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ORGANIZATIONS

The National Spinal Cord Injury Association. 8300 Colesville Road, Silver Spring, Maryland 20910. (301) 588-6959. <http://www.erols.com/nscia>.

Richard Robinson

Spinal muscular atrophy

Definition

Spinal muscular atrophies (SMAs) are a wide group of genetic disorders characterized by primary degeneration of anterior horn cells of the spinal cord, resulting in progressive muscle weakness. The most common form of spinal muscular atrophy is childhood proximal SMA. Other forms of SMAs include X-linked recessively inherited bulbospinal SMA, distal SMAs, scapuloperoneal SMAs, and others such as facioscapulohumeral, scapulohumeral, oculopharyngeal, and Ryukyuan SMAs.

Description

SMAs present with diverse symptoms and differ in age of onset, mode of inheritance, distribution of muscle weakness, and progression of symptoms.

Childhood proximal SMA is subdivided into three clinical groups: type I, type II, and type III SMA. SMA type IV designates adult form of proximal SMA. Although it is now apparent that the phenotype of SMA associated with mutations of the survival motor neuron (SMN1) gene spans a continuum without a clear delineation of subtypes, the classification is useful for prognosis and management.

SMA I (acute infantile SMA, Werdnig-Hoffman disease) manifests by decreased fetal movements in the last trimester of pregnancy in about one third of cases. About 65% of affected infants are floppy at birth, while delayed motor milestones are characteristic in all affected children by the age of six months. In addition to muscle weakness, clinical features include head lag, poor sucking and swallowing, weak cry, proximal limb weakness, and lack of reflexes. Affected children never raise their head, roll over, or walk. Sometimes weakness of the face and jaw muscles, finger tremor, and respiratory difficulty occur. Orthopedic abnormalities such as congenital dislocation of the hip, chest wall asymmetries, and flexion contractures are present in 25% of affected newborns.

SMA II (intermediate SMA) usually manifests itself between six and 12 months of age. Although poor muscle tone may be evident at birth or within the first few months of life, patients with SMA II may gain motor milestones slowly. Eighty percent are able to sit independently, although they are not able stand or walk alone. Limb girdle weakness, twitching, lack of reflexes, and weakness of tongue, face, and neck muscles are seen. **Tremors** affecting the upper extremities, musculoskeletal deformities, and respiratory failure occur.

SMA III (chronic SMA, Kugelberg-Welander disease) presents with the onset of symptoms after the age of 18 months. Patients walk independently, but may fall frequently or have trouble walking up and down stairs between age two to three years. Muscular weakness is present on both sides of the body, and the legs are more severely affected than the arms. Difficulty swallowing and difficulty speaking may occur in later stages of the disorder.

SMA IV manifests as muscle weakness usually in the second or third decade of life. The findings are similar to those described for SMA III.

Bulbospinal muscular atrophy (Kennedy disease) manifests as muscle weakness between the ages of 20 and 40 years. Weakness and atrophy in the lower extremities are usually followed by problems with the pectoral girdle, facial muscles, distal limb, and bulbar muscles. Muscle cramps on exertion often precede the weakness by several years. Fine tremors of the face are present in over 90% of patients. Type 2 diabetes mellitus, hand tremor, and infertility can also occur. Bulbar involvement predisposes the person with spinal muscular atrophy to recurrent aspiration pneumonia, due to weakening of the muscles necessary for efficient swallowing.

Other less common forms of SMAs include distal SMAs (10% of all SMA cases) and scapuloperoneal SMA (7% of all SMA cases). Distal SMAs are a group of disorders that manifest most commonly soon after birth, with muscle wasting in the hands and feet. Later in life, abnormal gait and foot deformities are seen. Similar clinical signs occur in adult-onset forms. Scapuloperoneal SMA has a characteristic pattern of muscle weakness, usually involving the heart and sensory neuropathy (Davidenkow's syndrome).

Demographics

SMAs are one of the most common groups of neuromuscular diseases in children, with an incidence of four to 10 per 100,000 live births. Other SMAs have a lower incidence, as a rule less than one per 100,000 live births.

Causes and symptoms

Spinal muscular atrophies are genetic diseases. Types I, II, and III SMAs have been mapped to chromosome 5q11.2-13.3. In 1994, the survival motor neuron (SMN1) gene was identified as responsible for SMA when mutations occur. The SMN1 gene has a duplicate copy called the SMN2 gene, but it is not able to compensate for the defects in the SMN1 gene. There is evidence that type I SMA is caused by deletion of the SMN1 gene, whereas type III is associated with a conversion event of SMN1 into SMN2, leading to an increased number of SMN2 genes. In addition to bulbospinal muscular atrophy, which has been shown to be caused by a defect in the androgen receptor gene, six other SMAs have already been mapped to corresponding chromosomal locations.

Inheritance pattern for most forms of SMA is autosomal recessive, meaning that both parents are carriers of the disorder, and the chance of having a child affected with the disorder is 25% with each pregnancy. Familial forms of the disorder that occur later in life are usually due to an autosomal recessive or autosomal dominant inheritance pattern.

Diagnosis

Diagnosis is based on the clinical presentation, family history, and genetic testing. The genetic test is based on the fact that approximately 95–98% of individuals with a clinical diagnosis of childhood SMA lack exon 7 in both copies of the SMN1 gene. Likewise, all patients with bulbospinal muscular atrophy have a defect in the androgen receptor gene.

Key Terms

Atrophy Wasting or degeneration of tissues.

Contractures Abnormal, usually permanent, stiffness or contractions of a muscle due to wasting of muscle fibers, extensive scar tissue over a joint, or other factors.

Distal muscles Muscles farthest away from the center of the body, such as muscles in the fingers and toes.

Proximal muscles Muscles closest to the center of the body, such as muscles used in breathing and sitting upright.

An electromyelogram may reveal damaged nerve impulses secondary to muscle fiber degeneration. Sensory nerve conduction studies are normal in all forms of SMA, the exceptions being bulbospinal muscular atrophy and Davidenkow's syndrome. Muscle **biopsy** is critical in the diagnosis of childhood SMA. If performed, it reveals atrophy of muscle fibers with a characteristic form of muscle fiber type grouping.

Treatment team

A multidisciplinary approach is essential for providing care and treatment of a person with spinal muscular atrophy, including specialists in the fields of neurology, physical therapy, occupational therapy, respiratory therapy, surgery, and genetic counseling.

Treatment

As no specific treatment is available for spinal muscular atrophies, the resulting complications of muscle deterioration are managed as best as possible. Treatment in severe childhood SMA includes prescription of antibiotics for respiratory infections and tube feeding in children with profound difficulty in sucking and swallowing. In children with SMA II, the goals of conservative therapy include maintaining the sitting posture, preserving or improving function, and reducing progression of deformity. This is achieved by regular active **exercise** monitored by physical therapists, gentle traction to prevent contractures (stiff muscles near the joints), splinting, bracing, and the use of spinal positioning devices and upright mobility systems. Orthopedic surgical interventions such as tendon transfer or spinal surgery can prevent disability in patients with expected prolonged survival.

Recovery and rehabilitation

As there is no recovery from spinal muscular atrophies, the emphasis is placed upon maintaining muscle function and mobility for as long as possible. Physical therapy is an integral part of maintaining movement in persons with spinal muscular atrophies. In children, range of motion exercises keep muscles and joints moving, while reaching games provide stimulation and aid in coordination. Water therapy also provides an enjoyable medium for working the muscles and joints.

As muscle weakness progresses and affects posture, occupational therapy can provide assistive devices and strategies to maintain positioning and movement, such as specialized wheelchairs and reaching devices. Respiratory therapy is also important to teach parents the chest therapy exercises and maneuvers that are necessary to remove accumulated secretions and mucous from the lungs.

Normal education should be encouraged for children with spinal muscular atrophies, especially in the more slowly progressive forms, as intelligence is preserved and even superior in many children with SMA.

Clinical trials

Riluzole, **gabapentin**, albuterol, phenylbutyrate, and thyrotropin-releasing hormone have so far been tested and have shown potential effects on improvement of muscle strength in children with SMA. Many different controlled trials are needed to confirm these preliminary findings.

Prognosis

Progressive muscle weakness usually leads to death by age four for persons with SMA I. Muscle weakness progresses at varying rates in SMA II, and many persons survive into adulthood. The life expectancy of patients with SMA III is close to that of the healthy population. Progression of the adult-onset SMAs is usually slow, and patients are ambulatory until late in the disease. Lifespan is only slightly reduced.

Special concerns

Genetic counseling is important in SMA, since prenatal and preimplantation genetic diagnoses offer the parents the possibility to prevent the disease.

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"Understanding Spinal Muscular Atrophy: A Comprehensive Guide." *Families of Spinal Muscular Atrophy.* May 5, 2004 (May 27, 2004). <http://www.fsma.org/booklet.shtml#taking>.

ORGANIZATIONS

Families of SMA. PO Box 196, Libertyville, IL 60048-0196. (847) 367-7623 or (800) 886-1762. sma@fsma.org. <http://www.fsma.org>.

Borut Peterlin, MD, PhD

Spina bifida

Definition

Spina bifida belongs to a group of disorders known as neural tube defects (NTDs). These all involve problems in the development and closure of the neural tube, a structure in the human fetus that begins forming very early in a pregnancy. The neural tube eventually becomes the spinal column. When the neural tube does not close properly, it can lead to spina bifida, a disruption in the spinal column. Spina bifida occurs to varying degrees of severity, and in various forms.

Description

Spina bifida is also known by the name spinal dysraphism. It generally occurs in two major types. One types is spina bifida cystica or spina bifida aperta, which involves a sac filled with spinal contents along the spine. The other type is spina bifida occulta, in which the spinal cord stays inside the spinal canal and there is no sac.

Spina bifida ranges from having no or mild effects, to having severe effects and a significant impact upon a person's life. Physical symptoms can include weakness of limbs, paralysis, lack of bowel or bladder control, learning problems, **hydrocephalus**, **seizures**, central apnea, clubfeet, impaired vision, and latex sensitivity.

Depending upon the involvement of the spinal problem, spina bifida can also have psychological and emotional impacts upon the affected person and his or her family.

Demographics

Spina bifida is fairly common; it is thought to occur in about one in 2,000 live births in the United States. NTDs in general occur in about one in 1,000 live births in the United States. Many areas have an even higher prevalence, for somewhat unknown reasons. A population with a higher prevalence for NTDs is the United Kingdom, with an estimated rate of 2.8 per 1,000 live births in the 1970s. A similar study in Ireland at that time estimated the rate to be about 7.1 per 1,000 live births. Through the advent of prenatal screening, prenatal diagnosis, pregnancy management options, and unknown factors the prevalence in the British Isles has fallen somewhat in recent years.

Higher rates of NTDs have been reported in the northwest British Isles, with lower rates in the southeast. In Canada, higher prevalence rates for NTDs have been reported in the eastern region of the country, as compared to the western region. A higher prevalence of NTDs has been seen in China in the provinces north of the Yangtze River, and these may be as much as six times higher than in the southern provinces. Pockets of higher prevalence have also been seen in India, but these do not fit any clear geographic areas or regions.

In the United States, people of Hispanic ancestry have a higher chance for NTDs than other ethnic groups. Conversely, African Americans and some Asians have a lower risk than other ethnic groups. When those with high NTD risks immigrate to other countries, they do not keep their high risk for NTDs. When those with low NTD risks migrate, they tend to maintain their low risk status, as a group.

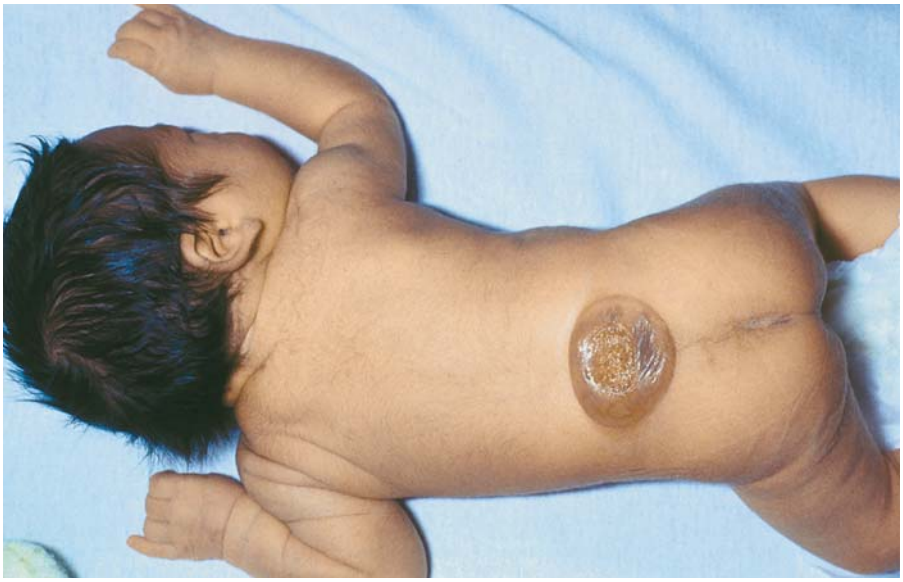
Spina bifida has been reported in males and females roughly equally.

Causes and symptoms

Spina bifida occurs because the neural tube, around the area of the spine, fails to close during fetal development. A multifactorial cause for this has been assumed, because multiple factors seem to be involved. It may best be described as an interaction between multiple genes and the environment. Many aspects of this interaction are still not well understood. As well, an exact neurological cause for spina bifida has not been identified.

Spina bifida can run in families. Multiple genes may be involved because identical twins, those with the exact same genetics, have been studied at length. Spina bifida also occurs as part of genetic syndromes and chromosome disorders.

Numerous families with NTDs have been studied to help identify recurrence risks. Generally, the risk is 3–5% for a couple to have another child with an NTD if they already have one. If a parent has an NTD, they have a 3–5% chance to have a child with one. If two or more children



An infant with spina bifida. *(© Custom Medical Stock Photo. Reproduced by permission.)*

already have NTDs, the risk is 6–9% for another one. If an NTD is in other more distant family members, the risk is somewhat higher than the average population, but probably not higher than 0.5%.

Environmental factors are also important in spina bifida. For example, taking the B vitamin folic acid before pregnancy conception has been shown to significantly reduce a woman's risk of having a child with the condition. Additionally, some medications can increase a woman's risk for spina bifida; these include some anti-seizures medications. As it turns out, many of these medications naturally reduce the levels of folic acid in one's body.

Neurological symptoms of spina bifida are varied. Many of them relate back to the early embryo's development, and how spina bifida occurs at this time. Three cell layers develop in the very early embryo; these are the ectoderm, mesoderm, and endoderm. The mesoderm normally sends signals to a region of the ectoderm to make it develop into neural tissue. Eventually, the neural ectoderm folds to form a tube, which runs for most of the length of the embryo. The top of the neural tube eventually forms the brain and top of the spinal column. The bottom of the neural tube eventually forms the lower back and bottom of the spinal column. This happens through very careful and controlled cell movements. The neural tube is usually completed forming by about 18 to 26 days after ovulation.

Failure of the neural tube to close causes spina bifida, and this disrupts the spinal column's structure and functioning. This disruption can be mild, as in spina bifida occulta. It may also be more severe with a large sac or cyst present, as in spina bifida cystica.

In about 80–90% of spina bifida cases, there is a cyst with parts of the spinal cord and spinal wall present. This is called a myelomeningocele (or meningomyelocele). This type of spina bifida can happen in a relatively high or low position on one's back. It often causes problems with bladder and bowel functioning, and sometimes paralysis or limb weaknesses. A neuropathic bladder can sometimes affect kidney functioning as well.

When a developing baby cannot move their limbs well *in utero*, this sometimes leads to feet and legs that turn inward, or clubfoot. As a result, some children with spina bifida are born with clubfoot.

Myelomeningoceles often cause spinal fluid to not flow properly through the system, and hydrocephalus may be a result. Head ultrasound scans may show hydrocephalus in about 90% of newborns with spina bifida. It is often associated with an **Arnold-Chiari malformation**, Type II. This occurs when the medulla pushes downward below the foramen magnum, and overlaps the spinal cord. This malformation is present in about 70% of people who have a meningomyelocele; it can cause distortion of the medulla and midbrain, as well as central apnea.

Hydrocephalus can eventually cause increased pressure to develop in the brain. This may ultimately lead to one's brain not being able to grow properly, and cause learning problems. Seizures may also be present. Learning problems are not a certainty with spina bifida, but when present they vary greatly. Their severity is impossible to predict. However, hydrocephalus and seizures put one at a higher risk for learning problems. Surveys on intellectual development have shown that children with hydrocephalus have lower IQs than their siblings without the condition.

In about 5% of spina bifida cases, there is no spinal tissue in the cyst wall; these are called meningoceles. Hydrocephalus is not usually present in this type of spina bifida, and a neurological examination may even be perfectly normal.

Optic atrophy and squinting may occur in people who have spina bifida, and a result of these may be poorer vision.

There is an association between spina bifida and latex sensitivity. Many have attributed this to the fact that people with the condition have a higher exposure to latex, since they may be in hospitals more often. Interestingly, a study in 2000 showed that 22% of children with spina bifida still had latex sensitivity, despite efforts to maintain latex-free environments for them.

Spina bifida occulta may cause mild symptoms, or none at all. Sometimes the only signs of it may in the lower spine area as a dimple, a small tuft of hair, or a small growth. If one has an imaging scan and a tethered spinal cord is noted, this can sometimes be a sign of spina bifida occulta as well.

Diagnosis

A early time to find spina bifida is during a detailed prenatal ultrasound scan, especially between 16 and 20 weeks gestation (from the last menstrual period). Ultrasounds cannot identify every structural problem in a developing baby, so some cases of spina bifida (especially mild forms) may be missed. However, it is a risk-free method to use that gives immediate results.

Prenatal blood screening is often offered to women between 15 and 21 weeks in a pregnancy. This screening measures the levels of various chemicals naturally found in a mother's blood, including alpha-fetoprotein (AFP). For this reason, the screening is often called AFP screening. AFP is a protein normally made by a developing fetus, so it is naturally present in maternal serum and called MS-AFP. When a fetus has spina bifida, the levels of MS-AFP may be higher than usual because it leaks out of the hole in the spine. If a woman's AFP screen comes back abnormal with a high MS-AFP value, she often is at a higher risk for having a baby with spina bifida. This may prompt her physician to offer her a detailed ultrasound, as well as other medical options that might give her more information about the baby.

One option to find spina bifida is a procedure called amniocentesis. Amniocentesis involves removing a small amount of fluid from around the baby, using a fine needle. This fluid naturally contains AFP, which may also be elevated if the baby has spina bifida. There is a small risk of miscarriage, about one in 200, with this procedure. As such, every women usually receives proper counseling through their doctor or a genetic counselor before having the test done.

Sometimes, spina bifida can only be seen at birth. A physical examination usually identifies spina bifida cystica fairly easily, especially if the sac is large. Spina bifida occulta can be more difficult to find, but clues can be a dimple in the lower back, a tuft of hair, or a small growth.

Once spina bifida is seen outwardly, imaging scans like x rays, ultrasound, **magnetic resonance imaging (MRI)**, or computed tomography (**CT**) can be helpful to see the extent of it. It is also a good way to identify whether someone has associated neurological complications like hydrocephalus.

Since spina bifida may occur as part of some genetic conditions, a medical geneticist should be involved to thoroughly examine a child with spina bifida. Identifying a particular syndrome in a child can help them receive more personalized medical care, and can help families identify a cause for why the spina bifida happened. It can also help to give families specific information about the chance of it happening again, for them or for other family members.

Some genetic testing, like chromosome studies, may identify a diagnosis or cause for the spina bifida. Abnormal genetic test results cannot be changed or reversed, but may provide answers about why the spina bifida occurred.

Treatment team

Treatment for people with spina bifida is highly dependent upon their symptoms. A multi-disciplinary team and approach is extremely helpful. Some hospitals offer day-long clinics devoted to people with spina bifida, which makes things much easier for families in terms of coordinating multiple appointments.

A treatment team for someone with spina bifida may include a **neurologist**, neurosurgeon, surgeon, **neuropsychologist**, medical geneticist, genetic counselor, orthopedic surgeon, physiatrist, physical therapist, occupational therapist, speech therapist, registered dietitian, social worker, nephrologist, ophthalmologist, audiologist, and a primary care provider. A neonatologist and pediatric specialists in those fields may be available to aid in the care for children. Those specializing in early childhood and development are particularly helpful, especially for issues related to attending school. Above all, good communication between the various specialists to coordinate care is essential.

Treatment

There is no known cure for spina bifida. Treatment primarily focuses on dealing with symptoms as they arise, since they vary so greatly from person to person.

Key Terms

Arnold-Chiari malformation, Type II Change in the brain when the medulla pushes downward below the foramen magnum, and overlaps the spinal cord.

Central apnea Abnormal breathing as a result of the medulla being pushed down, such as from an Arnold-Chiari malformation, Type II.

Chromosome Located in most cell nuclei, the genetic structure that contains all genes and DNA that make up an organism.

Clubfoot Abnormal positioning of the feet and legs, when they are turned inward towards each other.

Computed tomography (CT) scan Three-dimensional internal image of the body, created by combining x-ray images from different planes using a computer program.

Cyst Sac of tissue filled with fluid, gas or semi-solid material.

Foramen magnum Large opening in the back of the skull, where the spinal cord connects with the brain.

Hydrocephalus A state when fluid builds up in the brain, which may cause increased internal pressure and enlarged head size.

Magnetic resonance imaging (MRI) scan Three-dimensional internal image of the body, created using magnetic waves.

Medulla (spinalis) Elongated, cylindrical portion of the nervous system, which is contained in the spinal canal.

Neuropathic bladder Improper or lack of bladder function, due to a nerve problem.

Syndrome A well-recognized pattern of health problems or birth defects.

Ultrasound Two-dimensional internal image of the body, created using sound waves.

Ventriculoatrial (VA) shunt Tube that is placed from the brain to the chest cavity, in order to drain fluid.

Ventriculoperitoneal (VP) shunt Tube that is placed from the brain to the abdomen, in order to drain fluid.

X ray Two-dimensional internal image of the body, using radioactive waves.

Surgery to correct the spinal problem in spina bifida cystica is often done. This involves carefully tucking the spinal contents back into the spinal column, and closing the covering back up. This often happens shortly following birth to reduce the risk of developing an infection, and requires some time to heal afterward. Surgery has not been known to allow someone to regain functions they would not have had otherwise like movement, bowel, or bladder control.

A child with spina bifida is often carefully watched for signs of hydrocephalus. This may be done by measuring head circumference (which may enlarge) or with periodic head ultrasound or CT scans. If hydrocephalus is found, a procedure to put in a ventriculoperitoneal (VP) or ventriculoatrial (VA) shunt may be done. If a shunt is placed, it must be continually monitored and may need to be adjusted. Some people have their shunts removed later if the hydrocephalus never returns, and some people have a shunt for their entire lives.

Medications are widely available to treat those who develop seizures, and these may need periodic adjustments. Those who have problems with bowel or bladder control may require surgery, medications, or may never fully have these functions.

Babies and children with clubfoot often need to see an orthopedic surgeon and physiatrist, both of whom can recommend ways to correct them. Wearing braces on the legs can turn the feet back to their usual position, and this may be the only thing required. Sometimes surgery is necessary.

Surgery to correct the spinal problem during a pregnancy is experimental and not widely available. Since 1997, about 200 fetuses have had closure of myelomeningoceles during pregnancy. Since the surgery is so new, exact success rates, safety and long-term effects of the procedure are still not known as of early 2004.

Recovery and rehabilitation

Therapies and rehabilitation may be quite involved or relatively brief for people with spina bifida, depending on the severity of symptoms. Physical therapy is extremely important and can be ongoing. Speech and occupational therapies may be helpful if learning problems or delayed development are noted.

For those with wheelchairs, ramps and other assistive devices are helpful in their homes and places they frequent.

Clinical trials

As of early 2004, two **clinical trials** are under way in the United States to study spina bifida. National Institute of Child Health and Human Development (NICHD) sponsors both of these studies. One study is devoted to the genetics of spina bifida, recruiting many family members of an affected person to analyze and compare selected genes. The other study is attempting to identify the effectiveness and safety of spina bifida surgery during pregnancies. More information can be found at <http://www.clinicaltrials.gov>.

Prognosis

Prognosis in spina bifida is extremely varied and unpredictable. Years ago with far less intervention and fewer treatments available, someone with severe spina bifida had a high chance to die from complications. Mortality may still be high in complex cases even today. Conversely, those with a mild form of spina bifida may never even know they have it unless they have an internal imaging scan for an unrelated reason. As such, they may never have complications related to spina bifida and would have an average life span.

Today, there are far more options for helping those with spina bifida. Information can be learned during a pregnancy, allowing parents to make decisions and potentially prepare before birth. These treatments and therapies help maintain a better quality of life for those with spina bifida, and continue to offer hope.

Special concerns

Many couples who find their child has spina bifida during a pregnancy experience an array of emotional and psychological issues. They may be wondering how and why this happened, and may want some immediate answers. They also may be feeling guilt or wondering whether they could have caused it to happen. Issues related to these pregnancies, such as continuation or interrupting a pregnancy, can be complex and should be treated with sensitivity and care.

An important aspect of good prenatal care is regular folic acid supplementation, because this is known to reduce the risk for NTDs significantly. This can be gained through a prenatal vitamin, a separate supplement, or a healthy diet. Many breakfast cereals, breads, and other foods are now being supplemented with folic acid.

The current recommendation is for all women in their reproductive years to take 0.4 milligrams of folic acid daily, especially from about three to four months before conception. A woman with an affected child should take 4 milligrams of folic acid daily, beginning at least three to four months prior to conception. The reason for taking folic acid before conception is because the fetal spine forms very early, sometimes before a woman even knows she is pregnant.

Another tricky issue is managing the pregnancy of a woman with **epilepsy** or a seizure disorder. Many anti-seizure medications, like Depakote, cause an increased risk for NTDs and spina bifida. However, the risk of a woman having a seizure during pregnancy is also significant. The art is to find a balance between these two risks, in a way that makes everyone feel the most comfortable.

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March of Dimes. <www.modimes.org>.

National Institute of Neurological Disorders and Stroke. <www.ninds.nih.gov/index.htm>.

ORGANIZATIONS

Association for Spina Bifida & Hydrocephalus (U.K.). ASBAH House, 42 Park Road, Peterborough, United Kingdom PE1 2UQ. (01733) 555988. (01733) 555985. info@asbah.org. <http://www.asbah.org>.

Spina Bifida and Hydrocephalus Association of Canada. 977-167 Lombard Avenue, Winnipeg, Manitoba, Canada R3B 0V3. 204-925-3650 or 800-565-9488; Fax: 204-925-3654. spinab@mts.net. <http://www.sbhac.ca/index.php?page=main>.

Spina Bifida Association of America. 4590 MacArthur Boulevard N.W., Suite 250, Washington, DC 20007-4226.

202-944-3285 or 800-621-3141; Fax: 202-944-3295.
sbaa@sbaa.org. <http://www.sbaa.org>.

Deepti Babu, MS, CGC

Spinocerebellar ataxia

Definition

Spinocerebellar **ataxia** is a genetically inherited disorder characterized by abnormal brain function that represents a varied group of disorders. It is most commonly inherited as a dominant trait, which means that any individual who is a carrier of one of the many different gene mutations is affected. It also means that a carrier will have a 50% percent chance of having an affected offspring, regardless of the genetic background of the reproductive mate. In this group of disorders, the brain and spinal cord degenerate.

Description

Individuals affected with spinocerebellar ataxia develop a degenerative condition that affects a region in the base of the brain called the **cerebellum** located behind the brainstem. The primary function of the cerebellum is to coordinate the body's ability to move. Loss of this quintessential function leads to a progressive atrophy, or wasting away of muscles. The spine also atrophies and this can lead to **spasticity**.

Spinocerebellar ataxia can be physically devastating and the progressive loss of the ability to coordinate movements in emotional complications and significant lifestyle changes. The adverse effects involve the legs, hands, and the speech. Currently, there are 11 types of spinocerebellar ataxia. As there are many different genes mutations that cause this disease, there are different names for each type. The different types have numerical assignments as nomenclature. For example, Spinocerebellar ataxia type 1 is also known as SCA1. The numbers span from 1-25 (there is no SCA9) and are designated based on the time at which they were identified and characterized. Spinocerebellar ataxia is the same disease as spinal cerebellar ataxia.

Demographics

There are several gene mutations on different chromosomes that cause Spinocerebellar ataxia and the frequency of these gene within different populations varies considerably. In fact, due to the number of different types it is often difficult to estimate the incidence of a specific type in a specific population. In general, the incidence is thought to be approximately one to five per 100,000 people. There is no known predilection for sex. As with virtually all autosomal dominant disorders, males and females are equally likely to inherit a defective gene.

Causes and symptoms

Spinocerebellar ataxia is caused by a genetic defect that involves an expansion in the DNA sequence called a trinucleotide repeat expansion for SCA types 1-3, 6-10, 12, and 17. In general, the type of DNA expansion involves three DNA letters (nucleotides). In these cases, the sequence CAG (C=cytosine, A=adenine, G=guanine) is repeated above the normal repeat length. The normal repeat number differs for different types, as does the expanded repeat sizes. By repeating this sequence of DNA too many times, function of the protein it encodes can be disrupted. Other types of repeat expansions that cause SCA have been discovered. For example, SCA10 involves an ATTCT repeat expansion of the SCA10 gene and SCA8 involves an expansion in the SCA8 gene with the nucleotides CTG repeated. Finally, SCA14 involves a mutation in a gene that does not involve a trinucleotide repeat expansion.

The most common types are SCA1 (6%), SCA2 (14%), SCA3 (21%), SCA6 (15%), SCA7 (5%), and SCA8 (2–5%). Age of onset for all of these types is on average from 20–30 years of age except for SCA6, which usually occurs between the ages of 40 and 50. People with SCA8 usually develop symptoms between in their late 30s. SCA2 patients usually develop **dementia** and slow eye movements. SCA8, which has a normal lifespan, and SCA1 patients are both characterized as having active reflexes. SCA7 patients develop visual loss. SCA3 is also known as **Machado-Joseph disease**.

In SCA types 1–3 and 7, there can be an earlier age of onset with increased severity (called anticipation) as the defect is passed from one generation to the next. This means that children can be more severely affect at an earlier age than their affected parent. The size of the repeat of nucleotides in the affected genes is thought to correlate with the severity and age of onset in offspring. As the repeat size expands, the severity worsens and age of onset becomes earlier compared with the affected parent. However, repeat size does not predict the exact age of onset or the specific symptoms that will develop.

Penetrance refers to the likelihood that individuals with a genetic defect will develop the disease. In spinocerebellar ataxia, the penetrance is quite high; however, there are rare cases in which people do not develop symptoms. The reason for the lack of complete penetrance is currently unknown.

Key Terms

Ataxia A condition marked by impaired muscular coordination, most frequently resulting from disorders in the brain or spinal cord.

Atrophy The progressive wasting and loss of function of any part of the body.

Autosomal dominant A pattern of inheritance in which only one of the two copies of an autosomal gene must be abnormal for a genetic condition or disease to occur. An autosomal gene is a gene that is located on one of the autosomes or non-sex chromosomes. A person with an autosomal dominant disorder has a 50% chance of passing it to each of their offspring.

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.

Trinucleotide repeat expansion A sequence of three nucleotides that is repeated too many times in a section of a gene.

Affected individuals initially develop poor coordination of movement, which is the definition of ataxia. Developing poor movement coordination in patients is manifested clinically by difficulty in walking, abnormalities in hand or eye movements, and speech difficulties. Generally, the age of onset is usually after 18 years old, making it typically an adult-onset disorder. The severity of progressive degeneration depends primarily on the underlying defect.

Diagnosis

The diagnosis of spinocerebellar ataxia is initially suspected by the adult-onset of symptoms. An **MRI** scan can detect atrophy (wasting) of the cerebellum, a typical finding in patients with spinocerebellar ataxia. A clinical evaluation involves an extensive neurological examination. Genetic testing is a critical component of the diagnosis, as symptoms among the various types of spinocerebellar ataxia are similar. A molecular genetic test to determine the gene that has the trinucleotide repeat expansion can be helpful in quickly identifying other carriers in the family. Once the genetic defect is characterized, family members can also be tested. Unfortunately, genetic testing is not always 100% informative. There are rare cases of spinocerebellar ataxia diagnosed clinically that cannot be explained by any of the known genetic defects. It is estimated that in approximately 50–60% of Caucasian persons with a dominant familial form of cerebellar ataxia, DNA testing can provide a definitive diagnosis.

Treatment team

For people who begin to show symptoms and are later diagnosed with spinocerebellar ataxia, a careful evaluation by a **neurologist** is usually required. Treatment is based on lessening the symptoms as they develop. A fulltime caretaker and nursing support will eventually be required in the later stages of the disease. Psychological counseling is often needed depending on the family, the patient, and their needs.

Treatment

There is no cure for spinocerebellar ataxia. There is also no treatment to slow the progression of the disease. Treatment, therefore, remains supportive. Drugs that help control **tremors** are not effective for treating cerebellar tremors. Although dietary factors are not proven to be helpful, vitamin supplementation is recommended.

Recovery and rehabilitation

Researchers assume that physical therapy does not slow the progression of loss of coordination or muscle wasting. However, people with spinocerebellar ataxias are encouraged to remain as active as possible. Occupational therapy can be helpful in developing ways to accommodate the patient in performing daily activities. Walkers and other devices can assist in allow the patient to have mobility. Other modifications such as ramps for a wheelchair, heavy eating utensils, and raised toilet seats can make patients more independent. Speech therapy and computer-based communication aids often help as the person loses his or her ability to speak.

Clinical trials

As of early 2004, there are no approved **clinical trials** for the treatment or cure of spinocerebellar ataxia. There is, however, a clinical trial to determine the maximum tolerated dose of a drug called idebenone in children, adolescents, and adults with Friedreich's Ataxia, a disorder related to spinocerebellar ataxia (contacts: Patient Recruitment and Public Liaison Office, Building 61, 10 Cloister Court, Bethesda, Maryland 20892-4754; toll free: 1-800-411-1222). Additionally, there is also an ongoing study to determine the efficacy of high-dose intravenous immunoglobulin therapy in patients with cerebellar degeneration that are already enrolled.

Prognosis

There are many factors that determine the prognosis of an affected individual. These factors depend on the type of genetic mutation, the size of the repeat expansion, anticipation, and the age at which symptoms develop. Although these factors can help determine the prognosis, the exact age of onset and the specific symptoms are difficult to determine, especially for carriers with no symptoms. Ultimately, as with all progressive degenerative disorders, the disease is fatal. In the case of spinocerebellar ataxia, persons usually die one to two decades after symptoms develop. The prognosis for SCA11 and SCA6 is typically less severe, with a very slow worsening of symptoms, and persons with SCA8 and SCA11 have a normal lifespan.

Special concerns

Genetic testing of at-risk family members can be performed when an affected individual has a known genetic mutation. Testing of high-risk family members without symptoms raises many issues. For example, individuals who test negative usually feel guilty that they did not inherit the genetic defect, and parents who are affected feel guilty that they passed on the gene defect. These experiences can have a significant impact on the family dynamics, particularly in adult-onset disorders. Additionally, it is often unclear when (or if) family members who test positive for the mutation will develop symptoms and how severe the symptoms will be. It is generally considered not useful to test children with no symptoms. These issues and others are usually carefully evaluated by family members with the help of a genetic counselor.

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ORGANIZATIONS

National Ataxia Foundation (NAF). 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447. (612) 553-0020; Fax: (612) 553-0167. naf@mr.net. <http://www.ataxia.org>.

National Society of Genetic Counselors (NSGC). 233 Canterbury Drive, Wallingford, PA 19086-6617. (610) 872-7608; Fax: (610) 872-1192. nsgc@aol.com. <http://www.nsgc.org>.

WE MOVE (Worldwide Education and Awareness for Movement Disorders). 204 West 84th Street, New York, NY 10024. (212) 875-8389 or (800) 437-MOV2 (6683). wemove@wemove.org. <http://www.wemove.org>.

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Status epilepticus

Definition

Status epilepticus is a term describing a state of continuous seizure activity. In the past, 30 minutes of continuing seizure or frequent attacks that prevent recovery was required for the definition of status to be met. However, since most **seizures** last less than four to five minutes, it is now understood that any seizure that continues five minutes or longer should be potentially considered as status epilepticus, and managed accordingly.

Description

Nearly all types of seizures have the potential of occurring in a continuous or repeated fashion. There are two general categories: generalized status and focal status, depending on the clinical features of the situation. Generalized status can preferentially manifest with tonic, clonic, absence, and/or myoclonic seizures. Hence, status can be merely a prolongation of commonly observed individual seizure types. Non-convulsive status epilepticus can manifest with sustained or repeating complex partial seizures with a change in mental status, or simply as a focal seizure with limited physical signs but without alteration of consciousness. Status can occur in individuals who have **epilepsy** already. However, in some cases, the first seizure that a person experiences can be status epilepticus.

Demographics

The epidemiology of status epilepticus varies depending on the study. However, in the United States the incidence is approximately up to 40 per 100,000 individuals. Therefore more than 100,000 cases of status occur annually. Up to 10% of all first-time seizures are situations of status epilepticus. The mortality of status epilepticus is roughly 20%. Those most at risk are the very young or the elderly. The causes of death vary depending on the age of the patient, presence of medical complications, duration of

Key Terms

Absence A type of seizure that causes brief (shorter than 30 seconds) episodes of staring.

Clonic A type of seizure characterized by rhythmic jerking of the arms and legs.

Myoclonic A type of seizure that causes brief muscle jerks of the whole body or a limb.

Tonic A type of seizure characterized by episodes of stiffening in all the limbs for up to one or two minutes.

the uncontrollable seizures, and the underlying cause of the status epilepticus.

Causes and symptoms

The exact pathophysiology of why a seizure evolves into status is complex and not fully understood. However, status epilepticus has many causes, some of which are the same as causes of seizures in general. In infants, status can occur in the setting of perinatal **hypoxia** or anoxia (low oxygen or lack of oxygen) that injures the brain. Also, illness such as meningitis that can cause seizures can also be severe enough to cause status epilepticus. Metabolic disorders of infancy and childhood that can be causes of epilepsy can also produce status epilepticus. In adults, infections of the brain, strokes, brain tumors, and severe head trauma can cause seizures and hence status epilepticus.

Clinically, status epilepticus is basically a prolonged seizure situation. Individual seizures occurring frequently enough to impair full recovery to baseline function can be a manifestation of status epilepticus as well. A limited seizure such as an arm jerking without alteration of consciousness is called a simple or focal seizure. If it occurs continuously, the term epilepsy partialis continua is used. This is the least serious of the different types of status epilepticus. The more dangerous type is, of course, generalized tonic/clonic status. This is because cardiac arrhythmias or blood pressure changes can be life threatening. Also, breathing and oxygenation can be compromised, and patients may require ventilator assistance. Complex partial seizures and absence seizures are manifested with an alteration of consciousness. When these particular seizures become status, patients may simply appear confused or agitated. Since they are not having convulsions, they may be misdiagnosed as having a psychiatric symptom. Nevertheless, prompt and accurate diagnosis is important for proper management.

Diagnosis

When convulsions are occurring, status is typically easily recognized. However, subtle status, as in complex partial or absence status, may necessitate an electroencephalogram (EEG) for diagnosis. The EEG is not only used for initial diagnosis, but is often left running for longer periods to monitor response to treatment. The recognition of seizure activity is only one of the urgent tasks in the care of the patient. The other major issue is to rapidly identify the cause of seizures and the status epilepticus. This involves testing blood for at least glucose, electrolytes, liver function, and illicit substances. Very low blood glucose or extreme changes in sodium, for example, can cause seizures. Infections such as meningitis can cause status. Rapidly assessed levels of older, commonly used seizure medications such as phenytoin, **Phenobarbital**, **carbamazepine**, and valproic acid are sometimes sought in cases where there is no available history from the patient. Indeed, one of the most frequent causes of status is low anticonvulsant levels in a patient with a history of epilepsy.

Treatment team

Patients in status epilepticus will often necessitate a **neurologist** to guide the management from the emergency department through the rest of the hospital stay. **Social workers** are important for discharge plans because many patients who survive status epilepticus may need skilled nursing or rehabilitation to fully recover prior to being discharged home.

Treatment

The treatment of status depends on identifying quickly the underlying cause, if any. In cases of hypoglycemia, thiamine must be administered just prior to glucose supplementation. This is because some individuals, alcoholics for example, may be deficient in thiamine and a correction of glucose levels without thiamine supplementation can cause a condition known as Wernicke's **encephalopathy**. Sodium must be corrected slowly or a condition called central pontine myelinolysis can occur. A computed tomography (**CT**) scan of the brain is often ordered to evaluate for any brain trauma. A lumbar puncture may be performed to determine if there is meningitis so appropriate antibiotics can be used. Overall, in cases that an identifiable cause of status can be found, the key to successful treatment is the management of the underlying cause itself. There are published guidelines for the treatment of seizures themselves. Initially, a sedative such as lorazepam or **diazepam** is given, which can stop many seizures at least temporarily while a longer-acting anticonvulsant such as phenytoin takes effect. If seizures persist, then the addition of Phenobarbital is typically added. Since this particular medication, when fully loaded, causes respiratory **depression**, an

anesthesiologist is consulted to manage ventilator assistance. Status epilepticus is managed and treated in an intensive care unit with EEG monitoring to continually assess the response to seizure medications. When Phenobarbital fails to stop the ongoing seizures, a number of other medications are considered, such as a midazolam drip or propofol. Anesthetic dosages of these particular medications are usually effective in suppressing seizure activity. Approximately every 24 hours, the dosage is reduced to determine if seizures recur or not. The severity of status can vary widely. Sometimes, it is effectively treated within one to two hours and other times the status is severe and extremely resistant to treatment and lasts for weeks. In such cases, the mortality rate is significant because of risk of medical complications such as pneumonia and blood clots.

Recovery and rehabilitation

The recovery from status epilepticus will depend on its duration. If status can be effectively stopped in a relatively short period of time, complete neurological recovery is possible. The longer the seizures persist, the greater the chance of cerebral injury. Also, the longer the status epilepticus, the more difficult it is to stop. A complication of status epilepticus can actually be the development of epilepsy in a percentage of cases.

Prognosis

The prognosis with status epilepticus will depend on the duration of status and co-existing medical problems. The prognosis is good for recovery if status can be stopped in a relatively short period of time (hours) and there are no complications such as infection, active cardiac problems, or other active medical issues. However, prognosis for complete recovery is less favorable as status persists for long periods of time. Co-existing medical problems will complicate management and chance for a negative outcome.

Special concerns

It is important to be on the lookout for subtle status situations that may go unrecognized. An EEG is a relatively easy way to rule in or rule out presence of active seizures. It is crucial to respond urgently to status epilepticus because the longer the seizures continue the more difficult they are to stop.

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ORGANIZATIONS

American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. (860) 586-7505. <http://www.aesnet.org>.

Epilepsy Foundation of America. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

Internation League Against Epilepsy. Avenue Marcel Thiry 204, B-1200, Brussels, Belgium. + 32 (0) 2 774 9547; Fax: + 32 (0) 2 774 9690. <http://www.epilepsy.org>.

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Steele-Richardson-Olszewski syndrome *see* **Progressive supranuclear palsy**

Stiff person syndrome

Definition

Stiff person syndrome (SPS) is an extremely rare progressive neurological disorder characterized by persistent rigidity and spasms of certain voluntary muscles, especially those of legs and feet. In some cases, muscles of the neck, trunk, and shoulders may also be involved. SPS may begin as recurring (intermittent) episodes of stiffness and spasms, often precipitated by surprise or minor physical contact.

Description

SPS is a rare progressive neurological disorder characterized by constant painful contractions and spasms of voluntary muscles, particularly the muscles of the back and upper legs. In 1956, scientists at the Mayo Clinic also coined the term stiff man syndrome, and clearly described

the stiff person syndrome as a neurological disorder. The rigidity, which is characterized by tightness and stiffness, begins slowly over several months at the axial muscles, especially the thoracic and lumbar spine, and spreads to the legs. The stiffness may worsen when the affected individual is anxious or exposed to sudden motion or noise. Affected muscles may become twisted and contracted, resulting in bone fractures in the most severe cases.

Another abnormality in SPS is called co-contraction: when the person attempts to contract a muscle to move in one direction, muscles that pull in the opposite direction are involuntarily activated. Individuals with SPS may have difficulty making sudden movements and may have a stiff-legged unsteady gait (manner of walking). The muscle contractions are usually reduced with extra rest.

Eventually, persons with stiff person syndrome may develop a hunched posture (kyphosis) or a swayback (lordosis).

Key Terms

Antibody Proteins produced by the immune system in response to the introduction of foreign molecules called antigens. Antibodies neutralize these molecules to prevent infection or disease.

Autoimmune disorder A large group of diseases characterized by abnormal functioning of the immune system that produces antibodies against its own tissues.

Kyphosis Posterior curvature of the spine, creating a humpback appearance.

Lordosis Anterior curvature of the spine, creating a swayback appearance.

Demographics

The frequency of SPS worldwide or in the United States is unknown, but the syndrome is rare. Unlike many autoimmune diseases, which have a higher incidence in women, SPS is found more frequently in men, occurring in men in approximately 70% of all cases. The syndrome also occurs in children younger than three years, most commonly in infants. Onset in adults is most frequent in the third to fifth decades of life.

Causes and symptoms

The cause of stiff person syndrome is unknown, however, researchers theorize that SPS may be an autoimmune disorder. An autoimmune disorder involves a malfunction of the immune system, where the body produces antibodies against its own tissues. Antibodies are proteins produced by the body as part of its defense against foreign bacteria, viruses, or other harmful substances. Other autoimmune disorders such as diabetes, pernicious anemia (a chronic, progressive blood disorder), and thyroiditis (inflammation of the thyroid gland) may occur more frequently in patients with SPS.

Often SPS, antibodies are produced against glutamic acid decarboxylase (GAD), an enzyme largely found in the **central nervous system**. However, GAD antibodies alone appear to be insufficient to cause SPS, as some persons with stiff person disease do not have the GAD antibodies, and GAD antibodies are associated with a number of diseases.

Symptoms may occur gradually, spreading from the back and legs to involve the arms and neck. Initially, the patient has an exaggerated upright posture and may experience back discomfort, stiffness or **pain** in the entire back, which worsens with tension or stress. Some persons with SPS, in the early stages, show brief episodes of rather dramatic severe worsening that resolve spontaneously within hours or days. Later in the disease, upper limb muscles also begin to be involved, particularly when the person is stimulated, surprised, angered, upset, or frightened. This sort of stimulation may evoke painful severe spasms in the upper arm and leg muscles that resolve slowly. The person with SPS begins to move very slowly because rapid movement induces severe spasms. Even the lower extremities may become involved when moved rapidly. In the end stages of the disease, few muscles in the body are spared. However, facial and pharyngeal muscles may be especially affected.

Babies and young children are less rigid between attacks. Involvement of lower arm and leg muscles is often more evident, particularly during muscle spasms.

Diagnosis

During physical examination, the physician who suspects SPS looks for stiffness, rigidity or increased tone, spasm, or pain. The areas of involvement may include the face, neck, abdomen, or arms, but more typically the legs or lumbar spine are involved. Evaluation may include tests to rule out other causes of stiffness such as **multiple sclerosis**. When overwhelming anxiety and fear overshadow the stiffness, it may be difficult to distinguish SPS from an emotional disorder.

Laboratory procedures assess the presence of specific autoantibodies called anti-GAD, which are found at high levels in the blood of a person with SPS. These examinations include immunocytochemistry, Western blotting, ELISA (enzyme-linked immunosorbent assay), and radioimmunoassay (RIA). The last two procedures have the advantage of quantitatively assessing the amount of anti-GAD antibody a patient produces.

Electromyography (EMG) is an important diagnostic tool to determine an abnormal firing pattern in the muscles sometimes seen in persons with SPS. The EMG findings of SPS may be subtle in patients who are fully treated for symptoms of SPS. Except for global muscle stiffness, results of a neurological examination are usually normal. Results of conventional computed tomography and **magnetic resonance imaging** of the brain are also normal.

Treatment team

The treatment team for a person with SPS is often composed of physical and occupational therapists, nutritionists, neurosurgeons, and neurologists.

Treatment

SPS is clinically elusive, but potentially treatable. Traditional treatment for SPS starts with medications such as baclofen or a **benzodiazepine**. Commonly used benzodiazepines are **diazepam** (Valium) or lorazepam (Ativan). Both benzodiazepine and baclofen act increasing the activity of the central inhibitory systems. Although no studies have been performed, tizanidine (Zanaflex) may be a less sedating alternative, and prednisone is also a commonly prescribed drug for treatment of SPS.

In some patients, plasmapheresis, a process of filtering the blood to remove excess antibodies, has been demonstrated to be useful in removing anti-GAD antibodies from the bloodstream. In the hospital setting, intravenous immunoglobulin (IVIG) has also been used in the treatment of SPS.

Recovery and rehabilitation

Physical therapy and occupational therapy are critical to the recovery of patients under treatment. Medical treatment can make the patient feel weak, a feeling that may be alleviated by therapy. The person with SPS may also have problems with voluntary movements and fine motor skills. Occupational and physical therapists devise strategies to compensate for these weaknesses during the common daily activities of living.

Clinical trials

In 2004 there were two open **clinical trials** recruiting patients entitled "Cause, Development, and Progression of Stiff-Person Syndrome" and "Diagnostic Evaluation of Patients with Neuromuscular Disease," sponsored by National Institute of Neurological Disorders and Stroke (NINDS). For further and updated information, visit the website <www.clinicaltrials.gov>, sponsored by the National Institutes of Health.

Prognosis

There is no cure for SPS and the long-term prognosis is variable. Many patients have a slow course of the disorder that is mostly without symptoms, punctuated by occasional episodes of stiffness. Other patients may have a much more aggressive course, rapidly progressing to the late stages of disease. Other forms of the disease have been described that are accompanied by brain disorders and other central nervous system abnormalities, but whether they are separate diseases or different manifestations of the same disease is unclear. Management of the disorder with drug therapy usually provides significant improvement and relief of symptoms.

Special concerns

Many of the medications prescribed for SPS are not indicated during pregnancy. Elderly persons with SPS may have increased chances of falling and injury because of concurrent disability from other causes. As with all autoimmune disorders, dietary changes are sometimes helpful. For best results, dietary changes should be made under the supervision of a physician experienced in nutritional medicine.

Resources

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National Rehabilitation Information Center (NARIC). 4200 Forbes Boulevard; Suite 202, Lanham, Maryland 20706-4829. (301) 562-2400 or (800) 346-2742; (301) 562-2401. naricinfo@heitechservices.com. <http://www.naric.com>.

National Organization for Rare Disorders (NORD). 55 Kenosia Avenue, Danbury, Connecticut 06813-1968. (203) 744-0100; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Bldg. 31, Rm. 4C05, Bethesda,

Maryland 20892-2350. (301) 496-8188.
NIAMSInfo@mail.nih.gov. <http://www.nih.gov/niams>.

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Striatonigral degeneration

Definition

Striatonigral degeneration is a neurodegenerative disease caused by disruption of two areas, the striatum and substantia nigra, which work together to enable movement and balance.

Description

Striatonigral degeneration was described in 1961 and 1964. However, since the disorder has common manifestations seen in multiple diseases (e.g., the Shy-Drager syndrome, where autonomic nervous system failure predominates, and sporadic olivopontocerebellar degeneration, where **cerebellum** deficits predominate), it was necessary to clarify the nomenclature. In 1999, the name striatonigral degeneration was replaced with the accepted new names: multiple system atrophy-Parkinson (MSA-P), if **Parkinson's disease** symptoms predominate, or MSA-cerebellum (MSA-C), if cerebellar **ataxia** is the main feature. Patients who have MSA have characteristic pathological changes in common, but in variable degrees. Affected neurons in the brain have inclusion bodies that cause neuronal loss, by a mechanism of programmed cell death called apoptosis. The presence of inclusion bodies in neurons causes a reaction to self-destruct following a programmed sequence of chemical reactions that promotes cell death.

Demographics

The prevalence of MSA-P is difficult to establish with accuracy since the disorder is frequently misdiagnosed in the United States and internationally. It is estimated to account for 5–22% of cases in patients with Parkinson's or Parkinson-like disorders. Approximately 80% of patients present with MSA-P symptoms and 20% exhibit symptoms of cerebellar ataxia (MSA-C subtype). It is estimated that the prevalence of this disorder is 1.9–4.9 cases per 100,000. The age range of diagnosis is between 33 and 76 years of age. MSA-P has never been identified in a person younger than 30 years. The mean survival time after the onset of symptoms is 7–9 years. There is no racial predilection, and males and females are affected equally. The mean age of diagnosis is 53 years. For the majority of MSA-P affected persons, the full clinical picture evolves within five years after onset of symptoms.

Causes and symptoms

The cause of MSA has not been identified. MSA occurs in the general population in a sporadic manner. The disorder is degenerative and progressively worsens. The natural history of the disorder is chronic, symptoms progressively worsen, and the disorder often results in death, after multiple treatment efforts.

Common symptoms of MSA-P (which may be asymmetric) include bradykinesia (slowness of movement) characterized by an irregular jerky postural tremor. It is uncommon for the tremor to occur at rest. Additionally, patients often exhibit rigidity, postural instability, and a characteristic quivering high-pitched **dysarthria**. Many patients with MSA-P also develop orofacial and craniocervical **dystonia**. Patients with the MSA-C subtype also develop gait and limb ataxia, eye abnormalities, and scanning dysarthria. Other symptoms can include **depression**, emotional lability (fluctuations of emotional state), hyperreflexia, extensor plantar (sole) response, **myoclonus**, or laryngeal stridor. Failure of the autonomic nervous system (ANS) is a characteristic of both subtypes (MSA-P and MSA-C), which primarily consists of urogenital problems and **orthostatic hypotension**. ANS failure causes early male erectile dysfunction and urinary dysfunction, causing problems with frequency, urgency, retention, and incontinence. Additionally, patients frequently develop postprandial (after food) postural hypotension and episodes of syncope (loss of consciousness), due to lack of oxygen to the brain (cerebral hypoperfusion).

Diagnosis

No specific lab tests are indicated. High-resolution neuroimaging studies may demonstrate neuronal abnormalities and/or atrophy in the brain. The diagnosis is based on history, physical examination, and family history (to detect genetic correlations). A definite diagnosis can be obtained by pathological examination of brain neurons. A probable diagnosis is made by the presence of ANS failure, poor response to medications, or cerebellar dysfunction (cerebellar ataxia). Neuroimaging studies using **magnetic resonance imaging (MRI)** indicate that that there is volume loss (neuronal loss) in associated areas in the brain (the striatum and substantia nigra). Functional neuroimaging techniques (which take images of neuron function) indicate that neuron receptor binding is defective and there is low metabolism (low level of vital chemical reactions).

Key Terms

Ataxia Muscular incoordination and irregularity of muscular action.

Autonomic nervous system (ANS) Consists of neurons that are not under one's conscious control. The ANS is comprised of two subdivisions called the parasympathetic nervous system, which slows heart rate, increases intestinal and gland activity, and relaxes the sphincter muscles; and the sympathetic nervous system, which accelerates heart rate, raises blood pressure, and constricts blood vessels.

Cerebellar ataxia Disorders of the cerebellum that cause a loss of muscular coordination.

Dysarthria Nerve damage that causes disturbances in muscular control, resulting in impaired speech articulation.

Dyskinesias A group of disorders characterized by involuntary movements of muscles.

Dystonia Abnormal tone in a group of muscles.

Hyperreflexia An increased reaction to reflexes.

Incontinence Inability to control excretory functions such as defecation and urination.

Laryngeal stridor Constriction of the voice box, causing vocal hoarseness.

Myoclonus Spasm or twitching of a muscle or a group of muscles.

Orthostatic hypotension A reduction of blood pressure (systolic blood pressure that occurs when the heart contracts or diastolic pressure that occurs when the heart muscle relaxes).

Paresis A slight paralysis.

Parkinson's disease A neurodegenerative disorder characterized by slowness of voluntary movements, mask-like facial expression, and a rhythmic tremor of the limbs and stooped posture.

Receptor A structure located on the outside of a cell's membrane that causes the cell to attach to specific molecules; the molecules are then internalized, taken inside the cell.

Striatum Area located deep within the brain.

Substantia nigra An area located in the middle portion of the brain that can become depleted of a specific neurotransmitter called dopamine, causing symptoms of Parkinson's disease.

Syncope Loss of consciousness.

Tremor An involuntary movement characterized by quivering and trembling.

Treatment team

The treatment team can typically include a **neurologist** and respiratory care providers, when management of breathing difficulties requires professional intervention. A physical therapist can help with postural and movement difficulties. An audiologist is utilized for speech and eating difficulties.

Treatment

No surgical treatment exists for striatonigral degeneration, and pharmacological treatment is not effective in the long term. Approximately 30% of patients demonstrate initial improvement with a medication called levodopa-carbidopa. However, symptomatic improvement is temporary; approximately 90% patients are unresponsive to levodopa in the long term. Dystonia can be treated with **botulinum toxin**, which tends to control involuntary muscular movements. Affected persons who develop failure of the autonomic nervous system may develop orthostatic hypotension. Patients who develop low blood pressure symptoms should avoid activities such as overeating, straining at stool passage, and exposure to extreme heat. Elevating the head of the bed, use of pressure stockings, and increased sodium intake (which causes water retention, which in turn stabilizes blood pressure) are treatments for hypotension. Additionally, medication to correct hypotension can be prescribed, including fludrocortisone, ephedrine, and midodrine. Medication to treat postprandial hypotension (octreotide) or bladder symptoms (oxybutynin) can be given when needed. Overall, however, the result of medical treatment for MSA is poor.

Recovery and rehabilitation

Rehabilitation can include patient, family, and caretaker education concerning the possibilities of respiratory failure, aspiration pneumonia, trauma, and syncope. Patients can develop paresis of the larynx or pharynx, central chronic respiratory failure (a chronic respiratory failure due to destruction of neurons in the brain), or sudden death. Patients require physical therapy to help maintain mobility and prevent permanent muscular contractures. Speech therapy can improve speech impairments and difficulty with swallowing (dysphagia) mechanisms. Dysphagia may necessitate tube placement and feedings.

Patients eventually require occupational therapy to limit handicap from disability. A wheelchair is indicated depending on liability to falls due to gait (walking) ataxia and postural instability. Psychological support is necessary for the patient and family member caretakers.

Clinical trials

Clinical trials are being done to find methods to prevent and treat MSA-P. The Mayo Clinic in Rochester, Minnesota, currently has projects and investigations concerning new techniques for diagnosis using **PET** scan technology. This technology is likely to be available in the near future.

Prognosis

The disorder is degenerative and the mean survival time in confirmed cases is seven years. The range of survival for persons with MSA-P is 2–15 years. Approximately 50% of affected patients who receive levodopa develop side effects that can include **dyskinesia** of orofacial and neck muscles.

Special concerns

Episodes of syncope can cause severe trauma, usually from falls. Patients are advised to lie or sit down when symptoms appear. Family members and caretakers should be aware of the syncope and the dangers associated with falls and trauma.

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Worldwide Education & Awareness for Movement Disorders (WE MOVE). 204 West 84th Street, New York, NY 10024. (212) 875-8312 or (800) 437-6682; Fax: (212) 875-8389. wemove@wemove.org. <http://www.wemove.org>.

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Stroke

Definition

A stroke is the sudden death of brain cells in a localized area due to inadequate blood flow.

Description

A stroke occurs when blood flow is interrupted to part of the brain. Without blood to supply oxygen and nutrients and to remove waste products, brain cells quickly begin to die. Depending on the region of the brain affected, a stroke may cause paralysis, speech impairment, a loss of memory and reasoning ability, coma, or death. A stroke is also sometimes called a brain attack or a cerebrovascular accident (CVA).

Some important stroke statistics include:

- More than half a million people in the United States experience a new or recurrent stroke each year.
- Stroke is the third leading cause of death in the United States and the leading cause of disability.
- Stroke kills about 150,000 Americans each year, or almost one out of three stroke victims.
- Three million Americans are currently permanently disabled from stroke.
- In the United States, stroke costs about $30 billion per year in direct costs and loss of productivity.
- Two-thirds of strokes occur in people over age 65.
- Strokes affect men more often than women, although women are more likely to die from a stroke.
- Strokes affect blacks more often than whites, and are more likely to be fatal among blacks.

Stroke is a medical emergency requiring immediate treatment. Prompt treatment improves the chances of survival and increases the degree of recovery that may be expected. A person who may have suffered a stroke should be seen in a hospital emergency room without delay. Treatment to break up a blood clot, the major cause of stroke, must begin within three hours of the stroke to be effective. Improved medical treatment of all types of stroke has resulted in a dramatic decline in death rates in recent decades. In 1950, nine in 10 people died from stroke, compared to slightly less than one in three today.

Causes and symptoms

Causes

There are four main types of stroke. Cerebral thrombosis and cerebral embolism are caused by blood clots that block an artery supplying the brain, either in the brain itself or in the neck. These account for 70–80% of all strokes. Subarachnoid hemorrhage and intracerebral hemorrhage occur when a blood vessel bursts around or in the brain.

Cerebral thrombosis occurs when a blood clot, or thrombus, forms within the brain itself, blocking the flow

of blood through the affected vessel. Clots most often form due to "hardening" (atherosclerosis) of brain arteries. Cerebral thrombosis occurs most often at night or early in the morning. Cerebral thrombosis is often preceded by a **transient ischemic attack** (TIA), sometimes called a "mini-stroke." In a TIA, blood flow is temporarily interrupted, causing short-lived stroke-like symptoms. Recognizing the occurrence of a TIA and seeking immediate treatment are important steps in stroke prevention.

Cerebral embolism occurs when a blood clot from elsewhere in the circulatory system breaks free. If it becomes lodged in an artery supplying the brain, either in the brain or in the neck, it can cause a stroke. The most common cause of cerebral embolism is atrial fibrillation, a disorder of the heartbeat. In atrial fibrillation, the upper chambers (atria) of the heart beat weakly and rapidly, instead of slowly and steadily. Blood within the atria is not completely emptied. This stagnant blood may form clots within the atria, which can then break off and enter the circulation. Atrial fibrillation is a factor in about 15% of all strokes. The risk of a stroke from atrial fibrillation can be dramatically reduced with daily use of anticoagulant medication.

Hemorrhage, or bleeding, occurs when a blood vessel breaks, either from trauma or excess internal pressure. The vessels most likely to break are those with preexisting defects such as an aneurysm. An aneurysm is a "pouching out" of a blood vessel caused by a weak arterial wall. Brain **aneurysms** are surprisingly common. According to autopsy studies, about 6% of all Americans have them. Aneurysms rarely cause symptoms until they burst. Aneurysms are most likely to burst when blood pressure is highest, and controlling blood pressure is an important preventive strategy.

Intracerebral hemorrhage affects vessels within the brain itself, while subarachnoid hemorrhage affects arteries at the brain's surface, just below the protective arachnoid membrane. Intracerebral hemorrhages represent about 10% of all strokes, while subarachnoid hemorrhages account for about 7%.

In addition to depriving affected tissues of blood supply, the accumulation of fluid within the inflexible skull creates excess pressure on brain tissue, which can quickly lead to death. Nonetheless, recovery may be more complete for a person who survives hemorrhage than for one who survives a clot, because the blood deprivation effects are usually not as severe.

Death of brain cells triggers a chain reaction in which toxic chemicals created by cell death affect other nearby cells. This is one reason why prompt treatment can have such a dramatic effect on final recovery.

Risk factors

Risk factors for stroke involve age, sex, heredity, predisposing diseases or other medical conditions, and lifestyle choices, including:

- Age and sex. The risk of stroke increases with increasing age, doubling for each decade after age 55. Men are more likely to have a stroke than women.
- Heredity. Blacks, Asians, and Hispanics all have higher rates of stroke than do whites, related partly to higher blood pressure. People with a family history of stroke are at greater risk.
- Diseases. Stroke risk is increased for people with diabetes, heart disease (especially atrial fibrillation), high blood pressure, prior stroke, or TIA. Risk of stroke increases tenfold for someone with one or more TIAs.
- Other medical conditions. Stroke risk increases with obesity, high blood cholesterol level, or high red blood cell count.
- Lifestyle choices. Stroke risk increases with cigarette smoking (especially if combined with the use of oral contraceptives), low level of physical activity, alcohol consumption above two drinks per day, or use of cocaine or intravenous drugs.

Symptoms

Symptoms of an embolic stroke usually come on quite suddenly and are at their most intense right from the start, while symptoms of a thrombotic stroke come on more gradually. Symptoms may include:

- blurring or decreased vision in one or both eyes
- severe headache
- weakness, numbness, or paralysis of the face, arm, or leg, usually confined to one side of the body
- dizziness, loss of balance or coordination, especially when combined with other symptoms

Diagnosis

The diagnosis of stroke is begun with a careful medical history, especially concerning the onset and distribution of symptoms, presence of risk factors, and the exclusion of other possible causes. A brief neurological exam is performed to identify the degree and location of any deficits such as weakness, incoordination, or visual losses.

Once stroke is suspected, a computed tomography (**CT**) **scan** or **magnetic resonance imaging (MRI)** scan is performed to distinguish a stroke caused by blood clot from one caused by hemorrhage, a critical distinction that guides therapy. Blood and urine tests are done routinely to look for possible abnormalities.

Other investigations that may be performed to guide treatment include an electrocardiogram, **angiography**, ultrasound, and electroencephalogram.

Treatment team

Stroke treatment involves a multidisciplinary team. Physicians are responsible for caring for the stroke survivor's general health and providing guidance aimed at preventing a second stroke. Neurologists usually lead acute-care stroke teams and direct patient care during hospitalization. The team may include a physiatrist (a specialist in rehabilitation), a rehabilitation nurse, a physical therapist, an occupational therapist, a speech-language pathologist, a social worker, a psychologist, and a vocational counselor.

Treatment

Emergency treatment

Emergency treatment of stroke from a blood clot is aimed at dissolving the clot. This "thrombolytic therapy" is currently performed most often with tissue plasminogen activator, or t-PA. This t-PA must be administered within three hours of the stroke event. Therefore, patients who awaken with stroke symptoms are ineligible for t-PA therapy, as the time of onset cannot be accurately determined. The t-PA therapy has been shown to improve recovery and decrease long-term disability in selected patients. The t-PA therapy carries a 6.4% risk of inducing a cerebral hemorrhage, and is not appropriate for patients with bleeding disorders, very high blood pressure, known aneurysms, any evidence of intracranial hemorrhage, or incidence of stroke, head trauma, or intracranial surgery within the past three months. Patients with clot-related (thrombotic or embolic) stroke who are ineligible for t-PA treatment may be treated with heparin or other blood thinners, or with aspirin or other anti-clotting agents in some cases.

Emergency treatment of hemorrhagic stroke is aimed at controlling intracranial pressure. Intravenous urea or mannitol plus hyperventilation are the most common treatments. Corticosteroids may also be used. Patients with reversible bleeding disorders such as those due to anticoagulant treatment should have these bleeding disorders reversed, if possible.

Surgery for hemorrhage due to aneurysm may be performed if the aneurysm is close enough to the cranial surface to allow access. Ruptured vessels are closed off to prevent rebleeding. For aneurysms that are difficult to reach surgically, endovascular treatment may be used. In this procedure, a catheter is guided from a larger artery up into the brain to reach the aneurysm. Small coils of wire are discharged into the aneurysm, which plug it up and block off blood flow from the main artery.

A man who suffered a stroke is helped with his rehabilitation by a physical therapist. *(© 1993 ATC Productions. Custom Medical Stock Photo. Reproduced by permission.)*

Recovery and rehabilitation

Rehabilitation refers to a comprehensive program designed to help the patient regain function as much as possible and compensate for permanent losses. Approximately 10% of stroke survivors are without any significant disability and able to function independently. Another 10% are so severely affected that they must remain institutionalized for severe disability. The remaining 80% can return home with appropriate therapy, training, support, and care services.

Rehabilitation is coordinated by a team that may include the services of a **neurologist**, a physiatrist, a physical therapist, an occupational therapist, a speech-language pathologist, a nutritionist, a mental health professional, and a social worker. Rehabilitation services may be provided in an acute care hospital, rehabilitation hospital, long-term care facility, outpatient clinic, or at home.

The rehabilitation program is based on the patient's individual deficits and strengths. Strokes on the left side of the brain primarily affect the right half of the body, and vice versa. In addition, in left-brain-dominant people, who constitute a significant majority of the population, left-brain strokes usually lead to speech and language deficits, while right-brain strokes may affect spatial perception. Patients

Key Terms

Aneurysm A pouch-like bulging of a blood vessel.

Atrial fibrillation A disorder of the heartbeat associated with a higher risk of stroke. In this disorder, the upper chambers (atria) of the heart do not completely empty when the heart beats, which can allow blood clots to form.

Cerebral embolism A blockage of blood flow through a vessel in the brain by a blood clot that formed elsewhere in the body and traveled to the brain.

Cerebral thrombosis A blockage of blood flow through a vessel in the brain by a blood clot that formed in the brain itself.

Intracerebral hemorrhage A cause of some strokes in which vessels within the brain begin bleeding.

Subarachnoid hemorrhage A cause of some strokes in which arteries on the surface of the brain begin bleeding.

Tissue plasminogen activator (tPA) A substance that is sometimes given to patients within three hours of a stroke to dissolve blood clots within the brain.

with right-brain strokes may also deny their illness, neglect the affected side of their body, and behave impulsively.

Rehabilitation may be complicated by cognitive losses, including diminished ability to understand and follow directions. Poor results are more likely in patients with significant or prolonged cognitive changes, sensory losses, language deficits, or incontinence.

Preventing complications

Rehabilitation begins with prevention of stroke recurrence and other medical complications. The risk of stroke recurrence may be reduced with many of the same measures used to prevent stroke, including quitting smoking and controlling blood pressure.

One of the most common medical complications following stroke is deep venous thrombosis, in which a clot forms within a limb immobilized by paralysis. Clots that break free can often become lodged in an artery feeding the lungs. This type of pulmonary embolism is a common cause of death in the weeks following a stroke. Resuming activity within a day or two after the stroke is an important preventive measure, along with use of elastic stockings on the lower limbs. Drugs that prevent clotting may be given, including intravenous heparin and oral warfarin.

Weakness and loss of coordination of the swallowing muscles may impair swallowing (dysphagia), and allow food to enter the lower airway. This may lead to aspiration pneumonia, another common cause of death shortly after a stroke. Dysphagia may be treated with retraining exercises and temporary use of pureed foods.

Depression occurs in 30–60% of stroke patients. Antidepressants and psychotherapy may be used in combination.

Other medical complications include urinary tract infections, pressure ulcers, falls, and **seizures**.

Types of rehabilitative therapy

Brain tissue that dies in a stroke cannot regenerate. In some cases, other brain regions may perform the functions of that tissue after a training period. In other cases, compensatory actions may be developed to replace lost abilities.

Physical therapy is used to maintain and restore range of motion and strength in affected limbs, and to maximize mobility in walking, wheelchair use, and transferring (from wheelchair to toilet or from standing to sitting, for instance). The physical therapist advises on mobility aids such as wheelchairs, braces, and canes. In the recovery period, a stroke patient may develop muscle **spasticity** and contractures, or abnormal contractions. Contractures may be treated with a combination of stretching and splinting.

Occupational therapy improves self-care skills such as feeding, bathing, and dressing, and helps develop effective compensatory strategies and devices for activities of daily living. A speech-language pathologist focuses on communication and swallowing skills. When dysphagia is a problem, a nutritionist can advise alternative meals that provide adequate nutrition.

Mental health professionals may be involved in the treatment of depression or loss of thinking (cognitive) skills. A **social worker** may help coordinate services and ease the transition out of the hospital back into the home. Both social workers and mental health professionals may help counsel the patient and family during the difficult rehabilitation period. Caring for a person affected with stroke requires learning a new set of skills and adapting to new demands and limitations. Home caregivers may develop stress, anxiety, and depression. Caring for the caregiver is an important part of the overall stroke treatment program.

Support groups can provide an important source of information, advice, and comfort for stroke patients and for caregivers. Joining a support group can be one of the most important steps in the rehabilitation process.

Clinical trials

As of mid-2004, there were numerous open **clinical trials** for stroke, including:

- "Adjunctive Drug Treatment for Ischemic Stroke Patients," "E-Selectin Nasal Spray to Prevent Stroke Recurrence," "Improving Motor Learning in Stroke Patients," "Aspirin or Warfarin to Prevent Stroke," "Hand **Exercise** and Upper Arm Anesthesia to Improvements Hand Function in Chronic Stroke Patients," "Preliminary Study of Transcranial Magnetic Stimulation for Stroke Rehabilitation," and "Using fMRI to Understand the Roles of Brain Areas for Fine Hand Movements" are all sponsored by the National Institute of Neurological Disorders and Stroke.
- "Preventing Post-Stroke Depression" is sponsored by the National Institute of Mental Health (NIMH).
- "Walking Therapy in Hemiparetic Stroke Patients Using Robotic-Assisted Treadmill Training" is sponsored by the United States Department of Education.
- "Brain Processing of Language Meanings" is sponsored by Warren G. Magnuson Clinical Center.

Updated information on these and other ongoing trials for the study and treatment of stroke can be found at the National Institutes of Health Web site for clinical trials at <http://www.clinicaltrials.org>.

Prognosis

Stroke is fatal for about 27% of white males, 52% of black males, 23% of white females, and 40% of black females. Stroke survivors may be left with significant deficits. Emergency treatment and comprehensive rehabilitation can significantly improve both survival and recovery.

Prevention

Damage from stroke may be significantly reduced through emergency treatment. Knowing the symptoms of stroke is as important as knowing those of a heart attack. Patients with stroke symptoms should seek emergency treatment without delay, which may mean dialing 911 rather than their family physician.

The risk of stroke can be reduced through lifestyle changes, including:

- stopping smoking
- controlling blood pressure
- getting regular exercise
- keeping weight down
- avoiding excessive alcohol consumption
- getting regular checkups and following the doctor's advice regarding diet and medicines

Treatment of atrial fibrillation may significantly reduce the risk of stroke. Preventive anticoagulant therapy may benefit those with untreated atrial fibrillation. Warfarin (Coumadin) has proven to be more effective than aspirin for those with higher risk.

Screening for aneurysms may be an effective preventive measure in those with a family history of aneurysms or autosomal polycystic kidney disease, which tends to be associated with aneurysms.

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American Heart Association. 7320 Greenville Ave. Dallas, TX 75231. (214) 373-6300. (June 3, 2004). <http://www.americanheart.org>.

Richard Robinson

Sturge-Weber syndrome

Definition

Sturge-Weber syndrome (SWS) 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.

Description

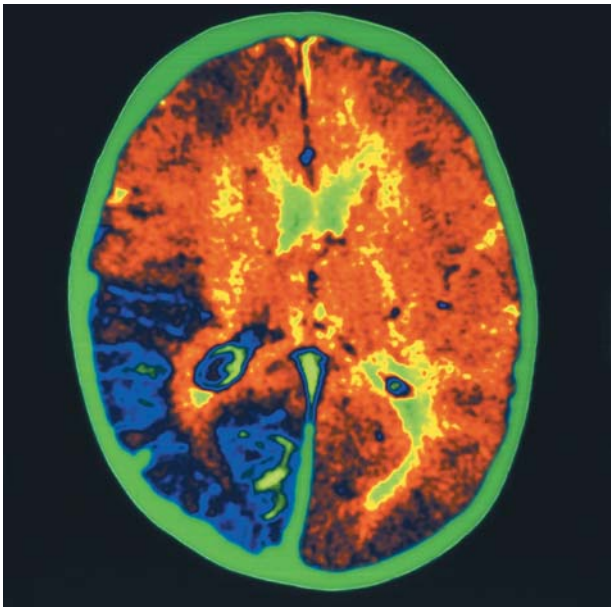
The brain finding in SWS is leptomeningeal angioma, which is a swelling of the tissue surrounding the brain and spinal cord. These angiomas cause seizures in approximately 90% of people with SWS. A large number of affected individuals are also mentally delayed.

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.

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, a gene known to cause SWS has not been identified. For now, SWS is thought to be caused by a random, sporadic event.



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.*

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.

Causes 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 SWS, 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 or brain

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.

calcifications, as well as any other associated white matter changes.

Treatment

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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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

Stuttering

Definition

Stuttering has no absolute definition that encompasses all the aspects of the disorder. In general, it is a condition in which a person trying to speak has difficulty in expressing words normally. Morphemes (actual individual sounds such as "mm" or the explosive "p") are not easily articulated. Two common symptoms of stuttering are the drawing out of the morpheme as in "mmmmmore" or the repetitious "l-l-l-look" of seemingly simple words.

Stuttering is not to be confused with another speech disorder called cluttering. Cluttering has a much more definitive cause and clearer symptoms. Its neurogenic link has been more thoroughly established, while the roots of stuttering have not. Cluttering involves a rapid speech pattern, while stuttering can take on a variety of levels of complexity.

Description

In the past, researchers and speech therapists assumed that stuttering was a developmental disorder. Increasing evidence points to a genetic cause in many patients, especially males. The results are far from clear and studies are conflicting in their data and conclusions. Many studies are focused on the fact that monozygotic (one egg) twins both seem to stutter when the disorder is present.

Key Terms

Clutter A fluency disorder where speech delivery is either abnormally fast, irregular, or both.

Stutter A speech disorder involving hesitations and involuntary repetitions of certain sounds.

Stuttering is usually identified in children. Unless the situation is extremely stressful, such as speaking in front of a large group of people, or an equally distressing condition is present, very few adults begin to stutter later in life. Stress and anxiety about the inability to easily express thoughts and words is very distressing for the child who stutters and can prolong recovery or even prevent it.

The social anxiety accompanying stuttering is one of the reasons researchers have historically cited the lack of emotional well-being or the production of high anxiety as the root cause of the disorder. While at an early age, when peer pressure and social acceptance is extraordinarily important, the lack of understanding by other children can be very difficult to overcome. At this point, stuttering does become an emotional as well as physical challenge.

Demographics

More than 1% of the population stutters. However, if every person who has, at some time, found themselves stuttering when anxious were included, the condition would be considered a great deal more common. Males are four times more likely than females to stutter. Stuttering is also more common in children than adults.

The Stuttering Foundation of America has provided facts on who is likely to stutter. They describe four of the most common factors that lead to stuttering. The first is genetics. Clinical results indicate that around 60% of those who stutter have a family member who also stutters. A second possible cause for stuttering involves developmental delays. Researchers claim that children with other speech and language problems are more likely to stutter than those who do not.

The third proposed reason for stuttering involves the physiology of the brain. With **magnetic resonance imaging (MRI)** and other such examinations, it appears that some people process speech and language in different regions of the brain than those who do not stutter. Early language acquisition occurs in the Broca's area of the brain, but this ability lasts only for a short time during childhood. After initial speech is acquired, language is learned in other regions of the brain. This may have an influence on those who stutter.

Finally, family dynamics are implicated as reasons for stuttering. Parents with high expectations and little patience may push a child to speak before he or she is ready. Without proper education, some parents may push their children to achieve certain goals by a particular age. If the goal is not, met a child may experience anxiety and it is possible this could result in stuttering.

Causes and symptoms

The actual physiological cause of stuttering is not conclusive.

Neurogenic stutterers are those people who have developed the disorder as a result of some sort of head injury or trauma. Their speech may be repetitious, prolonged, and they may even experience a mental block on certain words or phrases. However, they seem to lack the fears and anxieties of those who are designated as developmental stutterers. The severity of neurogenic stuttering is directly correlated with the degree of brain injury and degree of healing.

Diagnosis

A health professional or speech therapist trained in identifying varying speech disorders makes the diagnosis of stuttering. Stuttering must be isolated from anxious stammering, brain-related cluttering, and a variety of additional speech disorders.

Treatment team

The treatment team for a stutterer is multidisciplinary. Initially, a child's parent or teacher may identify a problem in communication and reading aloud. The pediatrician usually identifies and makes the diagnosis of stuttering as opposed to other vocal disturbances. A neurological consultation may be sought. Occurrences such as head trauma or lesions of the brain must be ruled out as a contributing factor.

Many speech and language pathologists have been trained and licensed to work with stutterers. They can provide exercises, vocal awareness, and support that the stutterer needs to begin a path to recovery. Many schools offer these types of support and are free to the students.

One of the best teams for the treatment of stuttering is the family and friends of the person who stutters. It is likely the stutterer feels embarrassment or guilt over the condition. Family and friends who take the time to understand the condition and show their patience and acceptance can help the person who stutters. Reading books about the condition and aiding in home therapies is a proven method of making the stutterer feel less shame and embarrassment. In turn, the benefits of therapy can be reached more quickly.

Treatment

Most clinicians recommend a holistic approach in which patients are allowed to find their own most useful therapy. A good rapport should exist between the speech therapist and patient.

Significantly, often when the person who stutters focuses on a related task such as singing, the individual fails to show any symptoms. When a prescribed set of words and additional distraction are employed, it appears the stutterer has fewer problems speaking clearly. Singing and rhyming are strategies used by speech therapists as confidence boosters to illustrate that the person has the ability to express language in a natural, easily flowing manner.

Recently, some electrical devices for the treatment of stuttering have come onto the market, but their success is still not well documented. The Delayed Auditory Feedback (DAF) and Frequency-Shifting Auditory Feedback (FAF) are electronic devices that pick up a voice from a microphone, delay the sound for a fraction of a second, and feed the voice back through earphones. Some clinicians claim the feedback machines can significantly reduce or eliminate stuttering.

Recovery and rehabilitation

Recovery from stuttering is unpredictable for several reasons. Many people must come to the aid of the stutterer. Family and friends, the therapist, schoolmates, and a variety of additional environmental conditions must be in place for the stutterer to gain control over the disorder. If all is in place, the chance of significant improvement is excellent.

Clinical trials

As of early 2004, the National Institute on Deafness and Other Communication Disorders and the National Institute of Neurological Diseases and Stroke were sponsoring several **clinical trials** on the nature and treatment of stuttering. Information about the studies can be found at the National Institutes of Health clinical trials website: <http://www.clinicaltrials.gov/ct/search?term=stuttering&submit=Search>.

Prognosis

The prognosis for people who stutter can be very good. The American Society of Stuttering lists some famous people who stutter and have proceeded to make careers in which their voice is an asset. The list includes James Earl Jones, Mel Tillis, Winston Churchill, Marilyn Monroe, Carly Simon, and many more celebrities who make their living by announcing, acting, or singing.

Special concerns

Many childhood stutterers are not receiving adequate treatment because of poverty or financially stretched school resources. The American Institute for Stuttering offers information on seeking financial resources for the treatment of stuttering, training of professionals to treat those who stutter, and additional information about stuttering.

Resources

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"Stuttering." *University of Maryland Medicine.* April 4, 2004 (June 3, 2004). <http://www.umm.edu/ent/stutter.htm>.

ORGANIZATIONS

American Speech-Language-Hearing Association. 10801 Rockville Pike, Rockville, MD 20852. (301) 897-5700 or (800) 638-8255; (301) 571-0457. actioncenter@asha.org. <http://www.nsastutter.org>.

National Stuttering Association. 471 East La Palma Avenue, Suite A, Anaheim Hills, CA 92807. (714) 693-7480 or (800) 364-1677; (714) 630-7707. nsastutter@asha.org. <http://www.nsastutter.org>.

Brook Ellen Hall, PhD

Subacute sclerosing panencephalitis

Definition

Subacute sclerosing panencephalitis (SSPE) is a long-lasting (chronic) infection of the **central nervous system** that causes inflammation of the brain. The infection is caused by an altered form of the measles virus. The symptoms appear years after the initial infection, following reactivation of the latent virus.

Description

SSPE is one of three types of encephalitis that can occur following infection with the measles virus. The other forms are an acute (sudden appearance of symptoms) form that is typically associated with the rash that forms during the measles infection. The other form of SSPE affects the myelin sheath surrounding nerve cells, and is likely part of an autoimmune reaction.

SSPE develops when the measles virus, which is still present but is in an inactive (or latent) form, is reactivated. The appearance of symptoms typically leads to a disease that last from one to three years.

The disease is also known as subacute sclerosing leukencephalitis and Dawson's encephalitis.

Key Terms

Antibody A special protein made by the body's immune system as a defense against foreign material (bacteria, viruses, etc.) that enters the body. It is uniquely designed to attack and neutralize the specific antigen that triggered the immune response.

Encephalitis Inflammation of the brain, usually caused by a virus. The inflammation may interfere with normal brain function and may cause seizures, sleepiness, confusion, personality changes, weakness in one or more parts of the body, and even coma.

Seizure A sudden attack, spasm, or convulsion.

Demographics

Children and young adults are primarily affected with SSPE. Males are also more affected than females, with a male-to-female ratio of 4:1. As well, there is a geographical component to the infection, with those in rural areas being much more susceptible (approximately 85% of cases arise in rural environments). Since the measles vaccine has been introduced, the disease has become rare in many areas of the globe, particularly the western world (about one in 1,000,000 people). Fewer than 10 cases per year occur in the United States. However, in the Middle East and India the incidence of the disease remains high (over 20 cases per 1,000,000 people).

Causes and symptoms

The disease is caused by the reactivated form of a mutated measles virus. The inactive form of the virus can be present in the body for up to 10 years following the initial bout of measles before the symptoms of SSPE develop. While normally the measles virus does not infect the brain, the mutated virus is capable of invading the brain.

When symptoms do develop, motor skills and mental faculties become progressively worse. Initial symptoms include a change in behavior, irritability, memory loss, and difficulty in forming thoughts and solving problems. Subsequently, a person can experience involuntary movements and **seizures** (also known as myoclonic spasms), loss of the ability to walk, difficulty speaking, and swallowing difficulty (dysphagia). Blindness can occur. In the final stages of the disease, a patient with SSPE may become mute and can lapse into a coma.

Monitoring the electrical activity of the brain has shown that SSPE causes disruptions that are consistent with the deterioration of the central nervous system. These changes tend to occur in stages, and so can be diagnostic of the progression of the disease. A different pattern of brain deterioration has been detected using the techniques of computed tomography and **magnetic resonance imaging**. However, this latter pattern is not yet refined enough for diagnostic use. Examination of brain tissue has shown that the disease is associated with the deterioration of the cortex and loss of white matter.

Diagnosis

SSPE is diagnosed based on the early symptoms, detection of antibodies to the measles virus, detection of protein in the spinal fluid, and the information gained from monitoring of the brain.

Treatment team

Initially, the family physician and local clinicians provide care. With the progression of the disease, specialists such as neurologists can become involved. Nurses are critical for those patients with advanced disease. Family and friends are an important source of care throughout the disease.

Treatment

There is no cure for SSPE. In the past, the primary means of treatment included therapy to curb seizures and the use of supportive measures such as feeding tubes when swallowing becomes difficult. During the 1990s, evidence accumulated in the medical literature to support the contention that SSPE can be stabilized and the progressive deterioration can be slowed by drug therapy. The drugs used lessen the damage inflicted by the immune system (immunomodulators such as the **interferons**), or attack the virus. The drugs used are an orally administered form of the antiviral drug inosine pranobex (oral isoprinosine),

oral isoprinosine combined with interferon alpha or beta, and interferon alpha combined with intravenous ribavirin (another antiviral). In particular, the isoprinosine-interferon alpha combination has been reported to produce up to a 50% rate of remission or improvement in symptoms. As promising as these results are, no controlled studies have yet been performed. Therefore, the treatments are not typically used.

Recovery and rehabilitation

As SSPE is almost always fatal, emphasis is placed upon maintaining comfort, rather than rehabilitation.

Clinical trials

There were no **clinical trials** in progress or planned in the United States as of January 2004. However, organizations such as the National Institute for Neurological Diseases and Stroke undertake and fund research aimed at furthering the understanding of the causes, prevention, and treatment of subacute sclerosing panencephalitis and related diseases.

Prognosis

Without treatment, death usually occurs within one to three years following the first appearance of symptoms. Treatment with immunomodulators and **antiviral drugs** has achieved remission of the disease in some cases. As well, remission can occur spontaneously in approximately 5% of cases.

Resources

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ORGANIZATIONS

National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders. 55 Kenosia Avenue, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-6673; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Brian Douglas Hoyle, PhD

Subarachnoid hemorrhage *see* **Aneurysm**

Subcortical arteriosclerotic encephalitis *see* **Binswanger disease**

Subdural hematoma

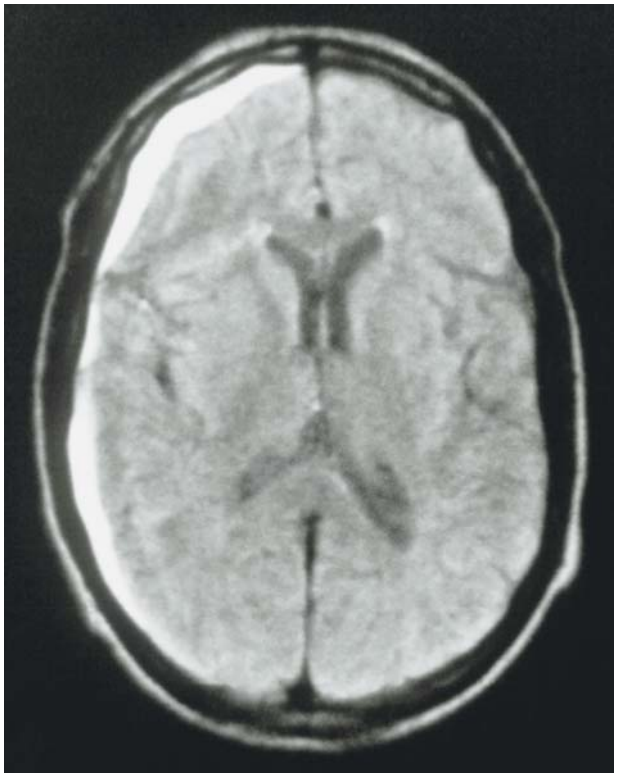
Definition

A subdural hematoma is a pooling of blood between the dura, which is a leathery membrane just under the skull, and the brain itself. Subdural hematomas usually occur following a head trauma that breaks the blood vessels that surround the brain. The pressure of the accumulated blood on the brain can cause a variety of symptoms including problems with speech, vision, or even a loss of consciousness.

Description

The bony skull encases the brain, protecting it from external damage. Between the skull and the brain itself is a tough leathery tissue, called the dura. This dura serves two purposes, forming a second layer of protection around the brain and providing vasculation that nourishes the brain with blood and spinal fluid. During a severe blunt head trauma, the bridging blood vessels that connect the dura to the skull may tear because of shear forces to the head. The broken vessels bleed into the space between the skull and the dura. This pooling of blood puts pressure on the brain, and it swells in response. Because the skull creates a defined volume, there is no extra room for the brain to swell and therefore, parts of the brain become compressed. This usually has neurological consequences including visual problems, speech dysfunction, and loss of consciousness.

The term subdural hematoma has a variety of synonyms including SDH, subdural hemorrhage, and blood clot on the brain. Physicians may use the adjectives acute, subacute, and chronic to describe the time course and volume of blood in subdural hematomas. Acute describes subdural hematomas that gather a large amount of blood



Nuclear magnetic resonance image of the head of a person suffering from a subdural hematoma. The two elongated white areas on the left side of the brain represent the blood that has been lost into the space between the brain and the skull. *(Hammersmith Hospital Medical School / Photo Researchers, Inc.)*

quickly. Subacute refers to subdural hematomas that occur between three and seven days following an injury to the head. In these patients, the blood clots will liquefy and in some cases the various cellular components of the blood clots will form layers that can be visualized using computerized tomography (**CT**). Chronic usually refers to subdural hematomas that produce symptoms two to three weeks following an injury. In these hematomas, the blood clot has become mostly blood serum. Additionally, subdural hematomas are classified as simple or complicated. About half of all cases are simple, which implies that there is no laceration or contusion in the brain. In complicated SDH, the brain has suffered some sort of traumatic injury.

Demographics

SDH can happen to anyone who experiences a head trauma. In the United States, between 15% and 30% of patients suffering from head injuries have SDH. About half of the cases of SDH are simple SDH. The other half of the cases involves other complications such as laceration of the brain, and the mortality rate is much greater in these individuals. SDH is more common in people older than 60 because their blood vessels are more fragile than those in younger people. SDH is also associated with child abuse. People with blood disorders, such as hemophiliacs, people on anticoagulants, and alcoholics, are at higher risk for developing subdural hematomas.

Causes and symptoms

Subdural hematomas are most often caused by head trauma. Rarely, they can occur spontaneously, especially in elderly persons. Often the person will lose consciousness following the trauma, but SDH can occur when the person has remained conscious. Signs indicating the presence of SDH include headaches, **dizziness**, nausea, pupil dilation, slurred speech, and weakness in the limbs. More severe symptoms include loss of consciousness, disorientation, amnesia, trouble with breathing, or even coma.

Diagnosis

Diagnosis of an acute or chronic subdural hematoma is most often accomplished by using a computerized tomography (CT) scan, which is a specialized x ray. The SDH appears as a white crescent shape that lies along the skull. In subacute SDH, the shape of the pooled blood looks more lens-like and **magnetic resonance imaging (MRI)** is recommended to distinguish it from an **epidural hematoma**.

Treatment

In many cases, small subdural hematomas may be treated with observation and a series of CT scans to ensure that the blood is reabsorbing and not becoming calcified. In more severe cases, surgical intervention is necessary. The surgeon will open the skull in a procedure known as a **craniotomy** and remove the blood clot to release the pressure on the brain. The clot is removed with suction and irrigation.

Recovery and rehabilitation

Following surgical removal of a subdural hematoma, a patient will most likely need to remain in the intensive care unit for a period of time. Diuretics to decrease swelling of the brain and **anticonvulsants** to prevent **seizures** will be administered. Some of the complications associated with surgery are swelling of the brain, infection, seizures, memory loss, **headache**, difficulty concentrating, and chronic SDH. In about 50% of the cases, a hematoma may recur following surgery.

Prognosis

The prognosis for someone who has suffered a subdural hematoma depends on the size and severity of the blood clot. Acute SDH may have very high rates of death

Key Terms

Craniotomy A surgical procedure in which part of the skull is removed (then replaced) to allow access to the brain.

Dura matter The strongest and outermost of three membranes that protect the brain, spinal cord, and nerves of the cauda equina.

Skull All of the bones of the head.

and long term disability. Subacute and chronic SDH usually have a better prognosis, with most symptoms abating following surgery. Mortality rates associated with simple SDH approach 20% as compared with 50% for complicated SDH. In all cases, persons who have experienced a subdural hematoma have a high risk of seizures, although this can usually be controlled with medication.

Resources

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ORGANIZATIONS

National Institute for Neurological Diseases and Stroke (NINDS). 6001 Executive Boulevard, Bethesda, MD 20892. (301) 496–5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

Juli M. Berwald, PhD

Succinamides

Definition

Succinamides are a sub-class of **anticonvulsants**, indicated for the treatment of **seizures** associated with **epilepsy**.

Purpose

Although there is no known cure for epilepsy, succinamides are used to control and prevent absence (petit mal) seizures associated with the disorder. Succinamides are most often used in conjunction with other anticonvulsant medications to control other types of seizures (such as other generalized tonic-clonic or grand mal seizures) as part of a comprehensive course of treatment for epilepsy and other disorders.

Description

Succinamides are sold under several names, including ethosuximide (Zarontin) and celontin. Zarontin is the only succinamide that is regularly used in the United States today, as celontin has a higher rate of side effects. Zarontin effectively controls partial seizures, but in some individuals may actually increase the likelihood of generalized seizures. It is often, therefore, prescribed in combination with other anticonvulsants to minimize the chances of generalized seizures.

Recommended dosage

Succinamides are taken orally and are available in tablet or suspension form. For the treatment of epilepsy, succinamides may be taken by both adults and children. Succinamides are prescribed by physicians in varying dosages, but typical total daily dosages range from 250mg to 1.5g.

When beginning a course of treatment that includes succinamides, most physicians recommend a gradual dose-increasing regimen. Patients typically take a reduced dose at the beginning of treatment. The prescribing physician will determine the proper initial dosage, and then will periodically raise the patient's daily dosage until seizure control is achieved.

A double dose of any succinamide should not be taken together. If a daily dose is missed, take it as soon as possible. However, if it is within four hours of the next dose, then skip the missed dose. Physicians typically direct patients to gradually taper their daily dosages when ending treatment that includes succinamides. Stopping the medicine suddenly may cause seizures to return, occur more frequently, or become more severe.

Precautions

A physician should be consulted before taking succinamides with certain non-prescription medications. Persons should avoid alcohol and CNS depressants (medicines that can make one drowsy or less alert, such as antihistimines, sleep medications, and some **pain** medications) while taking succinimides or any other anticonvulsants. They can exacerbate the side effects of alcohol and other medications. Succinamides are not habit-forming.

A course of treatment including succinamides may not be appropriate for persons with gastrointestinal disorders, **stroke**, anemia, mental illness, diabetes, high blood

Key Terms

Absence seizure A type of generalized seizure where the person may temporarily appear to be staring into space and/or have jerking or twitching muscles. Previously called a petit mal seizure.

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Seizure A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain, resulting in abnormal body movements or behaviors.

Tonic-clonic seizure A type of seizure involving loss of consciousness, generalized involuntary muscular contractions, and rigidity.

presure, angina (chest pain), irregular heartbeats, or other heart problems.

Succinamides may not be suitable for persons with a history of liver or kidney disease. In rare cases, succinamides may cause abnormalities in the blood and abnormal liver or kidney function. Periodic blood, kidney, and liver function tests are advised for all patients using the medicine. To check for rare blood disorders and symptoms of infection, periodic blood tests may be necessary while taking succinamides.

Before beginning treatment with succinamides, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant, nursing, or plan on becoming pregnant. Although succinamides have not been associated with problems during pregnancy, other anticonvulsant medications may cause birth defects. Patients are often advised to use effective birth control while taking succinamides in combination with other anticonvulsants. Women who become pregnant while taking succinamides should contact their physician immediately.

Side effects

Patients should discuss with their physicians the risks and benefits of treatment including succinamides before taking the medication. Succinamides are usually well tolerated, but may case a variety of usually mild side effects. Diziness, nausea, and drowsiness are the most frequently reported side effects. Most side effects do not require medical attention, and usually diminish with continued use of the medication. Possible side effects include:

- unusual tiredness or weakness
- clumsiness
- hiccups
- loss of appetite
- nausea, vomiting, stomach cramps

If any symptoms persist or become too uncomfortable, the prescribing physician should be consulted.

Other, uncommon side effects of succinamides can be serious or could indicate an allergic reaction. Patients who experience any of the following symptoms should immediately contact a physician:

- nightmares and sleeplessness
- rash or bluish patches on skin
- persistent nosebleed
- ulcers or white spots on lips
- extreme mood or mental changes
- shakiness or unsteady walking
- severe unsteadiness or clumsiness
- speech or language problems
- difficulty breathing
- chest pain
- irregular heartbeat
- faintness or loss of consciousness
- severe cramping
- persistant, severe headaches
- persistant sore throat, fever, or pain

Interactions

Succinamides may have negative interactions with some antihistimines, antidepressants, antibiotics, and monoamine oxidase inhibitors (MAOIs). Other medications such as **Diazepam** (Valium), **phenobarbital** (Luminal, Solfoton), nefazodone, metronidazole, and certain anesthetics may react with succinamides.

Resources

BOOKS

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ORGANIZATIONS

American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. <http://www.aesnet.org>.

Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

Adrienne Wilmoth Lerner

Sunsetting of eyes *see* **Visual disturbances**

Swallowing disorders

Definition

Swallowing disorders (also called dysphagia) are any conditions that cause impairment of the movement of solids or fluids from the mouth, down the throat, and into the stomach.

Description

Swallowing disorders are a significant source of disability. They can have a severe effect on overall calorie intake and nutritional status, and they can adversely affect an individual's enjoyment of eating and drinking and the ability to participate in related social interactions. Swallowing disorders may affect the ability to swallow liquids, solids, or both. In addition to complicating or preventing intake of liquids and solids, some swallowing disorders may make an individual susceptible to pneumonia, if any portion of the substances being swallowed are directed into the lungs.

Many conditions are associated with swallowing disorders. Any condition that interferes with one or more of the three normal phases associated with swallowing will impair an individual's swallowing ability. The three normal phases include the oral phase, the pharyngeal phase, and the esophageal phase. Oral refers to the mouth; pharyngeal refers to the pharynx (the area of the airway at the back of the mouth, and leading to the esophagus and the lungs); esophageal refers to the esophagus (the tube passageway between the mouth and the stomach).

The oral phase refers to the aspects of swallowing that rely on intact mouth functioning. The oral phase is itself divided into two phases, the oral preparatory phase and the oral transit phase. In the oral preparatory phase, solids are broken into smaller, softer bits through chewing and mixing with saliva. The resulting mass to be swallowed is referred to as the "bolus." The oral transit phase refers to the movement of the bolus to the back of the mouth, through the actions of the tongue.

The pharyngeal phase refers to the transit of the bolus into the pharynx, also called the swallowing reflex. During this phase, it is crucial that breathing cease and that the entry from the pharynx into the larynx (voice box) closes tightly, thus preventing food or fluid from entering into the lungs.

The esophageal phase refers to the transit of the bolus down the esophagus and into the stomach. The esophageal phase is guided primarily by a series of involuntary waves of muscular action, called peristalsis, that move the bolus down the esophagus towards the stomach. At the end of the esophagus is an area called the esophageal sphincter, which must relax sufficiently to allow the bolus to enter the stomach. The esophageal sphincter, however, must also quickly resume appropriate muscle tone to avoid allowing stomach contents to exit the stomach and go back up the esophagus (called reflux).

Of the three phases of swallowing, only the oral phase requires conscious input; both the pharyngeal and the esophageal phases occur outside of voluntary control. The amount of time required for the oral phase varies depending on the individual; some people eat or drink very slowly, chewing many times, while others seem to "inhale" their food. Under normal conditions, the pharyngeal phase is over in about one second, and the esophageal phase takes about three seconds. Various disorders may increase the duration (and relative success) of any of these phases.

Swallowing disorders can be caused by the following:

- mechanical obstruction at any point along the swallowing path
- problems with the nerves and muscles necessary for chewing and moving the food around the mouth
- decreased sensation, leading to inability to feel the food and organize its movement appropriately
- inability of the larynx to close tightly
- problems with coordinating breathing and its cessation
- problems with the involuntary muscle movements necessary for moving the bolus down the esophagus

These problems may occur at the actual level of functioning (for example, muscle defects) or at the level of the brain's organization of these functions.

Complications of swallowing disorders include dehydration, weight loss, malnutrition, social isolation, and aspiration pneumonia.

Causes and symptoms

A huge variety of disorders may cause problems with swallowing, including:

- progressive neurological conditions (such as **Parkinson's disease**, **multiple sclerosis**, **amyotrophic lateral sclerosis**, Huntington's **chorea**, **post-polio syndrome**, **myasthenia gravis**, muscular dystrophy)

Key Terms

Bolus A mass of a substance to be swallowed.

Esophagus The tube leading from the back of the mouth, down the throat, and into the stomach.

Larynx The "voice box," located between the pharynx (upper area of the throat) and the trachea (windpipe).

Peristalsis Waves of involuntary muscle contraction and relaxation.

Pharynx The part of the airway that is located at the back of the throat.

- mechanical blockage of the swallowing apparatus (by tumors; abnormal tissue growth called esophageal webs or rings; abnormal outpouchings of areas of the esopahagus called Zenker's diverticula; scar tissue or strictures due to **radiation** therapy, medications, toxic or chemical exposure, ulcers, or smoke inhalation)
- damage to the brain or spinal cord (due to **cerebral palsy** or after **stroke**, **spinal cord injury**, traumatic head injury, or direct injury to any of the structures necessary for swallowing)
- certain medications (nitrates, anticholinergic agents, aspirin, calcium tablets, calcium channel blockers, iron tablets, vitamin C, tetracycline)
- congenital defects (such as cleft palate)

Symptoms of swallowing difficulties include weight loss; dehydration; sensation of having a lump in the throat after having attempted to swallow; drooling; unintentional retention of food within the mouth, despite attempts to swallow; coughing; choking; change in voice; regurgitation of liquids or solids through the nose; difficulty chewing; difficulty breathing or talking while eating, drinking, and swallowing; recurrent bouts of pneumonia.

Diagnosis

A variety of tests can diagnose dysphagia. A thorough neurological examination may reveal deficits involving the cranial nerves responsible for the strength and coordination of the muscles of swallowing. Fiberoptic endoscopy uses a narrow lighted scope to examine the mouth, pharynx, and esophagus. Videofluroscopic swallowing studies require the patient to swallow a solution containing barium; a moving x-ray machine takes images to evaluate the swallowing mechanism. Ultrasound studies can examine the tongue and larynx during swallowing. Scintigraphy involves swallowing a radioactive substance, and then examining images to see if the patient is aspirating. Manometry is a test that measures the changes in pressure throughout the esophagus during swallowing, in order to evaluate peristalsis.

Treatment team

Neurologists, gastroenterologists, and otorhinolaryngologists may all work with patients suffering from dysphagia. Speech and language therapists are trained to evaluate and help individuals who have swallowing problems.

Treatment

Treatment ranges from simple changes in posture while eating to medications to surgical interventions.

When swallowing problems are mild, learning new eating techniques (smaller bites, more chewing) may be sufficient. Therapists can help individuals learn the most effective head and neck posture for successful swallowing. Exercises to strengthen muscles necessary for swallowing and improve coordination may be helpful. In order to improve their ease of swallowing, some people learn to avoid foods with certain textures, to thin or thicken liquids, or to avoid foods or beverages that are too hot or too cold. Medications may help improve swallowing. **Botulinum toxin** can relax spastic muscle that interfere with swallowing.

When no therapies or medications are helpful, and an individual's nutritional status is seriously compromised, alternative methods of providing nutrition (such as through a feeding or gastrostomy tube directly into the stomach) may be necessary.

Prognosis

Dysphagia can be a very serious condition. Its prognosis depends on how severe the swallowing problems are and how severely they interfere with proper nutrition, as well as on details of the underlying condition responsible for the dysphagia.

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Rosalyn Carson-DeWitt, MD

Sydenham's chorea

Definition

Sydenham's **chorea** is an acute but self-limited movement disorder that occurs most commonly in children between the ages of five and 15, and occasionally in pregnant women. It is closely associated with rheumatic fever following a throat infection. The disorder is named for Thomas Sydenham (1624–1689), an English doctor who first described it in 1686. Other names for Sydenham's chorea include simple chorea, chorea minor, acute chorea, rheumatic chorea, juvenile chorea, and St. Vitus' dance. The English word chorea itself comes from the Greek word *choreia*, which means "dance." The disorder takes its name from the rapid involuntary jerking or twitching movements of the patient's face, limbs, and upper body.

Description

Sydenham's chorea is best described as a neurologic complication of rheumatic fever triggered by a throat infection (pharyngitis) caused by particular strains of bacteria known as group A beta-hemolytic streptococci or as GAS bacteria. In general, streptococci are spherical-shaped anaerobic bacteria that occur in pairs or chains. GAS bacteria belong to a subcategory known as pyogenic streptococci, which means that the infections they cause produce pus.

The initial throat infection that leads to Sydenham's chorea is typically followed by a symptom-free period of one to five weeks. The patient then develops an acute case of rheumatic fever (ARF), an inflammatory disease that affects multiple organ systems and tissues of the body. In most patients, ARF is characterized by fever, arthritis in one or more joints, and carditis, or inflammation of the heart. In about 20% of patients, however, Sydenham's chorea is the only indication of ARF. Sydenham's is considered a delayed complication of rheumatic fever; it may begin as late as 12 months after the initial sore throat, and it may start only after the patient's temperature and other physical signs have returned to normal. The average time interval between the pharyngitis and the first symptoms of Sydenham's, however, is eight or nine weeks.

It is difficult to describe a typical case of Sydenham's chorea because the symptoms vary in speed of onset as well as severity. Most patients have an acute onset of the disorder, but in others, the onset is insidious, which means that the symptoms develop slowly and gradually. In some cases, the child's physical symptoms are present for four to five weeks before they become severe enough for the parents to consult a doctor. In other cases, emotional or psychiatric symptoms precede the clumsiness and involuntary muscular movements that characterize the disorder. The psychiatric symptoms that may develop in patients with Sydenham's chorea are one reason why it is sometimes categorized as a PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) disorder.

Demographics

Both ARF and Sydenham's chorea are relatively uncommon disorders in the United States. According to the Centers for Disease Control and Prevention (CDC), only 1–3% of people with streptococcal throat infections develop ARF; thus, the incidence of ARF in the United States is thought to be about 0.5 per 100,000 patients between five and 17 years of age.

In general, the incidence of Sydenham's chorea is lower in the developed countries than in others, largely because of the widespread use of antibiotics in these countries to treat childhood streptococcal infections in the 1960s and 1970s. In addition, the disorder appears to have been overdiagnosed in the past; whereas at one time doctors thought that as many as half of all patients with ARF developed Sydenham's, present reports estimate that about 26% of ARF patients develop chorea. On the other hand, however, there are signs that the incidence of rheumatic fever is rising again in the United States and Canada; since the late 1980s, outbreaks have been reported at military installations in California and Missouri as well as in various cities in Pennsylvania, Utah, and Ohio. It is thought that this increase is due to more virulent strains of group A streptococci.

With regard to age, the incidence of Sydenham's chorea is higher in childhood and adolescence than in

Key Terms

Anaerobic Able to grow or live in the absence of oxygen.

Antibody An immunoglobulin molecule that interacts with the specific antigen that stimulated the body to produce it.

Anticonvulsant A type of drug given to prevent seizures.

Antigen Any substance that induces the body to produce antibodies and reacts with them.

Basal ganglia (singular, ganglion) Groups of nerve cell bodies located deep within the brain that govern movement as well as emotion and certain aspects of cognition (thinking).

Carditis Inflammation of the heart tissue.

Chorea A term that is used to refer to rapid, jerky, involuntary movements of the limbs or face that characterize several different disorders of the nervous system, including chorea of pregnancy and Huntington's chorea as well as Sydenham's chorea.

Compulsion A repetitive or stereotyped act or ritual.

Hemichorea Chorea that affects only one side of the body.

Insidious Developing in a stealthy or gradual manner.

Obsession A persistent or recurrent thought, image, or impulse that is unwanted and distressing.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) A group of childhood disorders associated with such streptococcal infections as scarlet fever and strep throat. Sydenham's chorea is considered a PANDAS disorder.

Pharyngitis Inflammation of the throat, accompanied by dryness and pain. Pharyngitis caused by a streptococcal infection is the usual trigger of Sydenham's chorea.

St. Vitus' dance Another name for Sydenham's chorea. St. Vitus was a fourth-century martyr who became the patron saint of dancers and actors during the Middle Ages.

Streptococcus (plural, streptococci) A genus of spherical-shaped anaerobic bacteria occurring in pairs or chains. Sydenham's chorea is considered a complication of a streptococcal throat infection.

adult life. It occurs more frequently in females than in males; the gender ratio is thought to be about two females to one male. Since the peak incidence of rheumatic fever in North America occurs in late winter and spring, Sydenham's chorea is more likely to occur in the summer and early fall. There is no evidence that the disorder selectively affects specific racial or ethnic groups.

About 20% of patients diagnosed with Sydenham's chorea experience a recurrence of the disorder, usually within two years of the first episode. Most women who develop Sydenham's during pregnancy have a history of ARF in childhood or of using birth control pills containing estrogen.

Causes and symptoms

The basic cause of Sydenham's chorea is infection with GAS bacteria, which are usually transmitted from person to person through large droplets produced by coughing or sneezing, or by direct contact. GAS bacteria can also be transmitted through contaminated food, most commonly eggs, milk, or milk products. The bacteria then invade the patient's upper respiratory tract, producing the sore throat that precedes the movement disorder.

The next stage in the development of Sydenham's chorea is an abnormal response of the patient's immune system to the streptococcal infection. Streptococcal antigens resemble nerve tissue antigens. In some people, the immune system produces antibodies against the streptococcal antigens that then cross-react against the tissues in certain regions of the brain—specifically, areas of the brain known as the basal ganglia. The basal ganglia are paired clusters of nerve cells that lie deep within the brain; they serve to regulate a person's movements, although they also play a role in governing emotions and certain aspects of thinking. **Magnetic resonance imaging (MRI)** studies of patients with Sydenham's chorea indicate that the basal ganglia are abnormally large, suggesting that they have been affected by the inflammation caused by the infection.

Some people are at greater risk of developing Sydenham's chorea. The risk factors for the disorder include:

- Living in crowded living conditions, inadequate sanitation, and malnutrition. Streptococcal infections are most common among the poor or homeless.
- Genetic factors. Some families appear to be more susceptible to ARF, although no specific genes have been identified.

- Female gender. Some researchers think there is a link between female sex hormones and susceptibility to Sydenham's, given that girls are more likely than boys to develop the disorder, particularly during puberty. In addition, women who are pregnant or have taken birth control pills containing estrogen are more likely to have recurrences of Sydenham's. The disorder is virtually unknown in sexually mature males.

PHYSICAL SYMPTOMS Although the speed of onset varies, patients with Sydenham's chorea develop rapid and purposeless involuntary motions or gestures that may involve all the muscles of the body, except those around the eyes. Most patients are affected on both sides of the body; however, about 20% have symptoms on only side of the body, a condition called hemichorea. The movements disappear during sleep, but usually become more severe when the child is tired or under stress. The patient's intentional movements such as picking up objects or writing by hand may become clumsy or uncoordinated; in addition, the muscles may become generally weak or lose their tone. In milder cases of Sydenham's, the patient may have only facial grimacing and some difficulty putting on clothes or doing other tasks that require fine coordination. In more severe cases, however, the patient's life may be disrupted by movements that affect large groups of muscles, preventing the patient from walking, going to school, or doing most daily activities.

PSYCHIATRIC SYMPTOMS As has been mentioned earlier, some children develop psychiatric symptoms associated with Sydenham's chorea before the physical symptoms appear. They may start acting unusually restless, aggressive, or hyperemotional. Behavioral or emotional disturbances that have been observed with the disorder include:

- frequent mood changes
- episodes of uncontrollable crying
- behavioral regression, that is, acting like much younger children
- mental confusion
- general irritability
- difficulty concentrating
- impulsive behavior

The most common psychiatric syndrome observed in children with Sydenham's chorea, however, is obsessive-compulsive disorder (OCD). OCD is characterized by obsessions, which are unwanted recurrent thoughts, images, or impulses, and by compulsions, which are repetitive rituals, mental acts, or behaviors. Obsessions in children often take the form of fears of intruders or harm coming to a family member. Compulsions may include such acts as counting silently, washing the hands over and over, insisting on keeping items in a specific order, checking repeatedly to make sure a door is locked, and similar behaviors.

Diagnosis

The diagnosis of Sydenham's chorea is usually based on a combination of a recent history of a streptococcal infection and the doctor's observation of the patient's involuntary movements. Unlike tics, the movements associated with chorea are not repetitive, and unlike the behavior of hyperactive children, the movements are not intentional. The recent onset of the movements rules out a diagnosis of **cerebral palsy**. If Sydenham's is suspected, the physician may ask the patient to stick out the tongue and keep it in that position, or to squeeze the doctor's hand. Many patients with Sydenham's cannot hold their mouth open and keep the tongue out for more than a second or two. Another characteristic of Sydenham's is an inability to grip with a steady pressure; when the patient squeezes the doctor's hand, the strength of the grip will increase and decrease in an erratic fashion. This characteristic is sometimes called the "milking sign."

Although imaging studies are used by researchers to study Sydenham's chorea, they are not ordinarily used by themselves to diagnose the disorder. Blood tests may show elevated levels of antibodies against streptococcal bacteria, or the patient's throat culture may be positive, but more often these tests give negative results by the time the movement disorder develops.

Once the diagnosis has been made, the doctor will evaluate the patient's heart for any indications of damage caused by rheumatic fever. This evaluation includes listening for abnormal heart sounds through a stethoscope and taking x rays to determine whether the heart is enlarged. In some cases, the doctor may order an electrocardiogram (EKG) to assess any irregularities in the patient's heartbeat.

Treatment team

In most cases, a child with Sydenham's chorea will be examined and diagnosed by a pediatrician. A child or adolescent psychiatrist may be consulted if the patient has developed symptoms of OCD. Children with heart murmurs or other signs of carditis may be referred to a pediatric cardiologist for further evaluation.

Treatment

Adequate treatment of a streptococcal throat infection with antibiotics may help to prevent an attack of ARF or Sydenham's chorea.

If the chorea has already developed, most doctors do not advise treating the involuntary movements by themselves unless they are so severe that the child is disabled

or at risk of self-injury. The reason for this precaution is that some of the recommended drugs, which are known as dopamine antagonists or neuroleptics, have potentially severe side effects. Dopamine antagonists include such medications as haloperidol (Haldol), risperidone (Risperdal), and pimozide (Orap). Some doctors may prescribe an anticonvulsant (antiseizure) drug, most commonly sodium valproate (Depakene), to lower the risk of injury. If the patient does not respond to the anticonvulsant, the child may be prescribed the lowest effective dose of a neuroleptic. Some doctors may prescribe a benzodiazepine tranquilizer like **diazepam** (Valium) or lorazepam (Ativan) to control the movements. Another type of drug that appears to help some patients with Sydenham's is corticosteroids, which are given to lower the inflammation associated with ARF.

Most doctors recommend ongoing treatment with penicillin to prevent a recurrence of ARF or Sydenham's chorea, although there is some disagreement as to whether this treatment should continue for five years after an acute attack or for the rest of the patient's life. The penicillin may be given orally or by injection. Patients who cannot take penicillin may be given erythromycin or sulfadiazine.

Obsessive-compulsive disorder is treated with a combination of psychotherapy (usually cognitive behavioral therapy, or CBT) and medications (usually selective serotonin reuptake inhibitors or SSRIs).

Recovery and rehabilitation

Most patients with Sydenham's chorea recover after a period of bed rest and temporary limitation of normal activities. In most cases, the symptoms disappear gradually rather than stopping abruptly.

Clinical trials

As of early 2004, the National Institute of Mental Health (NIMH) is recruiting subjects for a study of **magnetic resonance imaging** (**MRI**) in assessing brain structure and function in patients with childhood-onset psychiatric disorders. Sydenham's chorea, as well as other PANDAS disorders, is one of the conditions included in the study.

Prognosis

Sydenham's chorea is a self-limiting disorder that usually runs its course within one to six months, although it occasionally lasts as long as one to two years. In most cases, the patient recovers completely, although the disorder may recur. In a very few cases—about 1.5% of patients diagnosed with Sydenham's—there may be increasing muscle stiffness and loss of muscle tone resulting in disability. This condition is occasionally referred to as paralytic chorea.

Special concerns

Many doctors recommend that children with Sydenham's chorea should not be kept out of school longer than is necessary. Some of the psychological side effects that were once thought to be caused by the chorea itself are now regarded as the result of missing school combined with worry about other people's reactions to the involuntary movements.

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National Institute of Neurological Disorders and Stroke (NINDS). 9000 Rockville Pike, Bethesda, MD 20892. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders (NORD). P. O. Box 1968, Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD; Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

WE MOVE—Worldwide Education and Awareness for Movement Disorders. 204 West 84th Street, New York, NY 10024. (212) 875-8389 or (800) 437-MOV2. wemove@wemove.org. <http://www.wemove.org>.

Rebecca J. Frey, PhD

Syncope *see* **Fainting**

Syphilitic spinal sclerosis *see* **Tabes dorsalis**

Syringomyelia

Definition

The term syringomyelia refers to a collection of differing conditions characterized by damage to the spinal cord that is caused by a formation of abnormal fluid-filled cavities (syrinx) within the cord. In 1827, French physician Charles-Prosper Ollivier d'Angers (1796–1845) suggested the term syringomyelia after the Greek *syrinx*, meaning pipe or tube, and *myelos*, meaning marrow. Later, the term **hydromyelia** was used to indicate a dilatation of the central canal, and syringomyelia referred to cystic cavities separate from the central spinal canal.

Description

The cavities may be a result of **spinal cord injury**, tumors of the spinal cord, or congenital defects. An idiopathic form of syringomyelia (a form of the disorder without known cause) is also described in medical literature. The fluid-filled cavity, or syrinx, expands slowly and elongates over time, causing progressive damage to the nerve centers of the spinal cord due to the pressure exerted by the fluid. This damage results in **pain**, weakness, and stiffness in the back, shoulders, arms, or legs. People with syringomyelia experience different combinations of symptoms. In many cases, the disorder is related to abnormal lesions of the foramen magnum, the opening in the occipital bone that houses the lower portion of the medulla oblongata, the structure that links the brain and spinal cord. An additional cause of syringomyelia involves a Chiari malformation, a condition in which excess cerebral matter extends downward towards the medulla oblongata, crowding the outlet to the spinal canal. Some familial cases of syringomyelia have been observed, although this is rare. Types of syringomyelia include:

- syringomyelia with fourth ventricle communication
- syringomyelia due to blockage of cerebrospinal fluid (CSF) circulation (without fourth ventricular communication)
- syringomyelia due to spinal cord injury
- syringomyelia and spinal dysraphism (incomplete closure of the neural tube)
- syringomyelia due to intramedullary tumors
- idiopathic syringomyelia

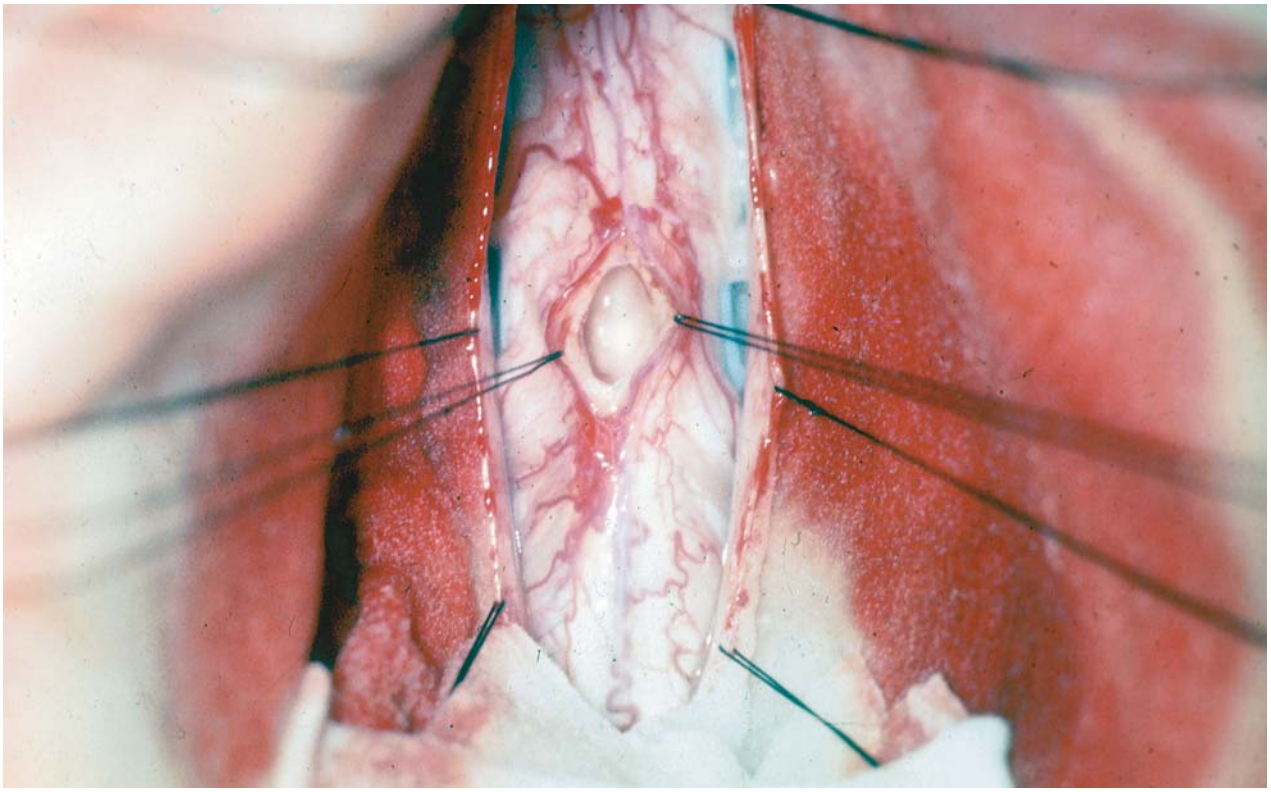
Demographics

Syringomyelia occurs in approximately eight of every 100,000 individuals. The onset is most commonly observed between ages 25 to 40. Rarely, syringomyelia may develop in childhood or late adulthood. Males are affected with the condition more often than females. No geographic difference in the prevalence of syringomyelia is known, and the occurrence of syringomyelia in different races is also unknown. Familial cases have been described.

Causes and symptoms

Most people with syringomyelia experience **headaches**, along with intermittent pain in the arms or legs, usually more severe on one side of the body. The pain may begin as dull or achy and slowly increases, or may occur suddenly, often as a result of coughing or straining. Pain in the extremities frequently becomes chronic. Additionally, numbness and tingling in the arm, chest, or back is often reported. The inability to feel the ground under the foot, or tingling in the legs and feet is also frequently experienced. Weakness of an extremity, leading to clumsiness in grasping objects or difficulty walking may also occur in individuals with syringomyelia. Eventually, functional use of the limb may be lost.

The cause of syringomyelia remains unknown. Not a single clear theory at the present can properly explain the basic mechanisms of cyst formation and enlargement. One theory proposes that syringomyelia results from pulsating CSF pressure between the fourth ventricle of the brain and the central canal of the spinal cord. Another theory suggests that syrinx development, particularly in people with Chiari



A spinal cord cyst associated with syringomyelia. *(Custom Medical Stock Photo. All Rights Reserved.)*

malformation, occurs after a difference in intracranial pressure and spinal pressure. A third theory contends that syrinx formation is caused by the cerebellar tonsils acting as a piston to produce large pressure waves in the spinal subarachnoid space, and this action forces fluid through the surface of the spinal cord into the central canal. Syringomyelia usually progresses slowly; the course may extend over many years. Infrequently, the condition may have a more acute course, especially when the brainstem is affected.

Diagnosis

Examination by a **neurologist** may reveal loss of sensation or movement caused by compression of the spinal cord. Diagnosis is usually reached by **magnetic resonance imaging (MRI)** of the spine, which can confirm syringomyelia and determine the exact location and extent of damage to the spinal cord. The most common place for a syrinx to develop is in the cervical spine (neck), with the second most common in the thoracic spine (chest and rib areas). The least likely place for a syrinx is in the lumbar spine (lower back). MRI of the head can be useful to determine the presence of any additional lesions present, as well as the presence of **hydrocephalus** (excess CSF in the ventricles of the brain). As the syrinx grows in size, it may cause scoliosis (abnormal curvature of the spine), which is best determined by x ray of the spine.

Treatment team

Diagnosis and treatment of syringomyelia require specialized physicians, including neurologists, radiologists, neurosurgeons, and orthopedists, along with specialized nurses. Physical therapy is often useful to maximize muscular function and assist with gait (walking).

Treatment

Treatment, usually surgery, is aimed at stopping the progression of spinal cord damage and maximizing functioning. Surgical procedures are often performed if there is an identifiable mass compressing the spinal cord. Additional surgical options to minimize the syrinx include correction of spinal deformities and various CSF-shunting procedures. Fetal spinal cord tissue implantation has recently been used in an attempt to obliterate syrinx. Surgery results in stabilization or modest improvement in symptoms for most patients. Many physicians advocate surgical treatment only for patients with progressive neurological deterioration or pain. Delay in treatment when the condition is progressive may

Key Terms

Cerebrospinal fluid (CSF) The clear fluid that circulates through the brain and spinal cord.

Medulla oblongata The lower part of the brain stem that borders the spinal cord and regulates breathing, heartbeat, and blood flow.

Syrinx Abnormal fluid-filled cavities within the spinal cord.

result in irreversible spinal cord injury, and post-traumatic syringomyelia remains difficult to manage.

Medications (vasoconstrictors) are often prescribed to help reduce fluid formation around the spinal cord. Avoiding vigorous activity that increases venous pressure is often recommended. Certain exercises such as bending the trunk so the chest rests on the thighs may reduce the risk of syrinx expansion. People with progressive symptoms of syringomyelia, whether or not surgically treated, usually are monitored by their physician and have MRI scans completed every six to 12 months.

Recovery and rehabilitation

Despite reports of neurological recovery following surgery, most people achieve stabilization or only mild improvement in symptoms. Syringomyelia in children has a much lower incidence of sensory disturbance and pain than occurs with adolescents and adults, and is associated with a high incidence of scoliosis that is more favorable to surgical treatment. Additionally, all cases of syringomyelia do not progress at the same rate. Some people, usually with milder symptoms, experience stabilization in their symptoms for a period of years. A frequent complication of symptom progression is the person's ongoing need to adjust to evolving functional losses that accompany syringomyelia. These adjustments may result in loss of independence and loss of personal privacy. Rehabilitation may focus on maintaining functionality for as long as practically possible with the use of exercises and adaptive equipment, or, especially in the case of children, may focus on recovery from scoliosis caused by the syringomyelia.

Clinical trials

As of February 2004, the National Institute of Neurological Disorders and Stroke (NINDS) was sponsoring three trials for the study of syringomyelia, including the physiology of syringomyelia, study and surgical reatment of syringomyelia, and genetic analysis of the Chiari I malformation.

Prognosis

The prognosis for persons with syringomyelia depends on the underlying cause of the syrinx and on the type of treatment. Untreated syringomyelia is compatible with long-term survival without progression in 35–50% of cases. In patients treated by shunting for syringomyelia due to spinal cord injury, long-lasting pain relief and improved strength are usually observed. Recent studies have revealed an unsatisfactory long-term prognosis due to high rates of syrinx recurrence in other forms of syringomyelia. Surgery (posterior fossa decompression) in syringomyelia associated with a Chiari malformation is described as a surgically safe procedure with a considerable chance of clinical improvement. In pediatric syringomyelia, surgery is effective in improving or stabilizing scoliosis.

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American Syringomyelia Alliance Project (ASAP). P.O. Box 1586, Longview, TX 75606-1586. (903) 236-7079 or (800) ASAP-282 (272-7282); Fax: (903) 757-7456. info@asap.org. <http://www.asap.org>.

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Antonio Farina, MD, PhD

Systemic lupus erythematosus *see* **Lupus**

T

Tabes dorsalis

Definition

Tabes dorsalis is a late manifestation of untreated syphilis and is characterized by a triad of clinical symptoms namely gait unsteadiness, lightning pains and urinary incontinence. It occurs due to a slow and progressive degeneration of nerve cells and fibers in spinal cord. It is one of the forms of tertiary syphilis or neurosyphilis.

Description

The first description of the disorder was given by a French **neurologist**, Guillame Duchenne in 1858 who called it *l'ataxie locomotrice progressive* (progressive locomotor **ataxia**). But the word tabes dorsalis was coined in 1836 even before the actual cause was discovered. *Tabes* in Latin means "decay" or "shriveling"; *dorsalis* means "of the back." These indicate the location and type of damage occurring in the spinal cord. It is also called "spinal syphilis" or "syphilitic myelopathy."

Syphilis was widespread in the early part of the twentieth century but there has been a ten-fold decrease in incidence since then due to better screening measures and effective antibiotic therapy. Therefore classic, full blown forms of tabes dorsalis are seldom seen in the twenty-first century.

Demographics

The Center for Disease Control (CDC) reports the annual incidence of syphilis and from this, an estimate of the number of tabes dorsalis cases can be made. In 2001, there was around 2.2 per 100,000 population, or 7,000 new cases of syphilis reported. Three to seven percent of untreated patients develop neurosyphilis, of whom about 5% develop tabes dorsalis. Normally, fifteen or twenty years elapse after the initial syphilis infection, but this is shortened in patients with **AIDS**. Tabes dorsalis is more common in middle-aged males, homosexuals and inner city population in New York, San Francisco and the southern part of the United States.

Causes and symptoms

Syphilis is a sexually transmitted disease caused by a bacteria named *Treponema pallidum*. During initial infection, the bacteria spread through the blood stream into remote sites like the brain and spinal cord, but remain silent in these areas. If proper treatment is not instituted, neurological disorders arise about a decade later and is called neurosyphilis. Damage to the spinal cord substance due to syphilis is called tabes dorsalis.

Inflammation occurs in the dorsal columns of the spinal cord. These columns are in the portion of the spinal cord closest to the back and have nerve fibers that carry sensory information like deep **pain** and position sense (proprioception) from the legs and arms to the brain. As a result of this, the nerve fibers lose their insulation and start atrophying. The pathological process starts in the lowermost portion of the spinal cord that receives information from the legs and spreads upwards. The inflammation can also involve other nerves that control vision, hearing, eye movements, bladder and bowel.

In the twenty-first century, mostly atypical cases of tabes dorsalis are seen due to previous partial antibiotic treatment. Much of the description of the classic disease comes from scientific articles and patient reports more than fifty years ago. The earliest and probably the most troublesome symptom is pain. This is often described as "stabbing" or "lightning-like" and is quite intense. It appears very suddenly, usually in the legs, spreads rapidly to other parts of the body and then disappears quickly. Unfortunately, this cycle can repeat itself several times a day and for days together, making the patient's life miserable. They also experience uncomfortable abnormal sensations or "paresthesias," like tingling, burning, or coldness. Later the feet become progressively numb. "Visceral crisis" develops either spontaneously or after stress in about 15% of patients due to autonomic nerve dysfunction. These

episodes are frightening and severe but rarely life threatening. They consist of excruciating abdominal pain and vomiting or vocal cord spasm or burning rectal pain.

A characteristic unsteady gait called "sensory ataxia" develops. Due to degeneration of nerves that carry position sense from the legs, patients are unable to judge the position of their feet in relation to the ground while walking. They become very unsteady especially while walking in a straight line, on uneven surfaces, or while turning suddenly. This becomes dramatically accentuated in the dark or while closing the eyes as visual compensation is removed. A person with tabes dorsalis walks stooped forward with a wide based "high-stepping" gait and eyes glued to the ground in order to prevent falling. With progression of the disease, they become unable to walk although muscle strength is intact.

Visual symptoms are quite common and include double vision, blurred vision, narrowed field of vision and finally blindness. The pupils are characteristically small and non-reactive to light and called "Argyll-Robertson" pupils. Urine overflow incontinence is very common as the bladder loses its muscular tone. Constipation, impotence, deafness, painless foot ulcers and painless hip and knee arthritis are other features. Decreased memory, disorientation, personality changes and sometimes frank psychiatric illness can also occur.

Diagnosis

Diagnosis is mainly clinical. Syphilis has often been called "the great mimicker" and requires an astute physician to diagnose. There are three steps in diagnosis.

First, the physician has to suspect the diagnosis. The classic signs seen in tabes dorsalis are a triad of 3A's; Argyll-Robertson pupil, areflexia (absent tendon reflexes), and ataxia. Poor visual acuity, asymmetrical eye movement, deafness, clumsy hand and leg movements are other tell-tale signs.

Secondly, it has to be differentiated from other disorders that can present similarly. This is done with the help of **CT scans**, **MRI** scans, spinal tap and certain screening blood tests. The most common screening blood test is called the Venereal Disease Research Laboratory (VDRL) test. This measures the level of certain antibodies that are elevated in the blood in syphilis. It reflects disease activity and therefore may be falsely negative in very late "burnt out" cases of tabes. On the other hand, it maybe falsely elevated in a host of other medical conditions. Therefore, it is a sensitive but not a very specific test. It is only a screening test and any positive result has to be confirmed with other blood tests. The cerebrospinal fluid (CSF) circulates around the brain and spinal cord and reflects underlying inflammation. In tabes, the white cell count and protein level in the CSF are elevated. A positive VDRL test in the CSF is a definitive diagnostic test for tabes dorsalis.

Thirdly, confirmatory tests should be done on the spinal fluid and blood. There are two confirmatory tests for syphilis, namely the Fluorescent Treponemal Antibody Absorption (FTA-ABS) and Micro Hemagglutination of Treponema Pallidum (MHA-TP). These detect very specific antibodies in the blood that are present when the person has syphilis and not otherwise. FTA-ABS in the CSF is a very sensitive test and a negative result virtually rules out tabes dorsalis. It is mandatory that all patients with syphilis undergo testing for HIV.

Elevated white cells and protein in the CSF with a positive CSF VDRL test in a person with appropriate clinical findings is diagnostic for tabes dorsalis.

Treatment team

The team consists of a neurologist, an internist, an infectious disease specialist, psychiatrist and sometimes a pain management specialist. They will closely interact with physical therapists and occupational therapists.

Treatment

Treatment is aimed at curing the infection and hopefully halting the progression of neurologic damage. Treatment is unfortunately limited in reversing the damage already done and the degree of recovery depends on the extent of damage when therapy is started. Appropriate treatment however does reduce future nerve damage, reduces symptoms and normalizes the CSF abnormalities.

The CDC of the United States Department of Health and Human Services has extensive guidelines for treatment of tabes. It recommends antibiotic treatment with intravenous aqueous crystalline penicillin G for two weeks. If the patient has penicillin allergy, he should be desensitized first before treatment. Otherwise, the antibiotic Ceftriaxone can be used as an alternative but the adequacy of this has not been fully approved by the CDC. Serum VDRL titers are checked every three months till they start declining. CSF is checked at six and twelve months and if still abnormal, rechecked at two years. Re-treatment is recommended if neurological damage progresses, if CSF white cell count does not normalize in six months, VDRL titers do not decline or show a four-fold increase and if the first course of treatment was suboptimal. Symptomatic analgesic treatment is given for pain. This can range from simple over the counter medications like aspirin or Tylenol or more potent analgesics like narcotics. Certain antiseizure medications like Phenytoin, **Carbamazepine** and Valproic acid are efficacious in treating resistant pain. If

Key Terms

AIDS Acquired Immune Deficiency Syndrome is a sexually transmitted disease caused by the Human Immunodeficiency Virus (HIV). It weakens the immune system and makes a person susceptible to many infections and malignancies.

Ataxia Clumsiness or loss of co-ordination of the arms and legs due a variety of causes. It is a symptom of an underlying disease process of the nervous system.

Cerebrospinal fluid This is a colorless fluid that is produced in the brain and circulates around the brain and spinal cord in the subarachnoid space.

Dementia This denotes a chronic condition where there is loss of mental capacity due to an underlying organic cause. It may involve progressive deterioration of thinking, memory, behavior and personality.

Dorsal columns This refers to nerve fiber tracts that run in the portion of the spinal cord that is closest to the back. It carries sensory information like position sense and deep pain from the legs and arms to the brain.

Locomotor Means of or pertaining to movement or locomotion.

Myelopathy Disease of the spinal cord.

Neurosyphilis This is slowly progressive destruction of the brain and spinal cord due to untreated tertiary syphilis. It can be asymptomatic or cause different disorders like tabes dorsalis, general paresis and meningovascular syphilis.

Paresthesia Abnormal sensation of the body like numbness or prickling.

Proprioception The ability to sense the location and postion and orientation and movement of the body and its parts.

Syphilis Sexually transmitted disease caused by a corkscrew shaped bacterium called Treponema pallidum. It is characterized by three clinical stages namely primary, secondary and tertiary or late syphilis.

Tendon reflex This is a simple circuit that consists of a stimulus like a sharp tap delivered to a tendon and the response is one of the appropriate muscle contraction. It is used to test the integrity of the nervous system.

Spinal cord The part of the central nervous system that extends from the base of the skull and runs through the vertebral column in the back. It acts as a relay to convey information between the brain and the periphery.

patients become demented and have behavioral issues, anti-psychotic medications can be given.

Primary and secondary prevention of syphilis is important to prevent development of tabes dorsalis. Safe sex (using a condom) is a way of primary prevention. Screening, detection and treatment of early syphilis are measures of secondary prevention. Sexually active people should consult a physician about any rash or sore in the genital area. Those who have been treated for another sexually transmitted infection like gonorrhea, should be tested for syphilis and HIV. Persons who have been exposed sexually to another person who has syphilis of any stage should be clinically evaluated, undergo testing and even be presumptively treated in certain instances.

Recovery and rehabilitation

Assistance or supervision may be needed for self-care activities like eating, showering, dressing etc. Patients may require assistive devices like a cane, walker or a wheelchair to overcome gait difficulty. Diapers or urinary catheters are used for urinary incontinence. Surgery can help replace joints destroyed by arthritis. Patients need a good bowel regimen to avoid constipation, which can trigger a visceral crisis. Since this is a chronic illness, **respite** care should be provided for the caregivers.

Clinical trials

There is no trial open for tabes dorsalis, but there is an ongoing phase III multicenter randomized trial as of early 2004 funded by the National Institute of Allergy and Infectious Diseases (NIAID) for assessing the antibiotic Azithromycin given orally in treatment of primary, secondary or early latent syphilis. The NIAID and the National Institute of Neurological Diseases and Stroke (NINDS) are carrying out research to develop a non-invasive test for detecting syphilis and to develop a vaccine. The genome of *Treponema pallidum* has been sequenced through NIAID-funded research. This is a wealth of information that will hopefully lead to clues to better diagnose, treat and vaccinate against syphilis.

Prognosis

Tabes dorsalis is a chronic, annoying and incapacitating disease but is *per se* seldom fatal. If tabes dorsalis is diagnosed in its very early stages, fairly good recovery is possible. Pain is quite bothersome and has a serious impact on quality of life. Ataxia, **dementia** and blindness are incapacitating. Death usually occurs due to rupture of enlarged blood vessels and damage to heart valves, which occur as a part of tertiary syphilis. Rarely, a urinary infection will lead to sepsis and death.

Special concerns

Tabes dorsalis can affect thinking and memory and all patients must have **neuropsychological testing** for dementia. They will need to get legal advice for estate and financial planning and their wishes for future medical care.

Resources

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National Institute of Allergy and Infectious Diseases. 31 Center Drive, MSC 2520, Bethesda, MD 20892-2520. (301) 496-5717. <http://www.niaid.nih.gov>.

Chitra Venkatasubramanian, MBBS, MD

Tacrine *see* **Cholinesterase inhibitors**

Tarlov cysts *see* **Perineural cysts**

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.

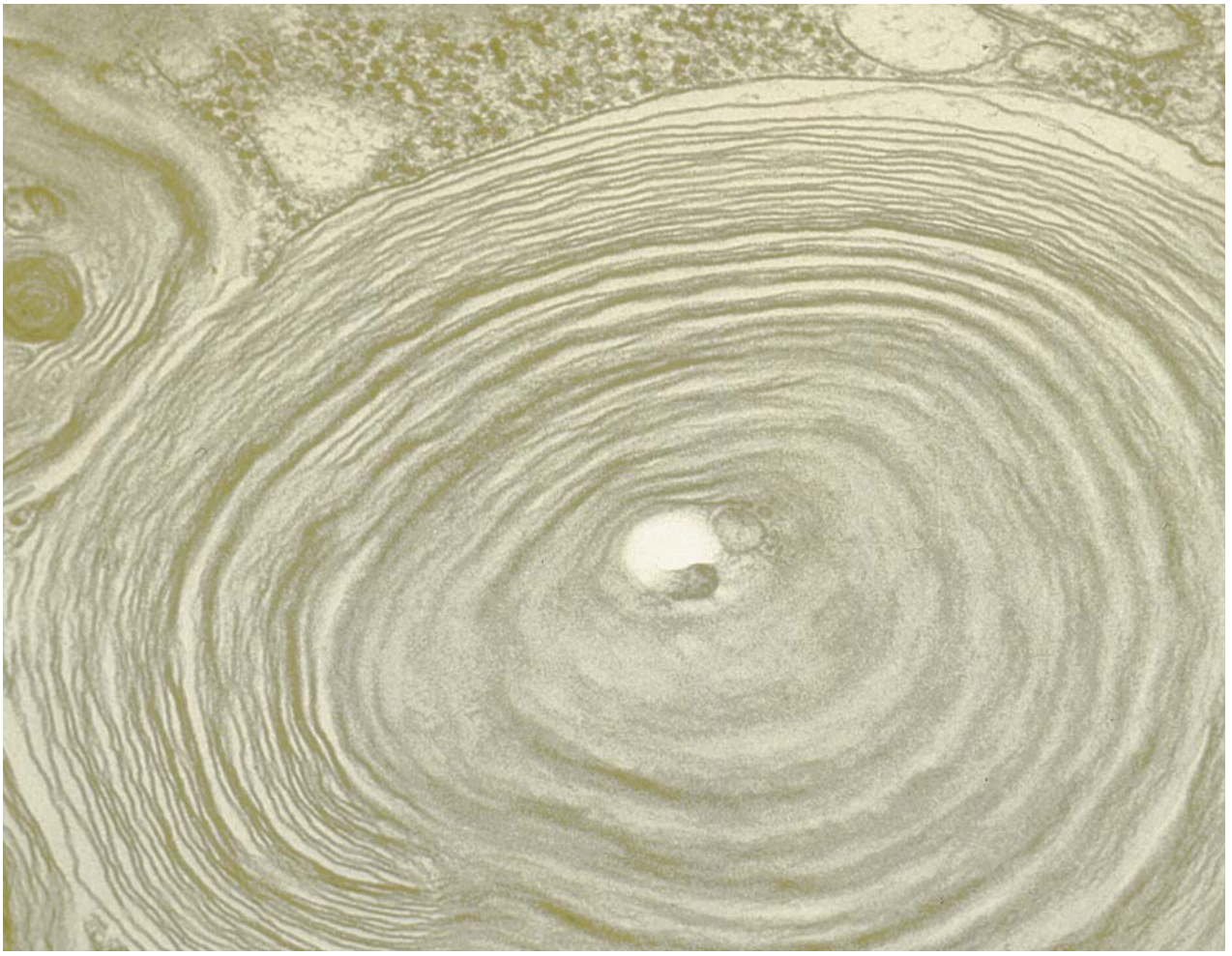
Tay-Sachs disease is particularly common among Jewish people of Eastern European and Russian (Ashkenazi) origin. About one out of every 3,600 babies born to Ashkenazi Jewish couples will have the disease. Tay-Sachs is also more common among certain French-Canadian and Cajun French families.

Causes and symptoms

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 genne, and a 25% chance of having two defective genes. The two defective genes cause the disease itself.

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



Scanning electron micrograph of cerebromacular degeneration as result of Tay-Sachs disease. *(Graph/Custom Medical Stock Photo. Reproduced by permission.)*

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 breath 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.
- 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.

Key Terms

Ganglioside A fatty (lipid) substance found within the brain and nerve cells.

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 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

Sadly, the prognosis for a child with classic Tay-Sachs disease is certain death. 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 (amniocentesis) or the placenta (chorionic villus sampling) to determine whether the baby will have Tay-Sachs disease.

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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>.

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Temporal arteritis

Definition

Temporal arteritis is a disease that causes inflammation and sometimes blockage of medium and large arteries in the head (often near the side of the head or temples).

Description

The mechanism responsible for temporal arteritis (also called giant cell arteritis) is complex and can affect medium and large size arteries, but commonly strikes the temporal artery causing temporal located **headaches**. In affected arteries there is an abnormal reaction that causes the infiltration of immune cells, such as lymphocytes, multinucleated giant cells, and plasma cells. Frequently the arteries in the head and neck are involved, but vasopathy can extend to the carotids and aorta. The abnormal mechanism is a cell-mediated immune response that is abnormally directed on an antigen (a foreign protein) near the elastic tissue component of an arterial wall. This immune response causes an infiltration of immune cells in an artery which could damage or even completely block the affected blood vessel. The exact cause of temporal arteritis (TA) is unknown. TA can be serious in cases where there is involvement of blood vessels that supply blood to the affected eye (i.e., posterior ciliary artery a branch of the ophthalmic artery) which can cause visual impairment.

Demographics

The disorder is more commonly observed in persons older than 50 years. TA occurs frequently with the occurrence ranging from 10 in 100,000 to 50 in 100,000. Internationally, there seems to be a higher incidence in countries higher in northern climates. The disorder occurs more frequently in Caucasian persons of northern European descent. TA rarely occurs in Blacks and Asians and it is four to six times more frequent in women than men. The mean age of onset is 70 years and the disorder is rarely seen in persons younger than 50 years. Long term survival is the same as for the general population. Visual loss is the most worrisome complication and can occur in over 50% of persons who are untreated, which could result in blindness for 20–50% of these patients.

Causes and symptoms

The cause of TA is not known. It is thought to be due to an immune cell response that attacks a foreign chemical (called an antigen) in the elastic layer of arteries in the head and neck.

In over 85% of affected persons, the most universal symptom is headache. The headache is severe and tends to

Key Terms

Erythrocyte sedimentation rate A test that measures the rate at which red blood cells settle out in a tube of anticoagulated blood, expressed in millimeters per hour; elevated sedimentation rates indicate the presence of inflammation.

Lymphocyte A type of white blood cell that participates in the immune response. The two main groups are the B-cells that have antibody molecules on their surface and T-cells that destroy antigens.

Ophthalmic artery The artery supplying the eye and adjacent structures with blood.

Plasma cell A type of white blood cell that produces antibodies; derived from an antigen-specific B-cell.

be on one side (unilateral), and worsens at night. The **pain** tends to increase as days go by. Visual impairment may be the first presenting symptom since approximately 50% of patients complain of a sudden and painless visual loss. Loss of vision may be transient or permanent and blindness can occur if the condition is untreated.

In approximately 65% of persons, jaw claudication is prominent when chewing, swallowing or talking. Patients may have low grade fever and the effected arteries may be tender, warm, pulseless, dilated and thickened. Other symptoms that can occur include cough, anorexia, muscle aches, malaise, difficulty hearing, **fatigue**, fever/sweats and **depression**.

Diagnosis

Criteria for the diagnosis of TA were established in 1990 by the American College of Rheumatology. A diagnosis based on criteria for giant cell arteritis includes the presence of three of the following five items:

- new onset of headache or localized pain in the head region
- temporal artery tenderness to palpation
- development of symptoms in a person over 50 years of age
- lab result of over 50 for a special test called the Westergren Erythrocyte Sedimentation rate (WESR)
- decreased pulsations in head arteries, which cannot be attributed to arteriosclerotic disease of neck (cervical) arteries

A definitive diagnosis is made by the temporal artery **biopsy** which can be performed as an outpatient procedure (same day surgery).

Blood tests may reveal a high white blood cell count (leukocytosis), mild anemia or an increase in platelet cells (thrombocytosis), which are responsible for blood coagulation. Approximately 50% of patients affected with temporal arteritis have abnormal liver function tests. Chest radiograph may be useful to detect involvement of a chest (thoracic) artery. Ocular pneumoplethysmography can help make the diagnosis of temporal arteritis. Multiple biopsies may be indicated if initial findings are negative, but the suspicion for this diagnosis remains high.

Treatment team

The condition can be diagnosed by a primary care provider. Consultations may be indicated with an ophthalmologist (if there are visual complications). Generally an internist or rheumatologist directs the general care for systemic symptoms.

Treatment

Oral steroids are effective treatment for TA. Treatment is critical and important to avoid vision loss. Treatment should be initiated based on clinical suspicion and should not be delayed for biopsy results. The use of steroid or prednisone can be initially given at a dose of 60 to 100 mg per day. The dose can be tapered down in an individualized manner at a rate of approximately 10% per week, while concurrently taking into account symptomatic state and lab result improvement.

Recovery and rehabilitation

Most patients can be treated on an outpatient basis, with steroids, and symptoms usually begin to resolve within one to three days. Patients may require oral steroid medication for up to one year, depending on individual response. Nonsteroidal anti-inflammatory drugs may provide some pain relief.

Clinical trials

A clinical trial sponsored by the Cleveland Clinic Foundation Hospital and the National Institute of Health concerning the treatment of TA. The study is a multi-institutional project which includes medical centers within the United States and in several countries overseas. Full details can be obtained from the website: <http://www.clinicaltrials.gov>.

Prognosis

The condition is self-limiting and can last up to two years. Treatment with corticosteroids produces relief of symptoms and can help with visual impairment.

Special concerns

A diagnosis of TA can be missed. The disorder should be suspected in older patients with a high erythrocyte sedimentation rate (ESR), even if other evidence is absent.

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National Heart, Lung, and Blood Institute, Building 31, Room 5A52. 31 Center Drive MSC 2486, Bethesda, MD 20892. (301) 592-8573; Fax: (301) 592-8563. nhlbiinfo@nhlbi.nih.gov. <http://www.nhlbi.nih.gov>.

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Temporal lobe epilepsy

Definition

Temporal lobe **epilepsy** (TLE) is a term that refers to a condition where **seizures** are generated in the portion of the brain called the temporal lobe. Either the right or the left temporal lobe can be involved, and in rare cases both temporal lobes can be involved in a particular individual.

Description

Under the broad category of TLE, there are a number of specific types. In mesial TLE (MTLE), there are characteristic abnormalities in the mesial aspect of the temporal lobe. This variably involves sclerosis (scarring), loss of nerve cells in the hippocampus and mossy cell fiber sprouting. Of course, there are other different pathologies that can be seen in the temporal lobe including tumors, **stroke**, **multiple sclerosis** plaques, and tubers (as seen in **tuberous sclerosis**). Another type of TLE is lateral TLE. This is where the seizures originate in the lateral portion of the particular temporal lobe. Again, various pathologies can be found such as cortical malformations and stroke. However, imaging studies, such as **magnetic resonance imaging (MRI)**, often may not show any obvious lesions or abnormalities. As more information is gathered regarding the genetics that may be involved in some cases, the classification of TLE will likely change.

Demographics

TLE, as a whole, constitutes a common type of epilepsy. The exact incidence is not clear but it is suspected to make up a significant proportion of medication-resistant epilepsy. Approximately 30% (of the 2.7 million cases of epilepsy in the United States) do not adequately respond to medications. Up to a half of these may be due to TLE. One of the risk factors that may predispose children to, in particular, mesial TLE is complicated or prolonged febrile convulsions before the age of five years. Mesial TLE can also run in some families.

Causes and symptoms

The abnormalities most associated with mesial TLE are sclerosis (scarring) of the hippocampus, neuronal cell loss in the hippocampal area, and inappropriate sprouting (growth) of mossy cell fibers. The cause of these variable pathological findings is still being studied. There is some evidence that mesial TLE may be a progressive condition where seizures become more resistant to medications over time. Likely, seizures over time play a role in the changes seen in the mesial temporal lobe. Likewise, the mesial temporal abnormalities contribute to the epileptogenicity (seizure potential) of that region. Although these pathologies are the most common findings in cases of mesial TLE, other lesions can be the suspected cause of epilepsy such as stroke, multiple sclerosis plaques, tumors, and cortical malformations. Lateral TLE can also be affected by strokes, cortical malformations, multiple sclerosis plaques, etc., and be the cause of seizures from this area. In the rare condition of benign familial TLE the cause is genetic and runs in families. Exactly how any of the previously mentioned abnormalities actually cause groups of neurons to generate seizure activity is complex and not fully understood. Because there can be different lesions, there can also be different mechanisms of generating a seizure. The temporal lobe epilepsies should not be considered as diseases. Rather, they are syndromes (groups of physical signs and symptoms) with many causes.

The age of onset of TLE is highly variable depending on the cause. In mesial TLE, seizure can begin as early as childhood or even later in adulthood. There is a characteristic remission that can occur during childhood, lasting a few years, but then seizures resume in adulthood.

The seizures that occur in TLE are simple partial seizures or complex partial seizures. Uncommonly, a generalized tonic-clonic seizure may occur. The simple partial seizures can take the form of auras. Although these are

viewed as seizure warnings, they are actually minor seizures that do not affect consciousness. The most common aura is a visceral sensation. This can take the form of a rising feeling in stomach. Other kinds of auras can be déjà vu (a sense of familiarity) or *jamais vu* (the opposite of déjà vu, a sense of unfamiliarity or uniqueness); distortion of perceptions of size, or movement (vertigo); or olfactory (odors) distortions and buzzing sounds depending on what portion of the temporal lobe is involved. Emotional auras can also occur; fear, for example. Still other auras are too difficult for patients to describe. All these minor seizures are usually not serious unless they are occurring frequently and are disturbing to the person.

Seizures that affect or alter consciousness are present in the majority of people with TLE. These complex partial seizures variably involve cessation of activity, a certain degree of starring off, lip smacking or other oral movements. Moreover, the arm contralateral (opposite) the temporal lobe displays a posturing action. The arm ipsilateral (same side) as the affected temporal lobe has automatisms (semi-purposeful motions). During this phase of the seizure, the person has little to no awareness of the environment and will virtually be unresponsive to those around him or her. The aura plus the complex-partial-seizure phase typically lasts less than two to three minutes. Then there is a variable period of confusion lasting longer. If the seizure involves primarily the dominant (usually left) hemisphere (where language is processed) then a so-called post-ictal (after seizure) **aphasia** (loss of language) can occur and last several minutes. All these behavioral features can help decide which hemisphere, if not temporal lobe, is involved.

Diagnosis

The diagnosis of TLE can be made by a careful history (of an accurate description of the seizures) coupled with abnormalities on high resolution magnetic resonance imaging (MRI) of the brain and electroencephalogram (EEG). Current MRIs are sensitive, but subtle lesions such as mesial temporal sclerosis can be missed either by routine MRIs or inexperienced radiologists. The routine EEG (usually 30 minutes of testing) can be normal between seizures but may sometimes show occasional characteristic wave patterns in the temporal regions suggesting the location of seizure generation. Long term monitoring with EEG/closed circuit T.V. (LTME) is extremely helpful to determining which temporal lobe is abnormal.

Treatment

The treatment goal of any epilepsy is freedom from seizures with no side-effects of medications. Although this is the goal, it is frequently not attained. There may be a highly variable response to medications. There are over 20 seizure medications available. It is important to understand, however, that if a trial of up to three different well-chosen medications alone or in combination fail to control seizures, then the likelihood that some other medication will work is slim. Therefore, the general concept is that not all medications and combinations need to be tried to know if an epilepsy will be resistant. A timely referral to a comprehensive epilepsy center should be done to explore other treatment options, such as surgery. In mesial TLE, medications frequently fail to adequately control the seizures. Fortunately, this particular epilepsy is most responsive to surgical treatment. Brain surgery should not be viewed as "a last resort" when pharmacoresistant epilepsies are considered. With modern screening methods and neurosurgical technique, complications are rare. The surgery for mesial TLE offers up to an 80% chance of cure. The surgery involves the removal of a portion of the affected temporal lobe. On the other hand, seizures that are generated from other areas of the temporal lobe are more complicated.

Recovery and rehabilitation

Recovery and rehabilitation are a consideration if epilepsy surgery is performed. If a partial temporal lobectomy has been done, the patient remains in the hospital for several days. Post-operatively, there can be headaches and nausea that are managed with medications and resolved in one to three days. Complications of surgery are rare but include infection (managed with antibiotics) and bleeding (which, if severe, may require a transfusion). Neurological deficits are uncommon; when they are present they are usually mild. This includes a limited visual field deficit, contralateral (opposite to surgical side) weakness or speech difficulty. When neurological complications occur, they usually improve with time and are not disabling.

Clinical trials

Currently there is a multicenter randomized controlled trial (Early Randomized Surgical Epilepsy Trial called ERSET) comparing epilepsy surgery and optimal **pharmacotherapy** in patients 12 years and older with mesial TLE within two years of determination of pharmacoresistance. The official website is <http://www.erset.org>. Information is also available from the National Institute of Neurological Disorders and Stroke <http://www.ninds.nih.gov> regarding other funded studies under the general heading of epilepsy.

Prognosis

The prognosis for TLE varies considerably depending on the type of TLE. Although medications should be tried initially, mesial TLE and many of the lateral TLEs are

often resistant. Timely referral to an epilepsy center that can determine the nature of the seizure disorder and offer other kinds of treatment approaches should be undertaken. Epilepsy surgery for mesial TLE offers up to an 80% chance of sustained seizure freedom and the possibility of discontinuing medications.

Special concerns

Long-standing, poorly controlled epilepsy has a number of psychosocial ramifications. These can include (but are not limited to) memory difficulty, reduced self-esteem, **depression**, reduced ability for gainful employment, and greater difficulty with interpersonal relationships. These issues may be underestimated in the setting of treating the seizure disorder. Recognizing the psychosocial well-being of the patient will greatly help in improving quality of life.

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ORGANIZATIONS

American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. (860) 586-7505. <http://www.aesnet.org>.

Epilepsy Foundation of America. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

International League Against Epilepsy. Avenue Marcel Thiry 204, B-1200, Brussels, Belgium. + 32 (0) 2 774 9547; Fax: + 32 (0) 2 774 9690. <http://www.epilepsy.org>.

Roy Sucholeiki, MD

Tension headache *see* **Headache**

Tethered spinal cord syndrome

Definition

Tethered spinal cord syndrome (TSCS), also known as occult spinal dysraphism sequence, is a congenital condition that causes the spinal cord, before or after birth, to become attached to the spinal column at some point along its length, most often in the lower (lumbar) portion. TSCS is related to **spina bifida**, since both disorders arise from a failure of the neural tube to close completely during embryonic development. There are differing forms and degrees of severity of TSCS, including tight filum terminale, lipomeningomyelocele, split cord malformations, and dermal sinus tracts.

Description

The normal spinal cord, a cable of nerves, extends vertically from the base of the brain to the lumbar region, or lower back, contained within the hollow cylinder formed by the bony vertebrae and soft tissues of the spinal column. The spinal cord hangs freely within the spinal column, cushioned by cerebrospinal fluid, and is attached at its lower end to a strand of elastic tissue, the filum terminale, which is in turn attached to the lower end of the spinal column and which secures the lower end of the cord but allows it to be stretched without injury. Beyond the lower end of the cord proper, the major afferent and efferent nerves for the muscles of the legs, lower bowel, and bladder, the cauda equina, continue down the spinal canal and branch to those areas.

TSCS is initiated by incomplete closure, during embryonic development, of the neural tube, the early embryonic foundation of the spinal cord and column, resulting in malformations of the spinal column and cord. One disorder brought about by the malformation is spina bifida, in which the spine is open on its dorsal surface, somewhere along its length. Spina bifida can range in severity from not being visible externally, or spina bifida occulta, to a visible, open cavity with major impairment of the spinal cord at and below that spot. Among these extremes, tethered spinal cord may occur in the invisible forms, or spina bifida occulta.

In cases of relatively mild spina bifida that result in TSCS, the flaw occurs most often along the lower (lumbar) portion of the spinal column and cord. Cases of tethered cord in the cervical and thoracic regions of the spinal column are known but are extremely rare.

The developmental flaw causes soft tissues of the spinal column to grow into the hollow containing the spinal cord and to attach to the spinal cord, anchoring it at

Key Terms

Neural tube A hollow column of ectodermal tissue that forms in early embryonic development and goes on to become the spinal cord and spinal column.

Spina bifida A defect in the spinal column, brought about by incomplete closure of the developing neural tube, in which the column is cleft on its dorsal side.

Spina bifida occulta A relatively mild form of spina bifida in which the defect is not visible from the surface.

Filum terminale The strand of elastic, fibrous tissue that secures the lower end of the spinal cord.

that spot. Since the spinal cord grows more slowly than the spinal column, a tethered spinal cord becomes stretched and stressed over time, causing neurological damage in the cord and the nerves of the cauda equina that results in physical problems that manifest in a range of diagnostic symptoms and signs. Bending or stretching movements of the body put additional tension on the tethered cord.

As the cord is stretched, circulation of blood to the lower portion and cauda equina may be reduced as the blood vessels there are compressed by the tension in the cord. This in turn results in hypoxia, or loss of oxygen, delivered in the blood to that part of the cord, eventually causing damage and loss of function in the neurons.

If left untreated, the stress induced in the tethered cord can cause permanent damage and malfunction to the nerves and muscles that control movements of the legs, feet, bowel and bladder. Severe consequences can be deformed feet and legs, paralysis and incontinence.

Other forms of tethered cord include tight filum terminale syndrome, in which malformations in the embryonic neural tube at its lowermost point result in a defective filum terminale, the normally flexible anchor of the cord's lower end. A defective filum terminale is short and fibrous, with reduced elasticity or none, thus tethering the spinal cord at its lower end.

A lipomeningomyelocele is an abnormal growth of fatty tissue at the base of the developing spinal cord that entangles the lower end of the cord and thus tethers it.

In diastematomyelia, or split cord syndrome, an abnormal growth of bony or fibrous tissue forms a spur within the spinal canal, parting longitudinally (not severing) the nerves of the spinal cord, which rejoin into a single tract below the spur. The spinal cord can become tethered at the location of the split.

A dermal sinus tract is a canal lined with epithelial (skin) tissue, one end of which shows as an opening in the lumbar skin, the other end connecting with the tissues of the spinal cord or canal, or with adjacent tissues. Tumors form in the internal end of the sinus in about half of all cases, the tumors often bringing about spinal cord tethering.

TSCS may also develop following surgery for spina bifida, when scar tissue resulting from surgery grows and snags the spinal cord, thus tethering it.

Demographics

TSCS is a relatively rare disorder. Its exact frequency is unknown, mostly because of a general lack of research on the disorder, and because the mildest forms may never be detected. TSCS in all forms affect both sexes and all races and ethnic groups.

Causes and symptoms

Congenital TSCS is initiated by incomplete closure of the neural tube during embryonic development. During the eighteenth to twenty-second day of embryonic development, the beginning structure of the neural tube, which will become the spinal column and cord, is formed by ectodermal tissue on the back of the embryo that forms a groove, which deepens and forms into a hollow tube, still open dorsally along its length. The tube begins to close itself, starting in the thoracic region, then moving on toward the head and lumbar regions. During the twenty-eighth to forty-eighth day of development, ectodermal tissue in the tail area of the embryo forms a separate, short length of neural tube, the conus medullaris, whose anterior end meets and fuses with the main neural tube while the posterior forms the filum terminale. The conus medullaris also produces the cauda equinae nerves.

Symptoms of TSCS may be visible at birth or appear later, even in adulthood, but most often in childhood. The symptoms may be visible or behavioral. Various visible signs on the skin of the lower back, along and near the spinal cord, are:

- lipomas, or fatty tumors below the skin
- hairy patches
- spots of increased pigmentation
- dimples that may indicate dermal sinus tracts

- skin lesions
- skin tags or outgrowths
- angiomas, or port-wine stains

Behavioral symptoms manifest as:

- chronic lower back pains
- progressive scoliosis, or curvature of the spine
- foot deformities
- numbness and loss of sensation in the legs or feet
- awkward gait and stumbling
- weakness in legs or feet
- unequal growth in the legs or feet
- progressive loss of control over bladder and bowel functions (incontinence)
- urinary tract infections

Diagnosis

The initial indicators of TSCS are the physical and behavioral ones listed above. A newborn that carries any of the symptomatic skin defects should be diagnosed further for possible TSCS. Among the behavioral signs, a child will likely complain to parents of lower back pains, while other behavioral symptoms will become obvious to parents. An adult who shows any of the physical or behavioral symptoms should bring these to the attention of his family physician, who should suspect TSCS as the cause. Symptoms, physical or behavioral, may not appear until many years after birth, including well into adulthood, depending on the time of tethering, degree of stretching of the spinal cord, and severity of damage to the nerves of the cord.

The next steps in diagnosis of TSCS are taking x-ray images of the spine to detect bone abnormalities, followed by the application of diagnostic neuro-imaging by means of **MRI** (**magnetic resonance imaging**) to produce three-dimensional images of the spinal column and spinal cord. Since a defect in the spinal cord or column makes it likely that there are other defects in the cord, column, or brain, an entire imaging of the brain and spinal column are recommended. **Electromyography** (EMG) can be used to check for or assess damage to nerve conduction in the spinal cord and the nerves of the cauda equinae. Ultrasound imaging can be used to monitor unborn infants for evidence of TSCS, should there be a reason to suspect it.

Since the muscles of the bladder are often affected by TSCS, urodynamics testing is recommended to discover the extent of the damage.

Treatment team

A family doctor is probably the person most likely to first link symptoms in a child or adult to TSCS, when parents bring in a child for a routine health check or because of the physical and behavioral signs and problems. Following the tentative diagnosis, the patient will be sent to neurologists, MRI imaging technicians, EMG technicians, urologists, surgeons and neurophysiologists if surgery is called for, and the personnel monitoring recovery.

Treatment

TSCS is corrected by surgery to detach the cord at its place of tethering. Follow-up examinations are necessary because the freed spinal cord sometimes becomes re-tethered to growing scar tissue.

In the case of tight filum terminale, the filum terminale is severed, allowing the cord to float freely.

Surgery for TSCS generally takes four to six hours, and is conducted according to the form of TSCS in the patient. The spinal column is opened from behind to reach the site of tethering. Neurophysiologists are present to monitor spinal cord and nerve functioning to reduce the risk of damage to nerves and other tissues.

Recovery and rehabilitation

The degree of recovery is based on the amount of damage induced by the TSCS and the success of the surgery. Nearly all patients improve or at least show no worsening of signs. A successful operation leaves 2% or less possibility of the symptoms getting worse, and a 50% likelihood of sensation and movement problems becoming normal. **Back pain** usually is reduced or eliminated and strength to the lower part of the body improves. On the other hand, bladder dysfunction usually does not improve.

Ongoing monitoring of a patient following surgery for TSCS is required, in case the spinal cord should retether.

Prognosis

The prognosis for tethered spine syndrome is favorable, since skin symptoms may be visible at birth or later, allowing early detection and treatment, while behavioral symptoms manifest slowly enough for diagnosis and treatment before the condition becomes severe.

Special concerns

Spinal surgery is always risky because of possible damage to the nerves of the spinal cord. The patient may also have to deal with permanent damage caused by TSCS that surgery cannot improve.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. 203-744-0100 or 800-999-NORD (6673); Fax: 203-798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

Spina Bifida Association of America. 4590 MacArthur Blvd. NW, Suite 250, Washington, DC 20007-4266. 202-944-3285 or 800-621-3141; Fax: 202-944-3295. sbaa@sbaa.org. <http://www.sbaa.org>.

Kevin Fitzgerald

Third nerve palsy

Definition

Third nerve palsy describes a condition involving the third cranial nerve (also called the oculomotor nerve), which is responsible for innervating some of the muscles responsible for eye movement.

Description

Third nerve palsy results in an inability to move the eye normally in all directions. Injury to the third nerve can occur anywhere along its path, from where it originates within the brain to where it innervates the muscles that move the eyeball. Third nerve palsy prevents the proper functioning of the medial, superior, and inferior recti, and inferior oblique muscles. As a result, the eye cannot move up, down, or in. When at rest, the eye tends to look down and to the side, due to an inequality of muscle functioning. The muscle responsible for keeping the upper eyelid open (levator palpebrae superioris) is also affected, resulting in a drooping upper eyelid (ptosis).

Causes and symptoms

A wide variety of conditions can result in third nerve palsy, including pressure and damage from tumors; blocked arteries or **aneurysms** leading to oxygen deprivation of nerves; meningitis; vascular complications of diabetes or high blood pressure; complications of migraine headaches; traumatic injury; birth injury; congenital defects; and conditions that strip nerve fibers of their myelin coating, resulting in slowed nervous transmission.

Some patients have severe **pain** and double vision (diplopia), in addition to problems moving their eyes normally. The affected eye tends to move down and out, due to an inequality in muscle functioning. The eye cannot move up, down, or in. In some cases, the pupil remains fixed in a dilated state. The upper eyelid is droopy (ptosis). The eyeball itself may actually be slightly displaced, pushed more forward than normal (proptosis).

Additionally, after the acute phase of third nerve palsy, as the nerve attempts to regenerate, a phenomenon called oculomotor synkinesis may take place. In this associated condition, nerve sprouts accidentally misdirect nerve transmission, so that efforts to utilize certain muscle groups accidentally prompt the functioning of other muscle groups. Therefore, attempts to accomplish certain muscular tasks actually result in different muscular tasks occurring. For example, as an individual with oculomotor synkinesis attempts to look down, the eyelid may raise up; when attempting to look up, the eye instead moves towards the midline; when attempting to look towards the midline, the pupil constricts.

Diagnosis

Eye muscle dysfunction is usually revealed during the course of a basic physical examination, which should always include testing of eye movements and examination of the pupils. **MRI**, **CT**, or **angiography** (a dye test that lights up the arteries throughout the brain, allowing the arteries to be better visualized on CT or MRI) may reveal the underlying cause of third nerve palsy.

Treatment team

Ophthalmologists and neurologists may work together to care for patients with third nerve palsy. In addition, physicians who manage diabetes, high blood pressure, or other underlying causative conditions will be involved in the patient's care.

Treatment

Steroids may treat pain and double vision. Special lenses with prisms may improve diplopia. Surgery on the eye muscles or eyelid may be necessary in some cases, although most clinicians recommend waiting six months from onset so that the patient's condition stabilizes.

Prognosis

In individuals who have no pupil involvement, and whose third nerve palsy is due to complications of diabetes or high blood pressure, symptoms may actually resolve within three to six months of onset. Other patients have a variable outcome, depending on the underlying condition responsible for the third nerve palsy.

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Thoracic radiculopathy *see* **Radiculopathy**

Thoracic outlet syndrome

Definition

Thoracic outlet syndrome refers to a condition that results in compression of neurovascular anatomical structures at the superior aperture of the chest (thorax).

Description

Thoracic outlet syndrome (TOS) refers to compression of nerves and blood vessels in the upper portion of the thorax. Neurologic symptoms occur in 95% of affected persons. The cause and treatment of TOS is controversial. In 95% of cases the brachial plexus is involved. The lower two nerves (C8 and T1) are most commonly affected in 90% of persons, following the ulnar nerve distribution. Blood vessels can also be affected. The subclavian vein is involved in 40% of cases and the subclavian artery in 1% of cases. The second most common nerve root involvement occurs in brachial plexus nerves C5, C6, and C7, and symptoms, if these nerves are affected, can be referred to upper back, upper chest, ear, neck, and outer arm that follows a radial nerve distribution.

Demographics

Reports concerning demographic information are controversial and range from three per 1,000 to 80 per 1,000 people. Overall the disorder is three times more common in women than men, with the exception of nervous system involvement which is more common in males. Some reports indicate that TOS is nine times more common in females than males. In the United States the incidence of vascular or neurogenic TOS is considered rare with only one new case per million population for the neurogenic TOS. The usual age of onset is from the second to eighth decade, with a peak age of onset in the fourth decade. Arterial involvement (arterial thoracic outlet syndrome) has no specific gender predilection.

Causes and symptoms

There are three major causes of TOS which include anatomic causes, trauma/repetitive activities, and neurovascular (nerve and blood vessels) entrapment in the chest. Certain anatomic abnormalities of the muscles in the neck and first rib (and a vertebral disk, C7) can cause compression of nerves and arteries. Anatomic abnormalities account for the majority of cases of neurologic and arterial thoracic outlet syndrome. Trauma such as hyperextension injury from motor vehicle accident or effort vein thrombosis (spontaneous thrombosis of the axillary veins following vigorous arm extension) may cause thoracic outlet syndrome. Repetitive activities similar to those of musicians are especially susceptible if they maintain the shoulder in abduction or extension positions for long periods. Nerves and blood vessels can be compressed anatomically in the costoclavicular space between the first rib and the head of the clavicle.

Neurologic **pain** can occur on either sides of the forearm, upper back and upper chest, neck and ear. Pain is especially evident on the ring and small finger. Patients often experience nocturnal paresthesias, awakening with numbness or pain (dysesthesia). There is often a loss of dexterity, cold intolerance and **headache**. Venous involvement causes pain, edema (swelling), cyanosis (bluish discoloration of the skin due to lack of oxygen), and distended superficial veins of the shoulder and chest. Arterial involvement causes pain and claudication, pallor, pulselessness, lower blood pressure in affected arm, and embolization (infarcts) of hand and finger. Patients usually have a subtle weakness of affected limb.

Key Terms

Brachial plexus A group of lower neck and upper back spinal nerves supplying the arm, forearm and hand.

Claudication Cramping or pain in a leg caused by poor blood circulation. This condition is frequently caused by hardening of the arteries (atherosclerosis). Intermittent claudication occurs only at certain times, usually after exercise, and is relieved by rest.

Clavicle Also called the collarbone. Bone that articulates with the shoulder and the breastbone.

Embolization A technique to stop or prevent hemorrhage by introducing a foreign mass, such as an air-filled membrane (balloon), into a blood vessel to block the flow of blood. This term also refers to an alternative to splenectomy that involves injecting silicone or a similar substances into the splenic artery to shrink the size of the spleen.

Hyperextension Extension of a limb or body part beyond the normal limit.

Ischemia A decrease in the blood supply to an area of the body caused by obstruction or constriction of blood vessels.

Thrombosis The formation of a blood clot in a vein or artery that may obstruct local blood flow or may dislodge, travel downstream, and obstruct blood flow at a remote location. The clot or thrombus may lead to infarction, or death of tissue, due to a blocked blood supply.

Diagnosis

Chest x ray may reveal an anatomic abnormality. Color flow duplex scanning (ultrasound analysis) is indicated for suspected case of vascular thoracic outlet syndrome. If symptoms suggest arterial involvement an arteriogram may be indicated as well as venography (in suspected cases of venous involvement). Nerve conduction evaluation by nerve root stimulation is the best approach to diagnose neurologic thoracic outlet syndrome.

Treatment team

The treatment team usually consists of appropriate specialists which depend on the presentation. Specialists that can be consulted include a **neurologist**, vascular surgeon or orthopedic surgeon. Physical medicine physicians are required for outpatient workup and evaluation.

Treatment

Neurologic TOS requires outpatient referral and conservative outpatient physiotherapy. Vascular thoracic outlet syndrome requires more urgent care that typically includes immediate heparinization, vascular surgery consultation, color flow (ultrasound), duplex scanning and **angiography** or venography. Neurologic thoracic outlet syndrome patients may also require surgery if conservative medical therapy fails for more than four months. However, surgical results are not encouraging since a study demonstrated that 60% of postsurgical patients were still work disabled one year after surgery. Outpatient medications can include Coumadin (a blood thinner or anticoagulant), analgesics or short-term antidepressants if there is protracted pain.

Recovery and rehabilitation

Recovery includes stress avoidance and work simplification and modifications on the job site. Recommendations include avoidance of sustained muscular contraction and repetitive or overhead work. **Exercise** programs may help with chronic pain. Exercises are recommended to maximize the potential outlet space through special stretching and strengthening maneuvers of the shoulder. These exercise can include maneuvers such as bilateral (both sides) shoulder retraction while standing or lying prone, standing corner pushups, hand circles and cervical and lumbar spine extension. Outpatient management typically includes occupational/physical therapy, and manipluation. Inpatient treatment is not indicated unless the patient is a surgical candidate.

Clinical trials

There are projects funded by the National Institute of Neurological Diseases and Stroke <http://www.ninds.nih.gov> concerning pain and pain management. The projects forcus on seeking new treatments for nerve damage and pain.

Prognosis

Neurologic TOS is not progressive and but requires treatment. Arterial or venous thoracic outlet syndrome respond well to adequate treatment and the results are generally good. Some patients can develop chronic pain (neurologic type) or thrombosis (venous and arterial thoracic outlet syndrome). Other complications that can develop include loss of functional ability of arms, neurologic deficit, **depression**, and ischemia.

Special concerns

Pregnancy can cause an increase in TOS symptoms, because of increased body size and displacement of the abdomen. Increased breast size common during and after pregnancy can displace the shoulder girdle and cause postural changes that can precipitate symptoms. Patients should be educated concerning precipitating factors of TOS, which can decrease the likihood of recurrence.

Resources

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American Chronic Pain Association. P.O.Box 850, Rocklin, CA 95677-0850. (916) 632-0922 or (800) 533-3231; Fax: (916) 632-3208. ACPA@pacbell.net. <http://www.theacpa.org>.

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Thyrotoxic myopathy

Definition

Thyrotoxic **myopathy** is a neuromuscular disorder that occurs due to overproduction of thyroid hormone and is characterized by excessive fatigability, muscle wasting and weakness. It mainly affects muscles of the shoulder, hips and hands. The adverse effects of thyroid hormone on the structure and function of muscles gives rise to this myopathy. Although diagnosis can be tricky, this disorder is reversible with appropriate treatment.

Description

Thyrotoxic myopathy is known by several other names like hyperthyroid myopathy, Graves and Basedow's myopathy or Basedow paraplegia. It was first recognized in the early nineteenth century by Graves and Von Basedow as occurring infrequently in severe hyperthyroidism. In the middle of the twentieth century, researchers found that up to 80% of hyperthyroid patients manifested at least some degree of muscle weakness and this was confirmed on electromyographic studies.

Myopathy or muscle disease is categorized based on the underlying cause, inheritance pattern, etc. One of the broader categories is endocrine myopathies, which occur when there is an abnormal level of endocrine hormones in the body. The thyroid gland produces the hormone thyroxine which regulates maturation of the nervous system, growth and metabolism. Of all the endocrine myopathies, the myopathy due to dysfunction of the thyroid gland is the most common.

Demographics

Although some degree of muscle weakness is common in most hyperthyroid patients, it is still a rare disorder overall and there are no accurate estimates of incidence. In a series of hyperthyroid patients studied by Ruurd Duyff in 2000, 67% had symptoms attributable to myopathy. From a series of over 100 hyperthyroid patients studied by Ramsay in 1974 and Puvanendran *et al* in 1979, it was found that only 33–64% percent of patients complained of weakness but 61–82% actually had demonstrable weakness on examination. Although hyperthyroidism is more common among women, symptomatic myopathy is more common among middle aged hyperthyroid men. Unlike the classic myopathy, **periodic paralysis**, which is an unusual neuromuscular complication of hyperthyroidism, is seen among young Asian males.

Causes and symptoms

Much research has been done to elucidate how thyroxine affects muscle function. Muscle is made up of thousands of individual muscle fibers and myofibrils. The latter have myofilaments that are composed of contractile proteins called actin and myosin. In order for a muscle to contract, a command originates from the brain, travels along the spinal cord and then the nerve to terminate on the muscle. This impulse is then transmitted via a complicated process to the myofilaments that contract and relax appropriately. Adenosine triphosphate (ATP) is a chemical that supplies the necessary energy for contraction. Calcium which is released during contraction is taken up to cause muscle relaxation. Muscle fibers are of two types, slow and fast twitch. The slow or type 1 fibers are needed for sustained effort like standing and are more responsive to thyroxine. The fast type 2 fibers are needed for short rapid bursts like sprinting.

In hyperthyroidism, there is an accelerated production of ATP and reuptake of calcium. This leads to very rapid contraction and relaxation. When this occurs repetitively, the structure and mechanics of the slow fiber is changed to

that of a fast fiber. Hyperthyroidism increases the body's basal metabolic rate and much of this energy is inefficiently used for muscle contraction. In turn, the muscles lose their endurance, **fatigue** easily, and become weak and wasted.

Hyperthyroidism can occur due to several causes. Of these, only two are commonly associated with myopathy. One of them is multinodular goiter, when the thyroid gland becomes studded with nodules, enlarges and overproduces thyroxine. The other is Graves disease, where the body launches an autoimmune attack on the thyroid gland and causes it to produce excess thyroxine.

A hyperthyroid person who has muscle weakness may or may not have other recognizable manifestations of hyperthyroidism. Myopathy can sometimes be the first presentation of the underlying hyperthyroid state. There are several types depending on the rapidity of symptom development and patterns of muscle involvement.

CHRONIC THYROTOXIC MYOPATHY The symptom onset is very insidious, so much so that patients very often do not notice the wasting or weakness. An average of six months elapses before the diagnosis is made, as the symptoms are subtle and the progress is very gradual. As mentioned earlier, only around 30% of patients complain of neuromuscular symptoms whereas around 80% show muscle weakness on testing. Patients complain of low **exercise** tolerance, easy fatigability, difficulty in doing certain tasks, muscle stiffness, muscle twitching and sometimes muscle wasting. Shoulder, hand and then pelvic muscles are affected and tasks like climbing stairs, getting up from a low chair or lifting arms above the shoulders become strenuous. Due to the weakness, movements become clumsy and effortful. The degree of wasting varies among individuals. It is usually mild to moderate but on occasions can be so severe that the scapulae look "winged." Despite a remarkable degree of wasting and weakness, patients remain ambulatory. If the myopathy progresses untreated, then facial muscles, swallowing, and respiratory muscles are involved with resultant difficulty swallowing and breathing. Muscles that control eye movement can also be affected, leading to double vision and squint.

ACUTE THYROTOXIC MYOPATHY This was first described by Laurent in 1944 and is a much rarer form than the chronic myopathy. It is rapidly progressive with profound muscle weakness developing over a few days. Muscle **pain**, cramps and muscle breakdown develop and lead to rhabdomyolysis. Patients are confused, have very weak respiratory muscles, and develop severe respiratory failure necessitating artificial ventilation.

OCULAR MYOPATHY This is also called "dysthyroid opthalmopathy" or "exopthalmic opthalmoplegia." It is more common in females, can be unilateral and may or may not be associated with chronic thyrotoxic myopathy. It can occur even after treatment for hyperthyroidism. The eye muscles become swollen and weak due to inflammation from an autoimmune attack. Eyes are bulging, the cornea is inflamed and eye movements are restricted especially in the horizontal direction. In severe cases, the cornea is ulcerated and blindness occurs. It progresses over six to 18 months and longer delays in treatment result in severe residual deficit.

THYROTOXIC PERIODIC PARALYSIS This is very rare and occurs mostly in young adult males of Asian ancestry around the third decade. It is characterized by sudden episodes of muscle weakness involving the trunk and limb muscles, developing over few minutes to hours and lasting for hours to a couple of days. It is due to altered muscle membrane excitability secondary to low potassium levels. Although it is reversible spontaneously or with administration of potassium, death can occur due to cardiac arrhythmias.

Diagnosis

The diagnosis is clinical and is usually made by a **neurologist** who has expertise in neuromuscular disorders. There should be a high index of clinical suspicion as the pattern of muscle weakness is nonspecific and often patients do not know that they are hyperthyroid. The combination of symptoms in a severe case of hyperthyroid myopathy, like muscle wasting, difficulty swallowing and muscle twitching can lead to a mistaken diagnosis of Lou-Gehrig's disease (ALS). A classic picture is that of a patient, who despite a ravenous appetite has significant muscle wasting, weakness and brisk tendon reflexes. Associated hyperthyroid features like enlarged thyroid gland, tremor, bulging eyes, and a fast heart rate may be seen.

Blood tests show an elevated thyroxine level. In Graves disease, antibodies against the thyroid gland are present. Levels of creatine phosphokinase (CPK), a muscle enzyme is normal except when there is acute muscle breakdown. **Electromyography** is a technique used to diagnose myopathies, by studying the response of muscle contraction to an electrical stimulus. In hyperthyroid myopathy, this may be normal or show a "polyphasic" or "myopathic" response. Muscle **biopsy** again may be normal or show some degenerating fibers in a non-specific pattern. **CT scans** or **MRI** scans can be used to see the swollen eye muscles.

Treatment team

Treatment for hyperthyroid myopathy involves the interaction between a neuromuscular specialist, endocrinologist, a surgeon, and an ophthalmologist. Physiatrists and

Key Terms

Amyotrophic lateral sclerosis ALS, also called Lou Gehrig's disease, is a progressive neuromuscular condition due to degeneration of the motor nerve cells and fiber tracts in the spinal cord. The cause is not yet well defined. It leads to progressive weakening of the limb muscles and that of swallowing and breathing. ALS leads to death within a couple of years of onset.

Autoimmune An immune response by the body against its own tissues or cells.

Contracture Loss of range of motion at a joint due to abnormal shortening of soft tissues around the joint.

Creatine phosphokinase A muscle enzyme present in various skeletal muscles and the heart which is released due to any type of muscle injury. This can be measured in the blood.

Electromyography Technique used to measure the function of muscles by studying their contraction response to an electrical stimulus. A needle is inserted into the muscle, an electrical stimulus is given, and the resulting contraction is recorded from which normal and abnormal patterns can be interpreted.

Euthyroid State of normal function of the thyroid gland.

Goiter A swelling or enlargement of the thyroid gland.

Hormone Chemical substance produced by certain endocrine glands that are released into the bloodstream where they control and regulate functioning of several other tissues.

Hyperthyroid State of excess thyroid hormone in the body.

Myofilament Ultrastructural microscopic unit of a muscle that is made up of proteins that contract.

Myopathy Disease of muscle.

Opthalmoplegia Paralysis of the muscles that control eye movements.

Paraplegia Paralysis of the legs and lower part of the body.

Rhabdomyolysis Breakdown of muscle fibers resulting in release of muscle contents into the blood.

Thyroxine Hormone produced by the thyroid gland.

physical and occupational therapists are also part of the team helping in rehabilitation.

Treatment

Hyperthyroid myopathy is fortunately reversible provided the underlying hyperthyroidism is corrected and a normal thyroid state (euthyroidism) is restored. This can be done with medications, **radiation**, or surgery. Treatment is also aimed at symptomatic relief, prevention, and treatment of complications.

Medications

Beta-blockers are used to block the effects of adrenaline on peripheral tissues, as adrenergic systems are unregulated in hyperthyroidism. This affords symptomatic but temporary relief. Definitive treatment however aims at reducing the output of thyroxine from the thyroid gland. Propylthiouracil and methimazole are medications that inhibit production and release of thyroxine and also block tissue effects of thyroxine. Radiation in the form of oral radio-iodine therapy destroys the overactive thyroid gland. Steroids, other anti-inflammatory medications, or radiation is used to treat the ocular myopathy. Artificial tears and lubricating ointments are used to prevent corneal ulceration. Potassium chloride given intravenously will reverse the thyrotoxic periodic paralysis.

Surgical treatment

Surgical removal of portions of the enlarged and unsightly thyroid gland can be done to restore euthyroid state. In severe cases of ocular myopathy, surgical widening of the walls of the orbit is done to allow the eyes to decompress. Corneal grafting can be done to treat corneal ulceration.

Recovery and rehabilitation

When proper treatment is given, full recovery of the myopathy is possible and complications can be avoided. Physical therapists can help in devising muscle strengthening exercises and in preventing muscle contractures. Protective eye glasses and eye patches are used to prevent corneal exposure and ulceration.

Clinical trials

There were no **clinical trials** ongoing as of early 2004, mainly because there is an effective treatment already available.

Prognosis

Prognosis is quite good. In two to four months after euthryoid state is achieved, muscle weakness improves. But it may take up to a year for muscle bulk to return. Respiratory failure is very rare. Patients have a normal life expectancy and lead normal lives if properly and promptly treated.

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Muscular Dystrophy Association. 3300 East Sunrise Drive, Tucson, AZ 85718-3208. (520) 529-2000 or (800) 572-1717; Fax: (520) 529-5300. mda@mdusa.org. <http://www.mdusa.org>.

National Institute of Health Neurological Institute. P.O. Box 5801, Bethesda, MD 20824. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov/>.

Chitra Venkatasubramanian, MBBS, MD

Tiagabine

Definition

Tiagabine is an anticonvulsant medication indicated for the control of **seizures** in the treatment of **epilepsy**. Epilepsy is a neurological disorder in which excessive surges of electrical energy are emitted in the brain, causing seizures.

Purpose

Tiagabine decreases abnormal electrical activity within the brain that may trigger seizures. Although tiagabine controls some types of seizures associated with epilepsy, especially partial seizures, there is no known cure for the disorder.

Description

In the United States, tiagabine is sold under the brand name Gabitril. While the exact mechanism by which tiagabine reduces seizures is unknown, the drug boosts the levels of GABA, a neurotransmitter, in the brain. **Neurotransmitters** such as GABA are naturally occurring chemicals that transmit messages from one neuron (nerve cell) to another. When one neuron releases GABA, it normally binds to the next neuron, transmitting information and preventing the transmission of extra electrical activity. When levels of GABA are reduced, there may not be enough GABA to sufficiently bond to the neuron, leading to extra electrical activity in the brain and seizures. Tiagabine works to block GABA from being re-absorbed too quickly into the tissues, thereby increasing the amount available to bind to neurons.

Recommended dosage

Tiagabine is taken by mouth in tablet form and is prescribed by physicians in varying dosages.

Beginning a course of treatment with tiagabine requires a gradual dose-increasing regimen. Adults and teenagers 16 years or older typical take 4 mg a day at the beginning of treatment. The prescribing physician may raise a patient's daily dosage gradually over the course of several weeks. The usual dose is not greater than 56 mg per day. The full benefits of tiagabine may not be realized until after several weeks of therapy.

A person should not take a double dose of tiagabine. If a daily dose is missed, the next dose should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose is skipped.

When discontinuing treatment including tiagabine, physicians typically direct patients to gradually reduce their daily dosages. Stopping the medicine suddenly may cause seizures to return or occur more frequently.

Precautions

A physician should be consulted before taking tiagabine with certain non-prescription medications. Patients should avoid alcohol and CNS depressants (medicines that can make one drowsy or less alert, such as

Key Terms

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Partial seizure An episode of abnormal activity in a localized (specific) part of the brain, causing temporary changes in attention and muscle movement.

Neurotransmitter A chemical that is released during a nerve impulse that transmits information from one nerve cell to another.

antihistimines, sleep medications, and some **pain** medications) while taking tiagabine. Tiagabine can exacerbate (potentiate) the side effects of alcohol and other medications.

Tiagabine may not be suitable for persons with a history of liver or kidney disease, mental illness, high blood presure, angina (chest pain), irregular heartbeats, or other heart problems. Before beginning treatment with tiagabine, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant, or plan to become pregnant. Physicians often advise the use of effective birth control while taking tiagabine. Studies in animals indicate that tiagabine may cause birth defects. Patients who become pregnant while taking tiagabine should contact their physician immediately.

Side effects

Patients and their physicians should weigh the risks and benefits of tiagabine before beginning treatment. Tiagabine is usually well-tolerated, but may case a variety of usually mild side effects. Dizziness, nausea and drowsiness are the most frequently reported side effects of tiagabine. Other possible side effects include:

- trouble sleeping
- fever
- **headache**
- unusual tiredness or weakness
- **tremors**
- abdominal pain
- increased appetite
- vomiting, diarrhea or constipation
- heartburn or indigestion
- aching joints and muscles or chills
- unpleasant taste in mouth or dry mouth
- tingling or prickly feeling on the skin

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication. However, if any symptoms persist or become too uncomfortable, the prescribing physician should be notified.

Other, uncommon side effects of tiagabine can be serious. A patient taking tiagabine who experiencs any of the following symptoms should contact their physician:

- rash or bluish patches on the skin
- mood or mental changes
- shakiness or unsteady walking
- excessive anxiety
- difficulty with memory
- double vision
- numbness in a limb.
- unsteadiness or clumsiness
- speech or language problems
- difficulty breathing
- chest pain
- irregular heartbeat
- faintness or loss of consciousness
- persistent severe headaches
- persistent fever or pain

Interactions

Tiagabine may have negative interactions with some antihistimines, antidepressants, antibiotics, and monoamine oxidase inhibitors (MAOIs). Other medications such as **diazepam** (Valium), **phenobarbital** (Luminal, Solfoton), nefazodone, metronidazole, **acetazolamide** (Diamox), phenytoin (Dilantin), **primidone**, and propranolol (Inderal) may also adversely react with triagabine. Tiagabine should be used with other other seizure prevention medications only if advised by a physician.

Many **anticonvulsants** may decrease the effectiveness of some forms of oral contraceptives (birth control pills).

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Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

Adrienne Wilmoth Lerner

Tic douloureux *see* **Trigeminal neuralgia**

Tinnitus *see* **Hearing disorders**

Todd's paralysis

Definition

Todd's paralysis is a brief period of paralysis that occurs in the aftermath of a seizure.

Description

The period of time directly following a seizure is called the "postictal state." During this time period, the individual's brain is still recovering from the major changes brought on by the seizure. Drowsiness and confusion are very common symptoms of the postictal state. In some cases, the symptoms are even more pronounced and dramatic, and may even involve severe weakness or paralysis of a limb or one side of the body (hemiparesis), odd sensations such as numbness, or pronounced vision changes or blindness.

Demographics

Todd's paralysis usually strikes individuals who have **epilepsy** (recurrent **seizures**), although it may occur after any seizure.

Causes and symptoms

A seizure is an episode of abnormal electrical activity in a particular part of the brain. There are many kinds of seizures, and they may affect any specific part of the brain, or may spread to affect a wider distribution of the brain. The behavior of an individual suffering from a seizure may range from a simple, brief staring episode to complete loss of consciousness, with involuntary jerking of the muscles. The aftermath of a seizure is referred to as the postictal state. During the postictal period, although the seizure itself has ended, the brain is still recovering from the abnormal electrical discharges that precipitated the seizure activity. During this time period, the individual may be drowsy, less responsive than normal, or confused. Todd's paralysis is thought to occur due to depressed activity in the area of the brain that underwent the seizure.

The symptoms of Todd's paralysis depend on the area of the brain where the seizure took place. For example, if the seizure occurred in the motor cortex (that part of the brain responsible for purposeful movement of the muscles), Todd's paralysis may result in hemiparesis, an inability to move the muscles of one-half of the body. Because the occipital lobe (the lower back part of the brain) is responsible for vision, an occipital lobe seizure may result in visual change or outright blindness during the postictal phase. In fact, tracking the specific symptoms of Todd's paralysis may actually help the physician diagnose the specific area of the brain in which an individual's seizures are occurring.

The symptoms of Todd's paralysis are often gone within minutes or hours of their onset. In some, more rare cases, the symptoms may last as long as 48 hours. Ultimately, however, full function is restored.

Diagnosis

Diagnosis of Todd's paralysis is crucial, because the symptoms can closely resemble those of a **stroke** (injury to the brain due to oxygen deprivation after bleeding or a blockage of an artery). It is important to distinguish between Todd's paralysis and a stroke, because the treatments are quite different.

Generally, Todd's paralysis can be easily diagnosed when it occurs in the aftermath of a documented seizure. The quick resolution of symptoms is another clue pointing to Todd's paralysis. When the diagnosis is unclear, however, tests may be run, including an electroencephalogram or EEG (a test that records information about the brain's electrical activity) or **MRI**. In the case of a seizure, the EEG may be abnormal; in the event of a stroke, the MRI may show an area of damage.

Treatment team

Todd's paralysis, like seizures and epilepsy, is usually treated by a **neurologist**.

Treatment

There is no specific treatment necessary for Todd's paralysis. The symptoms should fully resolve within minutes to hours or days.

Recovery and rehabilitation

Because of the quick and complete resolution of symptoms of Todd's paralysis, no rehabilitation is necessary.

Key Terms

Epilepsy A condition in which an individual has recurrent seizures.

Hemiparesis Severe weakness or paralysis affecting one side of the body.

Postictal The time period immediately following a seizure.

Seizure An episode of abnormal electrical activity in the brain.

Prognosis

The prognosis of Todd's paralysis is excellent, with full recovery to be anticipated.

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Topiramate

Definition

Topiramate is an anticonvulsant indicated for the control of **seizures** in the treatment of **epilepsy** (a neurological dysfunction in which excessive surges of electrical energy are emitted in the brain) and **Lennox-Gastaut syndrome** (a disorder which causes seizures and developmental delays).

In psychiatry, topiramate may also be used in the treatment of bipolar **affective disorders**.

Purpose

Topiramate is thought to decrease and balance the abnormal electrical activity within the brain that may trigger seizures. While topiramate controls some types of seizures associated with epilepsy, there is no known cure for the disorder.

In patients with bipolar disorders, topiramate stabilizes mood without producing a euphoric feeling or inducing manic episodes.

Description

In the United States, topiramate is sold under the brand name Topamax.

Topiramate is most commonly prescribed to treat patients who do not respond to other anticonvulsant medications, or is part of a combination of anticonvulsant medications used to treat intractable seizures. Although the precise mechanisms by which it exerts its therapeutic effects in epilepsy and other seizure disorders are unknown, topiramate has three specific seizure-reducing actions:

- topiramate decreases nerve-cell excitation by blocking targeted **neurotransmitters** from binding to certain receptors in the brain.
- topiramate blocks sodium channels in nerve cells, thus decreasing excessive nerve-cell firing.
- topiramate increases the availability of GABA, (gamma-aminobutyric acid), a neurotransmitter that inhibits nerve-cell excitation in the brain.

Recommended dosage

Topiramate is taken by mouth in tablet or sprinkle form. Topiramate is available in strengths of 25 mg, 100 mg, and 200 mg tablets, along with 15 mg and 25 mg sprinkle capsules. Patients usually take topiramate twice daily. Typical total daily doses are usually between 200 milligrams (mg) to 400 mg for treatment of seizure disorders. For the treatment of bipolar disorders, dosages vary.

Beginning a course of treatment which includes topiramate requires a gradual dose-increasing regimen. The prescribing physician determines the proper beginning dosage and may raise a patient's daily dosage gradually over the course of several weeks. It may take several weeks to realize the full seizure-reducing benefits of topiramate.

Key Terms

Bipolar affective disorder A psychiatric disorder marked by alternating episodes of mania and depression. Also called bipolar illness, manic-depressive illness.

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Lennox-Gastaut syndrome A severe form of epilepsy in children, resulting in intractable (difficult to control) seizures and developmental delays.

Seizure A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

A double dose of topiramate should not be taken to make up for a missed or forgotten dose. If a daily dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose is skipped. When discontinuing treatment with topiramate, physicians typically direct patients to gradually taper their daily dosages. Stopping the medicine suddenly may cause seizures to return or occur more frequently.

In the treatment of bipolar disorders, persons should not stop taking topiramate without consulting the prescribing physician. Stopping the medicine suddenly may cause seizures, or severely and suddenly alter a patient's mood.

Precautions

Topiramate is not habit-forming. A physician should be consulted before combining topiramate with certain non-prescription medications. Patients should avoid alcohol and CNS depressants (medicines that can make one drowsy or less alert, such as antihistimines, sleep medications, and some **pain** medications) while taking topiramate. Because topiramate may cause drowsiness, persons should not drive or operate heavy machinery until they know how they will react to the drug.

Persons taking topiramate, particularly those with predisposing factors, should maintain an adequate fluid intake in order to minimize the risk of kidney stone formation. Approximately 1.5% of people taking topiramate develop kidney stones.

Topiramate may not be suitable for persons with a history of liver or kidney disease, mental illness, high blood presure, angina (chest pain), irregular heartbeats, or other heart problems. Before beginning treatment with topiramate, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant or planning on becoming pregnant.

Topiramate may inhibit perspiration, causing body temperature to increase. Persons taking topiramate are at a greater risk for heat **stroke**, and should use caution during strenuous **exercise**, prolonged exposure during hot weather, and while using saunas or hot tubs.

Topiramate may cause birth defects. Use effective birth control while taking topiramate. Patients who become pregnant while taking topiramate should contact their physician immediately.

Side effects

Patients and their physicians should weigh the risks and benefits of topiramate before beginning treatment. Topiramate is usually well tolerated, but may cause a variety of usually mild side effects. **Dizziness** and drowsiness are the most frequently reported side effects of topiramate. Other possible side effects include:

- double vision
- tingling or prickly feeling of the extremeties
- language problems described as "trouble finding the right word"
- loss of appetite and nervousness (in children)

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication. However, if any symptoms persist or become too uncomfortable, the prescribing physician should be consulted.

Other, uncommon side effects of topiramate can lead to serious complications. A person taking topiramate who experiences any of the following symptoms should immediately contact their physician:

- blurred vision and eye pain
- extreme mood or mental changes
- shakiness or unsteady walking
- kidney stones
- difficulty breathing
- chest pain
- irregular heartbeat
- faintness or loss of consciousness

Interactions

Topiramate may have negative interactions with some antihistimines, antidepressants, antibiotics, and monoamine oxidase inhibitors (MAOIs). Other medications such

as **diazepam** (Valium), **phenobarbital** (Luminal, Solfoton), nefazodone, metronidazole, **acetazolamide** (Diamox), lanoxin (Digoxin, Digitek), phenytoin (Dilantin), **primidone**, and propranolol (Inderal) may also need to be adjusted and closely monitored if taken with topiramate. Topiramate, like many other anticonvulsant medications, may decrease the effectiveness of oral contraceptives (birth control pills).

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American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. <http://www.aesnet.org>.

Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

Adrienne Wilmoth Lerner

Tourette syndrome

Definition

Tourette syndrome (TS) is an inherited neurological disorder that typically appears in childhood. The main features of TS are repeated movements and vocalizations called tics. TS can also be associated with behavioral and developmental problems.

Description

Tourette syndrome is a variable disorder with onset in childhood. Though symptoms can appear anywhere between the ages of two and 18, typical onset is around age six or seven. Tics, which may be motor or vocal, tend to wax and wane (increase and decrease) in severity over time. Facial tics, such as rapid blinking or mouth twitches, are the most common initial sign of TS. Other early symptoms include involuntary sounds such as throat clearing and sniffing, or tics of the limbs. Symptoms usually intensify during teenage years and diminish in late adolescence or early adulthood. Patients may also develop co-occurring behavioral disorders, namely obsessive-compulsive disorder (OCD), **attention deficit hyperactivity disorder** (ADHD) or attention deficit disorder (ADD), poor impulse control, and/or sleep disorders. Though some children have learning disabilities, intelligence is not impaired. TS is not degenerative and life span is normal.

Tourette syndrome is classified by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision (DSM-IV-TR) as a "Tic Disorder." The *International Classification of Disease and Related Health Problems*, Tenth Revision (ICD-10) calls TS a "combined vocal and multiple motor tic disorder (de la Tourette's syndrome)." A French **neurologist**, Jean Marc Itard, described the first known case of Tourette syndrome in the 1825. He had recorded the ticcing and cursing behavior of an aristocratic woman, Madame de Dampierre. The disorder is named for another French physician, Georges Gilles de la Tourette, who reported a series of cases in 1885, the primary example of which was the marquise. Tourette syndrome may also be referred to as Gilles de la Tourette syndrome (GTS).

Demographics

Tourette syndrome occurs worldwide, in people of all racial and ethnic groups. It is thought that approximately 200,000 people in the United States have TS. About three-quarters of patients are males. Once thought to be a rare disorder, TS is one of the most common genetic conditions. Recent estimates of prevalence suggest that TS occurs in one in 1,000 to one in 100 male children. One report indicated that prevalence may be as high as 25% in children in special education classes.

Causes and symptoms

Genetic factors are believed to play a major role in the development of TS. Several chromosomal regions have been identified as possible locations of genes that confer susceptibility to TS. Some family studies have indicated that TS is inherited in an autosomal dominant manner. In an autosomal dominant condition, an individual has a 50% chance to pass the gene to his or her children. Not everyone who inherits a TS gene will show symptoms. Approximately 70% of females and 99% of males with a TS gene will express symptoms. An individual who inherits the TS gene may develop TS, a milder tic disorder, obsessive-compulsive disorder (OCD) without any tics, or no signs of TS. The gender of a person influences the expression (the disease symptoms and severity) of the TS gene; males are more likely to have TS or tics and females are more likely to have OCD. Approximately one in ten children who inherit the TS gene from a parent will show symptoms that are severe enough to warrant medical treatment.

Non-genetic factors are also believed to contribute to the development of TS. In about 10-15% of cases, TS is not genetic. Certain stressful processes during gestation (pregnancy) or at the time of birth may increase the chance for a person to develop TS. For example, it is known that when both twins have TS, the twin who weighed less at birth tends to have more severe tics. Other non-genetic factors that may predispose a person to TS include: severe psychological trauma, recurrent daily stresses, extreme emotional excitement, PANDAS (pediatric autoimmune neuropsychiatric disorder with streptococcal infection), drug abuse, and certain co-existing medical or psychiatric conditions. In PANDAS, children experience an abrupt onset of TS symptoms and/or obsessive-compulsive symptoms following a strep throat infection.

It is thought that TS is the result of abnormal metabolism of a neurotransmitter (a chemical in the brain that carries signals from one nerve cell to another) called dopamine and possibly of other **neurotransmitters** including serotonin and norepinephrine. As of December 2003, the exact mechanisms by which the TS gene or genes lead to disease symptoms were unresolved. It is hoped that locating the gene or genes responsible for TS will improve understanding of how TS develops and eventually will lead to more effective treatments.

Tics seen in patients with TS can range in intensity, frequency, duration, type and complexity. Although there is wide range of severity observed in TS, the majority of cases are mild. A minority of patients has symptoms that are severe enough to interfere with daily functioning. In the most severe cases, patients experience numerous debilitating tics during all waking hours. Tics usually occur in "bouts" with many tics over a short interval of time. Many patients experience waxing and waning (fluctuations in severity) of their tics over the course of weeks or months. Tics can be made worse by stress or **fatigue** and tend to improve when the individual is absorbed in an activity or task that requires concentration. Although the tics associated with TS are involuntary (not deliberate), people with TS can sometimes control their tics for a period of time ranging from minutes to hours. However the tic must eventually be expressed and will come out. Coprolalia, a sensationalized type of tic in which people make obscene or socially inappropriate comments, is present in less than 15% of TS patients.

Tics are classified as either simple or complex. Simple tics are sudden, repetitive movements that involve a limited number of muscle groups. Simple motor tics are fast and without purpose. They can cause both emotional and physical **pain** (such as head jerking or jaw snapping). Simple vocal tics are meaningless sounds or noises. Complex tics are coordinated patterns of stepwise movements that involve multiple muscle groups. Complex motor tics appear slower and more deliberate than simple motor tics. Complex vocal tics involve meaningful words, phrases or sentences.

Key Terms

Biofeedback A training technique that enables an individual to gain some element of control over involuntary or automatic body functions.

Dyslexia A type of reading disorder often characterized by reversal of letters or words.

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.

SIMPLE MOTOR TICS

- blinking eyes
- jerking head
- shrugging shoulders
- facial grimacing
- rolling eyes up
- squinting
- smacking lips
- jaw snapping

SIMPLE VOCAL TICS

- throat clearing
- yelping
- sniffing
- tongue clicking
- grunting
- coughing
- spitting
- humming
- whistling

COMPLEX MOTOR TICS

- jumping
- touching other people or things
- smelling
- twirling about
- thrusting of arms, groin, or torso
- pinching

- fiddling with clothing
- self-injurious actions including hitting or biting oneself (rare)

COMPLEX VOCAL TICS

- uttering words or phrases out of context
- repeating words or sounds
- stuttering
- repeating others' words (echolalia)
- repeating one's own last word or sound (palilalia)
- talking to oneself
- muttering
- vocalizing socially unacceptable words (a rare tic called coprolalia)

Co-occurring disorders

In addition to tics, patients with TS can also have additional problems that include:

- Obsessive-compulsive disorder (OCD). OCD is a condition characterized by the presence of obsessions (persistent involuntary thoughts, images or impulses that are experienced as unwanted and bothersome) and compulsions (the actual behaviors that are performed over and over in response to the obsessions). Examples of obsessive-compulsive behavior include excessive hand washing and repeatedly checking to see that a door is locked. In patients with TS, onset of OCD usually occurs before puberty and it may lead to serious impairment. It is thought that some forms of OCD have the same etiology (cause) as TS. Obsessive-compulsive behaviors can negatively impact a child's performance at school if they are time-consuming or distracting.
- Attention deficit disorder with or without hyperactivity (ADHD or ADD). Attention deficit disorder may precede symptoms of TS. It is estimated that ADD or ADHD occurs in as many as 75% of individuals with TS. Children with ADHD can be fidgety, have a very short attention span, be impulsive, and have difficulty completing tasks. ADD is similar except without the high level of activity seen in ADHD.
- Learning disabilities. Approximately one-third of patients with TS have a learning disability. Learning disabilities found in TS include difficulties with reading, writing and mathematics, and visual and auditory perception problems. Children with TS can also have **dyslexia** and problems with retaining information. Some tics seen in TS such as repetitive eye-blinking or head-jerking can make it difficult for the student with TS to read and thus interfere with learning.
- Sleep disorders. Sleep problems such as difficulty falling asleep, waking early, sleepwalking, night terrors and enuresis (bed-wetting) are fairly common in TS. For example, in one study the percentage of different grades of TS patients having trouble getting to sleep ranged from about 45% to 65% as compared to 15% of controls.
- Problems with impulse control. Individuals with TS may display overly aggressive behavior, socially inappropriate acts, self-injurious behavior such as lip biting or banging one's head, and defiant behaviors.

Diagnosis

There is no specific lab test or other medical study that can establish the definitive diagnosis of TS. Usually, diagnosis is made through observation of an individual's symptoms and by assessment of family history. Some patients may undergo blood tests, imaging studies such as **magnetic resonance imaging (MRI)**, or an electroencephalogram (EEG) scan in order to rule out other possible explanations for the symptoms. The process of making a TS diagnosis usually involves monitoring symptoms over a period of several months. The family may be asked to keep records. This period of observation will help determine to what extent the child's symptoms are interfering with ability to function at home, school, and in the community. A neurological examination may be performed. Assessment of cognitive functioning and school performance may be recommended if the child is having difficulty in school.

The American Psychiatric Association published diagnostic criteria, listed below, is from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision (DSM-IV-TR). Another similar set of criteria exists in the *International Classification of Disease and Related Health Problems*, Tenth Revision (ICD-10). The ICD-10 criteria are not as strict about the age of onset as the DSM-IV-TR criteria.

***Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition Text Revision (DSM-IV-TR) criteria**

- Both multiple motor and one or more vocal tics present at some time during the illness although not necessarily simultaneously.
- The occurrence of tics multiple times per day (usually in bouts), nearly every day or intermittently during a span of more than one year without a tic-free period of more than three consecutive months.
- The disturbance causes significant distress or impairment in social, occupational, or other important areas of functioning.
- Onset before age 18.
- The disturbance is not due to the direct physiological effects of a substance or a general medical condition.

Treatment team

Treatment of TS disorders requires a multidisciplinary approach. In addition to the patient's primary health care professionals, medical professionals involved in the care of patients with an MPS usually includes specialists in neurology, psychiatry, psychology, social work, genetics, and education. Tourette syndrome support groups may help families in coping with this condition.

Treatment

There is no cure for TS. Management of TS requires integration of behavioral, psychological and sometimes pharmacologic (medication) therapies. Occupational therapy may also be indicated for TS patients. The decision to treat an individual case of TS depends on the degree to which the symptoms interfere with that person's ability to function. Treatment is crucial in helping the affected child avoid **depression**, social isolation, and strained family relationships. In general, pharamacologic therapy is reserved for patients with severe symptoms. Education about the condition and reassurance are key components of any treatment program.

Behavior therapy

Various types of behavior therapy may benefit patients with TS. Using a technique known as habit-reversal training, individuals with severe tics are taught how to substitute one tic for another that is more socially acceptable. Also, since stress can exacerbate tics, individuals with TS may find that relaxation techniques and biofeedback can help alleviate stress reactions and reduce tics. Behavior modification may be necessary for children with poor impulse control.

Psychological therapy

Psychological counseling may help individuals with TS to cope with the social and emotional problems that occur as a result of their symptoms. Depression and self-esteem problems are common among persons with TS. Counseling is especially important for children with TS as they approach adolescence, a time in which tics tend to get worse. Affected children and their parents may also benefit from family therapy. Severe or frequent tics and the presence of co-occurring problems such as ADHD and OCD can negatively impact quality of life for people with TS, especially if family support is inadequate. Parents may have difficulty accepting a diagnosis and in deciding which how best to handle unwanted behaviors. The goal of family therapy is to educate family members about the disorder and to find ways to handle those symptoms that have a negative impact on family members.

Pharmacologic therapy

No single or combination (more than one) drug therapy offers complete cessation of symptoms without adverse effects.

Pharmacologic treatment of TS (alone, without OCD or ADHD) usually begins with a trial of clonidine. If clonidine is unsuccessful, treatment moves to one of the dopamine receptor antagonists. Haloperidol, a dopamine receptor antagonist, has been the main drug used in TS treatment since the 1960s. It has been reported that over 80% of patients show improvement of tics with this therapy. A similar drug known as pimozide has also been used as an anti-tic drug since the 1980s. Due to adverse effects associated with haloperidol and pimozide, other dopamine receptor antagonists, including risperidone, sulpiride (not available in North America as of 2003), and olanzipine have gradually displaced haloperidol and pimozide as the main drug therapies for tics. Newer drugs, ziprasidone and quetiapine, may also be effective; as of 2003, evidence regarding their efficacy was preliminary. For those individuals who are unable to tolerate the above medications, treatment with a related medication, tetrabenazine, may be recommended. Drug therapy with a dopamine agonist may be attempted if none of the above drugs are effective. There are preliminary reports of positive therapeutic effects with other treatments including nicotine, tetrahydrocannbinol (marijuana), baclofen, and **botulinum toxin** injection yet confirmation of safety and efficacy of these treatments awaits further study.

Clomipramine or one of the selective serotonin uptake inhibitors (SSRIs) are the first choice for treatment of OCD. Examples of SSRI's in use for OCD treatment include fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram. For those TS patients with OCD who do not respond to SSRIs alone, addition of a dopamine receptor antagonist such as haloperidol, pimozide, risperidine, or olanzipine may be indicated. New therapies under investigation for the treatment of OCD as of 2003 included neurosurgery, **deep brain stimulation** (DBS), transcranial magnetic stimulation (TMS), and injection with botulinum toxin.

Methylphenidate and dextroamphetamine, medications known as psychostimulants, have been shown to be safe and effective in the treatment of ADHD in TS patients. There has been controversy over the use of psychostimulants to treat ADHD due to concerns about worsening of tics. Results from a randomized, placebo-controlled clinical trial reported in 2002 indicated that methylphenidate and another drug, clonidine, do not adversely affect tics. The researchers also found that a combination of the drugs is more effective than either drug alone.

Recovery and rehabilitation

Children with TS may require academic and occupational interventions. For some TS students, modifying the school environment can help to minimize stress. For the student with vocal tics, untimed exams in a private room and permission to leave the classroom when tics become problematic may help. Children with auditory processing difficulties and fine motor skill problems may benefit from occupational therapy. For example, the use of tape recorders, typewriters, or computers may be recommended to help with reading and writing. Occupational therapy can also help with poor handwriting, a common problem in children with TS. Some students with TS may be eligible for an Individual Education Plan (IEP). An IEP provides a framework from which administrators, teachers, and parents can meet the educational needs of a child with TS. Depending upon severity of TS symptoms and the degree of learning difficulties, some children with TS may be best served by special education classes or a private educational setting.

Clinical trials

As of December 2003, thirteen **clinical trials** were actively recruiting patients with Tourette syndrome. The National Institute of Neurological Disorders and Stroke (NINDS) in Bethesda, Maryland, were sponsoring the following trials. Information on these trials can be found at <http://www.clinicaltrials.gov> or by contacting the Patient Recruitment and Public Liaison Office at 1-800-411-1222 or at prpl@mail.cc.nih.gov.

- Magnetic Resonance Spectroscopy (MRS) to Evaluate Tourette's Syndrome. This study will use **magnetic resonance imaging** (**MRI**) and magnetic resonance spectroscopy (MRS) of the brain to try to gain a better understanding of the disease process in Tourette's syndrome. More information can be found at the National Institutes of Health (NIH) web link, <http://clinicalstudies.info.nih.gov/detail/A_2002-N-0128.html>.
- Study of Tics in Patients with Tourette's Syndrome and Chronic Motor Tic Disorder. This study will investigate which areas of the brain are primarily involved in and responsible for tics in patients with Tourette's syndrome and chronic motor tic disorder. More information can be found at the National Institutes of Health (NIH) web link, <http://clinicalstudies.info.nih.gov/detail/A_2002-N-0175.html>.
- Study of GABA-A receptors in the Generation of Tics in Patients with Tourette's Syndrome. This study will investigate how the brain generates tics in patients with Tourette's syndrome and which areas of the brain are primarily affected. More information can be found at the National Institutes of Health (NIH) web link, <http://clinicalstudies.info.nih.gov/detail/A_2002-N-0181.html>
- Brain Dynamics Involved in Generating Tics and Controlling Voluntary Movement. This study will use **electroencephalography** (EEG) and **electromyography** (EMG) to examine how the brain generates tics and controls voluntary movement in patients with Tourette's syndrome and chronic motor tic disorder. More information can be found at the National Institutes of Health (NIH) web link, <http://clinicalstudies.info.nih.gov/detail/A_2003-N-0126.html>.
- Brain Activation in Vocal and Motor Tics. This study will investigate the brain areas that are activated by vocal and motor tics in patients with Tourette's syndrome and other tic disorders. More information can be found at the National Institutes of Health (NIH) web link, <http://clinicalstudies.info.nih.gov/detail/A_2002-N-0027.html>.

The following trials were being sponsored by the National Center for Research Resources (NCRR) and coordinated by the Yale University School of Medicine in New Haven, Connecticut. Information on these trials can be found at <http://www.clinicaltrials.gov> or by contacting the study chair, James F. Leckman at 203-785-7971.

- Study of the Neurobiology of Tourette Syndrome and Related Disorders. This study will investigate the pathobiology of Tourette syndrome and related disorders by measuring various compounds of interest in cerebrospinal fluid, plasma, and urine of patients with Tourette syndrome, obsessive compulsive disorder, and/or chronic tics; determine the pattern of familial aggregation of Tourette syndrome and obsessive compulsive disorder by systematic assessment of all first-degree family members of patients selected for cerebrospinal fluid studies; and establish the neurochemical and neuropeptide profile associated with the range of expression of the putative Tourette gene expression in adult and adolescent patients.
- Developmental Phenomenology of Obsessive Compulsive Disorder and Tourette Syndrome in Children and Adolescents. This study will characterize the natural history, associated features, and severity of symptoms of obsessive compulsive disorder and Tourette syndrome in children and adolescents, and identify factors that influence the clinical course and prognosis of these patients.

The National Institute of Mental Health (NIMH) in Bethesda, Maryland, was sponsoring the following trials. Information on these trials can be found at <http://www.clinicaltrials.gov>.

- Brain Tissue Collection for Neuropathological Studies. This study will collect and study the brain tissue of deceased individuals to learn more about the nervous system and mental disorders. More information can be found at the National Institutes of Health (NIH) web

page for this study at <http://clinicalstudies.info.nih.gov/detail/A_1990-M-0142.html> or by contacting Joel E. Kleinman, MD at (301) 402-7909 or kleinmaj@intra.nimh.nih.gov.

- Evaluation and Follow-up of Individuals with Obsessive-Compulsive Disorder and Related Conditions. This study will aim to better understand the long-term progress of people with obsessive-compulsive disorder (OCD) and related conditions such as anorexia nervosa, Tourette syndrome, and trichotillomania. More information can be found at the National Institutes of Health (NIH) web page for this study at <http://clinicalstudies.info.nih.gov/detail/A_2000-M-0067.html> or by contacting the patient recruitment and public liaison office at (800) 411-1222 or prpl@mail.cc.nih.gov.
- Brain Imaging of Childhood Onset Psychiatric Disorders, Endocrine Disorders, and Healthy Children. This study will use MRIs to assess **brain anatomy** and function in normal volunteers and patients with a variety of childhood onset psychiatric disorders. More information can be found at the National Institutes of Health (NIH) web page for this study at <http://clinicalstudies.info.nih.gov/detail/A_1989-M-0006.html> or by contacting the patient recruitment and public liaison office at (800) 411-1222 or prpl@mail.cc.nih.gov.
- Treatment of Obsessive-Compulsive Disorder. This study aims to find the best treatment for TS-spectrum obsessive-compulsive disorder (OCD), which includes symptoms of TS, e.g., repeated and involuntary body movements (tics). More information can be found by contacting the University of Florida at clintrls@psych.med.ufl.edu; the study chair, Wayne Goodman, MD at (877) 788-3994 or wkgood@psychiatry.ufl.edu; or Candy Hill at (352) 392-3681 or chill@psychiatry.ufl.edu.
- Genetics of Obsessive-Compulsive Disorder. This study to identify genes that affect susceptibility to obsessive-compulsive disorder (OCD). More information can be found at the National Institutes of Health (NIH) web page for this study at <http://clinicalstudies.info.nih.gov/detail/A_1996-M-0124.html> or by contacting Diane M. Kazuba at (301) 496-8977 or kazubad@intra.nimh.nih.gov.
- Central Mechanisms in Speech Motor Control Studied with H215O PET. This study will use radioactive water (H215O) and **Positron Emission Tomography** (PET scan) to measure blood flow to different areas of the brain in order to better understand the mechanisms involved in speech motor control, and is sponsored by the National Institute on Deafness and Other Communication Disorders (NIDCD) in Bethesda, Maryland. More information can be found at the National Institutes of Health (NIH) web page for this study at <http://clinicalstudies.info.nih.gov/detail/A_1992-DC-0178.html> or by contacting the patient recruitment and public liaison office at 1-800-411-1222 or prpl@mail.cc.nih.gov.

Prognosis

The majority of cases of TS are mild and as such they do not require medical attention. Most affected individuals show improvement of symptoms in late adolescence or early adulthood and up to one-third of people will experience remission of tic in adult years. In fewer than 10% of patients, tics become more severe in adulthood. TS is not a degenerative disease and patients can anticipate a normal life span.

Special concerns

All students with TS need an educational environment that is supportive and flexible. Children with TS frequently have problems in school because they are teased by peers and misunderstood by teachers. It is important to educate the students, the teachers, and other school personnel who come in contact with the child with TS about the disorder.

Resources

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Tourette's Disorder Home Page. <http://www.tourettes-disorder.com//home.html>.

ORGANIZATIONS

National Tourette Syndrome Association, Inc. 42-40 Bell Boulevard, Bayside, New York 11361-2820. (718) 224-2999 or (888) 4-TOURET (486-8738); Fax: (718) 279-9596. ts@tsa-usa.org. <http://www.tsa-usa.org>.

Tourette Syndrome Foundation of Canada. #206, 194 Jarvis Street, Toronto, Ontario M5B 2B7, Canada. (416) 861-8398 or (800) 361-3120; Fax: (416) 861-2472. tsfc@tourette.ca. <http://www.tourette.ca/index.shtml>.

Dawn J. Cardeiro, MS, CGC

Transient global amnesia

Definition

Transient global amnesia (TGA) is a temporary short-term memory loss that may result from the deactivation of the brain's temporal lobes and/or thalamus (the part of the brain that serves as a center for the relay of sensory information). Usually occurring in otherwise healthy persons, TGA triggers memory loss from external stresses such as strenuous exertion, high levels of anxiety, sexual intercourse, immersion in water, and other similar conditions. The event may also be triggered by a condition called the Valsalva maneuver. During this maneuver, a person performs the "breathe-in-bear-down" movement that is automatically performed during strenuous **exercise**. It is thought that this maneuver temporarily siphons blood from the temporal lobes of the brain. The temporal lobes are where the memories are stored. This loss of blood may induce the loss of memory by persons experiencing TGA. While this hypothesis is still under review, it has been accepted as a logical explanation for a condition that currently has no generally accepted causal explanation.

Description

Transient global amnesia was first identified and described around 1960. Since that time, there have been extensive writings and studies about the condition, but its etiology (causation) is still not clearly known or understood.

TGA affects memory function. People experiencing TGA can register information and there is no loss of social skills and sense of identity, but their ability to retain information is severely impaired. One of the puzzling associations with TGA is that many people who experience this disorder are also migraine **headache** sufferers. However, there is no report of a migraine prior to onset, nor is there any reported nausea, sensitivity to light or sound, or headache.

Demographics

There are no race or inherited conditions associated with TGA. Men experience the condition more often than women. In addition, the occurrence of this type of amnesia rarely happens before middle age, with about 12 out of 100,000 people ever experiencing the condition before age 50. The most likely ages in which to experience TGA are the 50s and 60s. About 3% of people who experience one episode of TGA will experience another episode sometime during their lifetime, but it is very rare for a person to experience more than three episodes of TGA.

The reason people in their 50s and 60s are more likely to experience TGA is not understood. No definitive links to any particular pathology or reaction to medication have been discovered. It is an elusive medical experience. For example, the connection of TGA with exposure to cold water cannot be explained in any convincing way. However, the condition has, as one of its major triggers, the exposure to cold water as in swimming, or prolonged exposure to cold rain or snow.

Causes and symptoms

The causes of this disorder are not yet fully understood. The hypotheses that the event is triggered by a temporary loss of blood to certain regions of the brain are most popular. In some cases, there is evidence of small strokes and local evidence of minor depressions on the surface of the brain. A well-accepted hypothesis suggests that blood is reduced to the temporal region of the brain during Valsalva, or weight-bearing movement.

People who have experienced TGA are also screened for current use of medications. Some drug interactions have been known to cause other types of amnesia, although not the type associated with TGA.

Another suggestion as a cause for TGA is that venous congestion (congested blood flow in the veins) inhibits blood flow to the thalamic or temporal regions of the brain. The support for this hypothesis is that increases in sympathetic nervous system activity and/or pressure within the thorax may exert pressure on the jugular veins. This, in turn, may disrupt arterial blood flow within the brain, resulting in ischemia (lack of oxygen) to memory

Key Terms

Amnesia A general medical term for loss of memory that is not due to ordinary forgetfulness. Amnesia can be caused by head injuries, brain disease, or epilepsy, as well as by dissociation. Includes: 1) Anterograde amnesia: inability to retain the memory of events occurring after the time of the injury or disease which brought about the amnesic state. 2) Retrograde amnesia: inability to recall the memory of events which occurred prior to the time of the injury or disease which brought about the amnesic state.

Anterograde amnesia Amnesia for events that occurred after a physical injury or emotional trauma but before the present moment.

Retrograde amnesia Amnesia for events that occurred before a traumatic injury.

Valsalva maneuver A strain against a closed airway combined with muscle tightening, such as happens when a person holds his or her breath and tries to move a heavy object. Most people perform this maneuver several times a day without adverse consequences, but it can be dangerous for anyone with cardiovascular disease. Pilots perform this maneuver to prevent black-outs during high-performance flying.

centers or other areas of the brain. While the common precipitating factors have been discussed, why these events might trigger a TGA episode are not well understood.

Diagnosis

TGA is sometimes a difficult condition to diagnose. It is extremely helpful for an observer to contribute information to the physician. Some of the criteria for identifying the event are the impairment of memory, both newly learned and past. There is no loss of consciousness or personal identity. There must be no recent experience of head trauma. Patients must not be epileptics nor can they have experienced any form of a seizure in the last two years.

The episode usually lasts for only a few hours and is usually completely resolved by the end of 24 hours. However, rare cases have been documented in which the patient experiences the amnesia for up to a month.

Anterograde amnesia, which sometimes also follows head trauma, is a component of TGA. With the anterograde types of amnesia, the person experiences a memory loss of recent experiences, however, long-term memory persists. Persons with anterograde amnesia often ask questions and, after receiving a response, immediately ask the same question again. Physicians examining a person with amnesia will rule out retrograde amnesia, which is not a part of TGA. Retrograde amnesia is somewhat the opposite of anterograde amnesia, whereby the affected person can remember events that occur after the head trauma, but not before.

With TGA, a person experiences temporary confusion and lack of memory. The person is disoriented and confused, but no loss of personal identity occurs and long-term memories are intact. The person may be frightened and sometimes mildly delusional, but this passes soon and the incidence of recurrence is rare.

The initial kinds of tests a physician will request are those that rule out infection, **stroke**, brain injury, and other physiological conditions.

Blood tests such as a CBC with differential help to rule out infection. Another test often performed is running an electrolyte panel. Eletrolytes are common salt minerals such as potassium, calcium, magnesium, etc. Most professional and amateur athletes are aware of how important proper electrolyte balances are for proper body functioning. A lowering of electrolytes may cause some of the symptoms described by a person experiencing TGA. Other types of blood tests, including the search for clotting potentials, are often performed. To determine whether the patient may be prone to blood clotting, a physician may request a pothrombin time (PT) and activated partial thromboplastin time (aPTT). Quick clotting times could indicate a propensity towards thrombosis (blood clotting), which could lead to stroke.

Part of the diagnosis involves conducting several types of imaging tests. The uses of **positron emission tomography (PET)** and diffusion-weighted **magnetic resonance imaging** (MRI-DWI) have shown a small degree of ischemia (lack of blood flow) to certain areas of the brain with TGA. However, these same tests have shown conflicting results in other patients. No definitive tests have been suggested to diagnose the condition.

Treatment team

Initially, most persons with TGA receive care from a physician in a hospital emergency department. A **neurologist** usually provides diagnosis and treatment. Both physicians usually order tests to differentiate TGA from other acute neurological events such as a stroke. As there is really no specific treatment for TGA, diagnosis and reassurance by a physician are important for a person experiencing TGA, as well as for family members.

Treatment

After ruling out trauma to the brain from accident, disease, or stroke, most people who have experienced TGA receive very little treatment because the condition is benign. A follow-up appointment with the neurologist is usually recommended.

Recovery and rehabilitation

Expected average times for recovery are within hours. A TGA patient rarely experiences the symptoms any longer than 24 hours. For most people, the condition lasts only 4–8 hours. Many people even report a shorter duration of one or two hours of disorientation and confusion. They may become frightened, but this is often alleviated with diagnosis and an explanation of the condition.

Prognosis

The prognosis for TGA patients is excellent. There are no debilitating side effects or any permanent loss of memory. TGA does not portend a serious stroke or similar condition involving the circulatory system. This is one of the reasons that TGA is such a perplexing syndrome for researchers; it is impossible to predict who will experience it. Because repeat occurrences are rare, numerous re-evaluations by a physician are usually not necessary.

Special concerns

It is important for people to be aware of the possibility of TGA. Seeking medical help, personal protection, and reassurance are the beneficial to offer someone displaying TGA symptoms.

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ORGANIZATIONS

National Institute for Neurological Disorders and Stroke. P.O. Box 5801, Bethesda, MD 20824. (301) 496-5761 or (800) 352-9424. <http://www.ninds.nih.gov>.

Brook Ellen Hall

Transient ischemic attack

Definition

A transient ischemic attack (TIA), or "mini-stroke," is a neurologic episode resembling a **stroke** but resolving completely within a short period of time. By definition, symptoms of TIA resolve within 24 hours, and symptoms lasting longer than that are termed a stroke. A TIA is caused by brief interruption of the blood supply to a specific brain region, and it may warn of impending stroke.

Description

Symptoms of TIA begin suddenly and are similar to those of stroke, but leave no residual damage. By definition, symptoms of TIA resolve within 24 hours, but typically they last less than five minutes, or about one minute on average.

The symptoms of TIA vary depending on what part of the brain is affected. Anterior circulation TIAs interrupt the blood supply to most of the front part of the brain known as the cerebrum, including the frontal, parietal, and temporal lobes.

Symptoms suggesting anterior circulation TIAs may include difficulty speaking or understanding speech. Blindness in one eye suggests amaurosis fugax, a type of TIA caused by decreased blood flow through the carotid artery. This large artery in the neck supplies blood to the optic nerve responsible for vision in the eye on the same side as the artery.

Posterior circulation TIAs involve the blood supply to the back part of the brain, including the occipital lobe, **cerebellum**, and brainstem. Symptoms suggesting posterior circulation TIAs include loss of consciousness, **dizziness**, ringing in the ears, and loss of coordination. Because nerve pathways involved in motor function and sensation pass through multiple brain regions, symptoms of weakness and numbness may occur with either anterior or posterior circulation TIAs.

Demographics

Every year in the United States, approximately 50,000 individuals experience a TIA, and about one-third of these patients will go on to have a stroke at some point in the future.

TIAs rarely affect persons younger than 60 years of age. For individuals 50 to 59 years of age, the incidence of TIA is estimated to be four to eight episodes per 1,000 persons per year.

In addition to advancing age, other factors increasing risk of TIA are a history of TIA or stroke in a family member, and black race, thought to be in part because of the

higher rates of high blood pressure and diabetes in this group. Although the risk of TIA in older men and women is approximately equal, younger men have a slightly higher risk of stroke than do women of the same age.

In a study from the Mayo Clinic reported in *Stroke* in 1998, the incidence of TIA in Rochester, Minnesota, from 1985 to 1989 was 16 cases per year per 100,000 people aged 45 to 54 years. After adjusting for age and sex, the incidence rate for any TIA was 68 per 100,000 people. These rates had not changed significantly from those determined during the years 1960 to 1972, suggesting no improvement in risk factors predisposing to TIA during the intervening time period.

In that study, about three-fifths of TIAs affected the anterior circulation, about one-fifth were amaurosis fugax, and the remaining one-fifth affected the posterior circulation. The incidence rate of TIA was 41% of the rate of stroke incidence, and it was higher than had been previously reported for other sites throughout the world.

Causes and symptoms

The symptoms of a TIA occur when there is temporary blockage of an artery supplying part of the brain, causing ischemia, or not enough blood supply to provide the brain with the oxygen and nutrients it needs to function properly. The ischemia does not last long enough to cause permanent damage as would occur with a stroke. When the arterial blockage is reversed, the symptoms of the TIA go away.

The underlying causes of the arterial blockage are the same for both TIAs and strokes. The most common cause is a buildup of atherosclerotic plaques, or fatty deposits containing cholesterol, in the wall of the artery.

Damage to the arterial lining may cause platelets to stick together around the injured area as a normal part of the clotting and healing process. When cholesterol and other fats are deposited in this area, a plaque forms within the lining of the artery and narrows the channel through which blood passes. This causes blood flow to slow down and become irregular, which increases the natural tendency of blood to clot.

If a thrombus, or clot, forms at the site of the plaque, it may block the blood vessel at that location. Pieces of the plaque or thrombus may break off and travel downstream to progressively narrower arteries, forming an embolus that can temporarily block these arteries and cause a TIA until it dissolves or is dislodged. In a similar fashion, an embolus moving to the brain from the heart or elsewhere in the body can also cause a TIA.

Diseases that increase the tendency of blood to clot may cause TIAs. These include cancer, disorders of blood clotting, sickle cell anemia, and hyperviscosity syndromes in which the blood is very thick.

Injury to or inflammation of blood vessels may cause them to narrow or to go into spasm. Inflammation affecting the blood vessels is called arteritis, with specific examples including fibromuscular dysplasia, polyarteritis, granulomatous angiitis, systemic **lupus** erythematosus, and syphilis.

In patients with atherosclerotic plaques, conditions which can increase the risk of TIA include low blood pressure, high blood pressure, heart disease, migraine headaches, smoking, diabetes, and increasing age.

The symptoms of TIA come on suddenly and can be the same as those of a stroke, except that they disappear rapidly, always within 24 hours and usually within five minutes, without leaving any permanent brain injury.

Because it is impossible to tell until the symptoms are over whether they were related to a TIA or a stroke, it is crucial to take these symptoms as a serious warning and to seek immediate medical attention. If the blood flow to part of the brain is interrupted for a sufficient length of time, nerve cells supplied by the affected blood vessel may die. Any delay in starting stroke treatment can result in additional irreversible brain damage or even death.

Symptoms of either TIA or stroke vary depending on what brain region is affected. Numbness, weakness, or a heavy sensation on one side of the face, arm, and/or leg usually represents an anterior circulation stroke or TIA, whereas these symptoms on both sides suggest posterior circulation stroke or TIA.

Confusion, garbled speech, or other difficulty in talking or in understanding speech may occur with decreased anterior circulation affecting the left half of the brain (in right-handed individuals). Difficulty with vision in one eye, often described as a curtain descending over the eye, is a classic symptom of amaurosis fugax. On the other hand, decreased vision involving both eyes usually indicates a posterior circulation disturbance.

Other symptoms of posterior circulation stroke or TIA may include loss of consciousness, dizziness, loss of balance and coordination, and vertigo (a sensation that the person or the room is moving). A sudden, severe **headache** with no known cause may occur with any stroke or TIA.

Diagnosis

The characteristic history or description of a TIA, with its sudden onset, rapid resolution, and typical symptoms, aid the doctor in diagnosis. Risk factors for atherosclerosis, such as smoking, heart disease, high blood pressure, and family history of heart disease or stroke also

suggest the diagnosis of TIA. The specific symptoms associated with the TIA will help the physician determine which portion of the brain and which blood vessels were involved.

By the time the person who had a TIA reaches medical attention, the neurological examination is usually normal, although there may be subtle signs related to previous strokes.

The general physical examination may indicate evidence of atherosclerotic plaques, such as a bruit or abnormal sound heard with the stethoscope placed over the carotid artery in the neck. Although an audible bruit may be present in the early stages of arterial narrowing when blood flow is turbulent, the sound may disappear when blood flow decreases further. Looking at the back of the eye through an instrument called an ophthalmoscope, the doctor may see cholesterol emboli in the tiny arteries of the retina.

Carotid **ultrasonography** helps determine if there is narrowing, also known as stenosis, or plaque formation in the carotid arteries. In this painless and harmless test, a transducer sends high-frequency sound waves into the neck, and deflections of these waves are analyzed as images on a screen.

Computed tomography (**CT**) scanning creates cross-sectional x-ray images of the brain. The CT may show strokes, but often fails to give sufficiently detailed views of the blood vessels. To improve blood vessel visualization, computerized tomography **angiography** (CTA) scanning uses injection of a contrast dye into a blood vessel.

Magnetic resonance imaging (MRI) uses a strong magnetic field to align water molecules in the brain, giving highly detailed cross-sectional images that are very good at detecting small strokes. Magnetic resonance angiography (MRA) uses similar technology to study the arteries in the neck and brain.

The clearest way to see the structure, course, and diameter of brain arteries is with arteriography. Unfortunately, this test is associated with a low rate of serious complications including bleeding, stroke, and even death. Therefore, it should be performed only if the results would change patient management, for example in guiding the decision of whether surgery is needed.

In this test, a radiologist inserts a thin catheter, or flexible tube, through a small groin incision into the large femoral artery supplying the leg. Using x-ray guidance, the radiologist threads the catheter through the major arteries and into the carotid or vertebral artery. An injection of contrast dye through the catheter then allows x-ray images of the arteries in the anterior or posterior circulation.

If the heart is thought to be the source of emboli causing the TIA, testing may include an electrocardiogram and Holter monitoring to detect any changes in heart rhythm, or arrhythmias, occurring during the course of a normal day's activities. After the technician attaches electrodes to the patient's chest, the patient can go home overnight with a portable tape recorder. The recordings are later analyzed for arrthymias, during which emboli might tend to leave the heart and cause TIAs.

Transesophageal echocardiography (TEE) allows clear, detailed ultrasound images of blood clots within the heart which could act as a source of emboli, but which might be missed by traditional echocardiography. During this test, the doctor passes a flexible probe containing a transducer into the esophagus, which is located directly behind the heart.

Other tests may determine if there are any underlying conditions causing TIA, including blood tests for arteritis, sickle cell anemia, diabetes, and hyperviscosity syndromes. Certain procedures may help to rule out other disorders that may cause symptoms resembling those of TIA.

For example, an electroencephalogram (EEG) may determine if there is abnormal electrical activity of the brain diagnostic of a **seizure** disorder, because the symptoms associated with some seizures may resemble those of a TIA. Other conditions that may be confused with TIA include **fainting** or migraine headache.

A study reported in the October 2003 issue of *Clinical Chemistry* describes a blood test which may help to diagnose TIA and to rule out bleeding into the brain, or intracerebral hemorrhage, which can sometimes be confused with TIA. The test analyzes antibodies to specialized receptors involved in communication between nerve cells. These N-methyl-D-aspartate receptor antibodies are thought to be key markers of nerve cell damage caused by lack of blood flow to the brain.

Treatment team

Because time is so critical in preventing damage from acute stroke, and because it is impossible to tell right away whether symptoms of brain ischemia are caused by TIA or acute stroke, the treatment team begins with those who are first aware of the symptoms.

The patient and their family must take these symptoms as a serious warning of impending neurologic disaster and seek immediate medical attention by calling 911, rather than by hoping the symptoms will go away. Public awareness of stroke symptoms and their significance is therefore just as important as knowing that crushing chest **pain** needs to be evaluated right away in the emergency room to rule out or to treat heart attack.

The emergency medical technician, internist, **neurologist**, cardiologist, and diagnostic technicians all play an important role in TIA management. At stroke centers

Key Terms

Amaurosis fugax A type of TIA caused by decreased blood flow through the carotid artery, characterized by blindness or decreased vision in one eye.

Anterior circulation The blood supply to most of the front part of the brain known as the cerebrum, including the frontal, parietal, and temporal lobes.

Antiplatelet agents Drugs that reduce the tendency of platelets to clump together, used to reduce the risk of TIA or stroke.

Atherosclerotic plaques Fatty deposits containing cholesterol that build up in the wall of arteries, causing narrowing and increased risk of TIA.

Atrial fibrillation A condition in which part of the heart is enlarged and beats irregularly, which may cause emboli to travel to the brain.

Bruit An abnormal sound heard with the stethoscope placed over the carotid artery in the neck, suggesting decreased blood flow through the vessel.

Carotid angioplasty (stenting) Surgery for carotid artery stenosis using a balloon-like device to open the clogged artery, followed by placing a stent, or small wire tube, within the artery to keep it open.

Carotid artery A large artery in the neck supplying blood to the brain.

Carotid endarterectomy Surgery for carotid artery stenosis in which the atherosclerotic plaques are removed through a neck incision.

Carotid ultrasonography A painless and harmless test using high-frequency sound waves to determine if there is narrowing or plaque formation in the carotid arteries.

Embolus A fragment of plaque or thrombus that breaks off from its original location and travels downstream to progressively narrower arteries, where it may block the vessel.

Ischemia Reduced blood supply to the brain, preventing it from getting the oxygen and nutrients it needs to function properly.

Posterior circulation The blood supply to the back part of the brain, including the occipital lobe, cerebellum, and brainstem.

Stenosis Narrowing of an artery which reduces blood flow through the vessel.

Thrombus A blood clot, which may form at the site of an atherosclerotic plaque and block the artery.

Transesophageal echocardiography (TEE) A test using sound waves to reveal blood clots or other abnormalities within the heart that might be missed by traditional echocardiography.

and larger hospitals, members of a specialized stroke team designated for rapid response may be the first health care professionals to see the patient with TIA.

Other providers who may become involved in helping the patient reduce their risk factors for TIA and stroke may include nutritionists, dieticians, and nurses specializing in lifestyle counseling for issues such as quitting smoking.

Neurosurgeons or vascular surgeons will become involved in management of the patient with carotid artery stenosis if surgery is needed to restore blood flow or to bypass the obstruction.

Treatment

Ideally, patients with symptoms suggesting TIA or acute stroke should be evaluated within 60 minutes. Even if the symptoms resolve by the time the patient reaches the emergency room, prompt evaluation is needed to identify the specific cause of the TIA and to begin appropriate treatment.

Patients who have had a TIA within 48 hours are usually admitted to the hospital for observation, diagnostic testing, and treatment planning in a controlled situation, in case the TIA recurs or a stroke develops. If there are any medical conditions causing the TIA, such as sickle cell anemia or arteritis, these should be treated.

Drugs that reduce the tendency of platelets to clump together, known as antiplatelet agents, may reduce the risk of future TIA or stroke. Within this drug class, aspirin is the most often prescribed, least expensive, and safest treatment in terms of possible side effects. Although the optimal dose of aspirin to prevent stroke and TIA has long been debated, there may not be a clear dose-response relationship.

Other antiplatelet agents include dipyridamole; Aggrenox, which is a combination of low-dose aspirin and dipyridamole; clopidogrel (Plavix), which may be given alone or together with aspirin; and ticlopidine (Ticlid).

If the medical evaluation reveals a condition called atrial fibrillation, in which part of the heart is enlarged and

beats irregularly, causing emboli to travel to the brain, blood thinners or anticoagulants may be prescribed. These drugs inhibit proteins involved in blood clotting but do not affect platelet function.

Warfarin (Coumadin) is the best known drug of this class for long-term use, whereas heparin is typically given only for a limited period, usually while the patient is still in the hospital. Because anticoagulants reduce blood clotting and hence TIAs, they can also cause serious bleeding. Drug levels must therefore be monitored with blood tests usually done at least once weekly.

Atrial fibrillation or other conditions in which the heart beats erratically, known as arrythmias, may be treated with antiarrhythmic agents that stabilize electrical impulses in the heart to allow a more regular heart beat.

A vital part of TIA treatment is to reduce treatable risk factors for stroke, including cardiovascular disease, smoking, diabetes, hyperlipidemia, and obesity. Heart disease caused by previous heart attack, abnormalities of the heart valve, and arrythmias may prevent the heart from pumping blood efficiently.

Cigarette smoking increases blood clotting and accelerates development of atherosclerotic plaques. Nicotine makes the heart work harder by increasing heart rate and blood pressure, and carbon monoxide in cigarette smoke decreases the amount of oxygen reaching the brain.

In a similar fashion to smoking, diabetes makes atherosclerosis worse and speeds its progression, as do high blood levels of low-density lipoprotein (LDL) cholesterol and low levels of high-density lipoprotein (HDL) cholesterol.

Increased homocysteine level is another risk factor for atherosclerosis that may be treatable. This amino acid occurs naturally in the blood, but in high concentrations it can cause arterial walls to become thicker and scarred, increasing the chances of plaque formation.

Supplementing the diet with B complex vitamins including B6, B12, and folic acid reduces blood levels of homocysteine and may protect against heart disease, but it is not yet known whether this will reduce stroke risk.

High blood pressure, heart disease, diabetes, and undesirable cholesterol levels may require treatment with specific drugs, or they may be controlled by lifestyle changes alone.

Whether or not medications are needed, lifestyle changes should include stopping smoking, weight control, avoiding heavy drinking, and eating a balanced diet low in saturated fats, salt, and sugar and high in vegetables, fruits, and fiber. Nutritional or lifestyle counseling, structured **exercise** programs, and/or support groups may help patients achieve these goals.

If carotid artery testing reveals moderate or severe narrowing or stenosis, surgery may be indicated to improve blood flow and prevent future stroke or TIA. Usually, there is a reduction in artery diameter of more than 70% before surgery is considered. The portion of the artery downstream from the site of blockage also needs to be relatively free of narrowing or obstruction for surgery to be successful.

Carotid endarterectomy involves opening the artery through a neck incision, removing atherosclerotic plaques, then closing the artery. In some cases, carotid angioplasty or stenting may be a viable alternative. Using a balloon-like device, the surgeon opens the clogged artery and then places a stent, or small wire tube, within the artery to keep it open.

According to a study by the Carotid Endarterectomy Trialists' Collaboration, published in the November 2003 issue of *Stroke,* blood pressure control needs to be more closely regulated in patients with **carotid stenosis** than in other patients. Overly aggressive reduction of blood pressure in these patients may actually decrease blood flow through the obstructed artery.

Clinical trials

The National Institutes of Neurological Disorder and Stroke (NINDS) is the primary sponsor of research on stroke and TIA in the United States, including patient studies and laboratory research into the biological mechanisms of strokes.

The NINDS is recruiting patients for a study evaluating whether a specific type of carotid artery surgery can reduce subsequent stroke risk in high-risk patients who have recently suffered from stroke or TIA. The surgical procedure, known as extracranial-intracranial bypass surgery, involves removing an artery from the scalp, making a small hole in the skull, and then connecting the scalp artery to a brain artery within the skull. By circumventing the carotid artery obstruction in the neck, the rationale is to provide more blood flow to the brain. Contact information is William J. Powers, MD, 314-362-3317 or wjp@npg.wustl.edu.

Another study for which the NINDS is recruiting patients is the "Aspirin or Warfarin to Prevent Stroke" study, designed to determine whether aspirin or warfarin is more effective in preventing stroke in patients with narrowing of one of the arteries in the brain. Contact information is Harriet Howlett Smith, RN, 1-404-778-3153 or hhowlet@emory.edu.

The pharmaceutical company AstraZeneca is currently recruiting patients for a study testing the safety and effectiveness of their drug NXY-059 when given within six hours of limb weakness suggesting TIA or acute

stroke. Contact information is the AstraZeneca Information Center, 800-236-9933.

Prognosis

A single TIA is by definition very brief, and recovery is complete, but that good outcome should not lull the patient into a false sense of security. After a first TIA, additional episodes may occur later on the same day or at some point in the future. Ironically, patients who recover substantially within 24 hours of acute brain ischemia may be at greater risk of subsequent neurological deterioration than those who take longer to recover, according to a report in the October 2003 issue of the *Annals of Neurology.*

TIAs are an ominous sign of increased risk for debilitating stroke. Although most strokes are not preceded by TIAs, approximately one-third of patients who have a TIA will have an acute, major stroke days, weeks, or even months later. About half of the time, the stroke occurs within one year of the TIA. Stroke risk is higher in a person who has had one or more TIAs than in someone of the same age and sex who has never suffered a TIA.

Even among patients given antiplatelet agents or anticoagulants after a TIA or stroke, 10% will have a stroke within 90 days. Stroke can have devastating consequences, as it is the third leading cause of death and the primary cause of disability in the United States.

Besides recurrent TIA and stroke, complications of TIA may include injury from falls, if the patient becomes weak or loses balance with the TIA, or bleeding from anticoagulant drugs used to treat the TIA.

Although a single episode of TIA is not fatal, the TIA reflects generalized atherosclerosis. The leading cause of death after a TIA is coronary artery disease causing a heart attack. For that reason, a patient with TIA should have a heart evaluation to determine cardiovascular risk and decide on management of potential coronary artery disease.

Special concerns

Preventing TIA is a worthwhile goal, especially since the same strategies will help prevent heart disease, stroke, high blood pressure, and diabetes. Healthy lifestyle, regular medical checkups, stopping smoking, avoiding alcohol and illegal drugs, regular exercise, and nutritionally sound diet all have additional benefits beyond their effects on cardiovascular and stroke risk.

When the symptoms of TIA strike, it is no time to be brave or stoic. It is a medical emergency demanding that 911 or other local emergency number be called immediately. Even if the symptoms resolve, they are an urgent warning that must not be ignored, and require immediate attention to prevent stroke. Having a TIA may in some ways be a blessing in disguise if the warning is heeded, as most patients who suffer a stroke do so without this warning sign.

Because the symptoms of TIA cannot be distinguished from those of acute stroke, these symptoms must be aggressively treated as soon as possible. Research suggests that emergency care of stroke within the first three to six hours of the first symptom may greatly reduce the disabling, long-term effects of stroke. Sadly, the average time elapsed between experiencing the first symptoms of stroke and seeking medical attention is 13 hours, and 42% of patients wait as long as 24 hours. Recognizing the symptoms of stroke and obtaining immediate emergency care can prevent disability and even death.

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Laurie Barclay

Transmissible spongiform encephalopathies

see **Prion diseases**

Transverse myelitis

Definition

Transverse myelitis is an inflammation of the full width of the spinal cord that disrupts communication to the muscles, resulting in **pain**, weakness, and muscle paralysis.

Description

The symptoms of transverse myelitis are due to damage and/or destruction of the myelin sheath, the fatty white covering of nerve fibers that serves both to insulate the nerve fibers and to speed nervous conduction along them. Areas of missing myelin and areas of scarring along the affected nerves result in slowed or disrupted nervous conduction and muscle dysfunction.

Transverse myelitis may have a gradual onset or a remarkably quick onset. Symptoms of transverse myelitis may reach their peak within 24 hours of onset for some patients (considered the hyperacute form of the condition). Other patients experience a more gradual increase in symptom severity, with peak deficits occurring days (acute form of transverse myelitis) to weeks (subacute form of transverse myelitis) after the initial symptoms first presented. Patients with the quicker onset form and who experience more severe initial symptoms tend to have more complications and a greater likelihood of permanent disability.

Transverse myelitis often occurs in people who are recovering from a recent viral illness, including chickenpox, herpes simplex, cytomegalovirus, Epstein-Barr, influenza, and measles. When this association is present, the condition often follows the more sudden hyperacute course.

Demographics

In the United States, there are only about 4.6 cases of transverse myelitis per million people per year. In the Unites States, about 1,400 people a year develop transverse myelitis; about 33,000 people in the United States have disabilities due to transverse myelitis. Individuals of all ages can be affected; reports have been made of patients ranging from the age of six months to 88 years. The peak ages appear to be 10-19 years and 30-39 years.

About 30-60% of all cases of transverse myelitis occur in individuals who have just recovered (within the previous 8 weeks) from a relatively minor viral infection. Recent vaccination is another risk factor for transverse myelitis. Other individuals at higher risk for transverse myelitis include patients with preexisting autoimmune diseases (such as **multiple sclerosis**, systemic **lupus** erythematosus, or Devic's disease); patients with recent histories of infections such as **Lyme disease**, tuberculosis, or syphilis; and intravenous drug abusers who inject heroine and/or amphetamines.

Causes and symptoms

Although the specific mechanism of transverse myelitis has not been delineated, the basic cause is thought to be an autoimmune response. Under normal conditions, the immune system reacts to the presence of a viral or bacterial illness by producing a variety of immune cells designed to attack the invading viruses or bacteria. Unfortunately, in the case of transverse myelitis, the immune cells mistake the body's own tissues as foreign, and attack those tissues as well. These errant immune cells are called autoantibodies; that is, antibodies that actually attack the body's own tissues.

Symptoms of transverse myelitis can develop over several hours, days, or weeks. The types of symptoms and their severity are dependent on the area of the spinal cord affected. When the transverse myelitis occurs in the neck, the arms and legs will be affected; when the transverse myelitis occurs lower in the back, only the legs will be affected.

Symptoms of transverse myelitis often begin with **back pain**, **headache**, achy muscles, flu-like symptoms, and stiff neck. Over hours or days, symptoms expand to include loss of sensation, numbness, dysesthesia (sensations of burning, lightning flashes of pain, prickly pinpoints), muscle weakness, partial or complete paralysis, and impaired bladder and bowel function. Symptoms of weakness and then paralysis usually begin in the feet, ascending over time to the legs, and then to the trunk and arms when the lesion is in the neck. Symptoms are bilateral, meaning that they affect both sides of the body simultaneously. Over time, muscles become increasingly tight and spastic, further limiting mobility. When the muscles of respiration are affected, breathing can be compromised.

Diagnosis

Diagnosis involves meeting specific symptom criteria, as well as demonstrating spinal cord involvement with **MRI** scanning and examination of cerebrospinal fluid.

Key Terms

Myelin The fatty white substance that wraps around nerve fibers, providing insulation and speeding electrical conduction of nerve impulses along the fibers.

Symptom criteria include the evolution of symptoms peaking over four hours to 21 days, with symptoms clearly traceable to spinal cord dysfunction, and including muscle weakness or paralysis and sensory defects such as numbness occurring on both sides of the body. The presence of a spinal cord tumor or another condition that is exerting pressure on the spinal cord, vitamin B12 deficiency, or a history of **radiation** therapy to or cyclophosphamide injection into the spinal cord excludes the possibility of a diagnosis of transverse myelitis.

Treatment team

The mainstay of the treatment team for patients with transverse myelitis will be a **neurologist**. A rheumatologist, specializing in autoimmune illness, may also be consulted. In order to regain maximum function, a physiatrist (a physician specializing in rehabilitation medicine) may be required, as well as the services of both physical and occupational therapists.

Treatment

Treatment is aimed at calming the immune response that caused the **spinal cord injury** in the first place. To this end, high doses of intravenous and then oral steroids are the first-line treatments for transverse myelitis. In severe cases of transverse myelitis, the very potent immunosupressant cyclophosphamide may be administered. In patients with moderately severe transverse myelitis unimproved by five to seven days of steroid treatment, a procedure called plasma exchange may be utilized. This procedure involves removing blood from the patient, and separating it into the blood cells and the plasma (fluid). The blood cells are then mixed into a synthetic plasma replacement solution and returned to the patient. Because the immune cells are in the plasma, this effectively removes the damaging immune cells from the body, hopefully quelling the myelin destruction.

Treatments to reverse the process involved in transverse myelitis should be attempted for about six months from the onset of the condition. After that point, treatment efforts should be shifted to effective rehabilitation.

Pain and other **dysesthesias** (uncomfortable sensations, such as burning, pins-and-needles, or electric shock sensations) are treated with a variety of medications, such as **gabapentin**, **carbamazepine**, nortriptyline, or tramadol. Another treatment for pain and dysesthesias is transcutaneous electrical nerve stimulation, called TENS therapy. This involves the use of a device that stimulates the painful area with a small electrical pulse, which seems to disrupt the painful sensation.

Because constipation and urinary retention are frequent problems in the patient with transverse myelitis, medications may be necessary to treat these problems. Oxybutinin, hyoscyamine, tolterodine, and propantheline can treat some of the bladder problems common to transverse myelitis patients. When urinary retention is an issue, sacral nerve stimulation may help the patient avoid repeated bladder catheterizations. Dulcolax, senekot, and bisacodyl can help improve constipation.

Tight, spastic muscles may improve with baclofen, tizanidine, or **diazepam**. When these medications are given orally, they sometimes result in untenable side effects.

Recovery and rehabilitation

Rehabilitation has both short- and long-term components. Even in the earliest stages of the condition, passive exercises should be performed. Passive exercises involve a physical therapist putting a particular muscle group or joint through range of motion and strengthening **exercise**, even when the patient cannot assist in its movement. During the recovery phase, the patient should be given progressive exercises to improve strength and range of motion, and to attempt to regain mobility. Physical therapists can also be helpful with pain management, using such techniques as heat and/or cold application, nerve stimulation, ultrasound, and massage. Physical therapy may also be helpful to retrain muscles necessary for improved bladder and bowel control and relief of constipation and urinary retention. Occupational therapists can help the patient relearn old skills for accomplishing the activities of daily living, or strategize new techniques that take into account the patient's disabilities.

Braces or assistive devices such as walkers, wheelchairs, crutches, or canes may be necessary during rehabilitation or permanently.

Prognosis

The area on the spinal cord affected by transverse myelitis will determine the individual's level of functioning. The higher-up the lesion, the greater the disability. High cervical lesions will require complete care; as lesions drop lower and lower in the cervical, thoracic, or lumbar region, the chance to participate in self-care or even to ambulate increases.

Recovery from transverse myelitis seems to follow the law of thirds: about a third of all patients make a full recovery from their level of functioning at the condition's peak, a third make a partial recovery, and a third make no recovery at all. Most patients make a good or even a complete recovery within one to three months of the onset of their symptoms. Patients who have not begun to improve by month three after symptom onset usually will not accomplish a complete recovery from their disability. Factors that do not bode well include abrupt onset of symptoms, prominent pain upon onset, and severe disability and deficit at the peak of the condition.

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ORGANIZATIONS

Transverse Myelitis Association. 1787 Sutter Parkway, Powell, OH 43065. (614) 766-1806. ssiegel@myelitis.org. <http://www.myelitis.org/index.html>.

The Johns Hopkins Transverse Myelitis Center. 600 N. Wolfe Street, Baltimore, MD 21287. (410) 502-7099; Fax: (410) 502-6736. dkerr@jhmi.edu. <http://www.hopkinsmedicine.org/jhtmc/>.

Rosalyn Carson-DeWitt, MD

Traumatic brain injury

Definition

Traumatic brain injury (TBI) is the result of physical trauma to the head causing damage to the brain. This damage can be focal, or restricted to a single area of the brain, or diffuse, affecting more than one region of the brain. By definition, TBI requires that there be a head injury, or any physical assault to the head leading to injury of the scalp, skull, or brain. However, not all head trauma is associated with TBI.

Description

TBI is sometimes known as acquired brain injury. The least severe and most common type of TBI is termed a concussion, which is technically defined as a brief loss of consciousness after a head injury without any physical evidence of damage on an imaging study such as a **CT** or **MRI** scan. In common parlance, concussion may refer to any minor injury to the head or brain.

Symptoms, complaints, and neurological or behavioral changes following TBI depend on the location(s) of the brain injury and on the total volume of injured brain. Usually, TBI causes focal brain injury involving a single area of the brain where the head is struck or where an object such as a bullet enters the brain. Although damage is typically worst at the point of direct impact or entry, TBI may also cause diffuse brain injury involving several other brain regions.

Closed head injury refers to TBI in which the head is hit by or strikes an object without breaking the skull. In a penetrating head injury, an object such as a bullet fractures the skull and enters brain tissue.

Diffuse brain damage associated with closed head injury may result from back-and-forth movement of the brain against the inside of the bony skull. This is sometimes called coup-contrecoup injury. "Coup," or French for "blow," refers to the brain injury directly under the point of maximum impact to the skull. "Contrecoup," or French for "against the blow," refers to the brain injury opposite the point of maximum impact.

For example, coup-contrecoup injury may occur in a rear-end collision, with high speed stops, or with violent shaking of a baby, because the brain and skull are of different densities, and therefore travel at different speeds. The impact of the collision causes the soft, gelatinous brain tissue to jar against bony prominences on the inside of the skull.

Because of the location of these prominences and the position of the brain within the skull, the frontal lobes (behind the forehead) and temporal lobes (underlying the temples) are most susceptible to this type of diffuse damage. These lobes house major brain centers involved in speech and language, so problems with communication skills often follow closed head injuries of this type.

Depending on which areas of the brain are injured, other symptoms of closed head injury may include difficulty with concentration, memory, thinking, swallowing,

walking, balance, and coordination; weakness or paralysis; changes in sensation; and alteration of the sense of smell.

Consequences of TBI can be relatively subtle or completely devastating, related to the severity and mechanism of injury. Diffuse axonal injury, or shear injury, may follow contrecoup injury even if there is no damage to the skull or obvious bleeding into the brain tissue. In this type of injury, damage to the part of the nerve that communicates with other nerves degenerates and releases harmful substances that can damage neighboring nerves.

When the skull cracks or breaks, the resulting skull fracture can cause a contusion, or an area of bruising of brain tissue associated with swelling and blood leaking from broken blood vessels. A depressed skull fracture occurs when fragments of the broken skull sink down from the skull surface and press against the surface of the brain. In a penetrating skull fracture, bone fragments enter brain tissue. Either of these types of skull fracture can cause bruising of the brain tissue, called a contusion. Contrecoup injury can also lead to brain contusion.

If the physical trauma to the head ruptures a major blood vessel, the resulting bleeding into or around the brain is called a hematoma. Bleeding between the skull and the dura, the thick, outermost layer covering the brain, is termed an **epidural hematoma**. When blood collects in the space between the dura and the arachnoid membrane, a more fragile covering underlying the dura, it is known as a **subdural hematoma**. An intracerebral hematoma involves bleeding directly into the brain tissue.

All three types of hematomas can damage the brain by putting pressure on vital brain structures. Intracerebral hematomas can cause additional damage as toxic breakdown products of the blood harm brain cells, cause swelling, or interrupt the flow of cerebrospinal fluid around the brain.

Demographics

Estimates for the number of Americans living today who have had a TBI range from between 2.5 and 6.5 million, making it a major public health problem costing the United States more than $48 billion annually. A recent review suggests that the incidence of TBI in the United States is between 180 and 250 per 100,000 population per year, with even higher incidence in Europe and South Africa.

Although TBI can affect anyone at any age, certain age groups are more vulnerable because of lifestyle and other risk factors. Males ages 15 to 24, especially those in lower socioeconomic levels, are most likely to become involved in high-speed or other risky driving, as well as physical fights and criminal activity. These behaviors increase the likelihood of TBI associated with automobile and motorcycle accidents or with violent crimes.

Infants, children under five years of age, and adults 75 years and older are also at higher risk for TBI than the general population because they are most susceptible to falls around the home. Other factors predisposing the very young and the very old to TBI include physical abuse, such as violent shaking of an infant or toddler that can result in **shaken baby syndrome**.

Causes and symptoms

Accidents, especially motor vehicle accidents, are the major culprit implicated in TBI. Because accidents are the leading cause of death or disability in men under age 35, and because over 70% of accidents involve injuries of the head and/or spinal cord, this is not surprising. In fact, transportation accidents involving automobiles, motorcycles, bicycles, and pedestrians account for half of all TBIs and for the majority of TBIs in individuals under the age of 75. At least half of all TBIs are associated with alcohol use. Sports injuries cause about 3% of TBIs; other accidents leading to TBI may occur at home, at work, or outdoors.

In those age 75 and older, falls are responsible for most TBIs. Other situations leading to TBI at all ages include violence, implicated in about 20% of TBIs. Firearm assaults are involved in most violent causes of TBI in young adults, whereas child abuse is the most common violent cause in infants and toddlers. In the shaken baby syndrome, a baby is shaken with enough force to cause severe countrecoup injury.

The symptoms of TBI may occur immediately or they may develop slowly over several hours, especially if there is slow bleeding into the brain or gradual swelling. Depending on the cause, mechanism, and extent of injury, the severity of immediate symptoms of TBI can be mild, moderate, or severe, ranging from mild concussion to deep coma or even death.

With concussion, the injured person may experience a brief or transient loss of consciousness, much like **fainting** or passing out, or merely an alteration in consciousness described as "seeing stars" or feeling dazed or "out of it." On the other hand, coma refers to a profound or deep state of unconsciousness in which the individual does not respond to the environment in any meaningful way.

When a person with TBI regains consciousness, some symptoms are immediately apparent, while others are not noticed until several days or weeks later. Symptoms which may be obvious right away after mild TBI include **headache**, changes in vision such as blurred vision or tired eyes, nausea, **dizziness**, lightheadedness, ringing in the ears, bad taste in the mouth, or altered sense of smell which is usually experienced as loss of the sense of taste.

Approximately 40% of patients with TBI develop postconcussion syndrome within days to weeks, with

symptoms including headache, dizziness or a sensation of spinning (vertigo), memory problems, trouble concentrating, sleep disturbances, restlessness, irritability, **depression**, and anxiety. This syndrome may persist for a few weeks, especially in patients with depression, anxiety, or other psychiatric symptoms before the TBI.

With more severe injuries, there may also be immediate numbness or weakness of one or more limbs, blindness, deafness, inability to speak or understand speech, slurred speech, lethargy with difficulty staying awake, persistent vomiting, loss of coordination, disorientation, or agitation. In addition to some of these symptoms, young children with moderate to severe TBI may also experience prolonged crying and refusal to nurse or eat.

While the injured person is preoccupied with headache or **pain** related to other physical trauma, symptoms such as difficulty in thinking or concentrating may not be evident. Often these more subtle symptoms may appear only when the individual attempts to return to work or to other mentally challenging situations. Similarly, personality changes, depression, irritability, and other emotional and behavioral problems may initially be attributed to coping with the stress of the injury, and they may not be fully appreciated until the individual is recuperating at home.

Seizures may occur soon after a TBI or may first appear up to a year later, especially when the damage involves the temporal lobes. Other symptoms which may appear immediately or which may be noticed only while the individual is returning to usual activities are confusion, **fatigue** or lethargy, altered sleep patterns, and trouble with memory, concentration, attention, and finding the right words or understanding speech.

Diagnosis

Recognizing a serious head injury, starting basic first aid, and seeking emergency medical care can help the injured person avoid disability or even death. When encountering a potential TBI, it is helpful to find out what happened from the injured person, from clues at the scene, and from any eyewitnesses. Because **spinal cord injury** often accompanies serious head trauma, it is prudent to assume that there is also injury to the spinal cord and to avoid moving the person until the paramedics arrive. Spinal cord injury is a challenging diagnosis; nearly one-tenth of spinal cord injuries accompanying TBI are missed initially.

Signs apparent to the observer that suggest serious head injury and mandate emergency treatment include shallow or erratic breathing or pulse; drop in blood pressure; broken bones or other obvious trauma to the skull or face such as bruising, swelling or bleeding; one pupil larger than the other; or clear or bloody fluid drainage from the nose, mouth, or ears.

Symptoms reported by the injured person that should also raise red flags include severe headache, stiff neck, vomiting, paralysis or inability to move one or more limbs, blindness, deafness, or inability to taste or smell. Other ominous developments may include initial improvement followed by worsening symptoms; deepening lethargy or unresponsiveness; personality change, irritability, or unusual behavior; or incoordination.

When emergency personnel arrive, they will stabilize the patient, evaluate the above signs and symptoms, and assess the nature and extent of other injuries, such as broken bones, spinal cord injury, or damage to other organ systems. Medical advances in early detection and treatment of associated injuries have improved the overall outcome in TBI. The initial evaluation measures vital signs such as temperature, blood pressure, pulse, and breathing rate, while the neurological examination assesses reflexes, level of consciousness, ability to move the limbs, and pupil size, symmetry, and response to light.

These neurological features are standardized using the Glasgow Coma Scale, a test scored from 1 to 15 points. Each of three measures (eye opening, best verbal response, and best motor response) is scored separately, and the combined score helps determine the severity of TBI. A total score of 3 to 8 reflects a severe TBI, 9 to 12 a moderate TBI, and 13 to 15 a mild TBI.

Imaging tests reveal the location and extent of brain injury and associated injuries and therefore help determine diagnosis and probable outcome. Sophisticated imaging tests can help differentiate the variety of unconscious states associated with TBI and can help determine their anatomical basis.

Until neck fractures or spinal instability have been ruled out with skull and neck x rays, and with head and neck computed tomography (CT) scan for more severe injuries, the patient should remain immobilized in a neck and back restraint.

By constructing a series of cross-sectional slices, or x ray images through the head and brain, the CT scan can diagnose bone fractures, bleeding, hematomas, contusions, swelling of brain tissue, and blockage of the **ventricular system** circulating cerebrospinal fluid around the brain. In later stages after the initial injury, it may also show shrinkage of brain volume in areas where neurons have died.

Using magnetic fields to detect subtle changes in brain tissue related to differences in water content, the magnetic resonance imaging (MRI) scan shows more detail than x rays or CT. However, it takes more time than the CT and is not as readily available, making it less suited for routine emergency imaging.

For patients with seizures or for those with more subtle episodic symptoms thought possibly to be seizures, the

Key Terms

Cerebrospinal fluid (CSF) A protective fluid surrounding and protecting the brain and spinal cord.

Closed head injury TBI in which the head strikes or is struck by an object without breaking the skull.

Coma A decreased level of consciousness with deep unresponsiveness.

Computed tomography (CT) scan A neuroimaging test that generates a series of cross-sectional x rays of the head and brain.

Concussion Injury to the brain causing a sudden, temporary impairment of brain function.

Contrecoup An injury to the brain opposite the point of direct impact.

Contusion A focal area of swollen and bleeding brain tissue.

Dementia pugilistica "Punch-drunk" syndrome of brain damage caused by repeated head trauma.

Depressed skull fracture A fracture in which fragments of broken skull press into brain tissue.

Diffuse axonal injury (shear injury) Traumatic damage to individual nerve cells resulting in breakdown of overall communication between nerve cells in the brain.

Epidural hematoma Bleeding into the area between the skull and the dura, the tough, outermost brain covering.

Glasgow coma scale A measure of level of consciousness and neurological functioning after TBI.

Hematoma Bleeding into or around the brain caused by trauma to a blood vessel in the head.

Intracerebral hematoma Bleeding within the brain caused by trauma to a blood vessel.

Increased intracranial pressure Increased pressure in the brain following TBI.

Magnetic resonance imaging (MRI) A noninvasive neuroimaging test using magnetic fields to visualize water shifts in brain tissue.

Penetrating head injury TBI in which an object pierces the skull and enters brain tissue.

Post-concussion syndrome A complex of symptoms including headache following mild TBI.

Post-traumatic amnesia (PTA) Difficulty forming new memories after TBI.

Post-traumatic dementia Persistent mental deterioration following TBI.

Post-traumatic epilepsy Seizures occurring more than one week after TBI.

Shaken baby syndrome A severe form of TBI resulting from shaking an infant or small child forcibly enough to cause the brain to jar against the skull.

Subdural hematoma Bleeding between the dura and the underlying brain covering.

Ventriculostomy Surgery that drains cerebrospinal fluid from the brain to treat hydrocephalus or increased intracranial pressure.

electroencephalogram (EEG) may reveal abnormalities in the electrical activity of the brain or brain waves. Other diagnostic techniques that may be helpful include cerebral **angiography**, transcranial Doppler ultrasound, and single photon emission computed tomography (SPECT).

Treatment team

The first responder at the scene of TBI is usually a paramedic or emergency medical technician (EMT). In the emergency department, a trauma specialist may determine the extent of associated injuries. The **neurologist** is usually the primary treating physician assessing and managing the symptoms and consequences of TBI. Diagnostic technicians involved in TBI management include radiological and EEG technicians and audiologists who assess hearing.

If surgery is needed to remove blood clots or to insert a shunt to relieve increased pressure within the skull, a neurosurgeon is needed. After surgery, or for any patient with loss of consciousness, intensive care is managed by a specialized treatment team including neurologists, neurosurgeons, intensivists, respiratory therapists, and specialized nurses and technicians.

After the physical condition has stabilized, a speech therapist and/or **neuropsychologist** may evaluate swallowing, cognitive, and behavioral abilities and carry out appropriate rehabilitation. Other specialized therapists include the occupational therapist, who addresses sensory deficits, hand movements, and the ability to perform activities of daily living such as dressing; and the physical therapist who directs **exercise** and other programs to rehabilitate weakness annd loss of coordination. Vocational planners, psychologists, and psychiatrists may help the individual with TBI cope with returning to society and to gainful employment.

Treatment

Although no specific treatment may be needed for a mild head injury, it is crucial to watch the person closely for any developing symptoms over the next 24 hours. Acetaminophen or ibuprofen, available over the counter, may be used for mild headache. However, aspirin should not be given because it can increase the risk of bleeding.

If the person is sleeping, he should be awakened every two to three hours to determine alertness and orientation to name, time, and place. Immediate medical help is needed if the person becomes unusually drowsy or disoriented, develops a severe headache or stiff neck, vomits, loses consciousness, or behaves abnormally.

Treatment for moderate or severe TBI should begin as soon as possible by calling 911 and beginning emergency care until the EMT team arrives. This includes stabilizing the head and neck by placing the hands on both sides of the person's head to keep the head in line with the spine and prevent movement which could worsen spinal cord injury. Bleeding should be controlled by firmly pressing a clean cloth over the wound unless a skull fracture is suspected, in which case it should be covered with sterile gauze dressing without applying pressure. If the person is vomiting, the head, neck, and body should be rolled to the side as one unit to prevent choking without further injuring the spine.

Although the initial brain damage caused by trauma is often irreversible, the goal is to stabilize the patient and prevent further injury. To achieve these goals, the treatment team must insure adequate oxygen supply to the brain and the rest of the body, maintain blood flow to the brain, control blood pressure, stabilize the airway, assist in breathing or perform CPR if necessary, and treat associated injuries.

About half of severely head-injured patients require neurosurgery for hematomas or contusions. Swelling of the injured brain may cause increased pressure within the closed skull cavity, known as increased intracranial pressure (ICP). ICP can be measured with a intraventricular probe or catheter inserted through the skull into the fluid-filled chambers (ventricles) within the brain. Placement of the ICP catheter is usually guided by CT scan. If ICP is elevated, ventriculostomy may be needed. This procedure drains cerebrospinal fluid from the brain and reduces ICP. Drugs that may decrease ICP include mannitol and barbiturates.

A recent review suggests that using intraventricular catheters coated with antibiotics reduces the risk for infection. Keeping the patient's body temperature low (hypothermia) also improves outcome after moderate to severe TBI. Increasing the level of oxygen in the blood beyond normal concentrations is also being explored as a treatment option for improving brain metabolism in TBI. Large, multicenter trials of these and other treatments, such as early surgery to relieve increased ICP, are still needed, and the quest continues for a therapy that could prevent nerve cell death in TBI.

Although some patients need medication for psychiatric and physical problems resulting from the TBI, prescribing drugs may be problematic because TBI patients are more sensitive to side effects.

Both in the immediate and later stages of TBI, rehabilitation is vital to optimal recovery of ability to function at home and in society. The Consensus Development Conference on Rehabilitation of Persons with TBI, held by the National Institutes of Health in 1998, recommended individualized rehabilitation based on specific strengths and abilities.

Problems with orientation, thinking, and communication should be addressed early, often during the hospital stay. The focus is typically on improving alertness, attention, orientation, speech understanding, and swallowing problems.

As the patient improves, rehabilitation should be modified accordingly. The panel suggested that physical therapy, occupational therapy, speech/language therapy, physiatry (physical medicine), psychology/psychiatry, and social support should all play a role in TBI rehabilitation. Appropriate settings for rehabilitation may include the home, the hospital outpatient department, inpatient rehabilitation centers, comprehensive day programs, supportive living programs, independent living centers, and school-based programs. Families should become involved in rehabilitation, in modifying the home environment if needed, and in psychotherapy or counseling as indicated.

Clinical trials

The National Institute of Neurological Disorders and Stroke (NINDS) supports research on the biological mechanisms of brain injury, strategies to limit brain damage following head trauma, and treatments of TBI that may improve long-term recovery. Research areas include mechanisms of diffuse axonal injury; the role of calcium entry into damaged nerves causing cell death and brain swelling; the toxic effects of glutamate and other nerve chemicals causing excessive nerve excitability; natural processes of brain repair after TBI; the therapeutic use of cyclosporin A or hypothermia to decrease cell death and nerve swelling; and the use of stem cells to repair or replace damaged brain tissue.

NINDS-supported clinical research focuses on enhancing the ability of the brain to adapt to deficits after TBI; improving rehabilitation programs for TBI-related

disabilities; and developing treatments for use in the first hours after TBI. Early treatments being investigated include hypothermia for severe TBI in children, magnesium sulfate to protect nerve cells after TBI, and lowering ICP and increasing blood flow to the brain.

To address the specific problems in thinking and communication following TBI, the NINDS is designing new evaluation tools for children, developing computer programs to help rehabilitate children with TBI, and determining the effects of various medications on recovery of speech, language, and cognitive abilities.

The NINDS website (www.clinicaltrials.gov/ct/action/GetStudy) lists specific contact information for ongoing trials. These include hypothermia to treat severe brain injury, open to subjects age 16 to 45 years with nonpenetrating brain injury with a post-resuscitation Glasgow Coma Score less than 8 (contact Emmy R. Miller, PhD, RN, 713-500-6145).

The Prospective Memory in Children with Traumatic Brain Injury study is open to children age 12-18 years, with a post-resuscitation Glasgow Coma Scale score of either 13 to 15 or 3 to 8. Contact information is Stephen R. McCauley, PhD, 713-798-7479, mccauley@bcm.tmc.edu.

The Measuring Head Impacts in Sports study will test a new device to measure the speed of head impact in football players. The study is open to college football players, age 18–24 years. Contact information is Rick Greenwald, PhD, RGreenwald@simbex.com.

A trial sponsored by Avanir Pharmaceuticals will be testing the safety of the drug AVP-923 in the treatment of uncontrolled laughter and crying associated with TBI as well as with other conditions. Study subjects must be age 18–75 years without any history of major psychiatric disturbance. Contact information varies by state and is available on the website; for Arizona it is Louis DiCave, 602-406-6292, ldicave@chw.edu.

Prognosis

Although the symptoms of minor head injuries often resolve on their own, more than 500,000 head injuries each year are severe enough to require hospitalization; 200,000 are fatal; and 200,000 require institutionalization or other close supervision. Each year in the United States, head injury causes one million head-injured people to be treated in hospital emergency rooms, 270,000 to have moderate or severe TBI, 70,000 to die, and 60,000 to develop **epilepsy**.

Outcome varies with cause: 91% of TBIs caused by firearms, two-thirds of which may represent suicide attempts, are fatal, compared with only 11% of TBIs from falls. Low Glasgow Coma Scale scores predict a worse outcome from TBI than do high scores.

The Swedish Council on Technology Assessment in Health Care concluded that of 1,000 patients arriving at the hospital with mild head injury, one will die, nine will require surgery or other intervention, and about 80 will have abnormal findings on brain CT and will probably need to be hospitalized.

Immediate complications of TBI may include seizures, enlargement of the fluid-filled chambers within the brain (**hydrocephalus** or post-traumatic ventricular enlargement), leaks of cerebrospinal fluid, infection, injury to blood vessels or to the nerves supplying the head and neck, pain, bed sores, failure of multiple organ systems, and trauma to other areas of the body.

About one-quarter of patients with brain contusions or hematomas and about half of those with penetrating head injuries develop seizures within the first 24 hours of the injury. Those that do are at increased risk of seizures occurring within one week after TBI.

Hydrocephalus usually occurs within the first year of TBI, and it is associated with deteriorating neurological outcome, impaired consciousness, behavioral changes, poor coordination or balance, loss of bowel and bladder control, or signs of increased ICP.

Long-term survivors of TBI may suffer from persistent problems with behavior, thinking, and communication disabilities, as well as epilepsy; loss of sensation, hearing, vision, taste, or smell; ringing in the ears (tinnitus), coordination problems, and/or paralysis. Recovery from cognitive deficits is most dramatic within the first six months after TBI, and less apparent subsequently.

Memory loss is especially common in severely head-injured patients, with loss of some specific memories and partial inability to form or store new memories. Anterograde post-traumatic amnesia refers to impaired memory of events that occurred after TBI, while retrograde post-traumatic amnesia refers to impaired memory of events that occurred before the TBI.

Personality changes and behavioral problems may include depression, anxiety, irritability, anger, apathy, paranoia, frustration, agitation, mood swings, aggression, impulsive behaviors or "acting out," social inappropriateness, temper tantrums, difficulty accepting responsibility, and alcohol or drug abuse.

Following TBI, patients may be at increased risk of other long-term problems such as **Parkinson's disease**, **Alzheimer's disease**, "punch-drunk" syndrome (**dementia** pugilistica), and post-traumatic dementia.

Because of all the above problems, some patients may have difficulty returning to work following TBI, as well as

problems with school, driving, sports, housework, and social relationships.

Special concerns

Unlike most other devastating neurological diseases, TBI can be prevented. Practical measures to decrease risk include wearing seatbelts, using child safety seats, wearing helmets for biking and other sports, safely storing firearms and bullets; using step-stools, grab bars, handrails, window guards, and other safety devices; making playground surfaces from shock-absorbing material; and not drinking and driving.

Because TBI follows trauma, it is often associated with injuries to other parts of the body, which require immediate and specialized care. Complications may include lung or heart dysfunction following blunt chest trauma, limb fractures, gastrointestinal dysfunction, fluid and hormonal imbalances, nerve injuries, deep vein thrombosis, excessive blood clotting, and infections.

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Laurie Barclay

Tremors

Definition

Tremor is an unintentional (involuntary) rhythmical alternating movement that may affect the muscles of any part of the body. Tremor is caused by the rapid alternating contraction and relaxation of muscles and is a common symptom of diseases of the nervous system (neurologic disease).

Description

Occasional tremor is felt by almost everyone, usually as a result of fear or excitement. However, uncontrollable tremor or shaking is a common symptom of disorders that destroy nerve tissue such as **Parkinson's disease** or **multiple sclerosis**. Tremor may also occur after **stroke** or **head injury**. Other tremor appears without any underlying illness.

Causes and symptoms

Tremor may be a symptom of an underlying disease, and it may be caused by drugs. It may also exist as the only symptom (essential tremor).

Underlying disease

Some types of tremor are signs of an underlying condition. About a million and a half Americans have Parkinson's disease, a disease that destroys nerve cells. Severe shaking is the most apparent symptom of Parkinson's disease. This coarse tremor features four to five muscle movements per second. These movements are evident at rest but decline or disappear during movement.

Other disorders that cause tremor are **multiple sclerosis**, Wilson's disease, mercury **poisoning**, thyrotoxicosis, and **liver encephalopathy**.

A tremor that gets worse during body movement is called an intention tremor. This type of tremor is a sign

Key Terms

Computed tomography (CT) scan An imaging technique in which cross-sectional x rays of the body are compiled to create a three-dimensional image of the body's internal structures.

Essential tremor An uncontrollable (involuntary) shaking of the hands, head, and face. Also called familial tremor because it is a sometimes inherited, it can begin in the teens or in middle age. The exact cause is not known.

Fetal tissue transplantation A method of treating Parkinson's and other neurological diseases by grafting brain cells from human fetuses onto the affected area of the human brain. Human adults cannot grow new brain cells but developing fetuses can. Grafting fetal tissue stimulates the growth of new brain cells in affected adult brains.

Intention tremor A rhythmic purposeless shaking of the muscles that begins with purposeful (voluntary) movement. This tremor does not affect muscles that are resting.

Liver encephalopathy A condition in which the brain is affected by a buildup of toxic substances that would normally be removed by the liver. The condition occurs when the liver is too severely damaged to cleanse the blood effectively.

Multiple sclerosis A degenerative nervous system disorder in which the protective covering of the nerves in the brain are damaged, leading to tremor and paralysis.

Magnetic resonance imaging (MRI) An imaging technique that uses a large circular magnet and radio waves to generate signals from atoms in the body. These signals are used to construct images of internal structures.

Pallidotomy A surgical procedure that destroys a small part of a tiny structure within the brain called the globus pallidus internus. This structure is part of the basal ganglia, a part of the brain involved in the control of willed (voluntary) movement of the muscles.

Parkinson's disease A slowly progressive disease of that destroys nerve cells. Parkinson's is characterized by shaking in resting muscles, a stooping posture, slurred speech, muscular stiffness, and weakness.

Thalamotomy A surgical procedure that destroys part of a large oval area of gray matter within the brain that acts as a relay center for nerve impulses. The thalamus is an essential part of the nerve pathway that controls intentional movement. By destroying tissue at a particular spot on the thalamus, the surgeon can interrupt the nerve signals that cause tremor.

Thalamus A large oval area of gray matter within the brain that relays nerve impulses from the basal ganglia to the cerebellum, both parts of the brain that control and regulate muscle movement.

Thyrotoxicosis An excess of thyroid hormones in the blood causing a variety of symptoms that include rapid heart beat, sweating, anxiety, and tremor.

Tremor control therapy A method for controlling tremor by self-administered shocks to the part of the brain that controls intentional movement (thalamus). An electrode attached to an insulated lead wire is implanted in the brain; the battery power source is implanted under the skin of the chest, and an extension wire is tunneled under the skin to connect the battery to the lead. The patient turns on the power source to deliver the electrical impulse and interrupt the tremor.

Wilson's disease An inborn defect of copper metabolism in which free copper may be deposited in a variety of areas of the body. Deposits in the brain can cause tremor and other symptoms of Parkinson's disease.

that something is amiss in the **cerebellum**, a region of the brain concerned chiefly with movement, balance, and coordination.

Essential tremor

Many people have what is called essential tremor, in which the tremor is the only symptom. This type of shaking affects between three and four million Americans.

The cause of essential tremor is not known, although it is an inherited problem in more than half of all cases. The genetic condition has an autosomal dominant inheritance pattern, which means that any children of an affected parent will have a 50% chance of developing the condition.

Essential tremor most often appears when the hands are being used, whereas a person with Parkinson's disease will most often have a tremor while walking or while the

hands are resting. People with essential tremor will usually have shaking head and hands, but the tremor may involve other parts of the body. The shaking often begins in the dominant hand and may spread to the other hand, interfering with eating and writing. Some people also develop a quavering voice.

Essential tremor affects men and women equally. The shaking often appears at about age 45, although the disorder may actually begin in adolescence or early adulthood. Essential tremor that begins very late in life is sometimes called senile tremor.

Drugs and tremor

Several different classes of drugs can cause tremor as a side effect. These drugs include amphetamines, antidepressants drugs, antipsychotic drugs, caffeine, and lithium. Tremor also may be a sign of withdrawal from alcohol or street drugs.

Diagnosis

Close attention to where and how the tremor appears can help provide a correct diagnosis of the cause of the shaking. The source of the tremor can be diagnosed when the underlying condition is found. Diagnostic techniques that make images of the brain, such as computed tomography scan (**CT scan**) or **magnetic resonance imaging** (**MRI**), may help form a diagnosis of multiple sclerosis or other tremor caused by disorders of the **central nervous system**. Blood tests can rule out metabolic causes such as thyroid disease. A family history can help determine whether the tremor is inherited.

Treatment

Neither tremor nor most of its underlying causes can be cured. Most people with essential tremor respond to drug treatment, which may include propranolol, **primidone**, or a benzodiazepine. People with Parkinson's disease may respond to levodopa or other **antiparkinson drugs**.

Research has shown that about 70% of patients treated with **botulinum toxin** A (Botox) have some improvement in tremor of the head, hand, and voice. Botulinum is derived from the bacterium *Clostridium botulinum*. This bacterium causes **botulism**, a form of **food poisoning**. It is poisonous because it weakens muscles. A very weak solution of the toxin is used in cases of tremor and **paralysis** to force the muscles to relax. However, some patients experience unpleasant side effects with this drug and cannot tolerate effective doses. For other patients, the drug becomes less effective over time. About half of patients don't get relief of tremor from medications at all.

Tremor control therapy

Tremor control therapy is a type of treatment using mild electrical pulses to stimulate the brain. These pulses block the brain signals that trigger tremor. In this technique, the surgeon implants an electrode into a large oval area of gray matter within the brain that acts as a relay center for nerve impulses and is involved in generating movement (thalamus). The electrode is attached to an insulated wire that runs through the brain and exits the skull where it is attached to an extension wire. The extension is connected to a generator similar to a heart pacemaker. The generator is implanted under the skin in the chest, and the extension is tunneled under the skin from the skull to the generator. The patient can control his or her tremor by turning the generator on with a hand-held magnet to deliver an electronic pulse to the brain.

Some patients experience complete relief with this technique, but for others it is of no benefit at all. About 5% of patients experience complications from the surgical procedure, including bleeding in the brain. The procedure causes some discomfort, because patients must be awake while the implant is placed. Batteries must be replaced by surgical procedure every three to five years.

Other surgical treatments

A patient with extremely disabling tremor may find relief with a surgical technique called thalamotomy, in which the surgeon destroys part of the thalamus. However, the procedure is complicated by numbness, balance problems, or speech problems in a significant number of cases.

Pallidotomy is another type of surgical procedure sometimes used to decrease tremors from Parkinson's disease. In this technique, the surgeon destroys part of a small structure within the brain called the globus pallidus internus. The globus is part of the basal ganglia, another part of the brain that helps control movement. This surgical technique also carries the risk of disabling permanent side effects.

Fetal tissue transplantation (also called a nigral implant) is a controversial experimental method to treat Parkinson's disease symptoms. This method implants fetal brain tissue into the patient's brain to replace malfunctioning nerves. Unresolved issues include how to harvest the fetal tissue and the moral implications behind using such tissue, the danger of tissue rejection, and how much tissue may be required. Although initial studies using this technique looked promising, there has been difficulty in consistently reproducing positive results.

Small amounts of alcohol may temporarily (sometimes dramatically) ease the shaking. Some experts recommend a small amount of alcohol (especially before dinner). The possible benefits, of course, must be weighed against the risks of alcohol abuse.

Prognosis

Essential tremor and the tremor caused by neurologic disease (including Parkinson's disease) slowly get worse and can interfere with a person's daily life. While the condition is not life-threatening, it can severely disrupt a person's everyday experiences.

Prevention

Essential tremor and tremor caused by a disease of the central nervous system cannot be prevented. Avoiding use of stimulant drugs such as **caffeine** and amphetamines can prevent tremor that occurs as a side effect of drug use.

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American Parkinson Disease Association. 60 Bay Street, Suite 401, Staten Island, NY 10301. (800) 223-2732. <http://www.apdaparkinson.org>.

International Tremor Foundation. 7046 West 105th St., Overland Park, KS 66212. (913) 341-3880.

National Parkinson Foundation. 1501 N.W. 9th Ave., Miami, FL 33136-1494. (800) 327-4545. <http://www.parkinson.org>.

Carol A. Turkington

Trigeminal neuralgia

Definition

Trigeminal neuralgia is a disorder of the trigeminal nerve that causes severe facial **pain**. It is also known as tic douloureux, Fothergill syndrome, or Fothergill's syndrome.

Description

Trigeminal neuralgia is a rare disorder of the sensory fibers of the trigeminal nerve (fifth cranial nerve), which innervate the face and jaw. The neuralgia is accompanied by severe, stabbing pains in the jaw or face, usually on one side of the jaw or cheek, which usually last for some seconds. The pain before treatment is severe; however, trigeminal neuralgia as such is not a life-threatening condition. As there are actually two trigeminal nerves, one for each side of the face, trigeminal neuralgia often affects only one side of the face, depending on which of the two trigeminal nerves is affected.

Demographics

There have been no systematic studies of the prevalence of trigeminal neuralgia, but one widely quoted estimate published in 1968 states that its prevalence is approximately 15.5 per 100,000 persons in the United States. Other sources state that the annual incidence is four to five per 100,000 persons, which would imply a higher prevalence (prevalence is the number of cases in a population at a given time; incidence is the number of new cases per year). In any case, the disorder is rare. Onset is after the age of 40 in 90% of patients. Trigeminal neuralgia is slightly more common among women than men.

Causes and symptoms

A number of theories have been advanced to explain trigeminal neuralgia, but none explains all the features of the disorder. The trigeminal nerve is made up of a set of branches radiating from a bulblike ganglion (nerve center) just above the joint of the jaw. These branches divide and subdivide to innervate the jaw, nose, cheek, eye, and forehead. Sensation is conveyed from the surfaces of these parts to the upper spinal cord and then to the brain; motor commands are conveyed along parallel fibers from the brain to the muscles of the jaw. The sensory fibers of the trigeminal nerve are specialized for the conveyance of cutaneous (skin) sensation, including pain.

In trigeminal neuralgia, the pain-conducting fibers of the trigeminal nerve are somehow stimulated, perhaps self-stimulated, to send a flood of impulses to the brain. Many physicians assume that compression of the trigeminal nerve near the spinal cord by an enlarged loop of the carotid artery or a nearby vein triggers this flood of impulses. Compression is thought to cause trigeminal neuralgia when it occurs at the root entry zone, a .19–.39 in (0.5–1.0 cm) length of nerve where the type of myelination changes over from peripheral to central. Pressure on this area may cause demyelination, which in turn may cause abnormal, spontaneous electrical impulses (pain).

Compression is apparently the cause in some cases of trigeminal neuralgia, but not in others. Other theories focus on complex feedback mechanisms involving the subnucleus caudalis in the brain. **Multiple sclerosis**, which demyelinates nerve fibers, is associated with a higher rate of trigeminal neuralgia. Brain tumors can also be correlated with the occurrence of trigeminal neuralgia. Ultimately, however, the exact mechanisms of trigeminal neuralgia remain a mystery.

Trigeminal neuralgia was first described by the Arab physician Jurjani in the eleventh century. Jurjani was also

Key Terms

Anticonvulsant Class of medications usually prescribed to prevent seizures.

Demyelination Destruction or loss of the myelin (a fatty substance) sheath that surrounds and insulates the axons of nerve cells and is necessary for the proper conduction of neural impulses.

Neuralgia Pain along the pathway of a nerve.

Trigeminal nerve The main sensory nerve of the face and motor nerve for chewing muscles.

the first physician to advance the vascular compression theory of trigeminal neuralgia. French physician Nicolaus André gave a thorough description of trigeminal neuralgia in 1756 and coined the term tic douloureux. English physician John Fothergill also described the syndrome in the middle 1700s, and the disorder has sometimes been called after him. Knowledge of trigeminal neuralgia slowly grew during the twentieth century. In the 1960s, effective treatment with drugs and surgery began to be available.

The pains of trigeminal neuralgia have several distinct characteristics, including:

- They are paroxysmal, pains that start and end suddenly, with painless intervals between.
- They are usually extremely intense.
- They are restricted to areas innervated by the trigeminal nerve.
- As seen on autopsy, nothing is visibly wrong with the trigeminal nerve.
- About 50% of patients have trigger zones, areas where slight stimulation or irritation can bring on an episode of pain. Painful stimulation of the trigger zones is actually less effective than light stimulation in triggering an attack.
- The disorder comes and goes in an unpredictable way; some patients show a correlation of attack frequency or severity with stress or menstrual cycle.

Stimulation of the face, lips, or gums, such as talking, eating, shaving, tooth-brushing, touch, or even a current of air, may trigger the severe knifelike or shocklike pain of trigeminal neuralgia, often described as excruciating. Trigger zones may be a few square millimeters in size, or large and diffuse. The pain usually starts in the trigger zone, but may start elsewhere. Approximately 17% of patients experience dull, aching pain for days to years before the onset of paroxysmal pain; this has been termed pretrigeminal neuralgia.

The pain of trigeminal neuralgia is severe enough that patients often modify their behaviors to avoid it. They may suffer severe weight loss from inability to eat, become unwilling to talk or smile, and cease to practice oral hygiene. Trigeminal neuralgia tends to worsen with time, so that a patient whose pain is initially well-controlled with medication may eventually require surgery.

Diagnosis

Trigeminal neuralgia is a possible diagnosis for any patient presenting with severe, stabbing, paroxysmal pain in the jaw or face. However, the most common causes of facial pain are dental problems and diseases of the mouth. Trigeminal neuralgia must also be differentiated from migraine headaches and from other cranial neuralgias (i.e., neuralgias affecting cranial nerves other than the trigeminal). Many persons with trigeminal neuralgia see multiple physicians before getting a correct diagnosis, and may have multiple dental procedures performed in an effort to relieve the pain.

There is no definitive, single test for trigeminal neuralgia. Imaging studies such as computed tomography (**CT**) scans or **magnetic resonance imaging (MRI)** may help to rule out other possible causes of pain and to indicate trigeminal neuralgia. High-definition MRI **angiography** of the trigeminal nerve and brain stem is often able to spot compression of the trigeminal nerve by an artery or vein. Trial and error also has its place in the diagnostic process; the physician may initially give the patient **carbamazepine** (an anticonvulsant) to see if this diminishes the pain. If so, this is positive evidence for the diagnosis of trigeminal neuralgia.

Treatment team

Many different sorts of health care professionals may be consulted by patients with trigeminal neuralgia, including dentists, neurologists, neurosurgeons, oral surgeons, and ear, nose, and throat surgeons. A referral to a **neurologist** should always be sought, as trigeminal neuralgia is essentially a neurological problem.

Treatment

Treatment is primarily with drugs or surgery. Drugs are often preferred because of their lower risk, but may have intolerable side effects such as nausea or **ataxia** (loss of muscle coordination). The two most effective drugs are carbamazepine (an anticonvulsant often used in treating **epilepsy**), used for trigeminal neuralgia since 1962, and **gabapentin**. Drugs are prescribed initially in low doses and increased until an effective level is found. Other drugs in use for trigeminal neuralgia are phenytoin, baclofen, clonazepam, **lamotrigine topiramate**, and trileptal.

Carbamazepine, which inhibits the activity of sodium channels in the cell membranes of neurons (thereby reducing their excitability), is deemed the most effective medication for trigeminal neuralgia. Unfortunately, it has many side effects, including vertigo (**dizziness**), ataxia, and sedation (mental dullness). This may make it harder to treat elderly patients, who are more likely to have trigeminal neuralgia. Carbamazepine provides complete or partial relief for as many as 70% of patients. Phenytoin is also a sodium channel blocker, and also has adverse side effects, including hirsutism (increased facial hair), coarsening of facial features, and ataxia.

For patients whose pain does not respond adequately to medication, or who cannot tolerate the medication itself due to side effects, surgery is considered. Approximately 50% of trigeminal neuralgia patients eventually undergo surgery of some kind for their condition. The most common procedure is microvascular decompression, also known as the Jannetta procedure after its inventor. This involves surgery to separate the vein or artery compressing the trigeminal nerve. Teflon or polivinyl alcohol foam is inserted to cushion the trigeminal nerve against the vein or artery. This procedure is often effective, but some physicians argue that since other procedures that disturb or injure the trigeminal nerve are also effective, the benefit of microvascular decompression surgery is not relief of compression but disturbance of the trigeminal nerve, causing nonspecific nerve injury that leads to a change in neural activity.

Other surgical procedures are performed, some of which focus on destroying the pain-carrying fibers of the trigeminal nerve. The most high-tech and least invasive procedure is gamma-ray knife surgery, which uses approximately 200 convergent beams of gamma rays to deliver a high (and highly localized) **radiation** dose to the trigeminal nerve root. Almost 80% of patients undergoing this procedure experience significant relief with this procedure, although about 10% develop facial paresthesias (odd, non-painful sensations not triggered by any external stimulus).

Clinical trials

As of mid-2004, one clinical trial related to trigeminal neuralgia was recruiting patients. This study, titled "Randomized Study of L-Baclofen in Patients with Refractory Trigeminal Neuralgia," was being carried out at the University of Pennsylvania, Pittsburgh, and was sponsored by the FDA Office of Orphan Products Development (dedicated to promoting the development of treatments for diseases too rare to be considered profitable by pharmaceutical companies). Its goal is to test the effectiveness and safety of the drug L-baclofen in patients with refractory (treatment-resistant) trigeminal neuralgia. The contact is Michael J. Soso at the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, 15261, telephone (412) 648-1239. Forms of baclofen have been used for the treatment of trigeminal neuralgia since 1980.

Prognosis

Trigeminal neuralgia is not life threatening. It tends, however, to worsen with time, and many patients who initially were successfully treated with medication must eventually resort to surgery. Some doctors advocate surgery such as microvascular decompression early in the course of the syndrome to forestall the demyelination damage. However, there is still much controversy and uncertainty about the causes of trigeminal neuralgia and the mechanism of benefit even in those treatments that provide relief for many patients.

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Trigeminal Neuralgia Association. 2801 SW Archer Road, Gainesville, FL 32608. (352) 376-9955; Fax: (352) 376-8688. tnanational@tna-support.org. <http://www.tna-support.org/>.

Larry Gilman

Tropical spastic paraparesis

Definition

Tropical spastic paraparesis (TSP) is a slowly progressive spastic paraparesis caused by the human T-cell lymphotropic virus-1 (HTLV-1), with an insidious onset in adulthood. It has been found all around the world (except in the poles), mainly in tropical and subtropical regions.

Description

For several decades the term tropical spastic paraparesis (TSP) was used to describe a chronic and progressive clinical syndrome that affected adults living in equatorial areas of the world. Neurological and modern epidemiological studies found that in some individuals no one cause could explain the progressive weakness, sensory disturbance, and sphincter dysfunction that affected individuals with TSP. During the mid-1980s, an important association was established between the first human HTLV-1 virus and idiopathic TSP. Since then, this condition has been named HTLV-1 associated myelopathy/tropical spastic paraparesis or HAM/TSP and scientists now understand that it is a condition caused by a retrovirus that results in immune dysfunction. The main neurological features of HAM/TSP consist of **spasticity** and hyperreflexia (increased reflex action) of the lower extremities, urinary bladder disturbance, lower-extremity muscle weakness, sensory disturbances, and loss of coordination. Patients with HAM/TSP may also exhibit arthritis, lung changes, and inflammation of the skin.

Co-factors that may play a role in transmitting the disorder include being a recipient of transfusion blood products, breast-feeding from an infected mother, intravenous drug use, or being the sexual partner of an infected individual for several years.

Demographics

Sporadic cases of TSP have been reported in the United States, mostly in immigrants from countries where this disease is endemic (naturally occurring). In the United States, the lifetime risk of an HTLV-1-infected person developing TSP/HAM has been calculated to be 1.7–7%, similar to that reported for United Kingdom, Africa, and the Caribbean.

The international incidence is difficult to estimate because of the insidious nature of this disease. HAM/TSP is common in regions of endemic HTLV-1, such as the Caribbean, equatorial Africa, Seychelles, southern Japan, and South America. However, it also has been reported from non-endemic areas, such as Europe and the United States. The prevalence in southern Japan is in the range of 8.6–128 per 100,000 inhabitants. An estimated 10–20 million individuals worldwide are carriers of HTLV-1.

HAM/TSP generally affects women more than men, with a female-to-male ratio of 3:1. This disease may occur at any age, with a peak in the third or fourth decade.

Causes and symptoms

The cause of HAM/TSP is still a matter of debate. Whereas only a small proportion of HTLV-1-infected individuals develop HAM/TSP, the mechanisms responsible for the progression of an HTLV-1 carrier state to clinical disease are not clear. However, three hypotheses are considered by scientists as the most likely cause of TSP: direct toxicity, autoimmunity, and bystander damage. The direct toxicity theory of HAM/TSP pathogenesis suggests that HTLV-1-infected cells are directly damaged by certain white blood cells. The autoimmunity theory postulates that the immune system attacks cells that react to HTLV-1 infected cells. In the bystander damage hypothesis, circulating antivirus-specific cells migrating through the **central nervous system** produce damage to nearby cells that is directed against the infected cells.

Key Terms

Paraparesis Weakness of the legs.

Retrovirus An RNA virus containing an enzyme that allows the viruses' genetic information to become part of the genetic information of the host cell as the virus replicates.

Spastic Involving uncontrollable, jerky contractions of the muscles.

Symptoms may begin years after infection. In response to the infection, the body's immune response may injure nerve tissue, causing symptoms including:

- spasms and loss of feeling or unpleasant sensations in the lower extremities, accompanied by weakness
- decreased sense of touch in mid-body areas
- a vibration sensation, especially in the lower extremities, resulting from spinal cord or peripheral nerve involvement
- low lumbar **pain** with irradiation to the legs
- increased reflexes of the upper extremities
- increased urinary frequency and associated increased incidence of urinary tract infection

Less frequently observed symptoms include **tremors** in the upper extremities, optical nerve atrophy, deafness, abnormal eye movements, cranial nerve deficits, and absent or diminished ankle jerk reflex.

Diagnosis

During the clinical examination, it is important to exclude other disorders causing progressive spasticity and weakness in the legs. Diagnosis of HAM/TSP criteria typically involve documenting the following:

- absence of a history of difficulty walking or running during school age

- within two years of onset: increased urinary frequency, nocturia, or retention, with or without impotence; leg cramps or low **back pain**; symmetric weakness of the lower extremities
- within six months of onset: complaints of numbness or **dysesthesias** of the legs or feet
- a clinical examination documenting increased reflexes; spasticity of both legs, abnormal gait (manner of walking), and absence of normal sensory level

Laboratory diagnosis using ELISA (enzyme-linked immunosorbent assay) detects the presence of antibodies against HTLV-1, confirmed by the western blot assay. Electrodiagnostic studies and **magnetic resonance imaging** may also be helpful to show evidence of active denervation, associated with HTLV-1.

Treatment team

Persons with TPS have multiple needs and the team should include a **neurologist** and a physical therapist. An occupational therapist can prescribe exercises designed to develop fine coordination or compensate for tremor or weakness, or suggest assistive devices. More advanced patients require continual nursing assistance.

Treatment

The US Food and Drug Administration (FDA) has not officially approved any drug for the specific treatment of HAM/TSP in the United States. Many patients benefit from oral prednisolone or equivalent glucocorticoid therapy. A response rate of up to 91% has been reported in less advanced cases. Oral treatment with methylprednisolone may produce excellent to moderate responses in around 70% of patients. Plasmapheresis, interferon, oral azathioprine, danazol, and vitamin C have been tried and also show transient effects. None of these treatments has been systematically studied in a controlled clinical trial. **Antiviral drugs** like AZT would be expected to help in reducing viral replication and associated direct cell injury.

Patients with HAM/TSP sometimes report neuropathic pain. Useful drugs include antiepileptics (e.g., **carbamazepine**, phenytoin, **gabapentin**, **topiramate**), baclofen, and tricyclic antidepressants. The dosages used usually are well below those used in the treatment of **epilepsy**. Physical therapy is commonly used in combination with medication for nerve pain.

Recovery and rehabilitation

The goal of a rehabilitation program for a person affected with HAM/TSP is to restore functions essential to daily living in individuals who have lost these capacities through injury or illness. Most rehabilitation programs are comprehensive in nature and have several different aspects.

Physical therapy is designed to help restore and maintain useful movements or functions and prevent complications such as frozen joints, contractures, or bedsores. Examples of physical therapy include:

- stretching and range of motion exercises
- exercises to develop trunk control and upper arm muscles
- training in walking and appropriate use of assistive devices, such as ambulatory aids, braces, and wheelchairs
- training in how to get from one spot to another, such as from the bed to a wheelchair or from a wheelchair to the car
- training in how to fall safely in order to cause the least possible damage

Occupational therapy focuses on specific activities of daily living that primarily involve the arms and hands. Examples include grooming, dressing, eating, handwriting, and driving.

Some rehabilitation centers have innovative programs designed to help people compensate for loss of memory or slowed learning ability. Rehabilitation may be carried out in a residential or an outpatient setting.

Clinical trials

In 2004 there were some open **clinical trials** for the study and treatment of TSP, including:

- "Evaluation of Patients with HAM/TSP," "Phase I/II Study of HTLV-I-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) Using the Humanized MiK-beta-1 Monoclonal Antibody," and "Assessment of Patients with Multiple Sclerosis," sponsored by National Institute of Neurological Disorders and Stroke (NINDS).
- "Phase I Study of T Cell Large Granular Lymphocytic Leukemia in Humanized MiK-Beta-1 Monoclonal Antibody Directed Toward the IL-2R/IL-15R Subunit (CD122)," sponsored by National Cancer Institute (NCI).

Further updated information on these clinical trials can be found at the National Institutes of Health website for clinical trials at <www.clinicaltrials.gov>.

Prognosis

HAM/TSP is usually a progressive neurological disorder, but it is rarely fatal. Most patients live for several decades after the diagnosis. Their prognosis improves if they take steps to prevent urinary tract infection and skin sore formation, and if they enroll in physical and occupational therapy programs.

Special concerns

An important component in the care of patients with TSP is the prevention of infections with the HTLV-1 virus. Several studies indicate that transmission of the HTLV-1 virus occurs through sexual or other intimate contact, intrauterine exposure, newborn exposure via breast milk, sharing of needles by drug abusers, and blood transfusion from infected persons. Transfusion of HTLV-1 antibody-positive blood causes infection in about 60% of recipients. Breastfeeding is contraindicated for mothers who are carriers of HTLV-1.

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National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD (6673); Fax: (203) 798-2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

National Institute of Allergy and Infectious Diseases (NIAID). 31 Center Drive, Rm. 7A50 MSC 2520, Bethesda, MD 20892-2520. (301) 496-5717. <http://www.niaid.nih.gov>.

Francisco de Paula Careta
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Tuberous sclerosis

Definition

Tuberous sclerosis (TS) is a hereditary neurological condition that affects all ages. The name arises from the potato stem-shaped growths that occur in the brain, also known as tubers. These growths often involve overgrowth of nerves or the connective tissue within them, which is described by the term sclerosis.

Description

TS is also known by the names tuberous sclerosis complex and Bourneville's disease. Neurological symptoms may include tubers and other non-cancerous growths in the brain, cancerous brain tumors, **seizures**, and **mental retardation** or developmental delay.

Nearly everyone with TS has some symptoms affecting their skin. These include light-colored patches called ash-leaf spots, acne-type growths on the face, nail beds, and the body, and shagreen patches. Other common symptoms of TS are kidney cysts, kidney growths, and heart tumors that may develop at a very young age or even before birth.

Demographics

According to the National Institute of Neurological Disorders and Stroke (NINDS), TS affects about 1 in 6,000 newborns. As many as 25,000 to 45,000 people in the United States and 1-2 million people worldwide have the disorder. Its true incidence may be higher because mildly affected individuals may not come to medical attention. TS has been reported in all ethnic groups and races with equal frequency.

Two genes for TS have been identified, and males and females are equally affected with the condition. About one third of people with TS have an affected parent as well.

Causes and symptoms

Always known to be hereditary, mutations in two different genes are now known to cause TS. These genes are TSC1 and TSC2, and were discovered in 1993 and 1997 on chromosomes 16 and 9 respectively. TS is inherited in an autosomal dominant manner, meaning that an affected individual has a 50/50 chance to pass a disease-causing mutation to his or her children, regardless of their gender. As a result, strong family histories of TS are common.

TSC1 and TSC2 normally code for specific proteins, hamartin and tuberin, which are felt to be necessary for neurological functioning. Reduced amounts of these proteins in the brains of people with TS may contribute to the neurological complications associated with the condition.

The most common neurological symptoms in TS include seizures, learning and behavioral problems, and **hydrocephalus**. Seizures affect about 85% of people at some point in their lives. They can begin in very early childhood as **infantile spasms**, sometimes with hypsarrhythmia. The presence of these spasms at an early age often means more significant learning problems and more significant **epilepsy** later on.

Key Terms

Aneurysm Increased size of a blood vessel like an artery, which may burst open.

Angiofibroma Non-cancerous growth of the skin, which is often reddish in color and filled with blood vessels.

Angiomyolipoma Non-cancerous growth in the kidney, most often found in tuberous sclerosis.

Computed tomography (CT) scan Three-dimensional internal image of the body, created by combining x ray images from different planes using a computer program.

"Confetti" skin lesions Small changes in the skin color and texture, which may be as small as pieces of confetti.

Connective tissue Supportive tissue in the body that joins structures together, lending strength and elasticity.

Cyst Sac of tissue filled with fluid, gas, or semi-solid material.

Echocardiogram Ultrasound of the heart, which shows heart structure in detail.

Electrocardiogram Test that shows a heart's rhythm by studying its electrical current patterns.

Electroencephalogram (EEG) Test that shows a brain's electrical wave activity patterns.

Gingival fibroma Small non-cancerous growth on the toe- or fingernail beds.

Hamartoma Abnormal growth that may resemble cancer, but is not cancerous.

Hydrocephalus A state when fluid builds up in the brain, which may cause increased internal pressure and enlarged head size.

Hypomelanotic macule Skin patch that is lighter in color than the area around it.

Hypsarrhythmia Typical brain wave activity found in infantile spasms.

Lymphangioleimyoma Non-cancerous growth in the lung, typical of tuberous sclerosis.

Magnetic resonance imaging (MRI) scan Three-dimensional internal image of the body, created using magnetic waves.

Mutation A change in the order of deoxyribonucleic acid (DNA) bases that make up genes, akin to a misspelling.

Periungual fibroma Small non-cancerous growth on the toe- or fingernail beds.

Plaque Another term to describe angiofibromas on the forehead.

Polyp Piece of skin that pouches outward.

Renal cell carcinoma A type of kidney cancer.

Retinal achromic patch Small area of the retina that is lighter than the area around it.

Rhabdomyoma Non-cancerous growth in the heart muscle.

Sequencing Genetic testing in which the entire sequence of deoxyribonucleic acid (DNA) bases that make up a gene is studied, in an effort to find a mutation.

Shagreen patches Patches of skin with the consistency of an orange peel.

Skin tag Abnormal outward pouching of skin, with a varying size.

Spasms Sudden involuntary muscle movement or contraction.

Subependymal giant cell astrocytoma Specific type of cancerous brain tumor found in tuberous sclerosis.

Tubers Firm growths in the brain, named for their resemblance in shape to potato stems.

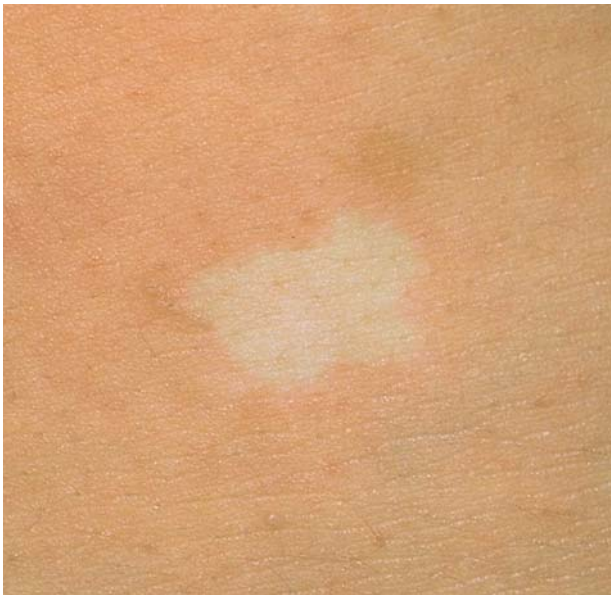
Ultrasound Two-dimensional internal image of the body, created using sound waves.

Vascular Related to the blood vessels.

White matter radial migration line White lines seen on a brain scan, signifying abnormal movement of neurons (brain cells) at that area.

Woods lamp Lamp that uses ultraviolet light, making subtle skin changes more obvious.

Learning problems are not a certainty with TS; about 50% of people with the condition are known to have developmental delay or mental retardation. People with TS have an increased chance to develop certain behavioral disorders. **Autism** is seen in about 25–50% of people with TS, and this is felt to have a major influence on an individual's daily functioning. Parents of children with TS often raise concerns about autism or autistic-type characteristics, because this has a significant impact on routine activities like attending school. Though scientific studies



Close-up of light-brown skin with a lighter patch in the center, known as an ash-leaf spot. Nearly everyone with tuberous sclerosis has some symptoms affecting the skin. *(© LI Inc./Custom Medical Stock Photo. Reproduced by permission.)*

have been done to find exact neurological causes for autism in TS, none has provided consistent results.

A unique brain finding in TS is the cortical tuber, which is seen in about 90% of people with the condition. The number and size of tubers in a person can correlate with the degree of learning problems and seizures they may experience. Other brain findings in TS include subependymal hamartomas. Some of these may grow in childhood and block the normal flow of spinal fluid, causing hydrocephalus. Brain tumors like subependymal giant cell astrocytomas are a cause of health complications and death in TS.

Since skin changes are so common in TS, they can be some of the first signs of the condition that are noticed. Ash-leaf spots are the most common skin finding, followed by facial angiofibromas. These angiofibromas may cause slight disfigurement, but more often are a cosmetic concern. Darkened skin patches called cafe-au-lait spots may also occur, along with skin tags. Fortunately, none of the skin symptoms usually cause serious medical complications.

Kidney disease can be a serious medical concern in TS; it is the most frequent cause of death in people with TS older than 30 years. The most common renal finding is the angiomyolipoma, which is more commonly found in women at a younger age. Though these growths are noncancerous, they can enlarge and disturb normal kidney function. Kidney cysts may occur, again more commonly in younger women. These cysts may be numerous and similarly disrupt normal kidney function as a result. Renal cell carcinoma can be a further symptom of TS, and kidney transplants may be necessary for any significant renal complication.

Cardiac rhabdomyomas are typically seen in early childhood, but occasionally may even be seen on a prenatal ultrasound. Most rhabdomyomas disappear with age, remaining stable and causing no symptoms; others may cause heart rhythm problems. Vascular disease may also be a part of TS, with some people having **aneurysms** of the abdomen and other areas of the body.

Lung problems are a part of TS, and affect women more often. Lymphangioleimyomas of the lung are common and affect about 1-4% of people with TS by interfering with normal lung function. Hormones may be a factor because pregnancy, menstruation, and estrogen have been associated with a worsening of these symptoms in some women. Interestingly, pulmonary problems have been associated with a milder case of TS, often with fewer learning problems and seizures.

Other symptoms of TS include growths on the retinas called hamartomas, which are not usually problematic. There have been no typical ages in which eye involvement occurs in TS.

Diagnosis

Up until the discovery of TSC1 and TSC2, the diagnosis of TS was made on a clinical basis. Criteria for clinical diagnosis were updated in 1998 at the Tuberous Sclerosis Complex Consensus Conference.

Revised diagnostic criteria for tuberous sclerosis complex (TSC)

The major features include:

- facial angiofibromas or forehead plaque
- non-traumatic ungual or periungual fibroma
- hypomelanotic macules (more than three)
- shagreen patch
- multiple retinal nodular hamartomas
- cortical tuber
- subependymal nodule
- subependymal giant cell astrocytoma
- cardiac rhabdomyoma, single or multiple
- lymphangioleimyomatosis
- renal angiomyolipoma

The minor features include:

- multiple randomly distributed pits in dental enamel

- hamartomatous rectal polyps
- bone cysts
- cerebral white matter radial migration lines
- gingival fibromas
- non-renal hamartoma
- retinal achromic patch
- "confetti" skin lesions
- multiple renal cysts

Definite TSC: Either two major features, or one major feature plus two minor features. Probable TSC: One major plus one minor feature. Possible TSC: Either one major feature, or two or more minor features.

Most brain findings in TS can be identified with **magnetic resonance imaging (MRI)** or computed tomography (**CT**) scans. Seizures can be documented from electroencephalogram (EEG) monitoring. Skin changes are often found by using a Woods lamp, which makes them more obvious during a physical examination. Routine ultrasounds of the kidney often find and help monitor cysts and angiomylipomas. Cardiac involvement may be seen as early as a prenatal ultrasound, or with an echocardiogram in early life. Electrocardiograms may be necessary to help detect heart rhythm problems. For women in particular, a CT scan of the chest is important to detect lung lymphangiomyomatosis. For all, an ophthalmology examination is important to detect retinal involvement.

Genetic testing is available for TS via gene sequencing. It is useful for confirming a clinical diagnosis, prenatal diagnosis, or family testing when there is an identified TSC mutation in the family. Sequencing of the TSC1 and TSC2 genes is not perfect; it detects about 80% of people with TS. An informative test result is one that identifies a known mutation in either gene, and this confirms that the person has TS. A negative test result does not identify a mutation in either gene. This either means that the tested individual does not have TS, or has a mutation that cannot be found through testing and truly has the diagnosis.

Treatment team

Treatment for people with TS is usually very specific to the person, since symptoms vary greatly. The typical treatment team for someone with TS may include a **neurologist**, neurosurgeon, medical geneticist, genetic counselor, dermatologist, cardiologist, pulmonologist, nephrologist, ophthalmologist, social worker, and a primary care provider. Often times there are pediatric specialists in these fields who aid in the care for children. Care providers in pediatric development are particularly important, such as speech-language therapists and pediatric neuropsychologists.

Treatment

There is no cure for tuberous sclerosis. Therefore, treatment is based upon symptoms.

Seizures may be treated with various anti-epilepsy medications. Those with significant seizures may be tried on a ketogenic diet, which consists of frequent meals of high-fat foods. While challenging, the ketogenic diet yields good results in some cases.

Learning or behavioral problems are often serious issues, but awareness and developmental interventions often help families with TS. Pediatricians who have an interest in child development are a good resource, particularly if a child with TS is showing signs of autism.

Hydrocephalus can be serious and even lead to learning problems if left untreated, so surgery to drain accumulated fluid in the brain may be necessary. While most growths in the brain are non-cancerous, brain tumors are typically treated as they would be in someone without TS.

Since most skin complications of TS cause no medical problems, treatment is not often necessary. Some angiofibromas, particularly on the face, may be problematic and require removal. Laser treatments may also be effective to reduce the appearance of some skin changes.

Many kidney growths cause no health problem in TS, but some individuals may have kidney cysts similar to those found in polycystic kidney disease (Type 1). In these cases, kidney function may be disturbed and the person might need a kidney transplant after some time. Those with renal cell carcinoma would be treated as anyone with this complication.

Most rhabdomyomas cause no problems, but some may need surgery to keep their hearts working well. Surgery may also be required for someone with a severe heart rhythm problem.

People with lung function problems may need to be treated with medications, hormone therapy, or surgery if necessary.

Visual complaints are not as common for people with TS, since retinal growths do not usually cause symptoms. In rarer cases, vision may be disturbed and treated like someone without TS.

Clinical trials

As of early 2004, there were two clinical studies recruiting subjects in the United States. Both were at the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health in Bethesda, Maryland. One study was studying skin tumors in people with TS, and the other was studying disease progression in people with TS who have lymphangioleimyomatosis. More information about these trials can be found at www.clinicaltrials.gov.

Prognosis

Prognosis for someone with tuberous sclerosis is highly dependent upon symptoms they experience. Those who die may do so as a result of significant neurological, pulmonary or cardiac complications. People with TS often have routine medical appointments dealing with symptoms as they arise.

Many people with TS survive into adulthood, and studies are attempting to learn more about long-term prognosis as people with TS age. It is challenging to gain this information because older people with milder forms of TS may not present for medical care frequently, or may not even know they have the condition.

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The Tuberous Sclerosis Association, U.K. Janet Medcalf, P.O. Box 9644, Bromsgrove, England B61 OFP. +44 (0)1527 871898; Fax: +44 (0)1527 579452. <http://www.tuberous-sclerosis.org>.

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U

Ulnar neuropathy

Definition

Ulnar neuropathy is an inflammation or compression of the ulnar nerve, resulting in paresthesia (numbness, tingling, and **pain**) in the outer side of the arm and hand near the little finger.

Description

The ulnar nerve transmits impulses to muscles in the forearm and hand. The nerve is responsible for the proper sensing of touch, texture, and temperature throughout the fourth and fifth digits of the hand, the palm, and the underside of the forearm. Ulnar neuropathy arises most commonly because of damage to the nerve as it passes through the wrist. The elbow is also a frequent site of nerve damage. Ulnar neuropathy is variously known as bicycler's neuropathy, cubital tunnel syndrome, Guyon or Guyon's canal syndrome, and tardy ulnar palsy.

Demographics

Ulnar neuropathy that originates at the elbow is very common. Estimates are that 40% of Americans experience some form of this neuropathy at some point in their lives. While the ulnar nerve is structurally identical in men and women, men tend to develop ulnar neuropathy more than women. This is because men generally do not have as much fat overlaying the elbow, and so the underlying nerve can be more susceptible to irritation and damage.

The onset of ulnar neuropathy can occur slowly. As a result, many of those who are affected are middle-aged or older adults. Demographic risk factors include a family history of diabetes, alcoholism, and presence of human immunodeficiency virus. Because leaning on the elbows can trigger ulnar neuropathy, people such as telephone operators, receptionists, and those who operate computers for extended periods of time are at risk for developing the disorder.

Causes and symptoms

Ulnar neuropathy is caused by nerve damage. The nature of the nerve damage is varied, and can result from inflammation or compression. Nerve damage at the elbow can result from compression of the nerve when sensation is obliterated during general anesthesia. As well, a blow to the elbow or even too much leaning on the elbow can be damaging, as can diseases (rheumatoid arthritis) and metabolic disturbances (diabetes). Even malnutrition can be a factor, as protective fatty deposits and muscle mass waste away. Damage to the nerve at the wrist can be caused by a blow, tumors, and impinging of an artery.

The nerve damage that results in ulnar neuropathy can involve the main body of the nerve, the branching region at the end of the nerve known as the axon (which is involved in the movement of the nerve impulse to the adjacent nerve), and the protective myelin coating around the nerve. When the main body of the nerve is involved, the problem is usually a block in the passage of the impulse down the nerve. Axon damage typically decreases the movement of the nerve impulse away from the nerve or the wavelength of the impulse. As a result, the impulse may not reach the adjacent nerve, or may not be recognized by the receptors of that adjacent nerve. Finally, damage to the myelin sheath (demyelination) also impedes the movement of signal down the body of the nerve.

Depending on the site of the neuropathy and whether the neuropathy arises suddenly (acute) or has been present for a long time (chronic), various symptoms can arise. Acute and chronic ulnar neuropathy of the elbow is always associated with numbness and weakness. Pain is present almost 40% of the time in the acute form of the disorder and almost 80% of the time in the chronic disorder. When the ulnar neuropathy involves the wrist, weakness is ever-present in a main muscle controlling wrist movement,

generalized weakness in the absence of pain in 50% of those afflicted, and finger numbness occurs in about 25% of cases.

Other physical signs include the adoption of a clawed shape by the hand and the inability of the entire thumb to move to the forefinger in a single motion.

Diagnosis

Typically, the development of weakness in the elbow or wrist is the sign that alerts a clinician to the possibility of ulnar neuropathy. Follow-up tests can include ultrasound or **magnetic resonance imaging** to visualize cysts or structural abnormalities. The functioning of the nerve can be assessed in a nerve conduction test. Laboratory analyses of blood can be done to detect the presence of diabetes or infections that can damage nerves (such as **Lyme disease**, human immunodeficiency virus, or hepatitis viruses).

Treatment team

Treatment can involve the family physician, family members, neurosurgeons, hand surgeon, pain specialist, and physical and occupational therapists. Therapists can often provide exercises that assist in maximizing muscular strength and orthotic devices to maintain proper positioning during repetitive or stressful movements, thereby reducing inflammation.

Treatment

Treatment can consist of the use of nonsteroidal anti-inflammatory drugs to control swelling around the nerve. The use of splints or cushions can ease the discomfort and the stress on the ulnar nerve. For some, surgery is a useful option, when relief can be gained by removal of a cyst or correction of damage caused by a blow.

Recovery and rehabilitation

Sports and other normal activity can be resumed when the person is able to perform normal hand-gripping tasks such as opening a jar, forcefully grip a tennis racquet or bicycle handlebars, or work at a keyboard without pain or tingling in the elbow or hand. Braces and other orthotic devices, if worn consistently, often prevent reoccurrence of ulnar neuropathy.

Prognosis

If nerve damage has been caused by a blow or by trauma such as putting too much pressure on the elbow or wrist, recovery can be complete.

Key Terms

Axon The long, slender part of a nerve cell that carries electrochemical signals to another nerve cell.

Electromyogram Often done after a nerve conduction velocity test, an electromyogram (EMG) is a diagnostic used test to evaluate nerve and muscle function.

Myelin sheath Insulating layer around some nerves that speeds the conduction of nerve signals.

Nerve impulse The electrochemical signal carried by an axon from one neuron to another neuron.

Neuron A nerve cell.

Orthotic device Devices made of plastic, leather, or metal which provide stability at the joints or passively stretch the muscles.

Paresthesia Abnormal physical sensations such as numbness, burning, prickling, or tingling.

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National Chronic Pain Outreach Organization (NCPOA). P.O. Box 274, Millboro, VA 24460. (540) 862-9437; Fax: (540) 862-9485. ncpoa@cfw.org. <http://www.chronicpain.org>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). 31 Centre Dr., Rm. 4Co2 MSC 2350, Bethesda, MD 20892-2350. (301) 496-8190 or (877) 226-4267. info@mail.nih.gov. <http://www.niams.nih.gov>.

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Brian Douglas Hoyle, PhD

Ultrasonography

Definition

Ultrasonography is a diagnostic technique that involves directing high frequency sound waves at tissues in the body to generate images of anatomical structures. Ultrasonography is also called sonography, diagnostic sonography, and echocardiography when it is used to image the heart.

Purpose

Ultrasonography has a variety of uses in medical diagnostics. It is most well suited for imaging soft tissues that are solid and uniform or filled with fluid. It does not perform well when imaging calcified objects such as bone or objects filled with air like the bowel. Some of the more common uses for ultrasonography include imaging fetus development during pregnancy, diagnosing gallbladder disease and some forms of cancer, and evaluating abnormalities in the scrotum and prostate, heart, and thyroid gland. Ultrasound can also be used to perform breast exams. A technique called Doppler imaging ultrasonography can also be used to view the movement of blood through blood vessels and to guide needles through anatomical structures for obtaining specimens for **biopsy**. Three-dimensional ultrasounds provide detailed images of fetuses in the uterus.

The majority of ultrasonic exams are performed externally by running a transducer over the surface of the skin. Usually a gel is applied to the skin on which the transducer will glide during the exam. The gel helps prevent the formation of air pockets between the transducer and the skin that interfere with the ultrasonic signal. Some ultrasound diagnostic tests require the insertion of a probe into a body orifice. For example, during a transesophageal echocardiogram a specialized transducer is placed in the esophagus to better image the heart. Transrectal exams require a transducer to be inserted into a man's rectum to obtain images of the prostate. Transvaginal ultrasounds are used to provide images of a woman's ovaries and uterus or of a fetus during the early weeks of pregnancy.

Ultrasound is generally a painless procedure. Some discomfort may be felt when the transducer is pressed against the skin or when the transducer is inserted in the body. Most ultrasonic procedures take less than half of an hour.

Cranial ultrasound

Cranial ultrasonography is most often used in infants to diagnose problems with the brain and the ventricles in the brain through which cerebrospinal fluid (the clear fluid that circulates through the brain and spinal cord) flows. These abnormalities are often associated with premature birth. Because ultrasound waves are poorly conducted through bones, cranial ultrasonography must be performed on infants before the fontanel (gaps between the bones of the cranium) have closed. Cranial ultrasonography is also performed on adults during brain surgery to help identify the location of brain tumors. In adults, the skull must be surgically opened in order to use ultrasonography.

In infants, cranial ultrasonography is most often used to diagnose two complications. Intraventricular hemorrhage (IVH) occurs when there is bleeding in the brain. This occurs more commonly in premature babies and is likely to happen within the first week of the infant's life. **Periventricular leukomalacia** (PVL) occurs when the tissue around the ventricles in the brain is damaged. This complication can occur within several weeks of birth. Both IVH and PVL are associated with mental disabilities and developmental delays. Cranial ultrasonography can also be used to evaluate brain abnormalities in babies, such as congenital **hydrocephalus** or tumors, or to detect infection.

Description

Ultrasonography relies on sound waves to create an image of the soft tissues in the body. Sound waves are a form of energy called longitudinal pressure waves that result when molecules are pushed together and then become rarified (less dense). The molecules through which the wave passes are not transported by the wave; rather, they vibrate back and forth around a neutral position. The number of times that a molecule moves through a compression and rarification cycle in one second is called the frequency of the wave. The unit of the frequency of a sound wave is the Hertz (Hz). Frequencies between about 20 Hz and 20,000 Hz are audible to the human ear and the greater the frequency, the higher a sound wave sounds. Frequencies above 20,000 Hz are called ultrasonic and the human ear cannot detect these sound waves. The frequencies of sound waves used in ultrasonography are between about one million and 15 million Hz (or one and 15 MHz).

An ultrasound machine typically consists of four parts: the transducer, which allows for the movement of the ultrasound machine over the body; the electronic signal processing unit, which controls the power to the transducer; the display unit, which is usually a computer screen; and a device for storing the images, which is usually a videotape or a camera.

The transducer is the most technologically interesting part of the ultrasonography machine. It is usually a handheld device that can be pushed against the skin or inserted into an orifice. The transducer is made up of a plastic or ceramic material that has piezoelectric properties. This

means that it is capable of generating and detecting ultrasound waves. If pulses of electric current are applied to the surface of a transducer, the piezoelectric surface will change in thickness in response to the pulses. This change in thickness causes a change in pressure in the molecules surrounding the piezoelectric surface, generating sound waves. If the pulses occur between one and 15 million times a second, then the result is a sound wave with an ultrasonic frequency. Similarly, the piezoelectric surface acts as a receptor for return waves. When sound waves collide with the piezoelectric surface, they cause a change in its thickness. This change in thickness is converted to a change in the electric current in the transducer, which is then interpreted as various shades of gray and used to form an image on the display unit. The electronics of the transducer are constructed so that ultrasound beams are generated, followed by a pause during which the return waves are detected; this cycle continues during the entire diagnostic procedure.

An ultrasonic wave that is directed out of the transducer and into tissues of the body has one of four outcomes: it can be absorbed by the material, in which case the transducer will receive no return signal; it can be reflected back to the transducer, in which case the transducer will receive a strong return signal; it can be refracted so that it changes direction and only a part of the signal will return to the transducer; finally, the wave can be scattered, greatly reducing the signal received by the transducer. At various tissue interfaces, different amounts of the wave energy are returned to the transducer as a result of various combinations of absorption, reflection, refraction, and scattering. For example, at a fat-muscle interface, about 1% of the incident wave is returned to the transducer, while at a bone-muscle interface, about 40% of the incident wave is returned. At any interface that involves air, such as a gas bubble in the bowel, nearly 100% of the incident wave will be returned to the transducer. Similarly, bones and other calcified objects like kidney stones and gallstones result in very high reflection of the incident wave. Because air acts as such a strong reflector of an ultrasonic wave, gel or some other lubricant is usually placed between the transducer and the skin during an ultrasonic exam.

Some ultrasonic machines take advantage of the Doppler effect in order to display color images of the flow of blood or other fluids. When an ultrasound wave is directed at a stationary object, the return wave will remain the same frequency as the incident wave, although it will be attenuated depending upon the structures with which it interacts. On the other hand, when an ultrasound wave is directed at a moving object, the return wave will have a different frequency than the incident wave depending on whether the moving object is in the same direction as, or in the opposite direction from, the incident wave. This change in frequency can be interpreted, for example, as the speed of blood flow within a vessel.

Key Terms

Sound waves Changes in air pressure that produce an oscillating wave that transmits sound.

Ultrasound High frequency sound waves directed at tissues in the body to generate images of anatomical structures.

The recent development of color Doppler sonography (CDS) has improved several diagnostic exams. In this technique, a black and white image of the anatomical structures resulting from traditional ultrasonography is overlaid with a color image showing the flow of a fluid within the tissues generated from a Doppler ultrasonograph. CDS has proven extremely useful for evaluating the blood flow to the placenta and uterus during pregnancy. It has also been used to quantify the blood flow to various tumors; malignant tumors tend to have greater rates of blood flow and longer residence times than benign ones.

Several other new technologies associated with ultrasonography are becoming available as diagnostic tools. Some physicians are using ultrasonography in conjunction with contrast agents that provide better resolution of internal structures. This is particularly useful for visualizing the heart and kidneys more effectively. Harmonic imaging is a technique that is used to improve the signal-to-noise ratio of an ultrasonic image. It is based on the idea that the tissues of the body resonate harmonically, similar to a musical instrument. Therefore, taking advantage of sound waves at two and three times the frequency of the incident wave should provide additional information about the internal structures of the body. For example, if the incident wave of the transducer is 4 MHz, then using return waves that are 8 MHz should improve the resolution of the image. Finally, three-dimensional sonography is available on some machines. In some cases, the three-dimensional image is reconstructed from several sweeps of the transducer at different levels through the body. In others, two transducers that are oriented perpendicular to each other are used to build a three-dimensional image. This technology has been used most frequently to visualize fetuses in the uterus.

Preparation

Preparation for ultrasonography differs depending on the type of exam being performed. For some exams, no preparation is necessary. For others, fasting and abstaining

from drinking for up to 12 hours prior to the exam is required. Some exams, like the transabdominal ultrasound, require that the patient have a full bladder because the ultrasonic waves are best transmitted through fluid. If a biopsy is required, antibiotics may be administered prior to the test. The physician or technician performing the exam usually provides instructions on proper preparation prior to the exam.

Risks

Because ultrasonography uses high frequency sound waves, and not x rays or other forms of **radiation**, there are very few risks associated with its use. Sound waves are either reflected back to the transducer, or the tissues of the body absorb them and they dissipate as heat. There may be a slight increase in heat in the body as a result, but no negative effects of this heat have been documented.

Normal results

Results of ultrasonic tests are usually sent to a physician and possibly to a radiologist. They are usually made available to the patient within one to two days.

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Juli M. Berwald, PhD

V

Valproic acid and divalproex sodium

Definition

Valproic acid is an anticonvulsant used to control **seizures** in the treatment of **epilepsy**, a neurological dysfunction in which excessive surges of electrical energy are emitted in the brain.

Valproic acid is closely related to divalproex sodium and valproate sodium. While these drugs are primarily used in the treatment of epilepsy, divalproex sodium is also indicated for the treatment of manic episodes (abnormally and persistently elevated mood) associated with bipolar disorder.

Purpose

Valproic acid is thought to depress activity in certain areas of the brain, suppressing the irregular firing of neurons to prevent seizures. Divalproex sodium is a stable coordination compound formed with valproic acid.

While valproic acid and divalproex sodium control the seizures associated with epilepsy, there is no known cure for the disease.

Description

In the United States, valproic acid and divalproex sodium are sold under the brand names Depekene and Depakote. Valproic acid is available in tablet and syrup form. Divalproex sodium is available in tablet, injection, or in sprinkle form.

Recommended dosage

Valproic acid usually requires two to four oral doses each day. The typical total daily dose is initiated at 15mg per kilogram (2.2 pounds) of body weight, and is increased in weekly intervals by 5–10 mg per kilogram of body weight until seizures are controlled. The frequency of adverse effects may increase with increasing doses, therefore, changes in dosage are made gradually. It may require several weeks of dosage titration (adjustment for maximum benefit and minimum risk) to realize the full benefits of valproic acid or divalproex sodium.

Persons should not take a double dose of anticonvulsant medications. If a daily dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped.

When discontinuing treatment including valproic acid or divalproex sodium, physicians typically direct patients to gradually reduce their daily dosages. Stopping the medicine suddenly may cause seizures to occur or become more frequent.

Precautions

Persons should avoid alcohol while taking valproic acid or divalproex sodium. It can exacerbate (heighten) the side effects of alcohol and other medications. A physician should also be consulted before taking valproic acid or divalproex sodium with certain non-prescription medications, such as medicines for asthma, appetite control, coughs, colds, sinus problems, allergies, and hay fever.

Valproic acid and divalproex sodium may not be suitable for persons with a history of liver or kidney disease, mental illness, high blood presure, angina (chest **pain**), irregular heartbeats, or other heart problems. Valproic acid and divalproex sodium may cause liver damage (hepatotoxicity), though the risk is low in adults. The prescribing physician may order routine blood tests to screen for liver damage.

Before beginning treatment with valproic acid or divalproex sodium, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant, or plan to become pregnant.

Valproic acid and divalproex sodium may cause birth defects, and have been linked to an increased risk of **spina**

bifida. Physicians often counsel their patients to use effective birth control while taking either of these medications. Unlike many other anti-convulsant medications, valproic acid will not decrease the effectiveness of oral contraceptives (birth control pills). Patients who become pregnant while taking valproic acid or divalproex sodium should contact their physician immediately.

Side effects

Research indicates that valproic acid and divalproex sodium are generally well tolerated. In certain individuals and especially children under two years of age, however, valproic acid may cause severe damage to the liver or pancreas. It is important to keep all appointments with the physician and laboratory to monitor the body's response to valproic acid. Temporary nausea, vomiting, stomach cramps, weight gain, temporary hair loss, shaking, and an irregular menstrual cycle are the most frequently reported side effects of valproic acid and divalproex sodium. Other possible side effects include:

- nervousness
- anxiety
- difficulty with memory
- double vision
- loss of appetite
- restlessness
- sleepiness or sleeplessness
- unusual drowsiness
- diarrhea or constipation
- heartburn or indigestion
- aching joints and muscles or chills
- unpleasant taste in mouth or dry mouth
- tingling or prickly feeling on the skin

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication.

Other, uncommon side effects of valproic acid and divalproex sodium can be potentially serious. A patient taking valproic acid who experiencs any of the following symptoms should contact their physician:

- jaundice (yellow tone to skin and eyes)
- facial swelling
- persistent fatigue
- rash
- mood or mental changes
- **depression**
- persistent trembling of the arms and hands
- restlessness
- excessive sleeplessness
- hallucinations
- difficulty breathing
- chest pain
- irregular heartbeat
- faintness
- persistent, severe **headaches**
- persistent fever or pain.

Key Terms

Bi-polar disorder A mood disorder characterized by periods of excessive excitability and energy alternating with periods of depression and lack of energy.

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Hepatotoxicity Damaging or destructive to the liver.

Seizure A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

Spina bifida A birth defect in which the neural tube fails to close during fetal development and a portion of the spinal cord and nerves fail to develop properly.

Interactions

Valproic acid and divalproex sodium may have negative interactions with some antacids, tricyclic antidepressants, antibiotics, monoamine oxidase inhibitors (MAOIs), and asprin and other non-steroidal anti-inflammatories (NSAIDs). Other medications such as **Diazepam** (Valium), **phenobarbital** (Luminal, Solfoton), nefazodone, metronidazole, **acetazolamide** (Diamox), phenytoin (Dilantin), **primidone**, propranolol (Inderal), and warfarin may also adversely react with volparic acid.

Volparic acid and divalproex sodium may react adversely with other **anticonvulsants** and anti-epilepsy drugs (AEDs). They should be used with other other seizure prevention medications only if advised by a physician.

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Adrienne Wilmoth Lerner

Vasculitic neuropathy

Definition

Vasculitic neuropathy refers to damage to the peripheral nerves (the nerves that are located outside of the brain and spinal cord) as a consequence of **vasculitis** (a condition characterized by inflammation and destruction of blood vessels).

Description

Vasculitis refers to a number of conditions that cause inflammation in the blood vessels of the body. This inflammation can prevent sufficient blood flow from reaching various organs and tissues of the body. Because adequate blood flow is required to provide the organs and tissues with oxygen, vasculitis causes damage to oxygen-deprived organs and tissues. When peripheral nerves are oxygen-deprived due to vasculitis, vasculitic neuropathy ensues.

Peripheral neuropathy can occur as the only symptom of vasculitis, or it can be part of a symptom complex.

Demographics

About 60-70% of all patients with vasculitis will experience peripheral neuropathy. In fact, about 34% of all patients with vasculitis will manifest peripheral neuropathy as the sole manifestation of their vasuclitis. The average age of an individual with vasculitic neuropathy is 62.

Causes and symptoms

Vasculitic neuropathy can accompany a number of types of vasculitis, including polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, Sjogren's syndrome, rheumatoid vasculitis, and vasculitis due to infections (such as **Lyme disease**, hepatitis, or HIV). Vasculitis occurs when the body's immune system accidentally misidentifies markers on the blood vessel walls as foreign. The immune system then begins to produce immune cells that attack and destroy the blood vessels. As the blood vessels become inflamed, blood flow through them is diminished, resulting in oxygen deprivation of the organs or tissues they normally serve. When the oxygen-deprived tissues are nerve cells, vasculitic neuropathy results.

Most people with vasculitic neuropathy notice **pain** and then weakness in a random, nonsymmetric distribution throughout their limbs; a smaller number (about one-third of all sufferers) notice pain and weakness that progress in a symmetric fashion, beginning with the feet or hands and progressing up the limbs. The pain of vasculitic neuropathy can include shooting, sharp pain, tingling, numbness, burning, and stinging. Some patients with vasculitic neuropathy will also experience fever, decreased appetite, weight loss, rash, **fatigue**, joint pain, and kidney problems.

Diagnosis

Examining a sample of an affected nerve cell (**biopsy**) will allow the diagnosis to be made. The biopsy will demonstrate the inflammation and destruction of blood vessel walls characteristic of vasculitis. Electrodiagnostic studies use needle electrodes to stimulate affected nerves or muscles, in order to demonstrate a slow or abnormal response.

Treatment team

Vasculitic neuropathy may be treated by a **neurologist** or a rheumatologist. Physical and occupational therapists can help optimize recovery of function.

Treatment

Treatment for vasculitic neuropathy involves medications that decrease inflammation and suppress the activity of the immune system. Such medications include corticosteroids and cyclophosphamide. Physical and occupational therapy can help restore functioning and can provide strategies to help overcome any permanent disabilities caused by the vasculitic neuropathy.

Prognosis

Once treatment for vasculitic neuropathy has been initiated, symptom progression should halt, and the condition should stabilize. Some improvement in already established

Key Terms

Neuropathy A disease of the nervous system.

Peripheral nerves Nerves outside of those in the brain and spinal cord.

Vasculitis A condition in which inflammation of the blood vessels deprives organs and tissues of oxygen, resulting in damage.

symptoms is possible; pain may decrease, and some degree of weakness may improve, although recovery of function is usually very slow and only partial.

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Rosalyn Carson-DeWitt, MD

Vasculitis

Definition

Vasculitis refers to a condition that causes inflammation of blood vessels (arteries, capillaries, and/or veins). When the blood vessels become inflamed, scarring, thickening of the vessel walls, and narrowing of the vessel caliber decrease the amount of blood flow through the blood vessels. When there is less blood flow, the organs or tissues that should be receiving blood flow are deprived of oxygen, causing damage to them. Because blood vessels anywhere in the body can be affected by vasculitis, organs and tissues anywhere in the body can be damaged by its consequences. Vasculitis can occur very focally (in a relatively small, circumscribed area) or diffusely (a widespread network of blood vessels are inflamed).

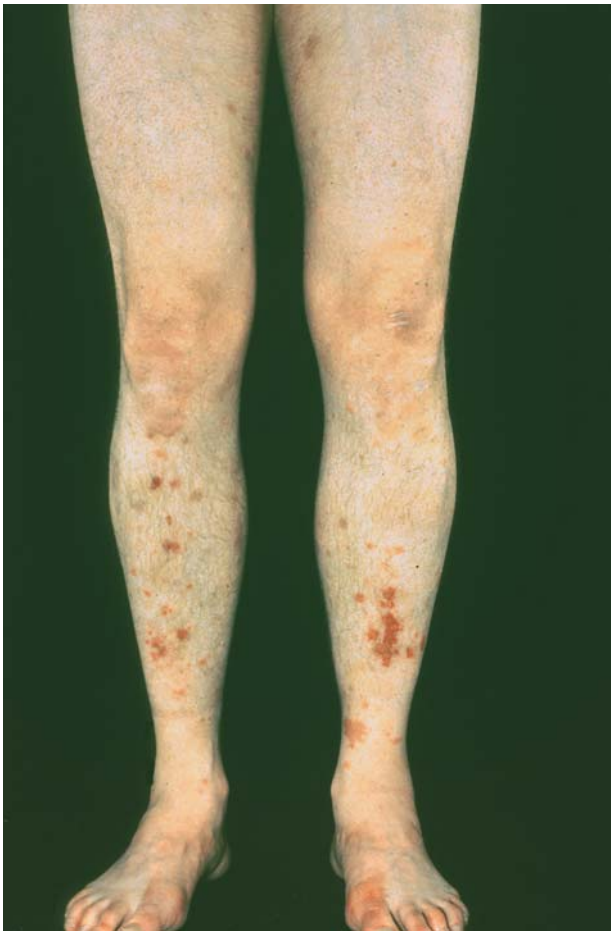
Description

Vasculitis describes a large number of conditions. Vasculitis can be primary (the vessel inflammation occurs spontaneously, with no other associated disease process) or secondary (the vessel inflammation occurs due to some other preexisting disease). Secondary vasculitis can be a manifestation of a large number of disease processes, including a variety of connective tissue or autoimmune diseases such as rheumatoid arthritis, systemic **lupus** erythematosus, Raynaud's phenomenon, Sjogren's syndrome, sclerodactyly, **polymyositis**, and **dermatomyositis**, as well as sarcoidosis, malignancy, hepatitis B and hepatitis C infections, allergic reactions to antibiotics and/or diuretics, and severe bacterial infections such as endocarditis, pneumonia, meningitis, gonorrhea, or syphilis.

Normally, inflammation is an immune system response to the presence of either an injury or an infection with an invading organism such as a virus, bacteria, or fungi. When faced with either of these threats, the immune system produces a variety of cells and chemicals that cause blood vessels in the injured or infected area to dilate and then become leaky. Fluid, protein, and blood cells leak out of the blood vessels and into the surrounding tissues, causing swelling. The affected area turns red, warm, and painful.

Inflammation causes a cascade of effects, both in the tissues adjacent to the initial area of inflammation and at distant sites throughout the body. Locally, the process of inflammation causes various chemicals of inflammation to leak out into the neighboring tissues, prompting the same cycle of vessel dilatation and leakiness, resulting in swelling of those neighboring tissues. Chemicals of inflammation traveling through the bloodstream can precipitate the cycle of inflammation in tissues and/or organs at a distance from the initial site of inflammation.

In vasculitis, the inflammation response has gone awry: it may be kicked off initially by the presence of an invader such as vasculitis secondary to a severe bacterial infection; it may be part of an overall immune system over-reactiveness as occurs when vasculitis occurs secondary to an autoimmune disease such as systemic lupus erythematosus and rheumatoid arthritis; or it may erupt spontaneously as in cases of primary vasculitis. The end results, however, are inflammation and destruction of blood vessel walls, blood clot blockages within blood vessels, **aneurysms** (weakened bulging areas of blood vessel walls which can rupture, causing catastrophic bleeding),



Some symptoms of vasculitis. *(Custom Medical Stock Photo. Reproduced by permission.)*

and oxygen deprivation of the affected organs and/or tissues, leading to damage and destruction of various tissue or organs throughout the body.

A variety of classification systems have been developed to describe and organize the various types of vasculitis. These include systems that are based on the specific organs affected, and systems that are based on the size and type of vessels affected, and the kinds of microscopic, cellular changes seen within those vessels. One of the most popular systems for classification of vasculitis is called the Chapel Hill system, named for the creators at the University of North Carolina-Chapel Hill. This system divides the types of vasculitis into three categories: large-vessel vasculitis (including giant cell or **temporal arteritis** and Takayasu's arteritis); medium-vessel vasculitis (including polyarteritis nodosa and Kawasaki's disease); and small-vessel vasculitis (including Wegener's granulomatosis, Churg-Strauss syndrome, microsopic polynagiitis, Henoch-Schonlein purpura, essential cryoglobulinemic vasculitis, and cutaneous leukocytoclastic angiitis).

Key Terms

Antibody A protein produced by the immune system in response to the presence of a foreign substance (antigen).

Antigen A protein marker that stimulates the immune system.

Diffuse Widespread.

Dilatation Increasing in caliber.

Focal Limited to a defined area.

Inflammation The body's response to injury, resulting in swelling, warmth, redness, and pain.

Demographics

Each type of vasculitis has its own primary demographic. Those that tend to strike older individuals include polyarteritis nodosa, giant cell or temporal arteritis, and Wegener's granulomatosis. Takayasu's arteritis tends to strike individuals in middle age. Henoch-Schonlein pupura and Kawaskai disease tend to strike children.

Causes and symptoms

Some researchers believe that vasculitis is prompted by the deposition of antibody-antigen complexes along the inside of blood vessel walls. Antibodies are immune cells that recognize and attach to specific markers (antigens) on foreign cells such as bacteria, viruses, and fungi. The presence of antibody-antigen complexes serves to jumpstart the immune cell response, prompting it to produce a variety of other cells and chemicals in an effort to rid the body of a foreign invader. Sometimes, however, the body accidentally produces antibodies that accidentally identify antigens on the body's own cells as foreign. When these antibodies bind to the body's antigens, the same immune response is provoked, but instead of being directed against a foreign invader, it is directed against the body itself.

Some researchers believe that the immune system is prompted into action by the presence of an actual threat (in the case of secondary vasculitis due to a bacterial infection), or is already overreacting (in the case of secondary vasculitis due to a preexisting autoimmune disease), or spontaneously swings into an overreactive state (in the case of primary vasculitis).

Symptoms of vasculitis depend on the specific organs or tissues affected. Affected body systems and potential symptoms include:

- Skin. Vasculitis of the skin may lead to a variety of rashes, bumps, bruises, or areas of subtle bleeding such

as petechia (tiny red dots), pupura (larger reddish purple spots), or ecchymoses (large, complexly colored areas of bruising). When areas of skin are completely deprived of any blood flow, and therefore of any oxygen delivery, the skin may die and turn black (gangrene).

- Joints. Vasculitis-induced arthritis occurs when the lining of the joints is affected by vasculitis, causing swelling, **pain**, decreased range of motion, and reduced functioning.
- Brain and nervous system. When vasculitis affects the nervous system, a variety of symptoms may result. Vasculitis of blood vessels in the brain can lead to headaches, confusion, personality changes, **seizures**, and coma. Depending on the area of the brain affected, other senses may suffer, including vision, hearing, and/or balance. Vasculitis of the nerves that provide sensation to the arms or legs can lead to pain and paresthesias (odd sensations of tingling, burning, pinpricks, lightning-flashes of pain, or numbness). A **stroke** occurs when an area of the brain tissue is completely deprived of oxygen, causing severe damage or destruction. The results of a stroke may be temporary or permanent, and the specific types of potential disability depend on what functions are normally controlled by the area of brain injured by the stroke.
- Gastrointestinal system. Any part of the gastrointestinal system can be affected by vasculitis, including the liver. Symptoms referable to the gastrointestinal system include pain, diarrhea, constipation, and vomiting. When blood flow is cut off to an area of the intestine, that area will become gangrenous or necrotic and die. This is a medical emergency.
- Heart. Vasculitis of the coronary arteries, which normally feed the heart muscle, can result in weakening of the heart muscle with compensatory enlargement, heart attack, or myocardial infarcation. When the walls of the arteries or the aorta undergo serious destruction due to vasculitis, weakened bulges called aneurysms may develop. If these aneurysms rupture, hemorrhage may occur.
- Lungs. Vasculitis of the complex network of blood vessels throughout the lungs can result in severe shortness of breath, cough, chest pain, and wheezing.
- Kidneys. When the kidney or renal arteries are damaged by vasculitis, high blood pressure results. The kidneys may fall behind in their normal role of filtering the blood, and kidney or renal failure may occur.

Diagnosis

Initial attempts to diagnosis vasculitis will depend on the area of the body affected and the kinds of symptoms exhibited. Blood tests that can demonstrate the presence of a strong inflammatory process include erythrocyte sedimentation rate, C-reactive protein, increased white blood cell count, and a variety of tests that can identify the presence of immune complexes or antibodies circulating within the blood. A variety of imaging techniques may reveal blood vessel inflammation, including ultrasound, echocardiography, computed tomography (**CT**), and **magnetic resonance imaging (MRI)** scanning. When the kidneys are involved, urine tests may reveal abnormalities. An x-ray procedure called **angiography** involves the injection of dye into a major artery to allow the detection of inflammation in the walls of blood vessels. Biopsies (tissue samples) may be taken from the blood vessels that serve affected organs or tissues to look for the presence of inflammation or scarring.

Treatment team

While rheumatologists specialize in the treatment of various autoimmune diseases (including various forms of vasculitis), patients may also be treated by specialists who concentrate on diseases that affect specific organs or tissues. For example, a patient may need to consult a cardiologist if the heart is affected; a nephrologist if the kidneys are affected; a **neurologist** if the nervous system is affected; a pulmonologist if the lungs are affected; a gastroenterologist if the gastrointestinal tract is affected; an ophthomologist if the eyes are affected; an otorhinolaryngologist if the ear, nose, and/or throat are affected; or a dermatologist if the skin is affected.

Treatment

Medications that calm the immune system and decrease inflammation are the mainstay of treatment for the various types of vasculitis. These include nonsteroidal anti-inflammatory medications (such as ibuprofen or aspirin) and corticosteroids (such as prednisone). More severe cases of vasculitis may require potent immunosuppressant drugs (such as cyclophosphamide or azathioprine).

Prognosis

The prognosis of vasculitis depends on the specific organ system affected and the severity of the particular case. In general, most people who receive appropriate treatment have a good recovery from vasculitis. However, when the disease causes kidney failure or affects the heart, the prognosis may be worse. Basic prognosis statistics of treated vasculitis include:

- Polyarteritis nodosa: about 90% of cases go into long-term remission.
- Hypersensitivity vasculitis: Most people recover completely, even without treatment.
- Giant cell arteritis: May require one to two years of steroid treatment, but most people recover completely.

- Wegener's granulomatosis: With treatment, 90% can expect symptom relief, and 75% go into complete remission.
- Takayasu's arteritis: 90% survive, with some spontaneous remission.
- Kawasaki disease: Under 3% of patients suffer fatal complications; most children recover uneventfully.

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Ventilatory assistance devices

Definition

Ventilatory assistance devices are mechanical devices that help a person breathe by replacing some or all of the muscular effort required to inflate the lungs.

Description

Ventilation is the process of inflating and deflating the lungs in order to breathe. Normally, a person uses several sets of muscles to accomplish this—the diaphragm at the base of the lungs, the muscles between the ribs (intercostals), and, to a small extent, the muscles of the lower neck and shoulder area. When these muscles are weakened through disease or injury, the ability to ventilate is impaired. As a result, a person cannot get sufficient oxygen into, and carbon dioxide out of, the lungs in order to maintain appropriate levels in the blood. In addition, weakened ventilation muscles also impair the ability to cough, which is an essential part of clearing lung secretions and preventing infection.

Ventilatory assistance devices may be needed due to:

- muscular dystrophies (progressive muscle weakening disorders)
- amyotrophic lateral sclerosis (ALS), a progressive disease causing muscle weakness
- polio
- high **spinal cord injury** (injury to the spinal cord in the neck)
- Guillain-Barré syndrome (a rapidly progressive but reversible loss of muscle control)
- myasthenia gravis, acute crisis (MG is a muscle-weakening disease, in which patients may experience a "crisis" of rapid and dangerous loss of muscle strength)
- head trauma
- botulism (poisoning by **botulinum toxin**, usually from improperly preserved food)
- tetanus (poisoning by tetanus bacteria, usually by a deep puncture wound)

Nighttime ventilators are also used for people with obstructive **sleep apnea**. This is a condition in which breathing is impaired during sleep by obstructions in the airway, most often extra tissue at the rear of the throat.

Ventilatory assistance is not the same as supplying extra oxygen, as is done for people whose lungs are damaged. The person who needs ventilatory assistance generally has normal gas exchange capacity, and simply needs help moving air in and out. Supplemental oxygen can worsen the situation in such cases, as it may depress the normal signals from the brain to stimulate breathing.

Ventilators

A ventilator is a machine that uses a tube to blow air into, and suck it out of, the body. The ventilator may be designed to deliver air at a set volume (volume ventilator) or at a set pressure (pressure ventilator).

Volume ventilator settings may be adjusted to deliver a variable volume of air depending on the patient's needs, and can either cycle automatically or be initiated by the patient's voluntary efforts.

Pressure ventilators come in two major styles. Continuous positive airway pressure (CPAP) delivers air at a steady pressure, which assists the patient while breathing in (inspiration) and resists breathing out (expiration). The purpose of CPAP is not to completely inflate the lungs, but

Key Terms

Neuromuscular disease Disease involving both the muscles and the nerves that control them.

rather to maintain an open airway. This makes it most appropriate for use in sleep apnea, in which a patient's airway closes frequently during sleep. In contrast, bi-level positive airway pressure (BiPAP) delivers a higher pressure on inspiration in order to allow the patient to completely inflate the lungs, and then switches to a low pressure on expiration, to allow easy exhalation. BiPAP is a common choice for patients with neuromuscular disease, whose respiratory muscles are weakened.

There are other rarer devices in use, which surround a patient's chest cavity and abdomen with a rigid shell, and change the pressure within. By lowering the pressure, air rushes into the lungs. The "iron lung" is one such device; smaller and more portable "cuirasses" are occasionally used to similar effect.

Interfaces

The air from a ventilator is delivered to the patient either through a face mask or directly into the lungs through a tracheostomy (trach) tube. Each has its advantages and disadvantages.

A tracheostomy is an opening in the airway in the middle of the throat through which a tube is inserted to deliver air. The properly chosen trach tube will fit comfortably. A widespread misunderstanding about tracheostomy ventilation is that it prevents talking, but this does not have to be so. Trach tubes are available that do not interfere with speech, and patients contemplating tracheostomy should ensure that their respiratory specialist is familiar with them. Trach tubes may provide the patient a greater sense of security and, unlike a face mask, it can easily be hidden from view with a well-placed scarf. Trach tubes do require daily lung hygiene, either by the patient or by a trained caregiver. This involves suctioning out secretions from the lungs, which tend to be increased due to the presence of the tube.

Face masks fit snugly over the mouth and nose, and are held on with a strap. Finding the right mask takes some time, but a well-fitting mask is comfortable and easy to tolerate for many hours per day. The mask usually must be removed to talk, but this does not present a problem for many patients who retain some use of their hands. The mask may also be used at night.

Other noninvasive interfaces are also available, including mouthpieces and "nasal pillows" that fit into one or the other orifice and are smaller than masks. These methods are usually chosen for patients who need fewer hours per day of ventilatory assistance.

Coughing

Patients with weakened respiratory muscles may be even more in need of cough assistance than they are of ventilatory assistance. Cough assistance may be delivered manually by a caregiver or by a machine (the in-exsufflator or cough assist) that is designed to inflate the lungs and then rapidly withdraw air, as occurs in a normal cough. This clears secretions that would otherwise accumulate and provide a locus for infection, as well as interfere with gas exchange.

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Richard Robinson

Ventricular shunt

Definition

A ventricular shunt is a tube that is surgically placed in one of the fluid-filled chambers inside the brain (ventricles). The fluid around the brain and the spinal column is called cerebrospinal fluid (CSF). When infection or disease causes an excess of CSF in the ventricles, the shunt is placed to drain it and thereby relieve excess pressure.

Purpose

A ventricular shunt relieves **hydrocephalus**, a condition in which there is an increased volume of CSF within the ventricles. In hydrocephalus, pressure from the CSF usually increases. It may be caused by a tumor of the brain

or of the membranes covering the brain (**meninges**), infection of or bleeding into the CSF, or inborn malformations of the brain. Symptoms of hydrocephalus may include **headache**, personality disturbances and loss of intellectual abilities (**dementia**), problems in walking, irritability, vomiting, abnormal eye movements, or a low level of consciousness.

Normal pressure hydrocephalus (a condition in which the volume of CSF increases without an increase in pressure) is associated with progressive dementia, problems walking, and loss of bladder control (urinary incontinence). Even though CSF is not thought to be under increased pressure in this condition, it may also be treated by ventricular shunting.

Demographics

The congenital form of hydrocephalus is believed to occur at an incidence of approximately one to four out of every 1,000 births. The incidence of acquired hydrocephalus is not exactly known. The peak ages for the development of hydrocephalus are in infancy, between four and eight years, and in early adulthood. Normal pressure hydrocephalus generally occurs in patients over the age of 60.

Description

The ventricular shunt tube is placed to drain fluid from the **ventricular system** in the brain to the cavity of the abdomen or to the large vein in the neck (jugular vein). Therefore, surgical procedures must be done both in the brain and at the drainage site. The tubing contains valves to ensure that fluid can only flow out of the brain and not back into it. The valve can be set at a desired pressure to allow CSF to escape whenever the pressure level is exceeded. In some cases where only brief drainage is needed, the shunt tube may simply drain to the outside.

A small reservoir may be attached to the tubing and placed under the scalp. This reservoir allows samples of CSF to be removed with a syringe to check the pressure. Fluid from the reservoir can also be examined for bacteria, cancer cells, blood, or protein, depending on the cause of hydrocephalus. The reservoir may also be used to inject antibiotics for CSF infection or chemotherapy medication for meningeal tumors.

Diagnosis/Preparation

The diagnosis of hydrocephalus should be confirmed by diagnostic imaging techniques such as computed tomography scan (**CT scan**) or **magnetic resonance imaging (MRI)** before the shunting procedure is performed. These techniques will also show any associated brain abnormalities. CSF should be examined if infection or tumor of the meninges is suspected. Patients with dementia or **mental retardation** should undergo **neuropsychological testing** to establish a baseline psychological profile before the shunting procedure.

As with any surgical procedure, the surgeon must know about any medications or health problems that may

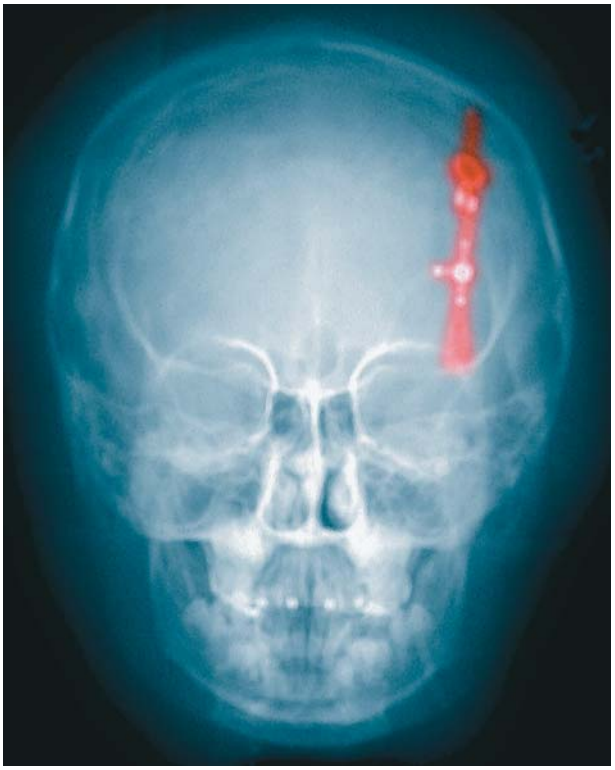
Key Terms

Cerebrospinal fluid Fluid bathing the brain and spinal cord.

Computed tomography (CT) scan An imaging technique in which cross-sectional x rays of the body are compiled to create a three-dimensional image of the body's internal structures.

Dementia Progressive loss of mental abilities.

Magnetic resonance imaging (MRI) An imaging technique that uses a large circular magnet and radio waves to generate signals from atoms in the body. These signals are used to construct images of internal structures.



A digitally enhanced x ray of the skull of a nine-year-old boy showing the shunt that was placed into the ventricle of the brain. *(Scott Camazine / Photo Researchers, Inc.)*

increase the patient's risk. Because infections are both common and serious, antibiotics are often given before and after surgery.

Aftercare

To avoid infections at the shunt site, the area should be kept clean. The physician should periodically check CSF to be sure there is no infection or bleeding into the shunt. CSF pressure should be checked to be sure the shunt is operating properly. The eyes should be examined regularly because shunt failure may damage the nerve to the eyes (optic nerve). If not treated promptly, damage to the optic nerve causes irreversible loss of vision.

Risks

Serious and long-term complications of ventricular shunting are bleeding under the outermost covering of the brain (**subdural hematoma**), infection, **stroke**, and shunt failure. When a shunt drains to the abdomen (ventriculoperitoneal shunt), fluid may accumulate in the abdomen or abdominal organs may be injured. If CSF pressure is lowered too much, patients may have severe headaches, often with nausea and vomiting, whenever they sit up or stand.

Normal results

After shunting, the ventricles get smaller within three or four days. This shrinkage occurs even when hydrocephalus has been present for a year or more. Clinically detectable signs of improvement occur within a few weeks. The cause of hydrocephalus, duration of hydrocephalus before shunting, and associated brain abnormalities affect the outcome.

Of patients with normal pressure hydrocephalus who are treated with shunting, 25–80% experience long-term improvement. Normal pressure hydrocephalus is more likely to improve when it is caused by infection of or bleeding into the CSF than when it occurs without an underlying cause.

Morbidity and mortality rates

Complications of shunting occur in 30% of cases, but only 5% are serious. Infections occur in 5–10% of patients, and as many as 80% of shunts develop a mechanical problem at some point and need to be replaced.

Alternatives

In some cases of hydrocephalus, certain drugs may be administered to temporarily decrease the amount of CSF until surgery can be performed. In patients with hydrocephalus caused by a tumor, removal of the tumor often cures the buildup of CSF. Approximately 25% of patients respond to therapies other than shunt placement.

Patients with normal pressure hydrocephalus may experience a temporary improvement in walking and mental abilities upon the temporary drainage of a moderate amount of CSF. This improvement may be an indication that shunting will improve their condition.

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Ventricular system

Definition

A ventricle is an internal cavity of the brain. Within the normal human brain, there is a connecting system of ventricles, commonly referred to as the ventricular system, which is filled with cerebrospinal fluid (CSF). The ventricular system within the brain develops from the cavity of the neural tube in the embryo.

Description

The ventricular system is composed of two lateral ventricles and two midline ventricles, referred to as the third and fourth ventricles. The chambers are connected to allow the flow of cerebrospinal fluid via two interventricular foramen (referred to as the foramen of Monro) and the cerebral aqueduct (referred to as the aqueduct of Sylvius).

The chambers of the ventricular system are lined or covered with ependymal cells and are continuous with the central canal enclosed within the spinal cord. Ependymal cells also line the central canal of the spinal cord.

Basic anatomy

The lateral ventricles

The lateral ventricles are separated by the septum pellucidum and do not communicate directly (i.e., do not allow the flow of cerebrospinal fluid) with each other. Cerebrospinal fluid within the individual lateral ventricles must flow to the third ventricle via the interventricular foramen associated with each lateral ventricle.

Lateral ventricles themselves are descriptively divided into a body with anterior, posterior, and inferior horns.

The third ventricle

The third ventricle is a narrow cavity or cleft located between the two thalami. The third ventricle also contains two saclike recesses called the anterior supraoptic recess and the infundibular recess. The massa intermedia, the neural tissue that connects both halves of the thalamus in some brains, runs through the third ventricle. Posteriorly, the third ventricle communicates with the fourth ventricle via the cerebral aqueduct, a narrow channel that allows the flow of cerebrospinal fluid from the third to the fourth ventricle. There is no choroids plexus within the cerebral aqueduct.

The fourth ventricle

The fourth ventricle is a wide and flattened space located just anterior to the **cerebellum** and posterior to the upper, or superior, half of the medulla oblongata and the pons. The fourth ventricle also has two lateral saclike pouches that are called the lateral recesses. The fourth ventricle is continuous with the upper (superior) terminal end of the central canal of the spinal cord. The fourth ventricle also connects with the subarachnoid space via three small foramina: the two foramina of Luschka (one in each of the lateral recesses) and the foramen of Magendie.

The subarachnoid space continues as the space between the arachnoid matter and the pia mater (meningal tissues that surround the brain and spinal cord) and is filled with CSF. The subarachnoid space also surrounds cranial and spinal nerves.

CSF flow and blockage of the ventricular system

The normal flow of cerebrospinal fluid—produced from brain surface tissue and the choroids plexuses within the ventricles—is from the two lateral ventricles through their respective interventricular foramina into the third ventricle. Then the CSF flows from the third ventricle through the cerebral aqueduct into the fourth ventricle and from there it can flow into the subarachnoid space where it is reabsorbed into the bloodstream.

Swellings or structures within the ventricular system may be due to congenital defect, trauma, or tumor.

If there is a blockage of the ventricular system the flow of CSF is interrupted. If, for example, there is a blockage within the cerebral aqueduct, the normal flow of fluid formed in the lateral ventricles and the third ventricle is interrupted, and the lateral ventricles and third ventricle begin to swell with cerebrospinal fluid. The swelling or enlargement is termed **hydrocephalus**. Hydrocephalus can also result from the formation of CSF (as can occur with a tumor in one of the choroid plexuses) that exceeds the amount that can flow through the ventricular system, or from a downstream-diminished capacity to absorb cerebrospinal fluid.

A tumor in one of the interventricular foramen connecting a lateral ventricle to the third ventricle obstructs the flow of cerebrospinal fluid from the same side lateral ventricle and results in an asymmetrical swelling of the blocked lateral ventricle.

Blockage of the flow of CSF through the foramen connecting the fourth ventricle to the subarachnoid space usually produces asymmetrical swelling or dilation of the entire ventricular system. The entire ventricular system can also swell in cases of meningitis in which the flow of cerebrospinal fluid over the outer surface of the brain is obstructed.

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Vertebrobasilar disease

Definition

Vertebrobasilar disease describes a broad spectrum of vascular abnormalities in the arterial supply to the brain stem.

Description

The vertebrobasilar circulation (VC, also called the posterior circulation) consists of the arterial supply to the brain stem, **cerebellum**, and occipital cortex. The vertebral arteries arise from the subclavian arteries in the neck. In the brain, the vertebral arteries lie deep in the base of the brain and unite in an area called the medullopontine junction to form the basilar artery. The basilar artery branches again to form the posterior cerebral arteries. Any interruption in blood flow in the VC may cause a broad spectrum of symptoms determined by the specific arterial branch or branches involved, and the degree of occlusion inside the blood vessels. The brain stem is a major area of neurologic activity since this area contains cranial nerves, neurosensory tracts, and the reticular activating system (RAS). Problems in blood flow to the VC result in several overlapping clinical syndromes.

Demographics

In the United States, approximately 25% of strokes and TIAs (transient ischemic attacks or "mini" strokes) occur in the vertebrobasilar circulation. Research with **magnetic resonance imaging (MRI)** studies estimates that 40% of patients with vertebrobasilar TIAs (transient ischemic attacks) have brain stem infarction. The disease affects men twice as often as women. Vertebrobasilar ischemic disease occurs in late life, usually between 70–80 years of age. The incidence (number of new cases) is 20–30 cases per 1,000 for persons over age 75. In the United States, the death rate for **stroke** is higher among blacks than whites. A severe form of the disorder, called basilar artery syndrome, caused by complete obstruction of the vertebrobasilar circulation (inside the brain) is fatal in 75–85% of cases. Approximately 50% of persons who have infarctions in the vertebrobasilar area report TIA events within days or months prior to onset of permanent deficit.

Causes and symptoms

The cause of vertebrobasilar disease (VD) is atherosclerosis that affects the vertebrobasilar (posterior) circulation at intracranial (inside the cranium and includes the basilar artery) sites and extracranial (outside the cranium and includes the vertebral artery) sites. Partial or complete occlusion can occur in major arteries or smaller arterial branches. The cause of VD is atherosclerosis and vertebrobasilar insufficiency in the brain caused by blockage (occlusion), and is more common among patients with cardiovascular risk factors that typically include obesity, smoking, use of oral contraceptives, advanced age, diabetes mellitus, hypertension (high blood pressure). and dyslipidemias (abnormalities that cause an increase in lipids in the blood). Other causes of vertebrobasilar disease can include destruction to arteries such as fibrotic changes in the muscular layer of arteries (a condition called fibromuscular dysplasia) and arterial dissection or **aneurysms**.

The symptoms of TIA have a short duration and usually last approximately eight minutes. Vertigo is the hallmark symptom of vertebrobasilar insufficiency. Other symptoms include visual defects (diplopia), syncope (drop attacks), dysphagia (difficulty swallowing), **dysarthria**, hoarseness, and facial numbness, or paresthesias. Patients with early stage vertebrobasilar insufficiency have transient episodes of neurologic symptoms. Persons with more advanced disease to the vertebrobasilar circulation may have eye deficits, limb **ataxia**, loss of taste, limb/trunk dysesthesia, nystagmus, and deficit in temperature/pain perception.

Diagnosis

Neuroimaging studies are the primary diagnostic tool necessary to confirm vertebrobasilar disease. Other tests are also indicated and include analysis of blood, electrolytes, glucose, urinalysis, thyroid function tests, and erythrocyte sedimentation rate (a special blood test that rules out other possible disorders). Computed tomography (**CT**) **scans** help to detect mass defects and MRIs can help visualize smaller areas of ischemia. Ultrasound studies can help assess and monitor vertebrobasilar patency (the degree of occlusion).

Key Terms

Cranial nerves The set of twelve nerves found on each side of the head and neck that control the sensory and muscle functions of the eyes, nose, tongue, face, and throat.

Dysarthria Slurred speech.

Hydrocephalus An abnormal accumulation of cerebrospinal fluid within the brain. This accumulation can be harmful by pressing on brain structures, and damaging them.

Infarction Death of tissue due to inadequate blood supply.

Nystagmus An involuntary, rhythmic movement of the eyes.

Paresthesia An abnormal sensation often described as burning, tickling, tingling, or "pins and needles."

Reticular activating system A network of structures, including the brain stem, medulla, thalamus, and nerve pathways, which function together to produce and maintain arousal.

Transient ischemic attack (TIA) A brief interruption of the blood supply to part of the brain that causes a temporary impairment of vision, speech, or movement. Usually, the episode lasts for just a few moments, but it may be a warning sign for a full-scale stroke.

Treatment team

A **neurologist** is typically required as the specialist coordinator of treatment. A neurosurgeon is used for surgical evacuation of hemorrhages complicated by **hydrocephalus**. An interventional neuroradiologist may be required to provide thrombolytic agents (chemicals that dissolve clots) by intra-arterial infusion delivery (injecting a chemical directly in an artery located in the brain using TV monitor-guided imagery).

Treatment

Treatment can be either supportive or interventional if arterial patency is an option. Emergency treatment for a bleeding patient includes airway preservation, control of blood pressure, and assessment of neurologic and mental status, intravenous fluid management, prevention of vomiting, and antiplatelet agents to prevent arterial occlusion. Additionally, a stroke patient may require treatment for hypertension if present, and mouth feedings should be avoided since the patient may be unable to swallow or chew. Antiplatelet medication is the first line treatment for vertebrobasilar disease, however, the usefulness is unclear. Anticoagulants (heparin) and antiplatelets (aspirin and ticlopidine) are typically given to prevent recurrent or ongoing occlusion (caused by blood clots) of the posterior (vertebrobasilar) circulation.

Recovery and rehabilitation

Recovery is variable depending on the degree of occlusion in the vertebrobasilar circulation. Persons with the severe form, basilar artery occlusion, often die in 75–85% of cases. Rehabilitation depends on the extent of damage and the deficits caused by permanent injury in the brain.

Clinical trials

Research in this area is diversified and abundant. Currently, the National Institute of Neurological Disorders and Stroke (NINDS) is investigating molecular mechanisms associated with neuronal injury. Research concerning the genetics of stroke and **gene therapy** is ongoing in experimental models. New research in high resolution neuroimaging techniques, and rehabilitation have demonstrated compensatory mechanisms (re-circuitry of neurons) as a result of stroke. Further information can be found at <http://www.clinicaltrials.gov>. or <http://www.ninds.nih.gov>.

Prognosis

Vertebrobasilar TIAs have a favorable outcome since the chance for complete stroke is minimal. Collateral circulation from smaller blood vessels may help to improve the outcome.

Special concerns

Clinicians must be vigilant to be suspicious of vertebrobasilar insufficiency in elderly patients who suffer from vertigo. Hemorrhage has to be ruled out before blood thinner (anticoagulation) treatment is initiated. Additionally, it is important to take special precautions when feeding persons with brain stem infarction, because patients can develop problems with normal swallowing mechanisms that can cause aspiration pneumonia (caused by food lodged in the lungs).

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Vertigo *see* **Dizziness**

Vestibular schwannoma

Definition

A vestibular schwannoma is a type of benign (noncancerous) tumor that affects the eighth cranial nerve.

Description

The eighth cranial nerve is involved in both hearing (the auditory or acoustic component of the nerve) and balance (the vestibular component of the nerve). Like all cranial nerves, the eighth cranial nerve (also called the acoustic or auditory nerve) is paired, meaning that there is one on each side of the body. Each eighth cranial nerve runs from the inner ear to the brain, passing through a bony canal called the internal auditory canal. This canal is shared with the seventh cranial nerve, the facial nerve.

Like many nerve fibers, the eighth cranial nerve is wrapped in a sheath composed of specialized Schwann cells that serve to speed the transmission of information along the nerve. When the Schwann cells grow in an uncontrolled fashion, they can develop into a tumor, called schwannoma or neuroma. Although a vestibular schwannoma is not malignant (cancerous), it can still result in serious symptoms caused by pressure on the eighth cranial nerve or on surrounding tissues or the adjacent facial nerve. Most cases of vestibular schwannoma are unilateral; that is, only one of the two eighth cranial nerves is affected.

Demographics

About 100,000 people in the United States develop vestibular schwannoma. Most people who develop a vestibular schwannoma are between the ages of 30 and 50; children rarely develop vestibular schwannoma. Women are slightly more likely than men to develop a vestibular schwannoma.

There is an increased risk of developing a vestibular schwannoma in individuals who have a disease called **neurofibromatosis**. In these cases, the tumors tend to develop on both sides (bilaterally). In fact, about 10% of all cases of vestibular schwannoma occur in individuals who have neurofibromatosis. People with neurofibromatosis who develop vestibular schwannoma may do so at a younger age, sometimes in their teens or early adulthood.

Causes and symptoms

No one knows exactly why some people develop a vestibular schwannoma. Most seem to occur sporadically, with no identifiable cause. There is an increased risk of developing a vestibular schwannoma in individuals with neurofibromatosis, and some research has suggested that individuals who are chronically exposed to loud noise may have an increased risk of developing a vestibular schwannoma.

The initial symptoms of vestibular schwannoma are caused by pressure on the eighth cranial nerve, and include gradually progressive one-sided hearing loss, buzzing in the ears (tinnitus), **dizziness**, and difficulty with balance. In particular, the hearing impairment greatly affects the ability to understand speech (speech discrimination). When the vestibular schwannoma puts pressure on the seventh cranial nerve, **pain** and numbness in the face may develop. Eventually, the facial muscles may become paralyzed. The individual may also experience difficulty chewing and/or swallowing, ear pain, and **headache**. When left untreated, hearing impairment may eventually lead to complete deafness in the affected ear. If the tumor begins to encroach on other brain tissues, the person may experience nausea, vomiting, fever, vision changes, and difficulty walking.

Diagnosis

A careful neurologic examination will reveal the deficits that are characteristic of vestibular schwannoma. Computed tomography (**CT**) or **magnetic resonance imagaing** (**MRI**) scan may help pinpoint the tumor. Audiometry and brain stem auditory evoked potential tests are performed to establish the degree of hearing deficit prior to treatment. Audiometry assesses hearing acuity by evaluating the ability to hear various volumes and tones. A brain stem auditory evoked potential test evaluates brain wave responses to clicking sounds, in order to assess the functioning of the auditory (hearing) pathways in the brain.

Key Terms

Acuity Sharpness.

Acoustic A term that refers to hearing.

Auditory A term that refers to hearing.

Benign Nonmalignant; not cancer.

Bilateral Occurring on both sides of the body.

Cranial nerve One of 12 pairs of nerves that leave the brain stem.

Neurofibromatosis Also called von Recklinghausen's disease; a disease in which tumors grow on nerve cells throughout the body.

Schwann cell A type of supportive cell in the nervous system that compose the myelin sheath around nerve fibers.

Unilateral Occurring on only one side of the body.

Vestibular A term that refers to the organs of balance.

Treatment team

When an individual is suspected of having a vestibular schwannoma, an otorhinolaryngologist and/or **neurologist** may be consulted to arrive at a diagnosis. An otorhinolaryngologist will be called upon if surgery is required.

Treatment

Surgery is nearly always necessary to treat vestibular schwannoma. There are several different types of surgery that are used to remove a vestibular schwannoma, classified by the anatomical pathway used to reach the tumor (called the "approach"). The surgeon will choose the approach based on tumor size, preoperative hearing acuity, and the patient's ability to tolerate surgical risk. In some cases, it is not possible to remove the entire vestibular schwannoma without considerable risk of damage to adjacent structures. In these cases, only part of the vestibular schwannoma may be removed, and the rest may be left in place (called "partial resection").

When a patient is medically frail, the surgeon may choose to simply monitor the growth of the vestibular schwannoma, delaying surgery until it becomes absolutely necessary. Occasionally, very small vestibular schwannoma may be treated with **radiation** therapy; when partial resection is necessary, surgery may be followed by radiation treatment.

Newer treatment techniques are called stereotactic radiosurgery or gamma knife surgery. Three-dimensional imaging allows the exact location of the tumor to be defined. The patient's head is held in a frame that allows high-dose radiation to be delivered from multiple angles directly at the tumor site.

Recovery and rehabilitation

In patients for whom the hearing impairment is not total, a hearing aid may be helpful. In patients who have completely lost hearing in one ear, a system called contralateral routing of sound (CROS) sends sound from the deaf ear through a microphone to the hearing ear, improving overall hearing acuity.

Prognosis

Without treatment, vestibular schwannoma will nearly always result in permanent deafness. Although surgery carries a high risk of hearing loss and facial nerve impairment, about 66% of patients who have small- to medium-sized vestibular schwannoma will have improved hearing acuity following surgery.

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Acoustic Neuroma Association. 600 Peachtree Pkwy, Suite 108, Cumming, GA 30041-6899. (770) 205-8211; Fax: (770) 205-0239. ANAUSA@aol.com. <http://anausa.org/>.

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Visual disturbances

Key Terms

Diplopia Also known as double vision, a visual disorder due to unequal action of the eye muscles causing two images of a single object to be seen.

Intracranial pressure The pressure inside the skull.

Nystagmus Involuntary rapid and repetitive movement of the eyes.

Optic nerve The bundle of nerve fibers that carry visual messages from the retina to the brain.

Optic neuritis Inflammation of the optic nerve.

Definition

Visual disturbances are abnormalities of sight. Visual disturbances associated with neurological disorders often include double vision (diplopia), moving or blurred vision due to nystagmus (involuntary rapid movements of the eyes), reduced visual acuity, reduced visual field, and partial or total loss of vision as in papilledema, a swelling of the optic disc, or in blindness. Visual disturbances are often symptoms of other disorders, in particular neurological disorders, but can also occur due to muscular disorders, vascular diseases, cancer, or trauma. Additionally, diseases such as diabetes and hyperthyroidism can contribute to the visual abnormalities. Some visual disturbances arise from congenital conditions that are often hereditary.

Description

Diplopia

Diplopia, or double vision, causes a person to see two objects instead of one. There are two main reasons for diplopia: one is a physical change in the lens, conjuctiva, or retinal surface; the second reason involves an inability of the brain to overlay the images seen with both eyes, which happens in a person with normal vision. The first type usually involves only one eye and is not corrected by covering of the eye. Scars or other physical defects in the eye cause the split of a single image, thus resulting in double vision. In contrast, the second type usually involves both eyes (binocular) and is corrected when one eye is covered. Binocular diplopia arises when the eye movement in one direction is prevented, and is often a congenital (present at birth) condition. Binocular diplopia is usually caused by misalignment of the eyes, which can be nerve or muscle related.

Abnormalities in eye movement can result from conditions such as cranial nerve paralysis (paresis), neuromuscular disease (e.g., **myasthenia gravis**), **multiple sclerosis**, infection, **stroke**, overactive thyroid (Grave's disease), or direct trauma to the eye. Diplopia can also be a result of a growing tumor, which presses on the nerves involved in eye movements.

The nerves involved in diplopia include three cranial nerves: the oculomotor nerve (third cranial nerve), the abducens nerve (sixth cranial nerve), and the trochlear nerve (fourth cranial nerve). These three nerves direct the movements of six extraocular muscles. Four muscles are innervated by the third cranial nerve, and the other two are innervated exclusively by either the fourth or the sixth cranial nerve. This arrangement allows the physician to determine the cause of visual disturbances observed in a patient. Misalignment of the eyes can be in any direction: inward, outward, upward, downward, or a combination. Damage to the third cranial nerve can cause outward and downward turning of the affected eye and the inability to pass midline in either of the two directions. Fourth cranial nerve damage will result in vertical diplopia, which is compensated by head tilting. Head turning is used to compensate for sixth cranial nerve damage that prevents outward movement of the eye.

Nystagmus

A different type of visual disturbance, nystagmus, is caused by abnormal eye movements and often results in blurred vision. Normal control of the eye movements depends on the neuronal connections between the eyes, brain stem, and the **cerebellum**. Changes in the **central nervous system** or peripheral labyrinthine apparatus can cause the uncontrolled, repetitive eye movements known as nystagmus. There are many types and subtypes of nystagmus depending on the underlying cause and movement involved. The most common form involves a jerking motion from side to side (horizontal nystagmus). The rapid eye movements can also appear in a vertical direction, usually indicating a problem with the central nervous system. Rotary movements are also sometimes observed in nystagmus.

Although nystagmus by itself does not cause loss of vision, it is often associated with poor vision. Nystagmus can develop in early childhood or in adulthood. Childhood nystagmus can be associated with eye defects (cataract or

retinal disorders) or result from unknown causes (congenital idiopathic nystagmus). Most cases of congenital nystagmus are not caused by a disease process and are familial.

If nystagmus develops later in life, it can be a sign of a serious underlying problem such as stroke, multiple sclerosis, or complication from head trauma. The direction of the eye movement can help the physician to diagnose the underlying neurological problem. For example, in an unconscious person, vertical nystagmus can indicate brain stem damage. This illustrates that eye movements not only cause visual disturbances, but are also an important diagnostic tool to determine if the brain is still alive.

The presence of the occulocephalic reflex (doll's eye movements) in people with coma shows that the brain stem is intact. The physician turns the patient's head from side to side or left to right to elicit the reflex. When the reflex is present, the eyes appear to move freely in the opposite direction from the direction the head was turned, thus moving in relation to the head. When the eyes remain fixated, this suggests lack of cerebral activity. Another important diagnostic test is the cold caloric test. The cold caloric test traces the direction of nystagmus to assess the oculovestibular reflex. An unconscious person's ear is injected with cold water, causing slow horizontal movement of the eyes towards the stimulation, which is followed by a fast return of the eyes to the midline.

Blindness

Blindness is the partial or complete loss of vision. The leading causes of blindness are glaucoma, cataracts, and diabetic retinopathy. Blindness can also result from eye diseases, optic nerve disorders, or brain diseases involving visual pathways or the occipital lobe of the brain. The patterns of visual field reduction depend on the area that is being affected by disease. Damage to visual pathways as a result of macular degeneration, retinal detachment, or optic nerve atrophy can affect one or both eyes. In contrast, damage to the optic nerve chiasm or the pathway beyond it affects both eyes. There are many eye diseases that can cause visual abnormalities or/and blindness, including retinal detachment, cataracts, retinal disorders (often inherited), and macular degeneration.

Macular degeneration is the leading cause of blindness for those over age 55 in the United States. The macula is the central portion of the retina that records images and sends them from the eye to the brain via the optic nerve. If the macula deteriorates, the eye loses the ability to see in fine detail. The cause of macular degeneration is not fully understood, but risks for the disorder increase with age. Other abnormalities in the central retina can lead to blurry vision or can affect color perception. Color blindness can also originate from the lack of one or more type of cones, a type of light receptor on the eye. Total color blindness (monochromatic vision) is very rare; most commonly, varying levels of single color deficits are found among people with color blindness. Central vision can also be destroyed by small hemorrhages in the retina as a result of the aging process or diabetic retinopathy.

The neuronal diseases affecting the optic nerve and causing blindness can result from developmental abnormalities (hereditary or sporadic), abnormalities in the blood vessels causing an insufficient blood supply to the eyes or optic nerve, glaucoma, and demyelinating and inflammatory diseases such as multiple sclerosis, tumors, toxic agents, and trauma.

Optic nerve damage

Papilledema, the swelling of the optic nerve, can result from increased intracranial pressure or optic nerve deterioration (optic neuropathy). Inflammation, lack of adequate blood supply to the optic nerve, and certain diseases such as multiple sclerosis can cause the optic nerve to deteriorate. A brain tumor, bleeding or blood clots in the brain, brain swelling due to encephalitis or trauma, or a blockage in cerebrospinal fluid circulation can cause an increase in pressure inside the skull (intracranial pressure). The condition is often life threatening, and correct diagnosis of papilledema is important.

Papilledema arising from increased intracranial pressure is often accompanied by other symptoms, including diplopia, nausea, **headache**, and reduction of the visual field. When diagnosing papilledema, the physician looks for swelling of the optic disc (the area where the optic nerve enters the eye). The early signs include slight changes in appearance of the edge of neural tissue. Later, the disc rises from the retinal surface and can appear pale or can show signs of hemorrhages in severe cases. Persistent, chronic papilledema can cause atrophy of the optic nerve head and result in blindness.

The optic nerve can also be damaged by increased intraocular pressure (IOP) as in glaucoma. The pressure develops in aqueous area of the eye and is transmitted to the back of the eye, causing an initial reduction in peripheral vision and leading eventually to blindness. Glaucoma is often a complication arising from diabetes.

Additionally, optic neuritis, or inflammation of the optic nerve, can cause permanent loss of vision. Demyelinating diseases such as multiple sclerosis, systemic infections, diabetes, and hereditary factors can cause optic neuritis. Optic neuritis can also be a secondary complication of diseases such as meningitis, sinusitis, or tuberculosis, or reactions to toxins or trauma.

Other important causes of blindness are tumors affecting the optic chiasm (the area in the brain where the optic nerves cross) such as gliomas, cerebral tumors, and

pituitary adenomas. In these cases, the transfer of visual stimuli through the optic nerve and visual pathways is directly affected and results in blindness.

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Vitamine B12 deficiency *see* **Vitamin/nutritional deficiency**

Vitamin/nutritional deficiency

Definition

Vitamins are substances that the human body requires but is unable to synthesize and therefore, must obtain externally. Deficiencies in three B vitamins, B1 or thiamine, B3 or niacin and B12 or cobalamin are known to cause neurological disorders. Thiamine deficiencies result in a disease called **beriberi**, which causes peripheral neurological dysfunction and cerebral neuropathy. Niacin deficiencies cause a wasting disease known as pellagra, which affects the skin, mucous membranes, gastrointestinal tract as well as the brain, spinal cord and peripheral nerves. Cobalamin deficiencies most often result in the disease pernicious anemia. Neurological symptoms of pernicious anemia include numbness in the extremities, impaired coordination and a ringing in the ears.

Description

Thiamine deficiency

Thiamine was the first water-soluble vitamin to be discovered, and is therefore, also known as vitamin B1. Thiamine deficiency, or beriberi, manifests itself as both wet beriberi, which affects the cardiovascular system, and dry beriberi, which causes neurological dysfunction. People suffering from beriberi exhibit muscle atrophy or wasting (especially in the legs), edema (swelling), mental confusion, intestinal discomfort and an enlarged heart. Severe cases of dry beriberi may result in Wernicke-Korsakoff syndrome and acute cases of wet beriberi may cause shoshin beriberi. Both of these extreme forms of the disease are sometimes fatal. In most cases, administering thiamine successfully reverses symptoms associated with thiamine deficiencies.

Niacin deficiency

Niacin deficiency results in a disease called pellagra. The major symptoms of pellagra include dermatitis, **dementia** (loss of intellectual functions) and diarrhea. Pellagra means rough skin in Italian and it was named because of the characteristic roughened skin of people who have the disease. Skin lesions generally appear on both sides of the body (bilaterally) and are found in regions exposed to sunlight. The disease also affects mucous membranes of the mouth, vagina, and urethra. Gastrointestinal discomfort is an early symptom, followed by nausea, vomiting, and diarrhea, often bloody. Neurological dysfunctions associated with niacin deficiencies include memory loss, confusion and confabulation (imagined memory). Although treatment with niacin usually reverses all of the symptoms, untreated niacin deficiencies can result in multiple organ failure.

Vitamin B12 deficiency

Vitamin B12, also called cobalamin or cyanocobalamin, has the most complex chemical structure of all vitamins. It is unique in that it contains a cobalt atom embedded in a ring, similar to the iron atom in hemoglobin. The cobalt gives the molecule a dark red color. Vitamin B12 is found bound to animal protein and is very rare in vegetables. A deficiency of vitamin B12 results in a blood disorder, also called an anemia, which enlarges red blood cells so that the immune system destroys them at an increased rate. Because the blood cells are enlarged, the disease is characterized as a macrocytic anemia. Vitamin B12 functions in many important cellular processes including synthesis of red blood cells, DNA synthesis and the formation of the myelin sheath that acts as insulation around nerve cells. One of the most common causes of vitamin B12 deficiency is pernicious anemia. Pernicious anemia is caused by a lack of a glycoprotein called intrinsic factor that is required for absorption of vitamin B12. Intrinsic factor is secreted by the stomach, where it binds to the vitamin and transports it to the small intestine for absorption. Symptoms of vitamin B12 deficiency progress

Key Terms

Amino acid An organic compound composed of both an amino group and an acidic carboxyl group. Amino acids are the basic building blocks of proteins. There are 20 types of amino acids. Eight are "essential amino acids" that the body cannot make and must therefore be obtained from food.

Anemia A condition in which there is an abnormally low number of red blood cells in the bloodstream. It may be due to loss of blood, an increase in red blood cell destruction, or a decrease in red blood cell production. Major symptoms are paleness, shortness of breath, unusually fast or strong heart beats, and tiredness.

Vitamins Small compounds required for metabolism that must be supplied by diet, microorganisms in the gut (vitamin K), or sunlight (UV light converts pre-vitamin D to vitamin D).

from weakness and **fatigue** to neurological disorders including numbness in the extremities, poor coordination, and eventually, to hallucinations and psychosis. Vitamin B12 deficiencies are usually treated with intramuscular injections of vitamin B12 initially and oral vitamin B12 supplements on an ongoing basis.

Demographics

Thiamine deficiency

Thiamine deficiencies have no sex or racial predilection. Thiamine deficiency is more common in developing countries where poor nutrition occurs frequently, although no accurate statistics on its occurrence are available. In many of these countries, cassava or milled rice acts as a major staple of the diet. While cassava does contain some thiamine, it contains so much carbohydrate relative to the thiamine that eating cassava actually consumes thiamine. Most of the thiamine in rice is found in the husk. When the husk is removed from the rice during milling, the result is a diet staple that is an extremely poor source of thiamine.

Beriberi is often associated with alcoholism, likely because of low thiamine intake, impaired ability to absorb and store thiamine, and acceleration in the reduction of thiamine diphosphate. People who strictly follow fad diets, people undergoing starvation, and people receiving large amounts of intravenous fluids are all susceptible to beriberi. Some physical conditions such as hyperthyroidism, pregnancy, or severe illness may cause a person to require more thiamine than normal and may put a person at risk for deficiency.

A form of beriberi specific to infants known as infantile beriberi can occur in babies between two and four months old that are fed only breast milk from mothers who are thiamine deficient.

Niacin deficiency

Pellagra is most common when maize is a major part of the diet. Although maize does contain niacin, it is not biologically available unless it is treated with basic compounds, such as lime. This process occurs in the making of tortillas, so populations in Mexico and Central America do not usually suffer from pellagra. Maize is also deficient in tryptophan, a precursor to niacin.

In the early 1900s, pellagra was epidemic in the southern United States because of the large amount of corn in the diet. After niacin was discovered to prevent pellagra in 1937, flour was fortified with niacin and reports of pellagra decreased dramatically. Currently, incidence rates of pellagra in the United States are unknown. People at risk for pellagra include alcoholics, people on fad diets, and people with gastrointestinal absorption dysfunction.

The group of people who most commonly suffer from pellagra live in the Deccan Plateau of India. Their diet is rich in millet or sorghum, which contains tryptophan, but also large concentrations of another amino acid, leucine. It is thought that leucine inhibits the conversion of tryptophan to niacin.

Vitamin B12 deficiency

Pernicious anemia is most common in patients of northern European descent and African Americans and less frequent in people of southern European descent and Asians. There is no sex predilection. Vitamin B12 deficiency occurs in 3–43% of people over the age of 65. A form of pernicious anemia is also found in children under the age of ten. It is more frequent in patients with other immune disorders such as Grave's disease or Crohn's disease. There is some evidence that relatives of people who have pernicious anemia are more likely to get the disorder, indicating some genetic component to the disease. Because vitamin B12 only occurs in animal proteins, vegetarians are susceptible to the disease and should take vitamin B12 supplements.

Causes and symptoms

Thiamine deficiency

Thiamine deficiencies are caused by an inadequate intake of thiamine. In most developed countries, getting enough thiamine is not a problem since it is found in all vegetables, especially the outer layer of grains. It is not

present in refined sugars or fats and is not found in animal tissue. Diets rich in foods that contain thiaminases, enzymes that break down thiamine, such as milled rice, shrimp, mussels, clams, fresh fish and raw meat may be associated with thiamine deficiencies.

Thiamine is absorbed through the digestive tract by a combination of active and passive absorption. It is stored in the body as thiamine diphosphate, also called thiamine pyrophosphate, and thiamine triphosphate. Thiamine diphosphate is the active form and it is used as a coenzyme in several steps in cellular respiration. Thiamine may also have an important role in the function of nerve cells independent of cellular respiration. It is found in the cell membranes of nerve axons, and electrical stimulation of nerve cells causes a release of thiamine.

Early thiamine deficiency produces fatigue, abdominal **pain**, constipation, irritation, loss of memory, chest pain, anorexia and sleep disturbance. As the deficiency progresses, it can be classified as dry beriberi or wet beriberi depending on the activity of the patient. Many persons experience a mixture of the two types of beriberi, although pure forms do occur.

When caloric intake and physical activity are low, thiamine deficiency produces neurological dysfunction termed dry beriberi. Symptoms occur with equal intensity on both sides of the body and usually start in the legs. Impaired motor and reflex function coupled with pain, numbness and cramps are symptomatic of the disease. As the disease advances, ankle and knee jerk reactions will be lost, muscle tone in the calf and thigh will atrophy and eventually the patient will suffer from **foot drop** and toe drop. The arms may begin to show symptoms of neurological dysfunction after the legs are already symptomatic. Histological (tissue) tests may indicate patchy degradation of myelin in muscle tissues.

Wernicke-Korsadoff syndrome, also called cerebral beriberi, occurs in extreme cases of dry beriberi. The early stage is called Korsakoff's syndrome and it is characterized by confusion, the inability to learn, amnesia and telling stories that bear no relation to reality. Wernicke's **encephalopathy** follows with symptoms of vomiting, nystagmus (rapid horizontal or vertical eye movement), opthalmoplegia (inability to move the eye outwards) and ptosis (eyelid droop). If untreated, Wernicke's encephalopathy may progress to coma and, eventually death.

If a person has a high caloric intake and reasonable levels of activity, but has a diet with insufficient thiamine, myocardial dysfunction termed wet beriberi may result. This disease consists of vasodilatation and high cardiac output, retention of salt and water, and eventual damage to the heart muscle. A person suffering from wet beriberi will exhibit rapid heartbeat (tachycardia), swelling (edema), high blood pressure, and chest pain.

Shoshin beriberi is a more acute form of wet beriberi and it is characterized by damage to the heart muscle accompanied by anxiety and restlessness. If no treatment is received, the damage to the heart may be fatal.

Niacin deficiency

Niacin, also called vitamin B3, is a general term for two molecules: nicotinic acid and nicotinamine. Nicotinic acid is very easily converted into biologically important molecules including nicotinamide adenine dinucleotide (NAD or coenzyme I) and nicotinaminamide adenine dinucleotide phosphate (NADP or coenzyme II), both of which are crucial to oxidation-reduction reactions in cellular metabolism. These reactions play key roles in glycololysis, the generation of high-energy phosphate bonds, and metabolism of fatty acids, proteins, glycerol, and pyruvate. Because niacin plays such an important role in so many different cellular functions, the effect of niacin deficiencies on the body is extremely broad.

The amino acid, tryptophan is a precursor to niacin, and therefore, niacin deficiency can be averted if tryptophan is included in the diet. Some of the psychological symptoms of pellagra are thought to be related to decreased conversion rates of tryptophan to serotonin (a neurotransmitter) in the brain.

Causes of pellagra include diets that are deficient in niacin or its precursor, tryptophan. These diets often rely heavily on unprocessed maize. Other diets that may cause pellagra contain amino acid imbalances. For example, diets that rely on sorghum as a staple contain excessive amounts of the amino acid leucine, which interferes with tryptophan metabolism. Other causes of pellagra include alcoholism, fad diets, diabetes, cirrhosis of the liver, and digestive disorders that prevent proper absorption of niacin or tryptophan. One such disorder is called Hartnup disease, which is a congenital defect that interferes with tryptophan metabolism.

Symptoms of pellagra occur in the skin, in mucous membranes, the gastrointestinal tract, and the **central nervous system**. Skin symptoms are usually bilaterally symmetric. They include lesions characterized by redness and crusting, thickening of the skin and skin inelasticity. Secondary infections are common, especially after exposure to the sun. Mucus membranes are also affected by pellagra. Typically, the tongue becomes bright red first and then the mouth becomes sore, coupled with increased salivation and edema of the tongue. Eventually, ulcers may appear throughout the mouth. Gastrointestinal symptoms include burning of the mouth, esophagus and abdominal

pain. Later symptoms include vomiting and diarrhea, often bloody.

The central nervous system is also affected by niacin deficiencies. Early symptoms include memory loss, disorientation, confusion, **hallucination**. More severe symptoms are characterized by loss of consciousness, rigidity in the extremities, and uncontrolled sucking and grasping.

Vitamin B12 deficiency

Vitamin B12 is required for the biochemical reaction that converts homocysteine to methionine, one of the essential amino acids required to synthesize proteins. Because vitamin B12 impairs DNA translation, cell division is slow, but the cytoplasm of the cell develops normally. This leads to enlarged cells, especially in cells that usually divide quickly, like red blood cells. In addition, there is usually a high ration of RNA to DNA in these cells. Enlarged red blood cells are more likely to be destroyed by the immune system in the bone marrow, causing a deficit of red blood cells in the blood. Methionine is also required to produce choline and choline-containing phospholipids. Choline and choline-containing phospholipids are a major component of cell membranes and acetocholine, which is crucial to nerve function.

Vitamin B12 requires several binding proteins in order to be absorbed properly. After ingestion into the stomach, it forms a complex with R binding protein, which moves into the small intestine. The stomach secretes another protein, intrinsic factor, which binds with vitamin B12 after R binding factor is digested in the small intestine. Intrinsic factor bound with vitamin B12 adheres to specialized receptors in the ileum, where it is brought inside of cells that line the intestinal wall. Vitamin B12 is then transferred to another protein, transcobalamin II, which circulates through the blood plasma to all parts of the body. Another protein, transcobalamin I, is found bound to vitamin B12; however its function is not well understood.

Because of the complexity of the steps required for vitamin B12 absorption, there are many different ways that deficiencies could arise. First, a person could have inadequate intake of vitamin B12. This is extremely rare, since it is found in most animal proteins, but it does occur in some strict vegetarians. If any of the proteins that usher vitamin B12 through the body are unavailable or damaged, vitamin B12 deficiencies could arise. The most common such problem is associated with inadequate production of intrinsic factor, which results in pernicious anemia. Inadequate production of intrinsic factor can occur because of atrophy (wasting) of the stomach lining, the removal of the part of the stomach that produces intrinsic factor, or in rare cases, because of a congenital defect. Rare cases of intestinal parasites such as a fish tapeworm and bacterial infections may also result in vitamin B12 deficiencies. Finally, acid is often required to hydrolyze vitamin B12 from animal proteins in the stomach. If the stomach is not sufficiently acidic, for example in the presence of antacid medicines, quantities of vitamin B12 available for absorption may be deficient.

The liver stores large amounts of vitamin B12. It is estimated that if vitamin B12 uptake is suddenly stopped, it would take three to five years to completely deplete the stores in a typical adult. As a result, vitamin B12 deficiencies develop over many years. Initial symptoms include weakness, fatigue, lightheadedness, weight loss, diarrhea, abdominal pain, shortness of breath, sore mouth and loss of taste, and tingling in the fingers and toes.

As the disease progresses, neurological symptoms begin to appear. These include forgetfulness, **depression**, confusion, difficulty thinking, and impaired judgment. Eventually, a person with vitamin B12 deficiency will have numbness in the fingers and toes, impaired balance and poor coordination, ringing in the ears, changes in reflexes, hallucinations, and psychosis.

Diagnosis

Thiamine deficiency

A patient with bilateral symmetric neurological symptoms, especially in the lower extremities may be suffering from thiamine deficiency, especially if there is an indication that the diet may be poor. Some diseases with symptoms that are similar to beriberi include diabetes and alcoholism. Other neuropathies, such as **sciatica**, are often not symmetric and are not usually associated with beriberi.

Laboratory tests may show high concentrations of pyruvate and lactate in the blood and low concentrations of thiamine in the urine. Because the disease responds so well to thiamine, it is often used as a diagnostic tool. After administration of thiamine diphosphate, an increase in certain enzyme activity in red blood cells is an excellent indicator of thiamine deficiency.

Niacin deficiency

There are no diagnostic tests currently available to detect niacin deficiencies. Concentrations of niacin and tryptophan in the urine of patients suffering from pellagra are low, but not lower than other patients with malnutrition. Diagnosis must be made given a patient's symptoms and dietary history. Because replacement of niacin is so effective, it may be used as a diagnostic tool.

Vitamin B12 deficiency

A person suspected of suffering from vitamin B12 deficiency will be subjected to a physical examination along with blood tests. These blood tests will include a complete

blood count (CBC). If blood analyses indicate that the red blood cells are enlarged, vitamin B12 deficiency may be diagnosed. Other disorders that exhibit enlarged red blood cells (macrocytes) include alcoholism, hypthyroidism, and other forms of anemia. White blood cells with segmented nuclei also indicate vitamin B12 deficiency. Other blood tests include a vitamin B12 test and folic acid tests. Low concentrations of both may indicate vitamin B12 deficiencies. Elevated levels of homocysteine, methylmalonic acid (MMA) or lactate dehydrogenase (LDH) indicate vitamin B12 deficiencies. Finally tests that indicate the presence of antibodies against intrinsic factor may indicate pernicious anemia.

Once a vitamin B12 deficiency has been established in a patient, the severity of the disease can be evaluated using a Schilling test. The patient is orally administered radioactive cobalamin and then an injection of unlabeled cobalamin is given intramuscularly. The ratio of radioactive to unlabeled cobalamin in the urine during the next 24 hours gives information on the absorption rate of cobalamin by the patient. If the rates are abnormal, pernicious anemia is diagnosed. As a final check, the patient is given cobalamin bound to intrinsic factor. With this, the patient's absorption rates should become normal if pernicious anemia is the cause of the symptoms.

Treatment

Thiamine deficiency

In most cases, rapid administration of intravenous thiamine will reduce symptoms of thiamine deficiency. Continued dosages of the vitamin should be continued for several weeks accompanied by a nutritious diet. Following recovery, a diet containing one to two times the recommended daily allowance of thiamine (1-1.5 mg per day) should be maintained. Shoshin beriberi requires cardiac support as well. Thiamine has not been found to be toxic for people with normal kidney function, even at high doses.

Niacin deficiency

Niacin deficiency can be treated effectively with replacement of niacin in the diet. In the case of Hartnup disease, large quantities of niacin may be required for effective reversal of symptoms.

Vitamin B12 deficiency

Vitamin B12 deficiency responds well to administration of cobalamin. Because absorption in the small intestine is often part of the problem, the best way to administer cobalamin is by intramuscular injection on a daily basis. After 6 weeks, the injections can be decreased to monthly for the rest of the patient's life. Usually, response to this treatment alleviates all symptoms of the disease. In severe cases, a blood transfusion may be needed and neurological conditions may not be completely reversed.

Resources

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"Thiamine deficiency and dependency." *The Merk Manual.* (January 16, 2004). <http://www.merck.com/mrkshared/mmanual/section1/chapter3/3j.jsp>.

ORGANIZATIONS

NIH/National Digestive Diseases Information Clearinghouse. 2 Information Way, Bethesda, MD 20892-3570. (301) 654-3810 or (800) 891-5389; Fax: (301) 907-8906. nddic@info.niddk.nih.gov. <http://www.niddk.nih.gov>.

National Heart, Lung, and Blood Institute (NHLBI). P. O. Box 30105, Bethesda, MD 20824-0105. (301) 592-8573; Fax: (301) 592-8563. NHLBIinfo@rover.nhlbi.nih.gov. <http://www.nhlbi.nih.gov>.

Juli M. Berwald, PhD

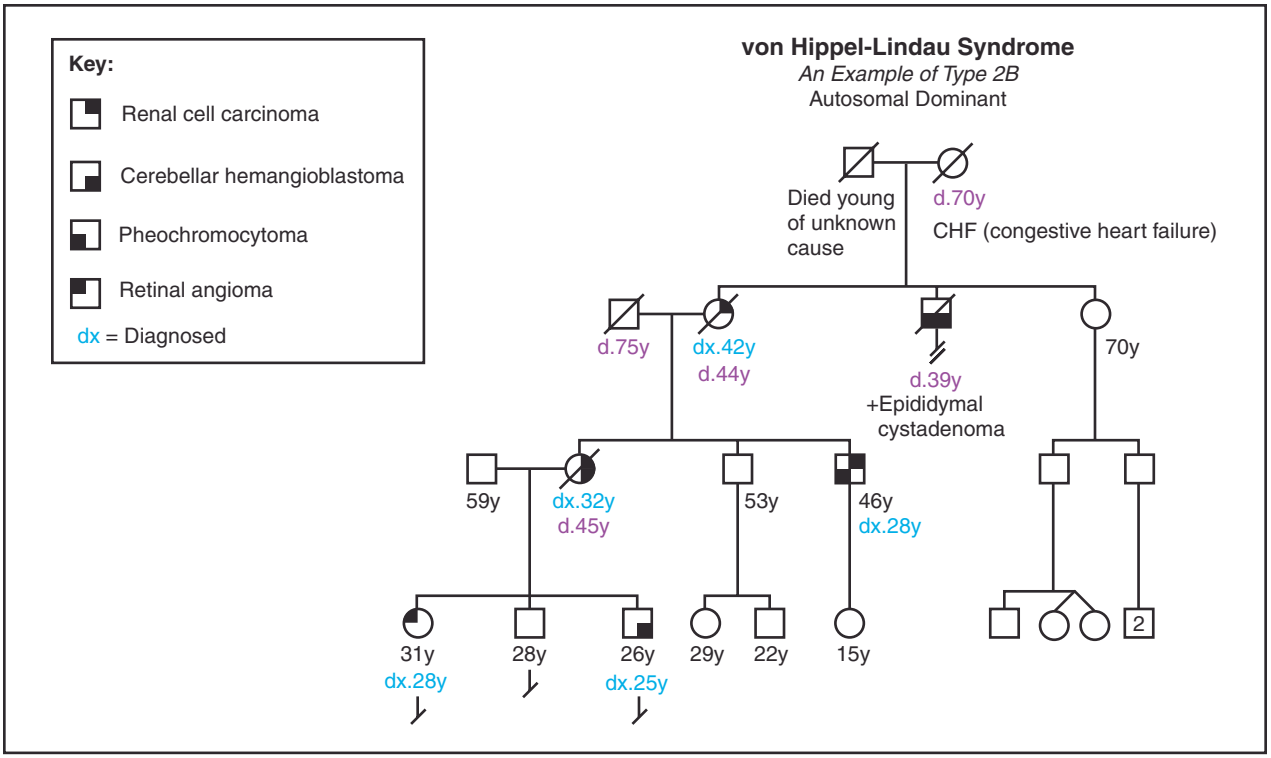
von Economo disease *see* **Encephalitis lethargica**

von Recklinghausen disease *see* **Neurofibromatosis**

Von Hippel-Lindau disease

Definition

Von Hippel-Lindau disease (VHL) is a hereditary condition that involves cancer and can affect people of all ages. It was named after the physicians to first describe aspects of the condition in the early 1900s, German ophthalmologist Eugen von Hippel and Swedish pathologist Arvid Lindau. It was not until 1964 that the term von Hippel-Lindau disease was coined.



See Symbol Guide for Pedigree Charts. *(Gale Group.)*

Description

VHL often involves symptoms in the **central nervous system** (CNS) and include hemangioblastomas of the **cerebellum**, spinal cord, brain stem, and nerve root. Retinal hemangioblastomas and endolymphatic sac tumors are CNS tumors that can also be seen. The kidneys, adrenal gland, pancreas, epididymis, and female broad ligaments may also be affected.

Behavioral and learning problems are not usually associated with VHL, but may be if the CNS tumors are quite significant. Symptoms of VHL do not usually cause concerns in very early childhood. However, VHL is a hereditary cancer syndrome for which screening is appropriate in late childhood and adolescence for those at risk.

Demographics

Studies from 1991 indicated an incidence of VHL of about one in 36,000 live births in eastern England. The condition affects people of all ethnic groups worldwide, with an equal proportion of males and females.

In 1993, the gene for VHL was identified. The majority of people with VHL also have an affected parent, but in about 20% of cases there is no known family history of VHL.

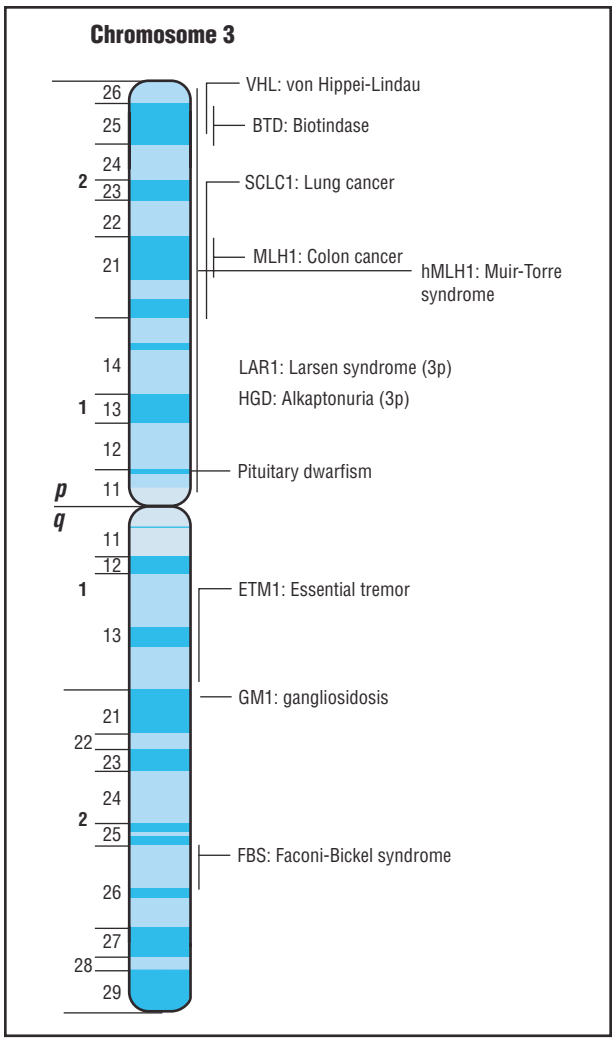
Causes and symptoms

Mutations in the VHL gene on chromosome 3 are now known to cause the condition. VHL is inherited in an autosomal dominant manner, meaning that an affected individual has a 50% chance to pass a disease-causing mutation to offspring, regardless of their gender.

VHL is a tumor-suppressor gene, or one whose normal function is to prevent cancer by controlling cell growth. Mutations in the VHL gene potentially cause uncontrolled cell growth in the gene, which is why a person with a VHL mutation is prone to developing cancer and other growths.

Hemangioblastomas of the CNS are the most common tumor in VHL; about 60–80% of people with VHL develop these tumors. The average age for CNS hemangioblastomas to develop is 33 years. The tubors are a frequent cause of death in people with VHL because they can disturb normal brain functioning. They can occur anywhere along the brain/spine areas, and swelling or cysts are often associated. The most common locations for CNS hemangioblastomas are in the spinal cord and cerebellum.

Symptoms from CNS hemangioblastomas depend on their size and exact location. Common symptoms include **headaches**, vomiting, gait disturbances, and **ataxia**, especially when the cerebellum is involved. Spinal hemangioblastomas often bring **pain**, but sensory and motor loss



von Hippel-Lindau disease, on chromosome 3. *(Gale Group.)*

may develop only if the tumor is so large that it is pressing into the spinal cord. Some hemangioblastomas never cause symptoms, and are only seen with special imaging techniques.

Retinal hemangioblastomas are seen in as many as 60% of people, and many times may be the first sign of VHL. There may be multiple hemangioblastomas in one eye, or even in both eyes. The average age for these to develop is about 25 years, but some develop in people younger than 10 years of age. When in the early stages and quite small, retinal hemangioblastomas may not cause symptoms. As they progress, they can cause retinal detachment, with partial or total vision loss.

Endolymphatic sac tumors are seen in about 11% of people with VHL, but are very rare in the general population. The first sign of this form of tumor may be partial hearing loss, which may progress to total hearing loss. Other symptoms can be tinnitus (buzzing in the ear), **dizziness**, and facial paresis. These tumors often erode or expand the inner bones of the ear, a major reason for the hearing loss.

Kidney involvement occurs in about 60% of people with VHL, which usually includes renal cell carcinoma and kidney cysts. The typical age that these symptoms develop is 39 years. One or both kidneys may be diseased, with multiple cysts or growths that may be seen in each kidney. Renal cell carcinoma is a major cause of death in VHL. Kidney disease may not cause symptoms, or may not cause a reduction in kidney function. In severe cases blood in the urine, a mass or pain may be felt in an affected person's side.

Adrenal gland pheochromocytomas occur in 10–20% of people with VHL; the average age of diagnosis is 30 years, though they have been seen in children under the age of 10. There may be a single tumor present, or multiple tumors. For people with a subset of VHL called type 2C, a pheochromocytoma is the only symptom they have. Five percent of all pheochromocytomas are cancerous, requiring treatment. Symptoms of pheochromocytomas may include intermittent or continuous high blood pressure, heart palpitations, a quickened heart rate, headaches, sweating episodes, nausea, and paleness of the skin. Pheochromocytomas may also cause the level of catecholamines to be elevated in urine.

Of all people with VHL, 35–70% have a pancreatic tumor, cyst, or cystadenoma. The masses often develop in the mid-30s, and are usually without symptoms. Pancreatic involvement is important to diagnose VHL, but is difficult to identify on its own because it may cause no medical problems.

Men with VHL have epididymal cystadenomas 25–60% of the time. There may be multiple masses, occurring in both sides. If occurring in both sides, in rare cases they may lead to infertility. Epididymal cystadenomas are non-cancerous and may show up in the teenage years. In women, a similar tumor to the epididymal cystadenoma in men is that of the broad ligaments. These are not very common, so the true frequency and age of development is unknown in VHL. They are non-cancerous and usually cause no specific symptoms.

Diagnosis

Until the discovery of the VHL gene, the diagnosis of the condition was made on a clinical basis. People with a family history of VHL need only have a CNS hemangioblastoma (including retinal), pheochromocytoma, or renal cell carcinoma to be given a diagnosis. Those without a family history must have two or more CNS

hemangioblastomas, or one CNS and a visceral finding (with the exception of epididymal and renal cysts) to have a diagnosis.

There has been the creation of subtypes within VHL. Type 1 families are at a very low risk for pheochromocytomas, but have the typical risk for all other tumors that are seen. All type 2 families have a risk for pheochromocytomas; type 2A families have a low risk for renal cell carcinoma, while type 2B families have a high risk for it; type 2C families only have pheochromocytomas and no other signs of VHL.

Hemangioblastomas of the brain and spine are typically found through **magnetic resonance imaging (MRI)** scans. Those found in the retina can be seen by examination of the dilated eye by an ophthalmologist. Endolymphatic tumors may be visualized using computed tomography (**CT**) and **MRI** scans of the internal ear canals. Audiograms can also be done to identify and track hearing loss.

Renal and pancreatic involvement is often found through abdominal CT scans, MRI scans, or ultrasounds of the kidneys and pancreas. Pheochromocytomas can be seen on CT or MRI scans, and occasionally meta-iodobenzylguanidine (MIBG) scintigraphy is required to detect them. Epididymal cystadenomas are usually felt by a physical examination and confirmation through an ultrasound. Broad ligament cystadenomas can be diagnosed by CT scans or an ultrasound.

Genetic testing is available for VHL through gene sequencing and other methods. Testing is useful for confirming a clinical diagnosis or for family testing when there is an identified VHL mutation in the family. Analysis of the VHL gene is not perfect, but it detects about 90% of mutations that cause VHL. An informative test result is one that identifies a known mutation in the gene, and this confirms that the person has VHL. A negative test result means a mutation was not found in the gene. This either means that the tested individual does not have VHL, or instead has a mutation that cannot be found through testing but actually has the diagnosis.

Genetic testing for children at risk for VHL is recommended because some symptoms can show up in childhood. Earlier screening may reduce the chance of serious future complications. As with all genetic testing in people who have no symptoms, the risks, benefits, and limitations of testing should be discussed through proper genetic counseling.

Treatment team

Treatment for people with VHL is often specific to the person. A multi-disciplinary team and approach are essential. A treatment team for someone with VHL may include a **neurologist**, neurosurgeon, medical geneticist, genetic counselor, endocrinologist, pulmonologist, nephrologist, ophthalmologist, social worker, urologist, and a primary care provider. Often there are pediatric specialists in these fields who aid in the care for children. The key is good communication between the various specialists to coordinate medical care.

Treatment

There is no cure for von Hippel-Lindau disease. Treatment and management are often based on symptoms. Genetic testing has helped to identify individuals without symptoms, so medical screening may begin earlier than usual.

Most brain and spine hemangioblastomas can be treated by removal through surgery. **Radiation** therapy is sometimes used, if surgery is not possible. Growth patterns of these tumors can be unpredictable, so monitoring through regular imaging is important. Screening by MRI is recommended yearly, beginning at age 11.

Treatment for retinal tumors varies. Many tumors respond to laser therapy or cryotherapy. In rare cases, removal of the eye is needed to reduce severe pain or the risk for irreversible glaucoma. The key is early diagnosis and monitoring to prevent vision loss or blindness. For this reason, an ophthalmology exam is recommended first in infancy, and yearly thereafter.

Surgery may be quite successful for endolymphatic sac tumors, often preserving the hearing of a person with VHL. Radiation therapy is sometimes used for treatment, but its effectiveness is still unknown. CT and MRI scans of the internal ear canals and audiology exams are recommended if any typical symptoms develop.

Treatment for renal cell carcinoma often includes surgery, depending on the size of the affected area. Percutaneous ablation or cryoablation are experimental treatments that may work well because they are less invasive than other therapies. An abdominal ultrasound is first recommended at age eight, and then an MRI if necessary, and yearly thereafter. An abdominal CT scan is first recommended at age 18 or earlier if needed, and yearly thereafter.

Treatment for pheochromocytomas is most often by surgical removal, with an attempt to keep as much of the adrenal gland as possible. Medications such as corticosteroids are used as a treatment. Since pheochromocytomas can cause significant symptoms, it is important for the person with VHL to be screened prior to any surgery or delivery of a child. Blood or 24-hour checks of urine catecholamine and metanephrine levels are recommended beginning at age two, and yearly thereafter. They are also recommended if a person's blood pressure is raised.

Key Terms

Ataxia Uncoordinated muscular movement; often causes difficulty with walking and other voluntary movements.

Brain stem The entire unpaired subdivision of the brain (rhombencephalon, mesencephalon, and diencephalon).

Catecholamines Chemicals such as epinephrine, dopa, and norepinephrine; often at high levels in the urine if a pheochromocytoma is present.

Cerebellum Large area in the posterior of the brain (above the pons and below the cerebrum) responsible for functions like coordination.

Chemotherapy Chemical medical treatment often used for cancer.

Computed tomography (CT) scan Three-dimensional internal image of the body, created by combining x-ray images from different planes using a computer program.

Corticosteroids Steroid normally produced by the adrenal gland.

Cryoablation Using very cold temperatures to remove a foreign substance or body.

Cryotherapy Using very cold temperatures to treat a disease.

Cyst Sac of tissue filled with fluid, gas, or semi-solid material.

Cystadenoma Non-cancerous growth, in which fluid-filled, gas, or semi-solid areas may be present.

Endolymphatic sac tumor Growths that develop within inner ear structures called endolymph sacs.

Epididymis Male genital structure usually connected to the testis; an area where sperm collect.

Gait The way in which one walks.

Glaucoma Condition of the eye with increased internal pressure, often causing vision problems.

Hemangioblastoma Tumor often found in the brain, as in von Hippel-Lindau disease.

Magnetic resonance imaging (MRI) scan Three-dimensional internal image of the body, created using magnetic waves.

Meta-iodobenzylguanidine (MIBG) scintigraphy A procedure to look at the amount of a radioactive chemical, meta-iodobenzylguanidine, injected into the body to find growths like pheochromocytomas.

Metanephrine A byproduct of epinephrine, found elevated in urine if a pheochromocytoma is present.

Mutation A change in the order of deoxyribonucleic acid (DNA) bases that make up genes.

Nerve root Two groups of nerves that run from the spinal cord to join and form the spinal nerves.

Palpitation A heartbeat that is more pronounced, often felt physically.

Paresis Partial or total loss of movement or sensation.

Percutaneous ablation Attempting to remove a foreign body by a method just above the skin, like using an ointment.

Pheochromocytoma Non-cancerous growth in the adrenal gland.

Renal cell carcinoma A type of kidney cancer.

Retina Structure in the eye that receives and processes light.

Sequencing Genetic testing in which the entire sequence of deoxyribonucleic (DNA) bases that make up a gene is studied, in an effort to find a mutation.

Tinnitus Abnormal noises in the ear, like ringing.

Ultrasound Two-dimensional internal image of the body, created using sound waves.

Visceral Generally related to the digestive, respiratory, urogenital, or endocrine organs.

Surgery is the typical treatment for pancreatic growths and cysts, depending on their specific location and size. A goal is to keep as much of the pancreas as possible. If the tumors spread, chemotherapy is sometimes necessary. As with screening of the kidneys, abdominal ultrasounds are recommended beginning at age eight, and yearly thereafter; abdominal CT scans are recommended beginning at age 18, and yearly thereafter.

Both epididymal and broad ligament cystadenomas are non-cancerous and usually cause no symptoms. Therefore, treatment for both is only recommended if symptoms arise. There are no routine screening recommendations for either type. Ultrasounds can be used to find epididymal cystadenomas, and to monitor their growth over time. Ultrasounds or CT scans can be used to identify and monitor broad ligament cystadenomas.

Recovery and rehabilitation

Though VHL typically does not affect a person's thinking, learning, or behavior, the disease can have a significant impact on a person's life. Medical appointments can be frequent, and the pain from tumors may be considerable. Feelings of guilt associated with passing a disease-causing mutation to children have been reported in families. Professional therapy or family counseling may be helpful for some people.

Clinical trials

As of early 2004, there are several clinical studies studying various aspects of VHL. Many are currently recruiting subjects in the United States. Trials are being conducted at several institutions, including the National Cancer Institute and National Institute of Neurological Disorders and Stroke. Further information may be obtained at <http://www.clinicaltrials.gov>.

Prognosis

Prognosis for someone with von Hippel-Lindau disease is highly dependent on symptoms. Those people who die may do so as a result of significant complications with tumors. Renal cell carcinomas and CNS hemangioblastomas have been the greatest causes for death in people with VHL.

The outlook for people with VHL has improved significantly. Before the advent of comprehensive medical screening, the median survival of patients with the condition was less than 50 years of age. Genetic testing now helps identify people at risk before they even develop symptoms, so screening can begin as early as possible. This has helped to reduce the risk of complications and increase the quality of life for many. Medical screening may be further tailored to the individual as scientific studies identify medical complications associated with specific VHL mutations in families.

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VHL Family Alliance. 171 Clinton Avenue, Brookline, MA 02455-5815. (617) 277-5667 or (800) 767-4VHL; Fax: (617) 734-8233. info@vhl.org. <http://www.vhl.org>.

Kidney Cancer Association. 1234 Sherman Avenue, Suite 203, Evanston, IL 60202-1375. (847) 332-1051 or (800) 850-9132; Fax: (847) 332-2978. office@kidneycancerassociation.org <http://www.kidneycancerassociation.org>.

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W

Walker *see* **Assistive mobile devices**

Wallenberg syndrome

Definition

Wallenberg syndrome is a type of brain stem **stroke** manifested by imbalance, vertigo, difficulty swallowing, hoarseness of voice, and sensory disturbance. It is caused by blockage in one of the arteries supplying the medulla and **cerebellum**.

Description

The first clinical description was given by Gaspard Viesseux in 1808 and published by Alexander John Gaspard Marcet in 1811. But it wasn't until 1895 that Adolf Wallenberg eloquently described the different symptoms and signs and confirmed the findings during autopsy. The syndrome is also known as lateral medullary infarct (LMI) or posterior inferior cerebellar artery syndrome (PICA).

It usually affects people over 40 years of age. They tend to have vascular risk factors such as hypertension, high cholesterol, and diabetes. Wallenberg syndrome can also occur in younger people, but the underlying causes are different.

Demographics

Wallenberg syndrome is rare, and accurate estimates about incidence are unavailable. In a large stroke registry in Sweden gathered by Norving and Cronquist in 1991, only about 2% of all strokes over a six-year period were caused by LMI.

Causes and symptoms

The stroke occurs in the medulla and cerebellum. The medulla controls such important functions as swallowing, speech articulation, taste, breathing, strength, and sensation. The cerebellum is important for coordination. The blood supply to these areas is via a pair of vertebral arteries and its branch, called the posterior inferior cerebellar artery (PICA).

Initially, the PICA was thought to be the blocked major artery, but this has been disproved from autopsy studies. In eight out of 10 cases, it is the vertebral artery that is occluded due to plaque buildup or because of a clot traveling from the heart. In younger patients, the vertebral artery dissection causes the infarct. The area of the stroke is only about 0.39 in (1 cm) vertically in the lateral part of the medulla and does not cross the midline.

Fully 50% of patients report transient neurological symptoms for several weeks preceding the stroke. During the first 48 hours after the stroke, the neurological deficit progresses and fluctuates. **Dizziness**, vertigo, facial **pain**, double vision, and difficulty walking are the most common initial symptoms. The facial pain can be quite bizarre with sharp jabs or jolts around the eye, ear, and forehead. Patients feel "seasick" or "off-balance" with nausea and vomiting. Objects appear double, tilted, or swaying. Along with gait imbalance, it becomes nearly impossible for the patient to walk despite good muscle strength. Other symptoms include hoarse voice, slurred speech, loss of taste, difficulty swallowing, hiccups, and altered sensation in the limbs of the opposite side.

The eye on the affected side has a droopy eyelid and a small pupil. The eyes jiggle when the person moves around; this is called nystagmus. There is decreased pain and temperature perception on the same side of the face. The limbs on the opposite side show decreased sensory perception. Voluntary movements of the arm on the affected side are clumsy. Gait is "drunken," and patients lurch and veer to one side.

Diagnosis

Accurate diagnosis usually requires the expertise of a **neurologist** or a stroke specialist. It is common for an inexperienced physician to dismiss the symptoms of nausea, vomiting, and vertigo as being caused by an ear infection or viral illness. Diagnosis requires a thorough

Key Terms

Brain stem The stalk-like portion of the brain that connects the cerebral hemispheres and the spinal cord. The brain stem receives sensory information and controls such vital functions as blood pressure and respiration.

Cerebellum Part of the brain that consists of two hemispheres, one on each side of the brain stem. It acts as a fine tuner for muscle tone, coordination of movement, posture, gait and skilled voluntary movement.

Dissection Tear in the wall of an artery that causes blood from inside the artery to leak into the wall and thereby narrows the lumen of the blood vessel.

Infarct Dead tissue resulting from lack of blood supply to brain; also called a stroke.

Medulla The lowermost portion of the brain stem that controls vital functions like respiration, blood pressure, swallowing, and heart rate.

Nystagmus Involuntary, uncontrollable, rapid, and repetitive movements of the eyeballs.

Stroke Also called as cerebrovascular accident (CVA) or cerebral infarction, it occurs when there is interruption of blood supply to a portion of the brain or spinal cord, resulting in damage or death of the tissue.

Vertigo Dizziness with a sense of spinning of self and/or surroundings with resultant loss of balance, nausea, and vomiting. Occurs due to a problem in the inner ears or the cerebellum and brain stem.

physical exam and neuroimaging. **CT scans** are insensitive and can detect only a large stroke or bleed in the cerebellum. **Magnetic resonance imaging (MRI)** scans are far superior, with the stroke showing up as a tiny bright spot in the medulla.

Treatment team

The team includes a neurologist or stroke specialist for initial diagnosis, workup, and medical management. Rehabilitation requires a physical therapist, occupational therapist, and speech therapist. Depending on whether complications arise, a neurosurgeon and a critical care physician may be involved.

Treatment

Treatment for Wallenberg syndrome is mostly symptomatic. The size of the underlying blocked artery is too small to allow any mechanical or chemical re-opening. Aim of treatment is to alleviate symptoms, modify underlying risk factors, and prevent complications and future strokes.

Medical therapy

Blood thinners like heparin are given intravenously in some patients for the first few days to stop further formation and propagation of the clot. Following that, the patient usually has to take other blood thinners such as aspirin for life. Medications are also used to control high blood pressure and cholesterol. Pain in Wallenberg syndrome can sometimes be quite severe and disabling. A variety of analgesics like Tylenol or narcotics are used. Some patients need anti-seizure medications like **gabapentin** for pain management. Medications are also used for symptomatic treatment of vomiting and hiccups.

Surgical therapy

If the stroke is sufficiently large, the dead tissue swells up and can push the medulla downwards, impairing its vital functions and causing death. In this case, a neurosurgeon can remove a part of the skull to allow for the brain to swell.

Recovery and rehabilitation

Physical therapy focuses on improving balance and coordination. Assistive devices such as a cane, walker, or wheelchair may be used. Occupational therapy is used to help with daily activities like eating, which may be difficult due to clumsiness and incoordination. Speech training helps with articulation that has been impaired due to vocal cord paralysis. Special attention should be paid to food consistency to prevent aspiration. Initially, patients require pureed or semi-solid food. After initial treatment in the hospital, patients will need short-term placement in a nursing home or rehabilitation facility before going home. Modifications in living environment may include hand rails, non-slip rugs, etc.

Prognosis

Prognosis is usually quite encouraging both in the short and the long term. Nausea and vomiting disappear within a week. Clumsiness, difficulty swallowing, and gait imbalance improve over six months to a year. However,

there is a 10% death rate due to complications like aspiration pneumonia, breathing difficulty, and cardiac arrhythmias.

Special concerns

Depression is very common among stroke survivors who face quite a challenge resulting from the abrupt change in lifestyle. They benefit from counseling, social support, and using antidepressant medications. There are several stroke support groups that help the patients and their families cope with the stroke and its aftermath.

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ORGANIZATIONS

National Stroke Association. 9707 East Easter Lane, Englewood, CO 80112. (303) 649-9299; Fax: (303) 649-1328. info@stroke.org. <http://www.stroke.org>.

American Stroke Association. 7272 Greenville Avenue, Dallas, TX 75231. (800) 242-8721 or (888) 4STROKE. <http://www.strokeassociation.org>.

National Rehabilitation Information Center. 4200 Forbes Blvd, Suite 202, Lanham, MD 20706-4829. (301) 562-2400 or (800) 346-2742; Fax: (301) 562-2401. naricinfo@heitechservices.com. <http://www.naric.com>.

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Werdnig-Hoffman disease *see* **Spinal muscular atrophy**

Wernicke-Korsakoff syndrome *see* **Beriberi**

West syndrome *see* **Infantile spasms**

West Nile virus infection

Definition

The West Nile virus is an arbovirus (meaning it is spread by mosquitos, ticks, or other arthropods) that can cause infections in animals and humans; in some cases, the infections can lead to fatal meningitis or encephalitis, which are inflammations of the spinal cord and brain. West Nile virus is considered a seasonal epidemic in North America, and it occurs mainly in the summer, but can continue into the fall. In many cases, it can be a serious illness that generally affects the **central nervous system**, leading to a variety of symptoms that differ from person to person. It is not contagious by touch, but can be spread by infected mosquitoes, transfusions, transplants, or from mother to child during pregnancy.

Description

West Nile virus infections usually begin with flu-like symptoms. Only approximately one in 150 people infected will develop severe symptoms, including **headaches**, neck stiffness, disorientation, **seizures**, fever, numbness, paralysis, and/or muscle weakness. In the worst cases, infection with West Nile virus can lead to death or permanent disability. These cases are usually due to either the age of the patient or the health status. Symptoms generally do not occur in healthy individuals.

Demographics

The West Nile virus has been observed mainly in temperate regions of Europe and North America, and has also been discovered to be the cause of human illness in the United States. The first known case in the United States was reported by the New York City Department of Health in late August 1999. Careful surveillance identified 59 patients who were hospitalized in New York City due to West Nile virus infections during August and September 1999. The median age of these patients was 71 years (range is five to 95). As of April 2004, only one case has been reported by the Centers for Disease Control. The West Nile virus has been observed in Africa, the Middle East, and west and central Asia. The first case was discovered in 1937 in an adult woman in the West Nile district of Uganda. The virus was characterized in Egypt during the 1950s.

An infection due to the West Nile virus does not produce symptoms in most people. In fact, only 20% of people who are infected will develop symptoms. Of these, the majority will recover and will not become infected again. The West Nile virus can infect males and females with equal frequency. There is no known predilection for people of specific ethnic backgrounds. People over 50 years

old are at the highest risk of having serious illness associated with the infection. There is a very low risk of contracting this illness by medical procedures such as transplantation and blood transfusions. Although pregnancy and breast-feeding do not increase the risk of becoming infected with the virus, the risk to the fetus or nursing infant of an affected mother is currently being investigated. Horses, birds, and other animals have also been shown to be susceptible to viral infection.

Causes and symptoms

When a person is infected with West Nile virus, usually via a mosquito bite from a mosquito harboring the virus, it is unlikely that the individual will develop symptoms. Of the infected individuals that develop symptoms, there are either mild or severe clinical manifestations. The majority of infections are mild.

Characteristics of mild infections include:

- mild illness, including fever
- fever and symptoms persist no more than six days, usually lasting only three days
- symptoms usually develop three to 14 days after exposure, consistent with the incubation period
- illness can be sudden and accompanied by anorexia (loss of appetite), nausea, headaches, rash, muscle weakness, vomiting, and/or lymphadenopathy (swollen lymph glands)

Characteristics of severe infections include:

- Severe symptoms can result in neurological disease in approximately one in 150 cases, with the elderly at highest risk.
- Neurological symptoms include disorientation, seizures, and cranial nerve abnormalities.
- Symptoms include high fever, weakness, significant alterations in behavior, eye problems, and stomach problems.
- In rare cases, flaccid paralysis along with severe muscle weakness can occur.
- Illness can be sudden and accompanied by anorexia (loss of appetite), nausea, headaches, rash, muscle weakness, vomiting, and/or lymphadenopathy (swollen lymph glands).

Diagnosis

Diagnosis requires clinical observation by an experienced physician as well as positive results from specific laboratory tests. Factors that assist in the diagnosis are recent travel experiences, the season that the symptoms developed, the age of the patient, and whether there are reports of other cases in the same geographical location that the patient was present during the time of exposure. Patients who have encephalitis, meningitis, or symptoms involving the central nervous system, which could lead a physician to suspect the West Nile virus, can be referred to health departments nationwide or the Centers for Disease Control (CDC) for testing. The CDC has confirmed all human cases.

The diagnostic test involves an assay that detects a virus-specific antibody (IgM) in the cerebral spinal fluid from patients. Blood can also be tested. If this test is negative, it is very unlikely that the infection is due to the West Nile virus; the other clinical explanations such as St. Louis encephalitis (SLE) should be considered. There is also a test that measures SLE virus-specific antibodies. Currently, there is a vaccination for horses, but not for humans.

Laboratory findings include normal to elevated white blood cell numbers with anemia (low red cell numbers). A deficiency of sodium in the blood (hyponatremia), which is usually associated with encephalitis, as well as normal glucose and a general increase in proteins can all be observed. A **magnetic resonance imaging (MRI)** scan can also be helpful, if specific areas of the brain show an abnormality, including the leptomeninges and/or the periventricular areas.

Treatment team

The treatment team might consist of the physician who initially sees the patient, usually a general practitioner, an infectious disease specialist, and **neurologist**. In severe cases, a complete medical team consisting of emergency room physicians and staff, nurses, and officers from the CDC might be necessary. Due to the risk of an epidemic, it is important for physicians to report these types of infections to the local health department.

Key Terms

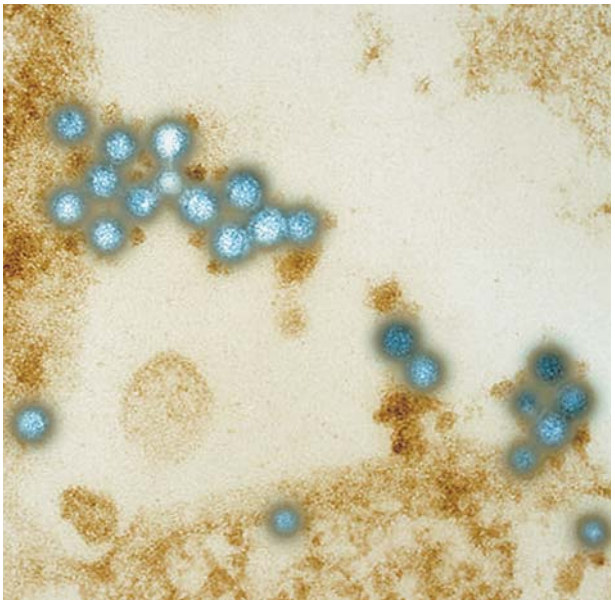
Arboviruses Viruses harbored by arthropods (mosquitoes and ticks) and transferred to humans by their bite. An arbovirus is the cause of West Nile infection.

Encephalitis Inflammation of the brain.

Flaccid paralysis Loss of muscle tone resulting from injury or disease of the nerves that innervate the muscles.

Lymphadenopathy Swelling of the lymph glands.

Meningitis Inflammation of the meninges, the membranes that surround the brain and spinal cord.



The West Nile virus. *(Scott Camazine/Photo Researchers, Inc.)*

Treatment

There is no cure for West Nile virus infection once the infection occurs. Treatment, therefore, is supportive and palliative. In the more severe cases, recurrent hospitalizations may necessitate life support services. The primary treatment is focused on lessening the symptoms and preventing secondary infections, which could include urinary tract infections and pneumonia in patients that develop severe illness. Intravenous fluids can be helpful during hospitalizations, along with airway management and good nursing care.

Recovery and rehabilitation

Most patients who develop symptoms recover from West Nile virus infections. The symptoms can be no worse than getting the flu. However, older patients and patients with health-related problems (particularly those that affect the immune system) have more difficulty recovering.

Clinical trials

The Warren G. Magnuson Clinical Center is currently recruiting participants for a clinical trial on the West Nile virus. The Patient Recruitment and Public Liaison Office's e-mail address is prpl@mail.cc.nih.gov.

The National Institutes of Health is conducting phase II **clinical trials** to investigate whether an experimental drug, Omr-IgG-am™IV, is a safe and effective treatment for West Nile virus-induced infections. This drug contains antibodies that help fight infection and is designed to target the West Nile virus. Another study by the same center has also been initiated to investigate the natural history of infection in patients with, or at risk of developing, West Nile virus-specific encephalitis or myelitis.

A third clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) in phase I and II is to test the tolerability of Omr-IgG-am, its efficacy as a vaccine, and its effectiveness in reducing morbidity and mortality (disability and death) in patients with a confirmed diagnosis of the West Nile virus disease. The contact is Walla Dempsey; the e-mail is wdempsey@niaid.nih.gov.

Finally, a clinical trial is ongoing to identify healthy individuals who might be eligible for a phase I vaccine clinical trial sponsored by the Vaccine Research Center at the National Institutes of Health. The Patient Recruitment and Public Liaison Office's e-mail address is prpl@mail.cc.nih.gov.

High doses of a drug called Ribavirin and another called interferon alpha-2b were found to be effective in research studies, but currently no controlled clinical trials in humans have been initiated for these or other types of medications in the therapeutic management of West Nile virus infections and encephalitis.

Prognosis

The prognosis for persons with West Nile virus infection is quite favorable in patients that are young and in otherwise good health. Older persons and patients with health complications can have a poorer prognosis. In rare cases, death is possible.

Special concerns

It is important to contact the local health department when finding dead birds or other animals that die suddenly of an unknown cause during suspected or confirmed local outbreaks of West Nile virus. Health officials monitor mosquito and bird populations to determine local risk for West Nile virus activity.

A person's exposure to mosquitoes and other insects that harbor arboviruses can be reduced by taking precautions when in a mosquito-prone area. Insect repellents containing DEET provide effective temporary protection from mosquito bites. Long sleeves and pants should be worn when outside during the evening hours of peak mosquito activity. When camping outside, intact mosquito netting over sleeping areas reduces the risk of mosquito bites. Communities also employ large-scale spraying of pesticides to reduce the population of mosquitoes, and encourage citizens to eliminate all standing water sources such as in bird baths, flower pots, and tires stored outside to eliminate possible breeding grounds for mosquitoes.

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ORGANIZATIONS

Centers for Disease Control and Prevention (CDC) Division of Vector-Borne Infectious Diseases. P.O. Box 2087, Fort Collins, CO 80522. (800) 311-3435. dvbid@cdc.gov. <http://www.cdc.gov/ncidod/dvbid/index.htm>.

U. S. Food and Drug Administration. 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <http://www.fda.gov/oc/opacom/hottopics/westnile.html>.

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Wheelchair *see* **Assistive mobile devices**

Whiplash

Definition

Whiplash is an injury resulting from a sudden extension or flexion of the neck. Whiplash can also be termed neck sprain or neck strain or, more technically, cervical acceleration/deceleration trauma. It is most often associated with being struck from behind in a car, although it also occurs during contact sports, falls, or other physical activities. Whiplash may also cause damage to vertebrae, ligaments, cervical muscles, or nerve roots.

Description

Whiplash occurs when the body is struck, usually from behind, and the head travels backwards to catch up with the body. The neck will flex until either the facet joints in the back of the vertebrae or the anterior longitudinal ligament in the front of the vertebrae stop the motion.

The muscles that are most often injured during an impact that causes whiplash are the sternocleidomastoids and the longus colli. The sternocleidomastoids are the large straplike muscles running down the front of the neck that pop out when the jaw is flexed. They are used to turn and support the head. The longus colli is a muscle that runs directly in front of the spine is used to turn the head from side to side and to bend the neck forward. The longus colli muscle aids the sternocleidomastoids in holding up the head and moving the neck. Often, the lognus colli muscle is weakened during whiplash and the sternocleidomastoid muscles become overworked as they compensate.

The facet joints in the anterior of the neck may also be damaged during a whiplash injury. There are two facet joints on the back of each vertebra. They are about a centimeter in size and guide the movement of the spine. When the neck bends backward during a whiplash impact, the joints can be compressed and then swell in response. This can cause **pain**, both in the neck and can also refer pain to other parts of the body. For example, if the facet joints between the second and third cervical vertebrae are compressed, pain may be felt in the back of the head.

A whiplash impact can also damage the anterior longitudinal ligament, which is a tough band of tissue that runs down the front of the vertebral column and holds the vertebral bones together. In automobile accidents, this ligament is often overstretched or torn. If it is torn, it can lead to vertebral **disc herniation** or to excessive movement of the spinal column. Such movement can result in pain spasms in the neck, cracking and grinding in the neck, or even numbness in the hands and feet.

Whiplash can also result in a herniated vertebral disc. The vertebral bones are cushioned between vertebral discs that are made up of an interior gel-like substance surrounded by a tougher outer layer. If this outer layer becomes damaged, the disc may rupture and the gel-like interior will be compressed out. The ruptured disc can put pressure on adjacent nerve roots and cause tingling, numbness or burning.

Damage to the **central nervous system** or the **peripheral nervous system** may occur during a whiplash injury. Most of the damage to the nervous systems involves compression injuries during which pressure is applied to nervous tissues, although damage can also be caused by

Key Terms

Herniated disc A blisterlike bulging or protrusion of the contents of the disk out through the fibers that normally hold them in place. It is also called a ruptured disk, slipped disk, or displaced disk.

Ligament A type of tough, fibrous tissue that connects bones or cartilage and provides support and strength to joints.

Vertebrae Singular, vertebra. The individual bones of the spinal column that are stacked on top of each other. There is a hole in the center of each bone, through which the spinal cord passes.

stretching or torquing (twisting) of nervous tissues. In severe cases, compression injuries can affect the brain resulting in subdural or extradural hematomas (pooling of blood between the brain and the skull). Symptoms of this complication include **anosmia** (loss of smell), double vision, brief loss of consciousness, confusion and loss of motor skills.

Compression, stretching, and torque injuries to the spinal cord may also occur during trauma associated with whiplash. The most frequently occurring is root syndrome. Nerve roots exit the spinal cord on both sides of the body between vertebrae. When the spaces between vertebrae, also called foramen, become compressed, the nerve roots can be compressed or damaged. This can result in slight numbness, burning or tingling in any of the parts of the body that the nerve enervates. In more severe car accidents, whiplash can cause more critical damage to the spinal cord resulting in major neurological dysfunction or paralysis below the location of the injury. The important variables controlling the severity of the symptoms appear to be the force and the direction of the impact on the spine. As the area impacted by the trauma increases due to increased force, a greater portion of the cord is involved resulting in greater neurological dysfunction.

The peripheral nervous system can also suffer damage in a whiplash injury. These nerves can be compressed in the vertebral foramen and can also be stretched or compressed by other anatomical structures along their path. Only a very small compression or stretching is required to interrupt blood flow to a nerve cell. For example, blood flow to a nerve cell can be completely stopped if the nerve cell is stretched to 15% more than its original length. Such trauma to a nerve cell can result in numbness or tingling in the region affected by the nerve, but usually not pain. It is the irritation of the nerve following the trauma that causes pain in the peripheral nervous system.

Demographics

Anyone can suffer from whiplash, in particular people who drive in automobiles. Whiplash has been documented in people who are driving as slowly as five miles per hour. About 20% of people who are involved in rear-end accidents in cars suffer symptoms of whiplash. In the United States, it is estimated that about 1.8 million people are subject to chronic pain and disability after an automobile accident, the majority of whom suffer from neck pain.

Causes and symptoms

Symptoms of whiplash include neck pain and stiffness, shoulder pain and stiffness, lower **back pain**, **headaches** in the back of the head, pain, and/or tingling in the hand or arm, **dizziness**, ringing in the ears and blurred vision. Often the pain associated with whiplash worsens several days following the injury. Some people suffer cognitive or psychological symptoms including difficulty concentrating, difficulty sleeping, memory loss, **depression** and irritability.

Symptoms of whiplash appear to follow one of two courses. In most people, symptoms will slowly abate within approximately three months. In a smaller proportion of people who experience whiplash, the symptoms become chronic and disability may result.

Diagnosis

Orthopedists (physicians specializing in the bones and joints) use a variety of diagnostic tools to evaluate the extent of injury following whiplash. This usually begins with a history of the accident and the symptoms experienced. A physical examination allows the physician to evaluate the range of motion in the neck, locations of pain in the neck, arms and legs, and function of nerves. An x ray is almost always used to determine if any vertebrae have been damaged in the accident. However, because many of the injuries are to soft tissues, they are not well visualized using a standard x ray. The orthopedist may then recommend other diagnostic procedures that visualize these tissues more effectively. **Magnetic resonance imaging (MRI)** allows for visualization of the spinal cord and nerve roots that emerge between the vertebrae. A **computed tomography** study (**CT**) gives precise information about the bone and spinal canal using specialized x ray technology. Another technology called a myelogram combines x rays with an injection of dye into the spinal canal and allows for detailed visualization of the spinal canal and nerve roots. An electromyogram (EMG) may

also be used to determine the health of nerves and muscles using electrical impulses.

Treatment

Treatment for whiplash includes a variety of techniques and medications including exercises, pain-relieving medications, traction, massage, heat and ice, and ultrasound, depending on the symptoms. Although a physician should evaluate people who suffer whiplash, most of the time whiplash can be treated using home treatments and extensive medical care is not prescribed.

Both heat and cold are useful for treatment of symptoms of whiplash. Initial treatment for whiplash usually includes cold packs of ice applied to the neck for the first 24 hours. Heat may then be used to relieve pain throughout the neck and shoulders either using heating pads or hot showers. Physical therapists can apply deep heat treatments using ultrasound equipment.

Medications are useful for relieving acute pain associated with whiplash. Non-steroidal anti-inflammatory medications can be very helpful in relieving pain. Antidepressants may be prescribed because they inhibit the transfer of nervous signals along pain pathways.

A soft cervical collar may provide some relief for symptoms of whiplash; however, most physicians recommend that the use of the collar be limited to two to three weeks. Using the cervical collar for long periods may cause muscle strength to decrease and inhibit muscle flexibility.

Physicians have found that movement is important in preventing chronic symptoms of whiplash. Many doctors assert that simple exercises such as walking, muscle strengthening, and range of motion exercises help improve symptoms more quickly than remaining sedentary. In 2000, a study reported in the journal *Spine* demonstrated that patients who frequently performed a set of exercises immediately following an injury that caused whiplash recovered faster than patients who exercised less. The more active group performed a set of repetitive motion exercises 10 times an hour beginning within 96 hours of injury, while the less active group performed exercises a few times a day beginning two weeks after the injury. Of the more active group, nearly 40% reported that they had no symptoms of whiplash six months following the accident, compared with only 5% of the less active group.

Traction, under the supervision of an orthopedic professional, removes the pressure from the neck, and some people report relief from pain for several hours to several days following treatments. Physical therapy and/chiropractic adjustments are often prescribed to treat symptoms of whiplash. In rare cases, surgery is required to correct whiplash injuries.

Clinical trials

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) conducting a study in 2004 focused on preventing acute pain, such as that associated with whiplash, from becoming chronic pain. Research suggests that the emotional response to an injury to the neck, particularly fear of reinjury, contributes significantly to the development of chronic pain from whiplash. The study focused on two anxiety-reducing treatments as a way to prevent such chronic pain from developing. The principal investigator on the two-year study is Dennis C. Turk, Ph.D. (telephone number: 206-543-3387, or email: wads@u.washington.edu). Information is available on the institute's website at <http://www.depts.washington.edu/wads>.

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American Chronic Pain Association (ACPA). P.O. Box 850, Rocklin, CA 95677. (916) 632-0922 or (800) 533-3231; Fax: (916) 632-3208. ACPA@pacbell.net.

National Chronic Pain Outreach Association (NCPOA). P.O. Box 274, Millboro, VA 24460. (540) 862-9437; Fax: (540) 862-9485. ncpoa@cfw.com.

National Headache Foundation. 820 N. Orleans, Suite 217, Chicago, IL 60610. (773) 388-6399 or (888) NHF-5552; Fax: (773) 525-7357. info@headaches.org. <http://www.headaches.org>.

Juli M. Berwald, Ph.D.

Whipple's disease

Definition

Whipple's disease is a rare infectious disorder that can affect many areas of the body, including the gastrointestinal and central nervous systems. Caused by the bacteria *Tropheryma whipplei,* it is typically diagnosed from malabsorption symptoms such as diarrhea and weight loss. If the **central nervous system** is infected, Whipple's disease can cause impairment of mental faculties and lead to **dementia**. It can be treated successfully with antibiotic therapy, but up to a third of patients suffer relapse.

Description

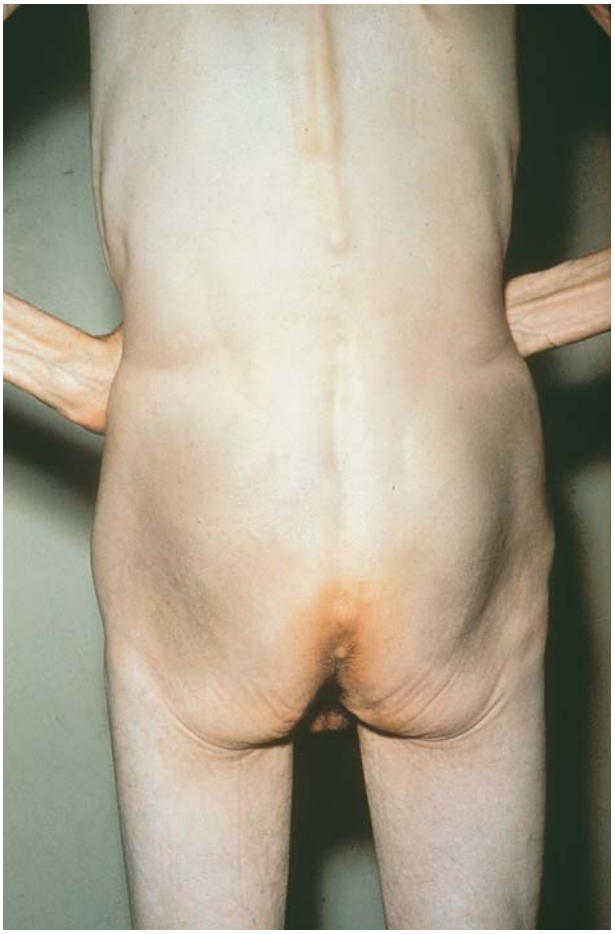
Whipple's disease, also known as intestinal lipodystrophy, was first reported in 1907 by George Hoyt Whipple (1878–1976). An autopsy on a thirty-seven year old male missionary revealed a granular accumulation of fatty acids in the walls of the small intestine and lymph nodes.

Historically, Whipple's disease has been considered an gastro-intestinal disorder, however, in the 1960s it was realized that other organs could be involved, with or without intestinal infection. It is now considered a systemic infection with a wide range of possible symptoms.

Demographics

The disorder typically affects middle-aged men of European descent. Most cases have been reported in North America and Europe. Many texts suggest the disorder affects eight times as many males as females, although there is some evidence to suggest the rate in females is rising.

The disease is extremely rare and no reliable estimate of incidence is known. Farmers and other rural people are most often diagnosed with Whipple's disease, but as yet, no specific environmental factors have been linked to the disorder.



The effects of Whipple's disease. *(Phototake, Inc. All rights reserved.)*

Causes and symptoms

The bacterium that causes Whipple's disease was only successfully cultured in 1997. *Tropheryma whipplei* belongs to the high G+C phylum of gram-positive bacteria, and its genome was sequenced in 2003.

Whipple's disease has traditionally been regarded as a malabsorption disease of the small intestine, but in most cases the first symptoms are arthritic joints, which can precede the malabsorption symptoms of Whipple's disease by many years. Commonly, the disease progresses to the small intestine. Symptoms then include diarrhea, anemia, weight loss, and there is often fat present in the stool, all due to the bacteria disrupting absorption of fat and nutrients. If untreated, other malabsorption problems, such as reductions in the levels of calcium and magnesium, may result. Fever and night sweats are common, as well as general weakness. There are many further possible symptoms depending on the organs affected.

In cases where the central nervous system is affected, there may be a decrease in intellectual abilities, insomnia,

Key Terms

Ataxia Inability to coordinate muscle control resulting in irregularity of movements.

Malabsorption The inability to adequately or efficiently absorb nutrients from the intestinal tract.

Tinnitus Ringing sensation or other noise in the ears.

hearing loss or tinnitus (ringing in the ears), and uncontrolled muscle movements (**ataxia**) or eye movements. If untreated, the disorder can lead to dementia and progressive brain cell death, leading to coma and death over a period of months to years.

Diagnosis

Diagnosis of Whipple's disease is difficult, and is commonly suspected only if the patient presents with malabsorption symptoms. Then, a small-bowel **biopsy** can be made to locate the presence of the bacteria and confirm the diagnosis. However, symptoms can vary greatly depending on the areas of the body that are affected, and up to a third of sufferers do not present with malabsorption ailments.

Treatment team

Once diagnosed, the treatment of Whipple's disease is often straightforward, and can be monitored with minor hospital procedures. However, due to the rarity of the disease and the recent developments in studying the disorder it is recommended that contact be made with specialized centers of research or a **neurologist**.

Treatment

Whipple's disease generally responds well to antibiotic therapy. The recommended treatment is two weeks of intravenous antibiotics followed by a year or more of oral antibiotics. If the malabsorption symptoms are pronounced, the patient may require intravenous fluids and electrolytes, and other dietary supplements. A diet high in calories and protein is often recommended, and should be monitored by a physician.

Recovery and rehabilitation

When treated, symptoms such as diarrhea and fever can resolve within days, and most symptoms typically improve within a few weeks. In most cases, symptoms of the disorder are lessened or ameliorated by treatment. The progress of therapy can be checked by biopsy of the small intestine. In about one third of cases, the disease relapses and is more likely to affect the central nervous system than the initial infection. Periodic monitoring over several years, therefore, is essential to prevent neurological damage.

Clinical trials

Although as of early 2004, there were no ongoing **clinical trials** in the United States specific for Whipple's disease, the National Institute of Diabetes and Digestive and Kidney Diseases supports research for similar disorders.

Prognosis

If untreated, Whipple's disease can be fatal, but when treated with antibiotic therapy most patients experience rapid recovery and lasting remission. However, up to a third of patients may suffer a relapse.

Special concerns

Knowledge of Whipple's disease is rapidly evolving, and there have been many recent developments that may lead to new diagnostic options and new treatments in the near future.

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National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744–0100 or (800) 999–NORD (6673); Fax: (203) 798–2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

David Tulloch,

Williams syndrome

Definition

Williams syndrome, first described in 1961, is a rare genetic condition with a wide array of clinical features.

Description

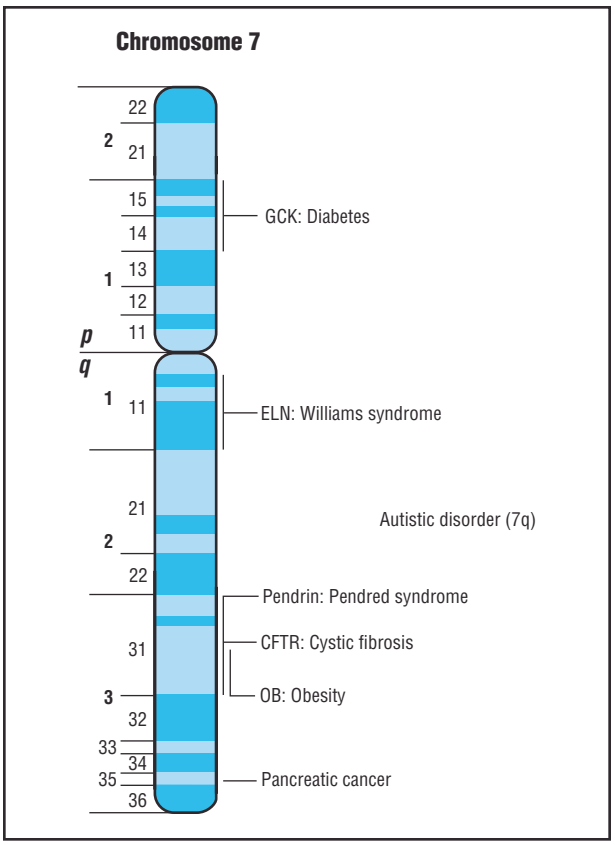
Typical facial features seen in children with Williams syndrome include a wide mouth with full lips, a small chin, and a short, slightly upturned nose. Children with blue or green eyes often times show a starburst pattern in the colored part (iris) of the eyes. An unusual narrowing of the aorta called supravalvular aortic stenosis is often present, and hernias are often seen in the inguinal area of the abdomen. The blood vessels and abdominal wall often show weakness or altered development. Muscle tone is typically low, and children are often on the low end of birth weight, with relatively poor weight gain and growth in their early years.

Most children with Williams syndrome have a remarkable contrast between verbal abilities and spatial abilities. While overall intellectual performance on standardized IQ tests will be in the general range found in Down syndrome, children with Williams syndrome show a complex pattern of strengths and deficiencies that would not be evident by counting IQ points. Verbal abilities, for example, are exceptionally strong, and people with Williams syndrome tend to show very strong social skills relative to what one might anticipate based on IQ scores. Long-term memory is also generally excellent. Musical interest and ability are often strong. In contrast, fine motor skills often lag behind their IQ-matched peers, and, the sense of spatial relationships is very poor. If a therapist, for example, were to ask a child with Williams syndrome for a picture of a boy on a bike, the child might not be able to identify many of the parts of the picture. The parts will not likely be spaced in a way that makes much sense. However, if the therapist asks for a description of what it is like to ride a bike, the child will likely describe the sensation with a detailed and imaginative story.

For reasons that are not well understood, children may have a problem with calcium levels that are too high. Irritability and colic are common in early development, especially in children with high calcium levels. Delays are typically seen in reaching developmental milestones, and children with Williams syndrome generally exhibit learning disabilities and may be easily distractible with some form of attention deficit disorder. Cognitive, verbal and motor deficits are universal, and about three quarters of children will be determined to have **mental retardation** in the course of their care. Young children with Williams syndrome often have extremely sensitive hearing, although this tends to become less significant as children get older.

Demographics

Williams syndrome is estimated to occur in one of every 20,000 births. In most families, only one child will be affected and there is no significant family history of Williams syndrome in other relatives.



Williams syndrome, on chromosome 7. *(Gale Group.)*

Causes and symptoms

Williams syndrome is most often caused by a chromosome deletion involving loss of a gene called elastin on chromosome number 7, and may involve the loss of other neighboring genes as well.

Diagnosis

Because of the variability in the way that Williams syndrome affects different people, it often goes undiagnosed for many years. Although there is a chromosome deletion in over 98% of children born with Williams syndrome, the deletions are so small that they are usually not detectable under the microscope using standard methods. Diagnosis requires the use of a special test called fluorescence in situ hybridization (FISH) in which a DNA probe for the elastin gene is labeled with a brightly colored fluorescent dye.

Treatment team

Medical care for children with Williams syndrome should be provided by a physician with specific knowledge or experience with Williams syndrome, and growth charts specific to children with Williams syndrome are

Key Terms

Autosomal dominant A pattern of inheritance in which only one of the two copies of an autosomal gene must be abnormal for a genetic condition or disease to occur. An autosomal gene is a gene that is located on one of the autosomes or non-sex chromosomes. A person with an autosomal dominant disorder has a 50% chance of passing it to each of their offspring.

Elastin A protein that gives skin the ability to stretch and then return to normal.

available. The services of a medical geneticist should be available to the treating physician.

Treatment

Treatment is supportive and varies according to the symptoms displayed. Special attention is given to monitoring for heart and blood vessel disease, along with blood calcium levels. Multivitamin supplementation should generally be avoided unless directed by a physician because of the potential for problems caused by vitamin D.

Recovery and rehabilitation

Teens and adults with Williams syndrome face a variety of challenges that come with aging. Involvement of the family in support groups with other families that have direct experience with Williams syndrome can be helpful in anticipating and avoiding the common pitfalls. Most adults with Williams syndrome continue to live at home with parents or in special group home situations, with rare individuals living and functioning independently.

Prognosis

There is no cure for Williams syndrome as it is a genetically determined disease. Research is underway to determine the roles of approximately 20 genes in the area of chromosome 7 that are critical to the development of Williams syndrome.

Special concerns

Individuals who have Williams syndrome have a 50% chance of passing it on to their offspring if they have children because one of their two copies of chromosome 7 is missing some vital information, and each sperm or egg will receive one copy of chromosome 7 at random. This inheritance pattern is called autosomal pseudodominant because it so closely resembles the pattern of transmission seen for autosomal dominant single gene traits.

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ORGANIZATIONS

Williams Syndrome Association. P.O. Box 297, Clawson, MI 48017-0297. (248) 244-2229 or (800) 806-1871; Fax: (248) 244-2230. info@williams-syndrome.org. <http://www.williams-syndrome.org>.

National Organization for Rare Disorders (NORD), P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813-1968. (203) 744-0100 or (800) 999-NORD (6673); Fax: (203) 798-2291. orphan@rarediseases.org, <http://www.rarediseases.org>.

Robert G. Best, PhD

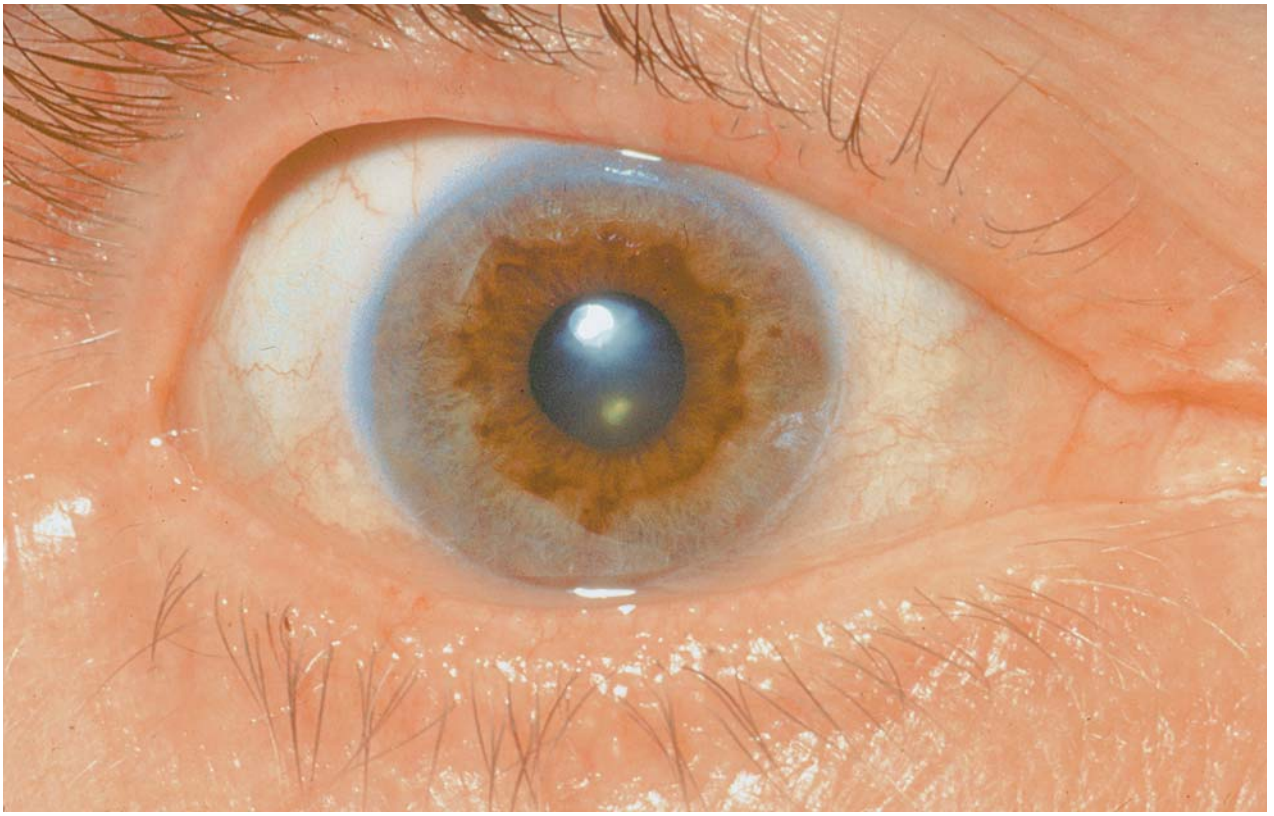
Wilson disease

Definition

Wilson disease (WD) is an inherited disorder of copper metabolism, transmitted as an autosomal recessive trait. This type of inheritance means unaffected parents who each carry the WD gene have a 25% risk in each pregnancy of having an affected child. The disorder is caused by a defective copper-binding protein found primarily in the liver, which leads to excess copper circulating through the bloodstream. Over time, the copper is deposited and increased to toxic levels in various body tissues, especially the liver, brain, kidney, and cornea of the eye. Left untreated, WD is invariably fatal.

Description

In 1912, Dr. Samuel Kinnear Wilson described a disorder he called "progressive lenticular degeneration." He noted the familial nature of the condition, and also that it was likely to be caused by a toxin affecting the liver. The toxin was later discovered to be excess copper. Another,



Eye afflicted with a Kayser-Fleischer ring, a brownish ring overlying the outer rim of the iris of the eye; it is caused by Wilson's disease. *(Photo Researchers, Inc. Reproduced by permission.)*

little-used name for the disorder is "hepatolenticular degeneration" (degeneration of the liver and lens), which omits the contribution of neurological symptoms.

The classic triad of signs for WD includes lenticular degeneration, cirrhosis of the liver, and neuropsychiatric symptoms. Errors in a specific gene produce a defective copper-binding protein in the liver, which results in an inability to excrete excess copper. While some copper is necessary for normal metabolic processes in the body, too much can be toxic. The disease is present at birth, but symptoms typically do not show until years later. WD is progressive because the underlying cause cannot be corrected. Effective treatments are available, but without treatment, people with WD will eventually die of liver failure.

Demographics

WD has an incidence of about one in 30,000, which means one in 90 individuals is a silent carrier of the WD gene. There seems to be no specific ethnic group or race that has a higher frequency of the disease. Only a man and woman who are both silent carriers of the WD gene can have a child with the condition. Unlike a disease with dominant inheritance, which usually implies a definite family history, WD only rarely has occurred in a previous family member.

Causes and symptoms

WD is caused by errors in a gene located on chromosome 13, which produces a protein named ATP7B. Errors in the ATP7B gene produce a protein with decreased ability to bind copper. Unused copper is then absorbed back into the bloodstream where it is transported to other organs. A person who is a carrier of WD has one normally functioning copy of the ATP7B gene, and this produces enough functional protein to rid the body of excess copper.

A little more than half of all patients with WD first show symptoms of hepatitis. In addition, those who have liver-related symptoms first, do so at a younger age than do those who first present with neuropsychiatric symptoms—15 years and 25 years on average, respectively. However, the symptoms and their severity are quite variable, and the diagnosis of WD has been made in children as young as three years old, and in adults in their 60s.

Neurological symptoms are primarily the result of copper's toxic effects in the basal ganglia, a portion of the brain that controls some of the subconscious aspects of

Key Terms

Ceruloplasmin A protein circulating in the bloodstream that binds with copper and transports it.

Cirrhosis A chronic degenerative disease of the liver, in which normal cells are replaced by fibrous tissue and normal liver function is disrupted. The most common symptoms are mild jaundice, fluid collection in the tissues, mental confusion, and vomiting of blood. Cirrhosis is associated with portal hypertension and is a major risk factor for the later development of liver cancer. If left untreated, cirrhosis leads to liver failure.

Chelation The process by which a molecule encircles and binds to a metal and removes it from tissue.

Hepatitis An inflammation of the liver, with accompanying liver cell damage or cell death, caused most frequently by viral infection, but also by certain drugs, chemicals, or poisons. May be either acute (of limited duration) or chronic (continuing). Symptoms include jaundice, nausea, vomiting, loss of appetite, tenderness in the right upper abdomen, aching muscles, and joint pain. In severe cases, liver failure may result.

Penicillamine A drug used to bind to and remove heavy metals (such as copper or lead) from the blood, to prevent kidney stones, and to treat rheumatoid arthritis. Brand names include Cuprimine and Depen.

voluntary movement such as accessory movements and inhibiting tremor. These symptoms include:

- Dystonia. Prolonged muscular contractions that may cause twisting (torsion) of body parts, repetitive movements, and increased muscular tone.
- Dysarthria. Difficulty in articulating words, sometimes accompanied by drooling.
- Dysphagia. Difficulty swallowing.
- Pseudosclerosis. Symptoms similar to multiple sclerosis.

Diagnosis

While the diagnosis of WD may be suspected on clinical grounds, it can only be confirmed using laboratory tests. An easily detectable physical sign is the presence of Kayser-Fleisher rings in the eye, which are bluish rings around the iris, caused by copper deposition in the cornea.

The easiest biochemical test is measurement of ceruloplasmin, a blood protein that is nearly always decreased in patients with WD. While low levels of ceruloplasmin are highly suggestive, a liver **biopsy** to detect excess copper levels is much more accurate. Testing for mutations in the ATP7B gene is nearly definitive, but the large number of mutations catalogued in the gene means that only certain individuals may benefit from testing. A consultation with a genetics professional is always recommended.

Treatment team

A gastroenterologist will treat and monitor liver disease, while a **neurologist** and psychiatrist (or neuropsychiatrist) should evaluate and treat neuropsychiatric symptoms. Since many individuals achieve remission of their neurologic symptoms once treatment is started, neuropsychiatric consultations may only be short term. If necessary, periodic consultations with a geneticist can provide updated information on genetic testing.

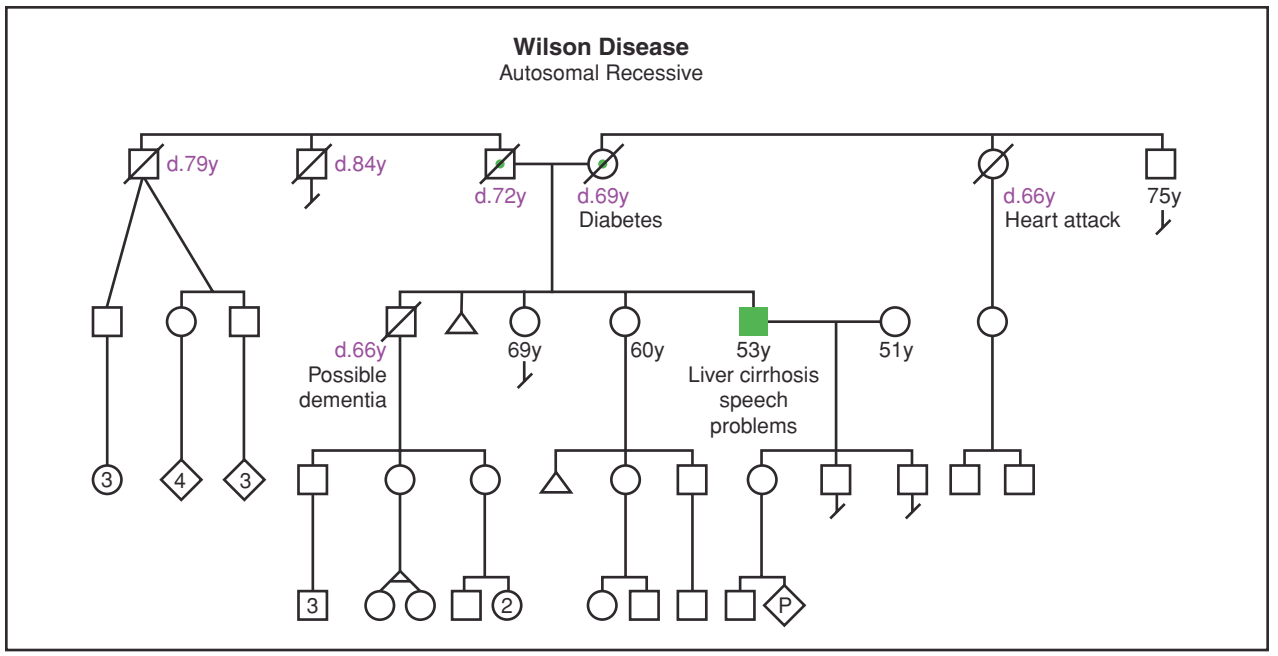
Treatment

Treatment of WD revolves around the process of copper chelation. A chelating agent binds to excess copper in the bloodstream so that it can be excreted from the body. Penicillamine is the most effective and commonly used medication, but about 20% of all patients suffer serious side effects, which may include joint **pain**, blood disorders, fever, an increase in neurologic symptoms, and systemic **lupus** erythematosus.

Trientine and zinc salts given orally are somewhat less effective, but have fewer side effects than penicillamine. In addition, zinc salts may take several months to have any noticeable effect. A diet low in copper will also have some preventive effect. Finally, for those patients in advanced stages of liver disease, liver transplantation may be the only method of averting liver failure and death.

Recovery and rehabilitation

The earlier in the course of the disorder that treatment is started, the more beneficial the effects will be. For some individuals, liver function may return to near normal, and often dramatic improvements in the neuropsychiatric symptoms can be seen shortly after beginning treatment. For others who have gone untreated for longer periods, or who have a more severe form of the disease, only modest improvements may be seen. Treatment must be lifelong.



See Symbol Guide for Pedigree Charts. *(Gale Group.)*

Clinical trials

A newer copper chelating agent currently being investigated is tetrathiomolybdate. The hope is that it will prove to have fewer side effects than penicillamine, yet be more effective than Trientine. Possible suppression of bone marrow function may yet be a risk for some patients.

Prognosis

For those who begin treatment early in the progression of the disorder, or even before symptoms are noted, the prognosis is excellent, as long as the patients comply with the treatment regimen. For others, the prognosis may be more difficult to predict, but nearly every patient with WD sees at least some improvement once treatment is begun. For those who go untreated, the prognosis is very poor.

Special concerns

The rarity of WD, combined with its diverse and varied symptoms that can mimic other conditions, makes it difficult to diagnose. This is of special concern because it is a progressive fatal condition; yet it can be easily and effectively treated if caught early. The autosomal recessive nature of the condition means that there is almost never a previous family history (other than a diagnosed sibling) to alert anyone to the risk. Because the diagnosis is easily established by measuring serum ceruloplasmin levels, with subsequent liver biopsy for copper levels, anyone contracting hepatitis or cirrhosis with no obvious cause, with or without neuropsychiatric symptoms, should be tested for WD.

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ORGANIZATIONS

Wilson's Disease Association. 4 Navaho Drive, Brookfield, CT 06804-3124. (800) 399-0266; Fax: (203) 775-9666. <http://www.wilsondisease.org>.

National Center for the Study of Wilson's Disease. 432 West 58th Street, Suite 614, New York, NY 10019. (212) 523-8717; Fax: (212) 523-8708.

Scott J. Polzin, MS, CGC

Z

Zellweger syndrome

Definition

Zellweger syndrome is a severe and fatal genetic disorder affecting the brain, liver, and kidneys. It can be inherited by children of individuals that carry mutations for a specific gene.

Description

Zellweger syndrome is a fatal disorder that damages the brain, liver, and kidneys. There are related syndromes that have Zellweger-like symptoms and involve defects in the distinct cytoplasm organelles of cells called the peroxisomes; these include neonatal **adrenoleukodystrophy**, infantile **Refsum disease**, and hyperpipecolic acidemia. Zellweger syndrome is the most severe of these related syndromes.

Demographics

The incidence of Zellweger syndrome worldwide is roughly one in 100,000 births.

Causes and symptoms

Mutations in one of the many genes that cause Zellweger syndrome lead to a dysfunctional protein that is important for the cells' ability to import newly synthesized proteins into small cytoplasmic organelles called peroxisomes. Zellweger syndrome is characterized by the reduction or absence of these peroxisomes. Key enzymes that are critical for various chemical reactions, in particular oxidation, are contained within the peroxisomes.

Functional and structural abnormalities of the peroxisomes can lead to the disease development observed in Zellweger syndrome. Because peroxisomes are abundant in the liver and the kidney, these organs are affected in Zellweger syndrome. Toxic molecules that enter the bloodstream are detoxified by the peroxisomes, although there are additional mechanisms for detoxification. For example, when consuming large amounts of ethanol from alcoholic beverages, roughly 5–25% of the ethanol can be oxidized by the peroxisomes. Peroxisomes can also function in the organic creation of key compounds and play important roles in the various chemical reactions.

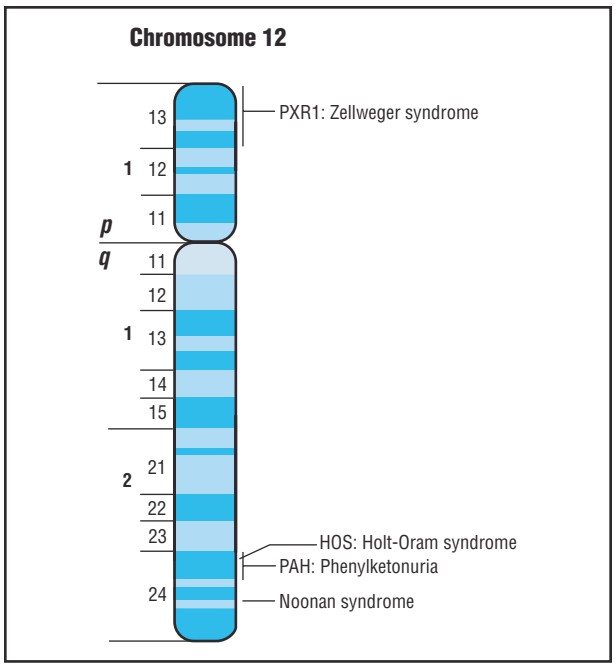
Zellweger syndrome is caused by mutations in any one of several different genes involved in the function of the peroxisome. These include peroxin-1 (PEX1), peroxin-2 (PEX2) peroxin-3 (PEX3), peroxin-5 (PEX5), peroxin-6 (PEX6), and peroxin-12 (PEX12). Each of these gene locations are biochemically and genetically distinct and are found on different chromosomes.

The observable clinical features of Zellweger syndrome can include facial, developmental, and ocular (eye) defects. Characteristic features commonly include a high forehead, upslanting eyes, and skin folds, called epicanthal folds, along the medial (nasal) borders of the palpebral fissures (space between upper and lower eyelids) of the eyes. Typically, babies with Zellweger syndrome have severe weakness, hyptonia (loss of muscle tone), and often have neonatal **seizures**. There are also several ocular abnormalities that can affect eyesight.

Diagnosis

Absent peroxisomes in the liver and kidney was initially demonstrated by American pathologist S. L. Goldfischer in 1985. The absence of these organelles in the liver is currently thought to be the hallmark of this disorder. Patients with Zellweger syndrome have been found to have remarkably fewer peroxisomes in both the brain and cultured skin fibroblasts. Fibroblasts are a type of skin cell and, in Zellweger syndrome, these cells appear to have ghost-like peroxisomes, which are caused by an absence of specific proteins inside the organelles that are recruited into the membranes.

Peroxisomes play an important role in organ development. Brain abnormalities can be explained by the disrupted migration of nerve cells called neurons (or



Zellweger syndrome, on chromosome 12. *(Gale Group.)*

neuroblasts at this stage of development) around the third month of gestation. This defect occurs in a specific area of the brain called the cerebrum and leads to small or thick convolutions in brain tissue. This brain abnormality allows Zellweger syndrome to be distinguished from other diseases that involve brain abnormalities. Other tissues involved in the disease development include the liver, kidney, cartilage, heart, and muscle. Most patients have cysts on their kidneys.

Zellweger syndrome is diagnosed by measuring metabolic compounds in blood samples from patients. Various fatty acids, plasmalogens, pipecolic acid, and bile acid intermediates are usually studied. Aside from plasmalogen levels, which are diminished, these compounds are typically increased in affected individuals. It is also possible to detect fatty acid levels and plasmalogen synthesis before birth by obtaining cells in the fluid of the amnion, a process called amniocentesis. Thus, pregnant mothers who have previously had an affected baby can opt to have prenatal diagnosis to determine if the fetus is affected.

Treatment team

Physicians, nurses, and therapists provide the basis of the treatment team for a person with Zellweger's syndrome. Geneticists also provide diagnostic and genetic counseling services. Support services are available for families.

Treatment

There is no cure for Zellweger syndrome and treatment is based solely on lessening the symptoms and supporting the involved organs.

Recovery and rehabilitation

Physical, occupational, respiratory, and speech therapists can provide supportive strategies and devices to maintain posture, independent breathing, speech, eating, and other daily activities according to the infant or child's developmental stage for as long as practically possible.

Clinical trials

As of 2004, there is one clinical trial sponsored by the FDA Office of Orphan Products Development for the treatment of Zellweger syndrome (which is under review by the National Institutes of Health). It involves determining the effectiveness of giving oral bile acids (cholic acid, chenodeoxycholic acid, and ursodeoxycholic acid) as therapy for affected individuals.

Prognosis

Persons with Zellweger syndrome rarely live more than one year after diagnosis, with death due mostly to severe feeding difficulties, liver complications, respiratory distress, and cardiac defects.

Special concerns

Because Zellweger syndrome is usually fatal within the first year of life, genetic counseling and prenatal diagnosis are usually assigned a high priority for parents identified or concerned that they may be at risk for having a baby with the syndrome.

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Key Terms

Cytoplasm The substance within a cell including the organelles and the fluid surrounding the nucleus.

Peroxisome A cellular organelle containing different enzymes responsible for the breakdown of waste or other products.

National Institute of Neurological Disorders and Stroke. *NINDS Zellweger Syndrome Information Page* January 3, 2004 (March 2, 2004). <http://www.ninds.nih.gov/health_and_medical/disorders/zellwege_doc.htm>.

ORGANIZATIONS

National Organization for Rare Disorders. P.O. Box 1968, Danbury, CT 06813-1968. (203) 744-0100. orphan@rarediseases.org. <http://www.rarediseases.org>.

United Leukodystrophy Foundation, Inc. 2304 Highland Drive, Sycamore, IL 60178. (800) 728-5483; Fax: (815) 895-2432. ulf@tbcnet.com. <http://www.ulf.org>.

Bryan Richard Cobb, PhD

Zonisamide

Definition

Zonisamide is an anti-convulsant used to control **seizures** in the treatment of **epilepsy**, a neurological dysfunction in which excessive surges of electrical energy are emitted in the brain.

Purpose

Zonisamide decreases abnormal activity and excitement within the brain that may trigger seizures. While zonisamide controls the partial seizures (focal seizures) associated with epilepsy, there is no known cure for the disease.

Some physicians have also used zonisamide in the treatment of mood disorders. As of 2004, zonisamide is additionally under study for the treatment of migraine **headaches** and neuropathic (nerve) **pain**.

Description

In the United States, zonisamide is sold under the brand name Zonegran. Zonisamide is classified as a sulfonamide anticonvulsant. The precise mechanisms by which it works are unknown.

Recommended dosage

Zonisamide is taken by mouth in tablet form. It is prescribed by physicians in varying dosages, usually from 100 mg to 400 mg daily.

Beginning a course of treatment which includes zonisamide requires a gradual dose-increasing regimen. Adults and teenagers 16 years or older typical take 100 mg per day for the first two weeks. Daily dosages of zonisamide may then be increased 100 mg once every two weeks until reaching the full daily dose (usually not more than 400 mg.) It may take several weeks to realize the full benefits of zonisamide.

Persons should not take a double dose of anticonvulsant medications. If a daily dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped.

When discontinuing treatment with zonisamide, physicians typically direct patients to gradually reduce their daily dosages. Stopping the medicine suddenly may cause seizures to occur or become more frequent.

Precautions

Persons taking zonisamide should avoid alcohol and **central nervous system** depressants (medications including antihistimines, sleep medications, and some pain medications). Combining these substances with zonisamide can exacerbate (heighten) the side effects of alcohol and other medications.

A physician should be consulted before taking zonisamide with certain non-perscription medications, such as medicines for asthma, appetite control, coughs, colds, sinus problems, allergies, and hay fever.

Zonisamide may inhibit perspiration, causing body temperature to increase during physical activity. Persons taking zonisamide are at a greater risk for heat **stroke**. Caution should be used during strenuous **exercise**, prolongued exposure during hot weather, and while using saunas or hot tubs.

Zonisamide may not be suitable for persons with a history of liver or kidney disease, mental illness, high blood presure, angina (chest pain), irregular heartbeats, or other heart problems.

Before beginning treatment with zonisamide, patients should notify their physician if they consume a large amount of alcohol, have a history of drug use, are pregnant, or plan to become pregnant. Most physicians recommend using effective birth control while taking zonisamide, as it may cause defects to a developing fetus. Patients who become pregnant while taking zonisamide should contact their physician.

Side effects

Research indicates that zonisamide is generally well tolerated. However, it may case a variety of usually mild side effects. Headache, nausea and **fatigue**, and weakness are the most frequently reported side effects of zonisamide. Other possible side effects include:

- difficulty sleeping
- nervousness
- anxiety
- abdominal pain
- difficulty with memory
- double vision
- loss of appetite
- restlessness
- drowsiness
- diarrhea or constipation
- indigestion
- aching joints and muscles
- unpleasant taste in mouth or dry mouth
- tingling or prickly feeling on the skin

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication. However, if any symptoms persist or become too uncomfortable, the prescribing physician should be consulted.

Other, uncommon side effects of zonisamide can be serious. A patient taking zonisamide who experiences any of the following symptoms should contact their physician:

- rash or bluish patches on the skin
- discouragement, feeling sad or empty
- mood or mental changes
- shakiness or unsteady walking
- lack of appetite
- kidney stones
- difficulty breathing
- chest pain
- slow or irregular heartbeat
- faintness
- confusion or loss of consciousness
- persistent, severe headaches
- persistent fever or pain

Interactions

Zonisamide may have negative interactions with some antifungal medications, antihistimines, antidepressants, antibiotics, and monoamine oxidase inhibitors (MAOIs). Other medications such as **diazepam** (Valium), fluoxetine (Prozac, Sarafem), fluvoxamine (Luvox), HIV protease inhibitors (indinavir), ritonavir (Norvir), ipratropium (Atrovent), isoniazid, **phenobarbital** (Luminal, Solfoton), nefazodone, metronidazole, **acetazolamide** (Diamox), phenytoin (Dilantin), **primidone**, propranolol (Inderal); and rifampin (Rifadin, Rimactane) may also adversely react with zonisamide.

Zonisamide is sometimes prescribed as part of a combination of drugs to prevent seizures. The physician will carefully monitor the combination drug therapy, as sometimes zonisamide will potentite (enhance) the effects of other anticonvulsant medications.

Zonisamide may decrease the effectiveness of some forms of oral contraceptives (birth control pills).

Zonisamide should not be taken by those allergic to sulfa drugs.

Key Terms

Epilepsy A disorder associated with disturbed electrical discharges in the central nervous system that cause seizures.

Seizure A convulsion, or uncontrolled discharge of nerve cells that may spread to other cells throughout the brain.

Sulfonamides A group of antibiotics used to treat a wide range of bacterial infections.

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ORGANIZATIONS

Epilepsy Foundation. 4351 Garden City Drive, Landover, MD 20785-7223. (800) 332-1000. <http://www.epilepsyfoundation.org>.

American Epilepsy Society. 342 North Main Street, West Hartford, CT 06117-2507. (860)586-7505. <http://www.aesnet.org>.

Adrienne Wilmoth Lerner

GLOSSARY

A

ABSCESS. A localized collection of pus or infection that is walled off from the rest of the body.

ABSENCE SEIZURE. A type of generalized seizure in which the person may temporarily appear to be staring into space and/or have jerking or twitching muscles. Previously called a petit mal seizure.

ABSTRACTION. Ability to think about concepts or ideas separate from specific examples.

ACALCULIA. The inability to perform basic calculation (addition, subtraction, multiplication, division).

ACETYLCHOLINE. A chemical called a neurotransmitter that functions primarily to mediate activity of the nervous system and skeletal muscles.

ACHALASIA. An esophageal disease of unknown cause in which the lower sphincter muscle is unable to relax normally, resulting in obstruction, either partial or complete.

ACOUSTIC. A term that refers to hearing.

ACOUSTIC NERVE. The cranial nerve VIII, involved in both hearing and balance.

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.

ACUITY. Sharpness.

ADJUVANT. A medication or other substance given to aid another drug, such as a tranquilizer given to ease the anxiety of a cancer patient in addition to an analgesic for pain relief.

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.

ADVANCED BONE AGE. The bones, on x ray, appear to be those of an older individual.

AFFECTIVE PSYCHOSIS. Abnormalities in mood, emotions, feelings, sensibility, or mental state.

AFLATOXIN. A toxin produced by a fungus that infests grains, peanuts, soybeans, and corn that have been stored in warm, moist conditions.

AGNOSIA. Inability to notice or process sensory stimuli.

AGRAPHIA. The inability to write.

AIDS. Acquired Immune Deficiency Syndrome is a sexually transmitted disease caused by the Human Immunodeficiency Virus (HIV). It weakens the immune system and makes a person susceptible to many infections and malignancies.

ALEXANDER TECHNIQUE. A form of movement therapy that emphasizes correct posture and the proper positioning of the head with regard to the spine.

ALGORITHMS. A sequence of steps designed to calculate or determine a task.

ALLERGEN. Any substance that irritates only those who are sensitive (allergic) to it.

ALZHEIMER DISEASE. A neurological disorder characterized by slow, progressive memory loss due to a gradual loss of brain cells.

AMAUROSIS FUGAX. A type of transient ischemic attack (TIA) caused by decreased blood flow through the carotid artery, characterized by blindness or decreased vision in one eye.

AMENORRHEA. The absence or abnormal stoppage of menstrual periods.

AMINO ACID. An organic compound composed of both an amino group and an acidic carboxyl group. Amino acids are the basic building blocks of proteins. There are 20 types of amino acids (eight are "essential amino acids" that the body cannot make and must therefore be obtained from food).

AMNESIA. A general medical term for loss of memory that is not due to ordinary forgetfulness. Amnesia can be caused by head injuries, brain disease, or epilepsy, as well as by dissociation. Includes: 1) Anterograde amnesia: inability to retain the memory of events occurring after the time of the injury or disease that brought about the amnesic state. 2) Retrograde amnesia: inability to recall the memory of events that occurred prior to the time of the injury or disease that brought about the amnesic state.

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.

AMNIOTIC SAC. Contains the fetus, which is surrounded by amniotic fluid.

AMYGDALA. An almond-shaped brain structure in the limbic system that is activated in stressful situations to trigger the emotion of fear. Hallucinations related to post-traumatic stress are thought to be caused by the activation of memory traces in the amygdala that have not been integrated and modified by other parts of the brain.

AMYLOID PLAQUE. A waxy, translucent, starch-like protein that is deposited in tissues during the course of certain chronic diseases such as rheumatoid arthritis and Alzheimer disease.

AMYLOIDOSIS. The accumulation of amyloid deposits in various organs and tissues in the body so that normal functioning is compromised. Primary amyloidosis usually occurs as a complication of multiple myeloma. Secondary amyloidosis occurs in patients suffering from chronic infections or inflammatory diseases such as tuberculosis, rheumatoid arthritis, and Crohn's disease.

AMYOTROPHIC LATERAL SCLEROSIS. ALS, also called Lou Gehrig's disease is a progressive neuromuscular condition due to degeneration of the motor nerve cells and fiber tracts in the spinal cord. The cause is not yet well defined. It is characterized by progressive weakening of the limb muscles and those involved in swallowing and breathing. It is fatal within a couple of years of onset.

AMYOTROPHY. A type of neuropathy resulting in pain, weakness, and/or wasting in the muscles.

ANAEROBIC. Describes an organism that grows and thrives in an oxygen-free environment.

ANALGESICS. A class of pain-relieving medicines, including aspirin and Tylenol.

ANEMIA. A condition in which there is an abnormally low number of red blood cells in the bloodstream. It may be due to loss of blood, an increase in red blood cell destruction, or a decrease in red blood cell production. Major symptoms are paleness, shortness of breath, unusually fast or strong heart beats, and tiredness.

ANEURYSM. A weakened area in the wall of a blood vessel that causes an outpouching or bulge. Aneurysms may be fatal if these weak areas burst, resulting in uncontrollable bleeding.

ANGINA PECTORIS. Chest pain caused by an insufficient supply of oxygen and decreased blood flow to the heart muscle. Angina is frequently the first sign of coronary artery disease.

ANGIOFIBROMA. Non-cancerous growth of the skin, which are often reddish in color and filled with blood vessels.

ANGIOGRAPHY. A mapping of the brain's blood vessels, using x-ray imaging.

ANGIOKERATOMA. Skin rash comprised of red bumps. Rash most commonly occurs between the navel and the knees.

ANGIOMYOLIPOMA. Non-cancerous growth in the kidney, most often found in tuberous sclerosis.

ANGULAR GYRUS. A ridge (outfolding) in the parietal lobe of the brain.

ANNULUS FIBROSUS. A fibrous and cartilage ring that forms the circumference of a vertebrae.

ANOREXIA. Loss of appetite.

ANOXIA. Lack of oxygen.

ANTERIOR CIRCULATION. The blood supply to most of the front part of the brain known as the cerebrum, including the frontal, parietal, and temporal lobes.

ANTERIOR VITREITIS. Inflammation of the corpus vitreum, which surrounds and fills the inner portion of the eyeball between the lens and the retina.

ANTEROGRADE AMNESIA. Amnesia for events that occurred after a physical injury or emotional trauma but before the present moment.

ANTIBODY. A special protein made by the body's immune system as a defense against foreign material (bacteria, viruses, etc.) that enters the body. It is uniquely designed to attack and neutralize the specific antigen that triggered the immune response.

ANTICHOLINERGIC DRUGS. Drugs that block the action of the neurotransmitter acetylcholine. They are used to lessen muscle spasms in the intestines, lungs, bladder, and eye muscles.

ANTICIPATION. Genetic phenomenon in which a triple repeat DNA mutation expands in a future generation, causing symptoms to develop earlier.

ANTICONVULSANT DRUGS. Drugs used to prevent convulsions or seizures. They often are prescribed in the treatment of epilepsy.

ANTIEMETIC. A type of drug given to stop vomiting.

ANTIEPILEPTIC. A drug that prevents or limits the spread of epileptic seizures.

ANTIGEN. A substance (usually a protein) identified as foreign by the body's immune system, triggering the release of antibodies as part of the body's immune response.

ANTIOXIDANT. Any substance that reduces the damage caused by oxidation, such as the harm caused by free radicals.

ANTIPLATELET AGENTS. Drugs that reduce the tendency of platelets to clump together, used to reduce the risk of transient ischemic attack (TIA) or stroke.

ANTIVIRAL. A drug that prevents viruses from replicating and therefore spreading infection.

ANXIETY. Worry or tension in response to real or imagined stress, danger, or dreaded situations. Physical reactions such as fast pulse, sweating, trembling, fatigue, and weakness may accompany anxiety.

ANXIETY DISORDER. A psychiatric disorder involving the presence of anxiety that is so intense or so frequently present that it causes difficulty or distress for the individual.

AORTA. The major artery that carries oxygenated blood from the heart to be delivered by arteries throughout the body.

APHASIA. Loss of the ability to speak or to understand written or spoken language. A person who cannot speak or understand language is said to be aphasic.

APHERESIS. A procedure in which the blood is removed and filtered in order to rid it of particular cells, then returned to the patient.

APNEA. An irregular breathing pattern characterized by abnormally long periods of the complete cessation of breathing.

APRAXIA. Inability to carry out ordinary purposeful movements in the absence of paralysis.

ARACHNOID MEMBRANE. One of the three membranes that sheath the spinal cord and brain; the arachnoid is the middle membrane. Also called the arachnoid mater.

ARBOVIRUSES. Viruses harbored by arthropods (mosquitoes and ticks) and transferred to humans by their bite. An arbovirus is the cause of West Nile infection, and arboviruses are one cause of encephalitis.

AREFLEXIA. Absence of a reflex; a sign of possible nerve damage.

ARTERIOGRAM. An x-ray study of an artery that has been injected with a contrast dye.

ARTERIOSCLEROSIS. A chronic condition characterized by thickening and hardening of the arteries and the build-up of plaque on the arterial walls. Arteriosclerosis can slow or impair blood circulation.

ARTERIOVENOUS MALFORMATION. Abnormal, direct connection between the arteries and veins. Arteriovenous malformations can range from very small to large.

ASPERGER SYNDROME. A developmental disorder of childhood characterized by autistic behavior but without the same difficulties acquiring language that children with autism have.

ASPIRATION. Inhalation of food or liquids into the lungs.

ASPIRATION PNEUMONIA. Infection of the lungs, caused by the presence of foreign material such as food.

ASTHENIA. Muscle weakness.

ASTHMA. A disease in which the air passages of the lungs become inflamed and narrowed.

ASTROCYTES. Types of neuroglial cells in the central nervous system that help support other nerve cells.

ATAXIA. A condition marked by impaired muscular coordination, most frequently resulting from disorders in the brain or spinal cord.

ATHEROSCLEROTIC PLAQUE. A deposit of fatty and calcium substances that accumulate in the lining of the artery wall, restricting blood flow. The disease is called atherosclerosis.

ATHETOSIS. A condition marked by slow, writhing, involuntary muscle movements.

ATONIC SEIZURE. A seizure characterized by a sudden loss of muscle tone, causing the individual to fall to the floor.

ATRIAL FIBRILLATION. A type of heart arrhythmia in which the upper chamber of the heart quivers instead of pumping in an organized way. In this condition, the upper chambers (atria) of the heart do not completely empty when the heart beats, which can allow blood clots to form.

ATROPHY. The progressive wasting and loss of function of any part of the body.

AUDIOLOGIST. A healthcare professional who specializes in diagnostic testing of hearing impairments and rehabilitation of patients with hearing problems.

AUDITORY. Pertaining to the sense of hearing.

AUDITORY NERVE. A bundle of nerve fibers that carries hearing information between the cochlea and the brain.

AURA. A group of visual or other sensations that precedes the onset of a migraine attack.

AUTISM. A developmental disability that appears early in life, in which normal brain development is disrupted and social and communication skills are retarded, sometimes severely.

AUTISTIC PSYCHOPATHY. Hans Asperger's original name for the condition now known as Asperger's disorder. It is still used occasionally as a synonym for the disorder.

AUTOANTIBODIES. Antibodies that attack the body's own cells or tissues.

AUTOIMMUNE. Pertaining to an immune response by the body against its own tissues or types of cells.

AUTOIMMUNE DISEASE. One of a group of diseases, like rheumatoid arthritis and systemic lupus erythematosus, in which the immune system is overactive and has lost the ability to distinguish between self and non-self. The body's immune cells turn on the body, attacking various tissues and organs.

AUTOMATISMS. Movements during a seizure that are semi-purposeful but involuntary.

AUTONOMIC FAILURE. Refers to failure in the autonomic nervous system, which comprises two divisions called the parasympathetic nervous system, which slows heart rate, increases intestinal and gland activity, and relaxes sphincter muscles; and the sympathetic nervous system, which accelerates heart rate, raises blood pressure, and constricts blood vessels.

AUTONOMIC NERVOUS SYSTEM. The part of the nervous system that controls so-called involuntary functions, such as heart rate, salivary gland secretion, respiratory function, and pupil dilation.

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 DOMINANT. A pattern of inheritance in which only one of the two copies of an autosomal gene must be abnormal for a genetic condition or disease to occur. An autosomal gene is a gene that is located on one of the autosomes or non-sex chromosomes. A person with an autosomal dominant disorder has a 50% chance of passing it to each of their offspring.

AUTOSOMAL RECESSIVE. A pattern of inheritance in which both copies of an autosomal gene must be abnormal for a genetic condition or disease to occur. An autosomal gene is a gene that is located on one of the autosomes or non-sex chromosomes. When both parents have one abnormal copy of the same gene, they have a 25% chance with each pregnancy that their offspring will have the disorder.

AXILLARY. Referring to the armpit.

AXON. The long, hairlike extension of a nerve cell that carries a message to a nearby nerve cell.

AXONTOMESIS. Loss of the protective sheet of tissue that covers the axon (the part of the nerve cell that carries a transmission).

B

BABESIOSIS. A disease caused by protozoa of the genus *Babesia* characterized by a malaria-like fever, anemia, vomiting, muscle pain, and enlargement of the spleen. Babesiosis, like Lyme disease, is carried by a tick.

BACILLUS. A rod-shaped bacterium, such as the diphtheria bacterium.

BALANCED CHROMOSOME TRANSLOCATION. A rearrangement of the chromosomes in which two chromosomes have broken and exchanged pieces without the loss of genetic material.

BALLISMUS. Involuntary violent flinging movements that may take the form of uncontrollable flailing. It is also called ballism. Ballismus that occurs with chorea is known as choreoballismus or choreoballism.

BARBITURATE. A class of drugs including phenobarbital that have sedative properties and depress respiratory rate, blood pressure, and nervous system activity.

BASAL GANGLIA. Brain structure at the base of the cerebral hemispheres involved in controlling movement.

BASILAR MIGRAINE. A type of migraine with aura that involves the basilar artery at the base of the brain. It occurs

most commonly in young women, and may include vision problems, confusion, and loss of consciousness as well as headache.

BATTERY. A number of separate items (such as tests) used together. In psychology, a group or series of tests given with a common purpose, such as personality assessment or measurement of intelligence.

BEHAVIOR DISORDERS. Disorders characterized by disruptive behaviors such as conduct disorder, oppositional defiant disorder, and attention-deficit/hyperactivity disorder.

BENIGN. In medical usage, benign is the opposite of malignant. It describes an abnormal growth that is stable, treatable, and generally not life-threatening.

BENZODIAZEPINES. A class of drugs with hypnotic, antianxiety, anticonvulsive, and muscle-relaxant properties. They are used in the treatment of anxiety and sleeping disorders, to relax muscles, and to control seizures. Diazepam (Valium), alprazolam (Xanax), and chlordiazepoxide (Librium) are all benzodiazepines.

BILATERAL. Occurring on both sides of the body.

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.

BIOFEEDBACK. A training technique that enables an individual to gain some element of control over involuntary or automatic body functions.

BIOLOGICAL MARKER. An indicator or characteristic trait of a disease that facilitates differential diagnosis (the process of distinguishing one disorder from other, similar disorders).

BIOPSY. The surgical removal and microscopic examination of living tissue for diagnostic purposes or to follow the course of a disease. Most commonly the term refers to the collection and analysis of tissue from a suspected tumor to establish malignancy.

BIOTRANSFORMATION. The conversion of a compound from one form to another by the action of enzymes in the body of an organism.

BIPOLAR DISORDER. A psychiatric disorder marked by alternating episodes of mania and depression. Also called bipolar illness, manic-depressive illness.

BLOOD VESSELS. General term for arteries, veins, and capillaries that transport blood throughout the body.

BODYWORK. Any technique involving hands-on massage or manipulation of the body.

BOLUS. A mass of a substance to be swallowed.

BOTULINUM TOXIN. A potent bacterial toxin or poison made by *Clostridium botulinum*; causes paralysis in high doses, but is used medically in small, localized doses to treat disorders associated with involuntary muscle contraction and spasms, in addition to strabismus. Commonly known as Botox.

BRACHIAL PLEXUS. A group of lower-neck and upper-back spinal nerves supplying the arm, forearm, and hand.

BRADYKINESIA. Extremely slow movement.

BRAIN STEM. The part of the brain that is continuous with the spinal cord and controls most basic life functions. It is the last part of the brain that is destroyed by Alzheimer's disease.

BREECH PRESENTATION. Buttocks presentation during delivery.

BRONCHITIS. Inflammation of the air passages of the lungs.

BRUIT. An abnormal sound heard with the stethoscope placed over the carotid artery in the neck, suggesting decreased blood flow through the vessel.

BRUXISM. Habitual clenching and grinding of the teeth, especially during sleep.

BULBAR MUSCLES. Muscles of the mouth and throat responsible for speech and swallowing.

C

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

CAPILLARY BED. A dense network of tiny blood vessels that enables blood to fill a tissue or organ.

CAPSAICIN. An alkaloid derived from hot peppers that can be used as a topical anesthetic.

CARBIDOPA. A drug combined with levodopa to slow the breakdown of the levodopa, used to treat the symptoms of Parkinson's disease.

CARBONIC ANHYDRASE. An enzyme that shifts the rate of reaction to favor the conversion of carbon dioxide and water into carbonic acid, bicarbonate ions, and free protons.

CARCINOGEN. A substance known to cause cancer.

CARDIAC TAMPONADE. A condition in which blood leaking into the membrane surrounding the heart puts pressure on the heart muscle, preventing complete filling of the heart's chambers and normal heartbeat.

CARDIOMYOPATHY. A disease of the heart muscle that leads to generalized deterioration of the muscle and its pumping ability.

CARDITIS. Inflammation of the heart tissue.

CAROTID ARTERY. One of the major arteries supplying blood to the head and neck.

CAROTID ENDARTERECTOMY. Surgical procedure designed to reduce the accumulation of plaque in the carotid artery and thus, prevent stroke.

CAROTID ULTRASONOGRAPHY. A painless and harmless test using high-frequency sound waves to determine if there is narrowing or plaque formation in the carotid arteries.

CARPAL TUNNEL SYNDROME. A condition caused by compression of the median nerve in the carpal tunnel of the hand, characterized by pain.

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.

CATAPLEXY. A symptom of narcolepsy marked by a sudden episode of muscle weakness triggered by strong 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.

CATARACTS. Abnormal clouding or opacities within the lens of the eye.

CATATONIA. A fixed, motionless stupor.

CATECHOLAMINES. Chemicals such as epinephrine, dopa, and norepinephrine; often at high levels in the urine if a pheochromocytoma is present.

CATHETER. A long, thin, flexible tube used in angiography to inject contrast material into the arteries.

CAUDATE. A region of gray matter near the lateral ventricle of the brain; also called caudate nucleus.

CENTRAL APNEA. Abnormal breathing as a result of the medulla being pushed down, such as from an Arnold-Chiari, Type II malformation.

CENTRAL NERVOUS SYSTEM. The brain, spinal cord and the nerves throughout the body.

CENTRAL SLEEP APNEA. A less-common form of sleep apnea in which the brain does not properly signal respiratory muscles to begin breathing.

CEPHALALGIA. The medical term for headache.

CEREBELLAR ATAXIA. Unsteadiness and lack of coordination caused by a progressive degeneration of the part of the brain known as the cerebellum.

CEREBELLUM. The part of the brain involved in the coordination of movement, walking, and balance.

CEREBRAL ANEURYSM. An abnormal, localized bulge in a blood vessel that is usually caused by a congenital weakness in the wall of the vessel.

CEREBRAL COLLATERAL BLOOD FLOW. Anatomical and physiological mechanisms that allow blood destined for one hemisphere of the brain to crossover and nourish tissue on the other side of the brain when the supply to the other side of the brain is impaired.

CEREBRAL CORTEX. The thin, convoluted surface of the brain consisting mainly of nerve cell bodies. This brain region is responsible for reasoning, mood, and perception.

CEREBRAL DOMINANCE. The preeminence of one cerebral hemisphere over the other in the control of cerebral functions.

CEREBRAL EMBOLISM. A blockage of blood flow through a vessel in the brain by a blood clot that formed elsewhere in the body and traveled to the brain.

CEREBRAL HERNIATION. Movement of the brain against the skull.

CEREBRAL INFARCTION. Brain-tissue damage caused by interrupted flow of oxygen to the brain.

CEREBRAL ISCHEMIA. Lack of oxygen to the brain, which may result in tissue death.

CEREBRAL OXIDATIVE METABOLISM. Using oxygen to generate energy by complex chemical reactions that occur in brain cells.

CEREBRAL PALSY. A nonprogressive movement disability caused by abnormal development of or damage to motor control centers of the brain.

CEREBRAL THROMBOSIS. A blockage of blood flow through a vessel in the brain by a blood clot that formed in the brain itself.

CEREBRAL VASCULAR ACCIDENT. Damage to brain cells caused by lack of blood flow in the brain from emboli (clots) plaque, or hemorrhage.

CEREBROSPINAL FLUID. The clear, normally colorless fluid that fills the brain cavities (ventricles), the subarachnoid space around the brain, and the spinal cord and acts as a shock absorber.

CEREBRUM. The main portion of the brain (and the largest part of the central nervous system), occupying the upper portion of the cranial cavity. It is responsible for higher functions such as speech, thought, vision, and memory.

CERULOPLASMIN. A protein circulating in the bloodstream that binds with and transports copper.

CERVICAL. Referring to the neck. Cervical vertebrae are the first 7 bones of the spine.

CHELATION. The process by which a molecule encircles and binds to a metal and removes it from tissue.

CHEMOTHERAPY. Chemical medical treatment often used for cancer.

CHOREA. A term that refers to rapid, jerky, involuntary movements of the limbs or face that characterize several different disorders of the nervous system, including chorea of pregnancy, Huntington's chorea, and Sydenham's chorea.

CHOREA GRAVIDARUM. Chorea occurring in the early months of pregnancy.

CHORIONIC VILLUS SAMPLING. A medical procedure done during weeks 10-12 of a pregnancy. A needle is inserted into the placenta and a small amount of fetal tissue is withdrawn for analysis.

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.

CHROMATIN. The readily stainable portion of a cell nucleus, consisting of DNA, RNA, and various proteins. It coils and folds itself to form chromosomes during the process of cell division. Rett syndrome (RS) is sometimes described as a chromatin disease.

CHROMOSOME. A microscopic thread-like structure found within each cell of the human body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Chromosomes contain the genetic information necessary to direct the development and functioning of all cells and systems in the body. They pass on hereditary traits from parents to child (like eye color) and determine whether the child will be male or female. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

CHRONIC. Refers to a disease or condition that progresses slowly but persists or recurs over time.

CIRCLE OF WILLIS. Also known as the circulus arteriosus; formed by branches of the internal carotid arteries and the vertebral arteries.

CIRRHOSIS. A chronic degenerative disease of the liver, in which normal cells are replaced by fibrous tissue and normal liver function is disrupted. The most common symptoms are mild jaundice, fluid collection in the tissues, mental confusion, and vomiting of blood. Cirrhosis is associated with portal hypertension and is a major risk factor for the later development of liver cancer. If left untreated, cirrhosis leads to liver failure.

CLAUDICATION. Cramping or pain in a leg caused by poor blood circulation. This condition is frequently caused by hardening of the arteries (atherosclerosis). Intermittent claudication occurs only at certain times, usually after exercise, and is relieved by rest.

CLAVICLE. Also called the collarbone. Bone that articulates with the shoulder and the breast bone.

CLEFT PALATE. A birth defect in which the roof of the mouth (palate) has an abnormal opening (cleft).

CLONIC. A type of seizure characterized by rhythmic jerking of the arms and legs.

CLOSED HEAD INJURY. Traumatic brain injury (TBI) in which the head strikes or is struck by an object without breaking the skull.

CLUBFOOT. Abnormal positioning of the feet and legs, when they are turned inward towards each other.

CLUSTER HEADACHE. A painful recurring headache associated with the release of histamine from cells.

CLUTTER. A fluency disorder where speech delivery is either abnormally fast, irregular, or both.

COCHLEA. A spiral-shaped tubular structure resembling a snail's shell that forms part of the inner ear.

COCHLEAR IMPLANT. A device used for treating deafness that consists of one or more electrodes surgically implanted inside or outside the cochlea, an organ in the inner ear that transforms sound vibrations in the inner ear into nerve impulses for transmission to the brain.

COGNITIVE DELAY. Impairment or slowing of the mental processes of thinking and acquiring knowledge.

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

COMA. A decreased level of consciousness with deep unresponsiveness.

COMMAND HALLUCINATION. A type of auditory hallucination in which the person hears voices ordering him or her to perform a specific act.

COMMUNITY MENTAL HEALTH CENTERS. Organizations that manage and deliver a comprehensive range of mental health services, education, and outreach to residents of a given community.

COMORBID. A term used to refer to a disease or disorder that is not directly caused by another disorder but occurs at the same time.

COMPULSION. A repetitive or stereotyped act or ritual.

CONCUSSION. Injury to the brain causing a sudden, temporary impairment of brain function.

CONDUCTIVE HEARING LOSS. A type of medically treatable hearing loss in which the inner ear is usually normal, but there are specific problems in the middle or outer ears that prevent sound from getting to the inner ear in a normal way.

CONGENITAL. Present at birth.

CONGENITAL MYOPATHY. Any abnormal condition or disease of muscle tissue that is present at birth; it is characterized by muscle weakness and wasting.

CONNECTIVE TISSUE. Supportive tissue in the body that joins structures together, lending strength and elasticity.

CONSTRUCTIONAL APRAXIA. Difficulty or inability to copy a drawing.

CONTRACTURE. A tightening or shortening of muscles that prevents normal movement of the associated limb or other body part.

CONTRECOUP. An injury to the brain opposite the point of direct impact.

CONTUSION. A focal area of swollen and bleeding brain tissue.

CORDOTOMY. Surgery to relieve pain by destroying bundles of nerve fibers on one or both sides of the spinal cord.

CORNEA. The clear, dome-shaped outer covering of the eye that lies in front of the iris and pupil. The cornea lets light into the eye.

COROLLARY DISCHARGE. A mechanism in the brain that allows one to distinguish between self-generated and external stimuli or perceptions.

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.

CORPUS STRIATUM. Region of the brain that contains the caudate nucleus and putamen.

CORTICAL ATROPHY. A wasting away and decrease in size of the outer portion of the brain, or cerebral cortex.

CORTICOSPINAL TRACT. A tract of nerve cells that carries motor commands for voluntary body movements from the brain to the spinal cord.

CORTICOSTEROIDS. A group of hormones produced naturally by the adrenal gland or manufactured synthetically. They are often used to treat inflammation. Examples include cortisone and prednisone.

CORTISOL. A steroid hormone secreted by the adrenal cortex that is important for maintenance of body fluids, electrolytes, and blood sugar levels. Also called hydrocortisone.

CRANIAL NERVES. The set of twelve nerves found on each side of the head and neck that control the sensory and muscle functions of the eyes, nose, tongue, face, and throat.

CRANIAL SUTURES. The fibrous joints (sutures) that hold together the five bones comprising the skull of a newborn.

CRANIOSYNOSTOSIS. A birth defect of the brain characterized by the premature closure of one or more of the cranial sutures, the fibrous joints between the bones of the skull

CRANIOTOMY. A surgical procedure in which part of the skull is removed (then replaced) to allow access to the brain.

CRANIUM. Skull; the bony framework that holds the brain.

CREATININE PHOSPHOKINASE. A chemical normally found in the muscle fibers that is released into the bloodstream when the muscles undergo damage and breakdown. Testing for it can prove the occurrence of a heart attack or other muscle damage. It used to be called creatine kinase.

CRYOABLATION. Using very cold temperatures to remove a foreign substance or body.

CRYOTHERAPY. Using very cold temperatures to treat a disease.

CUTANEOUS. Relating to the skin.

CYST. An abnormal sac or enclosed cavity in the body that is filled with liquid or partially solid material. Also refers to a protective, walled-off capsule in which an organism lies dormant.

CYSTADENOMA. Non-cancerous growth, in which fluid-filled, gas, or semi-solid areas may be present.

CYTOGENETICS. The branch of biology that combines the study of genetic inheritance with the study of cell structure.

CYTOMEGALOVIRUS (CMV). A common human virus causing mild or no symptoms in healthy people, but permanent damage or death to an infected fetus, a transplant patient, or a person with HIV.

CYTOPLASM. The substance within a cell including the organelles and the fluid surrounding the nucleus.

CYTOSKELETON. A network of filaments that give structure and shape to the cell.

CYTOTOXIC T-CELLS. A type of white blood cells, T-lymphocytes, that can kill body cells infected by viruses or transformed by cancer.

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.

DECEREBRATE POSTURE. Stiff, rigid posture indicative of severe damage to brain stem.

DECONDITIONING. Loss of physical strength or stamina resulting from bed rest or lack of exercise.

DECORTICATE POSTURE. A stiff, rigid posture indicative of damage to nerve tracts that run between spinal cord and brain.

DEINSTITUTIONALIZATION. The process of moving people out of mental hospitals into treatment programs or halfway houses in local communities. With this movement, the responsibility for care shifted from large (often governmental) agencies to families and community organizations.

DELIRIUM. A condition characterized by waxing-and-waning episodes of confusion and agitation.

DELTOID MUSCLE. A muscle near the clavicle bone that is responsible for arm movement.

DELUSION. A false belief that a person maintains in spite of obvious proof or evidence to the contrary.

DEMENTIA. Loss of memory and other higher functions, such as thinking or speech, lasting six months or more.

DEMENTIA PUGILISTICA. Syndrome of brain damage caused by repeated head trauma. People with this kind of damage are sometimes described as "punch drunk."

DEMYELINATING DISEASES. A group of diseases characterized by the breakdown of myelin, the fatty sheath surrounding and insulating nerve fibers. This breakdown interferes with nerve function and can result in paralysis. Multiple sclerosis is a demyelinating disorder.

DEMYELINATION. Disruption or destruction of the myelin sheath, leaving a bare nerve. It results in a slowing or stopping of the impulses that travel along that nerve.

DEPOLARIZATION. Occurs when a neuron exchanges ions, causing an influx of sodium and calcium inside the cell and an efflux of potassium out of the cell.

DEPOT. A type of drug preparation and administration that involves the slow, gradual release from an area of the body where the drug has been injected.

DEPRESSED SKULL FRACTURE. A fracture in which fragments of broken skull press into brain tissue.

DEPRESSION. A psychiatric disorder in which the mood is low for a prolonged period of time, and feelings of hopelessness and inadequacy interfere with normal functioning.

DEPRESSIVE DISORDER. A psychiatric disorder of varying degrees characterized by feelings of hopelessness, physical responses such as insomnia, and withdrawal from normal activities.

DERMATOME. An area of skin that receives sensations through a single nerve root.

DESMIN. A protein that provides part of the structure to heart, skeletal, and smooth muscle cells.

DEVELOPMENTAL DELAY. The failure to meet certain developmental milestones such as sitting, walking, and talking at the average age. Developmental delay may indicate a problem in development of the central nervous system.

DEVELOPMENTAL DISABILITIES. Disabilities that are present from birth and delay or prevent normal development, such as mental retardation or autism.

DIABETES MELLITUS. The clinical name for common diabetes. It is a chronic disease characterized by the inability of the body to produce or respond properly to insulin, a hormone required by the body to convert glucose to energy.

DIABETIC NEUROPATHY. A complication of diabetes mellitus in which the peripheral nerves are affected. Diabetic neuropathy is primarily due to metabolic imbalance and secondarily to nerve compression.

DIALYSIS. Process by which special equipment purifies the blood of a patient whose kidneys have failed.

DIENCEPHALON. A part of the brain that binds the mesencephalon to the cerebral hemispheres, it includes the thalmus and the hypothalmus. It acts as a relay station for impulses concerning sensation and movement.

DIFFUSE. Widespread.

DILATATION. Increasing in caliber.

DIPLOPIA. Also known as double vision, it is a visual disorder resulting from unequal action of the eye muscles, which causes two images of a single object to be seen.

DISCECTOMY. Surgery to relieve pressure on a nerve root caused by a bulging disc or bone spur.

DISCOGRAPHY. A test in which dye is injected into a disc space thought to be causing back pain, allowing the surgeon to confirm that an operation on that disc will be likely to relieve pain.

DISEASE ERADICATION. A status whereby no further cases of a diseases occur anywhere, and continued control measures are unnecessary.

DISSECTION. Tear in the wall of an artery that causes blood from inside the artery to leak into the wall and thereby narrows the lumen of the blood vessel.

DISSEMINATED. Scattered or distributed throughout the body. Lyme disease that has progressed beyond the stage of localized erythema migrans (EM) is said to be disseminated.

DISTAL. Situated away from the center of the body.

DISTAL MUSCLES. Muscles farthest away from the center of the body, such as muscles in the fingers and toes.

DIURETIC DRUGS. A group of medications that increase the amount of urine produced and relieve excess fluid buildup in body tissues. Diuretics may be used in treating high blood pressure, lung disease, premenstrual syndrome, and other conditions.

DIZYGOTIC TWINS. Twins that share the same environment during development in the uterus.

DNA. Deoxyribonucleic acid; 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.

DOMINANT DISORDER. A disorder resulting from an inheritance pattern where one parent has a single, faulty dominant gene, and has a 50% chance of passing on that faulty gene to offspring with each pregnancy.

DOPAMINE. A neurotransmitter made in the brain that is involved in many brain activities, including movement and emotion.

DORSAL. Pertaining in direction to the back or upper surface of an organ.

DORSAL COLUMNS. This refers to nerve fiber tracts that run in the portion of the spinal cord that is closest to the back. They carry sensory information like position sense and deep pain from the legs and arms to the brain.

DORSAL HORN. The part of the spinal cord that receives and processes pain messages from the peripheral nervous system.

DOUBLE BLIND STUDY. A study or clinical trial designed to minimize any bias, in that neither participant or study director knows who is assigned to the control group and who is assigned to the test group until the end of the study.

DOWN SYNDROME. A genetic disorder characterized by an extra chromosome 21 (trisomy 21), mental retardation, and susceptibility to early-onset Alzheimer's disease.

DUPLICATION. Extra genetic material due to a duplicate copy.

DURA MATTER. The strongest and outermost of three membranes that protect the brain, spinal cord, and nerves of the cauda equina.

DYNATOME. An area in which pain is felt when a given spinal nerve is irritated.

DYSARTHRIA. Imperfect articulation of speech (slurred speech) due to muscular weakness resulting from damage to the central or peripheral nervous system.

DYSAUTONOMIA. A disorder or dysfunction of the autonomic nervous system.

DYSCALCULIA. Difficulty with basic arithmetic and calculations.

DYSESTHESIA. A painful feeling of numbness, tingling, or heat.

DYSGRAPHIA. Difficulty writing.

DYSKINESIA. Impaired ability to make voluntary movements.

DYSLEXIA. A type of reading disorder often characterized by reversal of letters or words.

DYSPHAGIA. Difficulty in swallowing.

DYSPHONIA. Disordered phonation or voice production.

DYSPLASIA. The abnormal growth or development of a tissue or organ.

DYSTHYMIA. A chronic mood disorder characterized by mild depression.

DYSTONIA. Painful involuntary muscle cramps or spasms.

DYSTROPHIN. A large protein that stabilizes the plasma membrane of a muscle cell during muscle contractions. Dystrophin is absent or reduced in the most common forms of muscular dystrophy.

E

ECHOCARDIOGRAM. Ultrasound of the heart, which shows heart structure in detail.

ECHOLALIA. Involuntary echoing of the last word, phrase, or sentence spoken by someone else.

EDEMA. An accumulation of watery fluid that causes swelling of the affected tissue.

ELASTIN. A protein that gives skin the ability to stretch and then return to normal.

ELBOW EXTENSION. Movement away from the body at a jointed point.

ELECTROACUPUNCTURE. A variation of acupuncture in which the practitioner stimulates the traditional acupuncture points electronically.

ELECTROCARDIOGRAM. Test that shows a heart's rhythm by studying its electrical current patterns.

ELECTROENCEPHALOGRAM (EEG). A record of the tiny electrical impulses produced by the brain's activity picked up by electrodes placed on the scalp. By measuring characteristic wave patterns, the EEG can help diagnose certain conditions of the brain.

ELECTROLYTES. Salts and minerals that produce electrically charged particles (ions) in body fluids. Common human electrolytes are sodium chloride, potassium, calcium, and sodium bicarbonate. Electrolytes control the fluid balance of the body and are important in muscle contraction, energy generation, and almost all major biochemical reactions in the body.

ELECTROMYOGRAPHY (EMG). A diagnostic test that records the electrical activity of muscles. Small electrodes are placed on or in the skin and the patterns of electrical activity are projected on a screen or over a loudspeaker. This procedure is used to test for muscle disorders, including muscular dystrophy.

ELECTRON. One of the small particles that make up an atom. An electron has the same mass and amount of charge as a positron, but the electron has a negative charge.

ELISA PROTOCOLS. ELISA is an acronym for "enzyme-linked immunosorbent assay"; it is a highly sensitive technique for detecting and measuring antigens or antibodies in a solution.

EMBOLISM. A blood clot, air bubble, or clot of foreign material that travels and blocks the flow of blood in an artery. When blood supply blocks a tissue or organ with an embolism, infarction (death of the tissue the artery feeds) occurs. Without immediate and appropriate treatment, an embolism can be fatal.

EMBOLIZATION. A technique to stop or prevent hemorrhage by introducing a foreign mass, such as an air-filled membrane (balloon), into a blood vessel to block the flow of blood. This term also refers to an alternative to splenectomy that involves injecting silicone or a similar substances into the splenic artery to shrink the size of the spleen.

EMBOLUS. A fragment of plaque or thrombus that breaks off from its original location and travels downstream to progressively narrower arteries, where it may block the vessel.

EMPHYSEMA. An irreversible lung disease in which breathing becomes increasingly difficult.

ENCEPHALITIS. Inflammation of the brain, usually caused by a virus. The inflammation may interfere with normal brain function and may cause seizures, sleepiness, confusion, personality changes, weakness in one or more parts of the body, and even coma.

ENCEPHALOGRAM. Machine that detects brain activity by measuring its electrical impulses.

ENCEPHALOPATHIC. Widespread brain disease or dysfunction.

ENCEPHALOPATHY. Any abnormality in the structure or function of brain tissues.

ENDODONTIST. A dentist who specializes in the treatment of diseases and injuries that affect the tooth root, dental pulp, and the tissues surrounding the tooth root.

ENDOLYMPH. The fluid contained inside the membranous labyrinth of the inner ear.

ENDOLYMPHATIC HYDROPS. Another term for Ménière's disease. It defines the disorder in terms of increased fluid pressure in the inner ear.

ENDOLYMPHATIC SAC TUMOR. Growths that develop within inner ear structures called endolymph sacs.

ENDORPHINS. A group of chemicals resembling opiates that are released in the body in response to trauma or stress. Endorphins react with opiate receptors in the brain to reduce pain sensations.

ENDOSCOPY. A clinical technique using an instrument called an endoscope, used for visualization of structures within the body.

ENDOTHELIUM. A layer of cells called endothelial cells that lines the inside surfaces of body cavities, blood vessels, and lymph vessels.

ENKEPHALINS. Polypeptides that serve as neurotransmitters and short-acting pain relievers. Enkephalins also influence a person's perception of painful sensations.

ENTRAPMENT NEUROPATHY. A disorder of the peripheral nervous system in which a nerve is damaged by compression as it passes through a bony or fibrous passage or canal. Many repetitive motion disorders are associated with entrapment neuropathies.

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

EPIDIDYMIS. Male genital structure usually connected to the testis; an area where sperm collect.

EPIDURAL HEMATOMA. Bleeding into the area between the skull and the dura, the tough, outermost brain covering.

EPIDURAL SPACE. The space immediately surrounding the outermost membrane (dura mater) of the spinal cord.

EPILEPSY. A neurological disorder characterized by recurrent seizures with or without a loss of consciousness.

EQUINUS. Excess contraction of the calf, causing toe walking.

ERB POINT. A point 2-3 centimeters above the clavicle.

ERGONOMICS. The branch of science that deals with human work and the efficient use of energy, including anatomical, physiological, biomechanical, and psychosocial factors.

ERGOT. A compound produced by a fungus that grows on rye plants. It is used in the production of some abortive antimigraine drugs.

ERYTHEMA. Redness of the skin due to congestion of the capillaries, usually due to injury, infection, or inflammation.

ERYTHROCYTE SEDIMENTATION RATE. A test that measures the rate at which red blood cells settle out in a tube of anticoagulated blood, expressed in millimeters per hour; elevated sedimentation rates indicate the presence of inflammation.

ESOPHAGUS. The tube leading from the back of the mouth, down the throat, and into the stomach.

ESSENTIAL TREMOR. An uncontrollable (involuntary) shaking of the hands, head, and face. Also called familial tremor because it is sometimes inherited, it can begin in the teens or in middle age. The exact cause is not known.

ETIOLOGY. The cause or origin of disease.

EUDYNIA. The medical term for acute pain, or pain that is a symptom of an underlying disease or disorder.

EUPHORIA. An exaggerated state of psychological and physical well being.

EUTHYROID. State of normal function of the thyroid gland.

EXCISIONAL BIOPSY. Removal of an entire lesion for microscopic examination.

EXCLUSION CRITERIA. A predetermined set of factors that make a potential participant not eligible for inclusion in a clinical trial or study.

EXECUTIVE FUNCTIONS. A set of cognitive abilities that control and regulate other abilities and behaviors. Necessary for goal-directed behavior, they include the ability to initiate and stop actions, to monitor and change behavior as needed, and to plan future behavior when faced with novel tasks and situations.

EXTENSIVE SUPPORT. Ongoing daily support required to assist an individual in a specific adaptive area, such as daily help with preparing meals.

EXTRAPYRAMIDAL SYSTEM. A functional rather than anatomical unit, it is comprised of nuclei and nerve fibers that are chiefly involved with subconscious, automatic aspects of motor coordination, but which also assist in the regulation of postural and locomotor movements.

F

FACIAL NERVE. A cranial nerve that controls the muscles in the face.

FAILURE TO THRIVE. Significantly reduced or delayed physical growth.

FASCICULATIONS. Small involuntary muscle contractions visible under the skin.

FAST FOURIER TRANSFER. A digital processing of the recorded signal resulting in a decomposition of its frequency components.

FATAL FAMILIAL INSOMNIA . A rare, progressive neurological disease that is believed to be transmitted via an abnormal protein called a prion.

FEBRILE CONVULSION. Seizures occurring mainly in children between three months and five years of age that are triggered by fever.

FEMORAL ARTERY. An artery located in the groin area that is the most frequently accessed site for arterial puncture in angiography.

FETAL. Refers to the fetus. In humans, the fetal period extends from the end of the eighth week of pregnancy to birth.

FETAL TISSUE TRANSPLANTATION. A method of treating Parkinson's and other neurological diseases by grafting brain cells from human fetuses onto the affected area of the human brain. Human adults cannot grow new brain cells but developing fetuses can. Grafting fetal tissue stimulates the growth of new brain cells in affected adult brains.

FIBROMYALGIA. A condition characterized by aching and stiffness, fatigue, and sleep disturbance, as well as pain at various sites on the body.

FILUM TERMINALE. The strand of elastic, fibrous tissue that secures the lower end of the spinal cord.

FINGER AGNOSIA. Inability to identify a particular finger.

FLACCID PARALYSIS. Loss of muscle tone resulting from injury or disease of the nerves that innervate the muscles.

FLAIL. To swing freely.

FLASHBACK. A vivid sensory or emotional experience that happens independently of the initial event or experience. Flashbacks resulting from the use of LSD are sometimes referred to as hallucinogen persisting perception disorder, or HPPD.

FLUORESCEIN DYE. An orange dye used to illuminate the blood vessels of the retina in fluorescein angiography.

FLUOROSCOPE. An imaging device that displays x rays of the body. Fluoroscopy allows the radiologist to visualize the guide wire and catheter moving through the patient's artery.

FOCAL. Limited to a defined area.

FORAMEN MAGNUM. Large opening in the back of the skull, where the spinal cord connects with the brain.

FORAMINOTOMY. Surgery to enlarge the bony hole, or foramen, where a nerve root enters or exits the spinal canal.

FRAGILE X SYNDROME. A genetic condition related to the X chromosome that affects mental, physical, and sensory development. It is the most common form of inherited mental retardation.

FREE RADICAL. An unstable molecule that causes oxidative damage by stealing electrons from surrounding molecules, thereby disrupting activity in the body's cells.

FRONTAL CORTEX. The part of the human brain associated with aggressiveness and impulse control. Abnormalities in the frontal cortex are associated with an increased risk of suicide.

FRONTAL LOBE. The area of the brain responsible for higher thinking.

G

GAIT. The way in which one walks.

GAMMA RAY. A high-energy photon emitted by radioactive substances.

GANGLION. A mass of nerve cells usually found outside the central nervous system, from which axons arrive from the periphery and proceed to the spinal cord or brain; plural form: ganglia .

GANGLIOSIDE. A fatty (lipid) substance found within the brain and nerve cells.

GANGRENE. The death of tissue caused by loss of blood supply. Gangrene is a serious potential side effect of taking ergot alkaloids.

GASTROPARESIS. Nerve damage of the stomach that delays or stops stomach emptying, resulting in nausea, vomiting, bloating, discomfort, and weight loss.

GELASTIC SEIZURES. Seizures manifesting with brief involuntary laughter

GENE. A building block of inheritance, it 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.

GENERALIZED ANXIETY DISORDER. An anxiety disorder characterized by excessive worry or fear about a number of activities or events.

GENOME. The entire collection of genes of an individual.

GENOTYPE. The genetic makeup of an organism or a set of organisms.

GINGIVAL FIBROMA. Small non-cancerous growth on the toe or finger nail beds.

GLASGOW COMA SCALE. A measure of level of consciousness and neurological functioning after traumatic brain injury (TBI).

GLAUCOMA. A common eye disease characterized by increased fluid pressure in the eye that damages the optic nerve, which carries visual impulses to the brain. Glaucoma can be caused by another eye disorder, such as a tumor or congenital malformation, or it can appear without obvious cause. If untreated it generally leads to blindness.

GLIAL CELL. Nerve tissue of the central nervous system other than the signal-transmitting neurons. Glial cells are interspersed between neurons, providing support and insulation.

GLIOMA. A tumor that originates in the cells supporting and nourishing brain neural tissue (glial cells).

GLOBOID CELLS. Large cells containing excess toxic metabolic "waste" of galactosylceramide and psychosine.

GLUCOCORTICOID MEDICATIONS. A group of medications that produces effects of the body's own cortisone and cortisol. Glucocorticoids are commonly called steroids and, among other functions, work to reduce inflammation,

GLUCOSYLCERAMIDE. A chemical substance composed of glucose (sugar) and lipid (fat).

GLYCOGEN. The principle form of carbohydrate energy (glucose) stored within the muscles and liver.

GOITER. A swelling or enlargement of the thyroid gland.

GRAY MATTER. Areas of the brain and spinal cord that are comprised mostly of unmyelinated nerves.

GUIDE WIRE. A wire that is inserted into an artery to guide a catheter to a certain location in the body.

GUSTATORY. Pertaining to the sense of taste.

H

HALLUCINATION. A false or distorted perception of objects, sounds, or events that seems real. Hallucinations usually result from drugs or mental disorders.

HALLUCINOGEN. A drug or other substance that induces hallucinations.

HAMARTOMA. Abnormal growth that may resemble cancer, but is not cancerous.

HANDEDNESS. The preference of either the right or left hand as the dominant hand for the performance of tasks such as writing.

HAPTIC. Pertaining to the sense of touch.

HEMANGIOBLASTOMA. Tumor often found in the brain, as in von Hippel-Lindau disease.

HEMATOMA. A localized collection of blood, often clotted, in body tissue or an organ, usually due to a break or tear in the wall of blood vessel.

HEMICHOREA. Chorea that affects only one side of the body.

HEMIPARESIS. Muscle weakness of one side of the body.

HEMIPLEGIA. Paralysis on one side of the body.

HEMIPLEGIC MIGRAINE. Migraine accompanied by temporary paralysis on one side of the body.

HEMISPHERE. One side of the brain, right or left.

HEMOPHILIAC. A person with the blood disorder hemophilia, an inherited deficiency in blood-clotting ability. Hemophiliacs require regular administration of blood products, and were especially at risk of acquiring AIDS from HIV-contaminated blood during the early years of the evolving AIDS epidemic, before tests were developed to identify the HIV virus in donated blood.

HEMORRHAGE. Severe, massive bleeding that is difficult to control. The bleeding may be internal or external.

HEPATIC ENCEPHALOPATHY. A change in mental state due to toxic substance buildup in the blood that is caused by liver failure.

HEPATITIS. An inflammation of the liver, with accompanying liver cell damage or cell death, caused most frequently by viral infection, but also by certain drugs, chemicals, or poisons. May be either acute (of limited duration) or chronic (continuing). Symptoms include jaundice, nausea, vomiting, loss of appetite, tenderness in the right upper abdomen, aching muscles, and joint pain. In severe cases, liver failure may result.

HEPATOSPLENOMEGALY. Enlargement of the liver and spleen.

HEPATOTOXICITY. Damaging or destructive to the liver.

HEREDITARY ATAXIA. One of a group of hereditary degenerative diseases of the spinal cord or cerebellum. These diseases cause tremor, spasm, and wasting of muscle.

HERNIATED DISC. A blisterlike bulging or protrusion of the contents of the disk out through the fibers that normally hold them in place. It is also called a ruptured disk, slipped disk, or displaced disk.

HERPES. A virus that causes cold sores, sexually transmitted diseases, shingles, or chicken pox.

HERPES SIMPLEX VIRUS. A virus that can cause fever and blistering on the skin and mucous membranes. Herpes simplex 1 infections usually occur on the face (cold sores) and herpes simplex 2 infections usually occur in the genital region.

HERPES VARICELLA ZOSTER VIRUS. The virus that typically causes chicken pox in children; then may reactivate later in life to cause shingles.

HIB DISEASE. An infection caused by *Haemophilus influenza*, type b (Hib). This disease mainly affects children under the age of five. In that age group, it is the leading cause of bacterial meningitis, pneumonia, joint and bone infections, and throat inflammations.

HIPPOCAMPUS. A part of the brain that is involved in memory formation and learning. The hippocampus is shaped like a curved ridge and belongs to an organ system called the limbic system.

HISTAMINE. A substance released by immune system cells in response to the presence of an allergen. It stimulates widening of blood vessels and increased porousness of blood vessel walls so that fluid and protein leak out from the blood into the surrounding tissue, causing localised inflammation of the tissue.

HISTOLOGIC. Pertaining to histology, the study of cells and tissues at the microscopic level.

HISTOLOGY. The study of tissue structure.

HOLOPROSENCEPHALY. Brain, cranial, and facial malformations present at birth that are caused by incomplete cleavage of the brain during embryologic development.

HOMEOSTASIS. The balanced internal environment of the body and the automatic tendency of the body to maintain this internal "steady state." Also refers to the tendency of a family system to maintain internal stability and to resist change.

HORMONE. Chemical substance produced by certain endocrine glands that is released into the bloodstream where it controls and regulates functioning of several other tissues.

HUMAN IMMUNODEFICIENCY VIRUS (HIV). A transmissible retrovirus that causes AIDS in humans. Two forms of HIV are now recognized: HIV-1, which causes most cases of AIDS in Europe, North and South America, and most parts of Africa; and HIV-2, which is chiefly found in West African patients. HIV-2, discovered in 1986, appears to be less virulent than HIV-1 and may also have a longer latency period.

HYDROCEPHALUS. An abnormal accumulation of cerebrospinal fluid within the brain. This accumulation can be harmful by pressing on brain structures and thereby damaging them.

HYPERCAPNIA. Excess carbon dioxide in the blood.

HYPEREMESIS GRAVIDARUM. Uncontrollable nausea and vomiting associated with pregnancy. Acupuncture appears to be an effective treatment for women with this condition.

HYPEREXTENSION. Extension of a limb or body part beyond the normal limit.

HYPERFUNCTION. Term used to describe excess effort or strain involved in producing an action.

HYPERHIDROSIS. Excessive sweating. Hyperhidrosis can be caused by heat, overactive thyroid glands, strong emotion, menopause, or infection.

HYPERLIPIDEMIA. A condition characterized by abnormally high levels of lipids in blood plasma.

HYPERPIGMENTATION. An excess of melanin, leading to abnormal areas of increased dark skin color.

HYPERREFLEXIA. An increased reaction to reflexes.

HYPERTENSION. Abnormally high arterial blood pressure, which if left untreated can lead to heart disease and stroke.

HYPERTHERMIA. Elevated body temperature.

HYPERTHYROID. State of excess thyroid hormone in the body.

HYPERTHYROIDISM. Abnormally high levels of thyroid hormone. About 2% of patients with this condition develop chorea.

HYPERTONUS. Increased tension of a muscle or muscle spasm.

HYPERVENTILATION. A pattern of rapid but shallow breathing that is frequently found in patients with Rett syndrome.

HYPNOGOGIC. Pertaining to drowsiness. It is usually used to describe hallucinations that occur as a person falls asleep.

HYPNOGOGIC HALLUCINATION. A vivid, dream-like hallucination, such as the sensation of falling, that occurs at the onset of sleep.

HYPNOPOMPIC. Persisting after sleep. It is usually used to describe hallucinations that occur as a person awakens.

HYPNOTICS. A class of drugs that are used as sedatives and sleep aids.

HYPOCALCEMIA. A condition characterized by an abnormally low level of calcium in the blood.

HYPOMELANOTIC MACULE. Skin patch that is lighter in color than the area around it.

HYPOPIGMENTATION. A deficiency of melanin, leading to abnormal areas of lighter skin color.

HYPOPITUITARISM. A condition characterized by underactivity of the pituitary gland.

HYPOTHALAMUS. The lowermost part of the diencephalon, containing several nuclei, nerve tracts, and the

pituitary gland; it is the regulatory seat of the autonomic nervous system, controlling heartbeat, body temperature, thirst, hunger, blood pressure, blood sugar levels, and other functions.

HYPOTHYROIDISM. A disorder in which the thyroid gland produces too little thyroid hormone causing a decrease in the rate of metabolism with associated effects on the reproductive system. Symptoms include fatigue, difficulty swallowing, mood swings, hoarse voice, sensitivity to cold, forgetfulness, and dry/coarse skin and hair.

HYPOTONIA. Having reduced or diminished muscle tone or strength.

HYPOTONUS. Decreased tension of a muscle, or abnormally low muscle tone.

HYPOXEMIA. Abnormally low blood oxygen.

HYPOXIA. A condition characterized by insufficient oxygen in the cells of the body

HYPOXIC. Oxygen deficient.

HYPSARRHYTHMIA. Typical brain wave activity found in infantile spasms.

I

ICHTHYOSIS. Dry, thickened, rough, coarse skin, sometimes with evident scaling.

ICTAL EEG. An electroencephalogram (EEG) done to determine the type of seizure characteristic of a person's disorder. During this EEG, seizure medicine may be discontinued in an attempt to induce as seizure during the testing period.

IDIOPATHIC. Of unknown cause or spontaneous origin. Ménière's disease and some headaches are considered idiopathic disorders.

ILLUSION. A false visual perception of an object that others perceive correctly. A common example is the number of sightings of UFOs that turn out to be airplanes or weather balloons.

IMMUNOADSORPTION. A procedure that can remove harmful antibodies from the blood.

IMMUNOCOMPROMISED. A state in which the immune system is suppressed or not functioning properly.

IMMUNOGLOBULIN. A protein molecule formed by mature B-cells in response to foreign proteins in the body; the building blocks for antibodies.

IMMUNOHISTOCHEMISTRY. A method of detecting the presence of specific proteins in cells or tissues.

IMMUNOSUPPRESSANTS. Drugs that reduce or eliminate the body's ability to make an immune response.

INBORN ERROR OF METABOLISM. One of a group of rare conditions characterized by an inherited defect in an enzyme or other protein. Inborn errors of metabolism can cause brain damage and mental retardation if left untreated. Phenylketonuria, Tay-Sachs disease, and galactosemia are inborn errors of metabolism.

INCISIONAL BIOPSY. Removal of a small part of a sample tissue area for microscopic examination.

INCLUSION BODY. A small intracellular body found within the cytoplasm or nucleus of another cell, characteristic of disease.

INCLUSION CRITERIA. A predetermined set of factors that make a potential participant eligible for inclusion in a clinical trial or study.

INCONTINENCE. Inability to control excretory functions such as defecation and urination.

INCOORDINATION. Loss of voluntary muscle control resulting in irregular movements.

INCREASED INTRACRANIAL PRESSURE. Increased overall pressure inside the skull.

INFARCT. An area of dead tissue caused by inadequate blood supply; in the brain, this condition is called a stroke.

INFLAMMATION. The body's response to injury, resulting in swelling, warmth, redness, pain.

INGUINAL. Referring to the groin area.

INNERVATION. Distribution or supply of nerves to a structure.

INSIDIOUS. Developing in a stealthy or gradual manner.

INSULIN. A hormone or chemical produced by the pancreas that is needed by cells of the body in order to use glucose (sugar), a major source of energy for the human body.

INTENTION TREMOR. A rhythmic purposeless shaking of the muscles that begins with purposeful (voluntary) movement. This tremor does not affect muscles that are resting.

INTERFERON ALFA. A potent immune-defense protein that is used as an anti-cancer drug.

INTERLEUKINS. Chemicals released in the body as a result of stress.

INTERMEDIATE CARE FACILITY. An inpatient facility that provides periodic nursing care.

INTERVERTEBRAL DISCS. Gelatinous structures separating the spinal vertebrae and acting as shock absorbers.

INTRACEREBRAL HEMATOMA. Bleeding within the brain caused by trauma to a blood vessel.

INTRACEREBRAL HEMORRHAGE. A cause of some strokes in which vessels within the brain begin bleeding.

INTRACRANIAL HYPERTENSION. Increase in pressure in the brain.

INTRACRANIAL PRESSURE. The overall pressure within the skull.

INTRAOCULAR. Inside the eye.

INTRAVENTRICULAR HEMORRHAGE. Bleeding into the brain, specifically into the ventricles.

IONIZING RADIATION. High-energy radiation such as that produced by x rays.

IRIS. The circular membrane that forms the colored portion of the eye and expands or contracts around the pupil.

IRITIS. Inflammation of the iris, the membrane in the pupil, the colored portion of the eye. It is characterized by photophobia, pain, and inflammatory congestion.

IRRITATIVE HALLUCINATIONS. Hallucinations caused by abnormal electrical activity in the brain.

ISCHEMIA. A decrease in the blood supply to an area of the body caused by obstruction or constriction of blood vessels.

J

JAUNDICE. Yellowing of the skin or eyes due to excess of bilirubin in the blood.

K

KARYOTYPE. A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

KETOACIDOSIS. Usually caused by uncontrolled type I diabetes, when the body isn't able to use glucose for energy. As an alternate source of energy, fat cells are broken down, producing ketones, toxic compounds that make the blood acidic. Symptoms of ketoacidosis include excessive thirst and urination, abdominal pain, vomiting, rapid breathing, extreme tiredness, and drowsiness.

KI. The Japanese spelling of qi, the traditional Chinese term for vital energy or the life force.

KINETIC. Word taken from the Greek (kinesis): motion.

KYPHOSIS. An abnormal convex (outward) curvature of the upper portion of the spinal column, sometimes called a humpback or hunchback.

L

LABYRINTH. The inner ear. It consists of the membranous labyrinth, which is a system of sacs and ducts made of soft tissue; and the osseous or bony labyrinth, which surrounds and contains the membranous labyrinth.

LABYRINTHECTOMY. Surgical removal of the labyrinth of the ear. It is done to treat Ménière's disease only when the patient has already suffered severe hearing loss.

LACINATING PAIN. Piercing, stabbing, or darting pain.

LAMINA. Flat plates of bone that form part of a vertebrae.

LARYNGEAL STRIDOR. Constriction of the voice box, causing vocal hoarseness.

LARYNX. The "voice box," located between the pharynx (upper area of the throat) and the trachea (windpipe).

LATERAL FLEXION. To flex toward a side.

LATERAL GENICULATE NUCLEI. A structure that receives and processes impulses from the optic nerve; it sends these impulses farther into the brain for more processing.

LEFT VENTRICULAR ENLARGEMENT. Abnormal enlargement of the left lower chamber of the heart.

LEPTOMENINGEAL ANGIOMA. A swelling of the tissue or membrane surrounding the brain and spinal cord, which can enlarge with time.

LESION. A disruption of the normal structure and function of a tissue by an injury or disease process. Wounds, sores, rashes, and boils are all lesions.

LEUKEMIA. A cancer of the blood-forming organs (bone marrow and lymph system) characterized by an abnormal increase in the number of white blood cells in the tissues. There are many types of leukemias and they are classified according to the type of white blood cell involved.

LEUKOCYTOSIS. An elevated white blood cell count.

LEUKODYSTROPHY. A disease that affects the white matter called myelin in the central nervous system (CNS).

LEUKOMALACIA. Softening of the brain's white matter.

LEVODOPA. A substance used in the treatment of Parkinson's disease. Levodopa can cross the blood-brain barrier that protects the brain. Once in the brain, it is converted to dopamine and thus can replace the dopamine lost in Parkinson's disease.

LEWY BODIES. Spheres, found in the bodies of dying cells, that are considered to be a marker for Parkinson's disease.

LIGAMENT. A type of tough, fibrous tissue that connects bones or cartilage and provides support and strength to joints.

LIMBIC SYSTEM. A group of structures in the brain that includes the hypothalamus, amygdala, olfactory bulbs, and hippocampus. The limbic system plays an important part in the regulation of human moods and emotions. Many psychiatric disorders are related to malfunctioning of the limbic system.

LIMITED SUPPORT. A predetermined period of assistance required to deal with a specific event, such as training for a new job.

LIPIDS. Organic compounds not soluble in water but soluble in fat solvents such as alcohol. Lipids are stored in the body as energy reserves and are important components of cell membranes. Commonly known as fats.

LIPOPIGMENTS. Substances made up of fats and proteins found in the body's tissues.

LIPOPROTEINS. Compounds of protein that carry fats and fat-like substances such as cholesterol in the blood.

LISCH NODULE. A benign growth within the iris of the eye.

LIVER ENCEPHALOPATHY. A condition in which the brain is affected by a buildup of toxic substances that would normally be removed by the liver. The condition occurs when the liver is too severely damaged to cleanse the blood effectively.

LOCOMOTOR. Means of or pertaining to movement or locomotion.

LORDOSIS. Anterior curvature of the spine, creating a swayback appearance.

LUMBAR. Referring to the lower back. There are five lumbar vertebrae.

LUMBAR PUNCTURE. A diagnostic procedure in which a needle is inserted into the lower spine to withdraw a small amount of cerebrospinal fluid.

LYME BORRELIOSIS. Another name for Lyme disease.

LYMPHADENOPATHY. Swelling of the lymph glands.

LYMPHANGIOLEIMYOMA. Non-cancerous growth in the lung, typical of tuberous sclerosis.

LYMPHOCYTE. A type of white blood cell that participates in the immune response. The two main groups are the B-cells that have antibody molecules on their surface and T-cells that destroy antigens.

LYMPHOCYTIC MENINGITIS. Benign infection of brain coverings that protect the brain

LYMPHOMA. A malignant tumor of the lymph nodes.

LYSOSOME. Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

M

MACROPHAGE. A large, versatile immune cell that acts as a scavenger, engulfing dead cells, foreign substances, and other debris.

MACULE. A small, flat area of abnormal color on the skin.

MAGNETIC RESONANCE IMAGING (MRI). An imaging technique used in evaluation and diagnoses of the brain and other parts of the body.

MAJOR DEPRESSIVE DISORDER. A mood disorder characterized by overwhelming and persistent feelings of hopelessness, often accompanied by sleep disturbances, withdrawal from normal social and personal care activities, and an inability to concentrate.

MALABSORPTION. The inability to adequately or efficiently absorb nutrients from the intestinal tract.

MALDYNIA. The medical term for chronic pain, or pain that has become a disease in and of itself as a result of changes in the patient's nervous system.

MALINGERING. Knowingly pretending to be physically or mentally ill in order to get out of some unpleasant duty or responsibility, or for economic benefit.

MANIC. A period of excess mental activity, often accompanied by elevated mood and disorganized behavior.

MASTOID BONE. The bony areas behind and below the ears. Also called the mastoid process.

MEDIAN NERVE. A nerve that runs through the wrist and into the hand. It provides sensation and some movement to the hand, the thumb, the index finger, the middle finger, and half of the ring finger.

MEDICAID. A program jointly funded by state and federal governments that reimburses hospitals and physicians for the care of individuals who cannot pay for their own medical expenses. These individuals may be in low-income households or may have chronic disabilities.

MEDULLA. The lowermost portion of the brain stem (it borders the spinal cord) that controls vital functions like respiration, blood pressure, swallowing, and heart rate. Also called the medulla oblongata.

MENINGES. The three-layered membranous covering of the brain and spinal cord.

MENINGIOMA. A tumor made up of cells of the lining of the brain and spinal cord (meninges).

MENINGITIS. An infection or inflammation of the membranes that cover the brain and spinal cord (the meninges). It is usually caused by bacteria or a virus.

MERIDIANS. In traditional Chinese medicine, the channels that run beneath the skin through which the body's energy, chi (sometimes spelled "qi" or "ki") flows.

METABOLIC. Refers to the chemical reactions in living organisms.

METABOLIC ACIDOSIS. Overly acidic condition of the blood.

METABOLISM. The group of biochemical processes within the body that release energy in support of life.

METANEPHRINE. A byproduct of epinephrine, found elevated in urine if a pheochromocytoma is present.

METASTASIS. The spread of cancer from one part of the body to another. Cells in the metastatic (secondary) tumor are like those in the original (primary) tumor.

MICROCEPHALY. An abnormally small head and underdeveloped brain.

MICROTUBULES. Slender, elongated, anatomical channels.

MIGRAINE. Recurrent severe headaches generally accompanied by an aura (classic migraine), nausea, vomiting, and dizziness.

MILLIGRAM. One thousandth of a gram; the metric measure that equals 0.035 ounces.

MINERALOCORTICOID. A steroid hormone, like aldosterone, that regulates the excretion of salt, potassium, and water.

MITOCHONDRIA. Spherical or rod-shaped structures of the cell. Mitochondria contain genetic material (DNA and RNA) and are responsible for converting food to energy.

MITOCHONDRIAL DNA. The genetic material found in mitochondria, the organelles that generate energy for the cell. Because reproduction is by cloning, mitochondrial DNA is usually passed along female lines.

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.

MONOAMINE OXIDASE INHIBITORS. A class of antidepressants used to treat certain types of mental depression. MAO inhibitors are especially useful in treating people whose depression is combined with other problems such as anxiety, panic attacks, phobias, or the desire to sleep too much.

MONONEUROPATHY. Disorder involving a single nerve.

MONOZYGOTIC TWINS. Twins that are genetically identical and are always of the same gender.

MOTOR. Of or pertaining to motion, the body structures involved in movement, or the brain functions that direct such deliberate movement.

MOTOR FUNCTION. The ability to produce body movement by complex interaction of the brain, nerves and muscles.

MOTOR NERVES. Motor or efferent nerve cells, they carry impulses from the brain to muscle or organ tissue.

MOTOR NEURON. A nerve cell that specifically controls and stimulates voluntary muscles.

MOTOR NEURON DISEASE. A neuromuscular disease, usually progressive, that causes degeneration of motor neuron cells and loss or diminishment of voluntary muscle control.

MOTOR UNIT ACTION POTENTIALS. Spikes of electrical activity recorded during an electromyogram (EMG) that reflect the number of motor units (motor neurons and the muscle fibers they transmit signals to) activated when the patient voluntarily contracts a muscle.

MOVEMENT EDUCATION. A term that refers to the active phase of bodywork, in which clients learn to move with greater freedom and to maintain the proper alignment of their bodies.

MOXIBUSTION. A technique in traditional Chinese medicine that involves burning a "Moxa," or cone of dried wormwood leaves, close to the skin to relieve pain. When used with acupuncture, the cone is placed on top of the needle at an acupuncture point and burned

MUCOPOLYSACCHARIDE. A complex molecule made of smaller sugar molecules strung together to form a chain. It is found in mucous secretions and intercellular spaces.

MULTIPLE MONONEUROPATHY. Neuropathy affecting several individual nerve trunks.

MULTIPLE SCLEROSIS. A progressive, autoimmune disease of the central nervous system characterized by damage to the myelin sheath that covers nerves. The disease, which causes progressive paralysis, is marked by periods of exacerbation and remission.

MUSCLE TONE. Also termed tonus; the normal state of balanced tension in the tissues of the body, especially the muscles.

MUTATION. A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease. It can be transmitted to offspring.

MYASTHENIA. Muscular weakness or a group of chronic muscular diseases characterized by muscle weakness.

MYASTHENIA GRAVIS. A chronic, autoimmune, neuromuscular disease with symptoms that include muscle weakness and sometimes paralysis.

MYELIN. A fatty sheath surrounding nerves throughout the body that helps them conduct impulses more quickly.

MYELOGRAM. An x-ray exam of the spinal cord, nerves, and other tissues within the spinal cord that are highlighted by injected contrast dye.

MYELOGRAPHY. A test in which dye is injected into the spinal canal and the patient is then tilted in different directions on a special table, allowing dye to outline the spinal cord and nerve roots and to show areas of compression.

MYELOMENINGOCELE. A sac that protrudes through an abnormal opening in the spinal column.

MYELOPATHY. A disorder in which the tissue of the spinal cord is diseased or damaged.

MYOCARDIAL INFARCTION. Commonly known as a heart attack, a myocardial infarction is an episode in which some of the heart's blood supply is severely cut off or restricted, causing the heart muscle to suffer and die from lack of oxygen.

MYOCLONUS. Involuntary contractions of a muscle or an interrelated group of muscles. Also known as myoclonic seizures.

MYOFILAMENT. Ultrastructural microscopic unit of a muscle that is made up of proteins that contract.

MYOPATHY. Any abnormal condition or disease of muscle tissue, characterized by muscle weakness and wasting.

MYOSITIS. Inflammation of a muscle.

MYOTONIA. The inability to normally relax a muscle after contracting or tightening it.

N

NARCOLEPSY. A life-long sleep disorder marked by four symptoms: sudden brief sleep attacks, cataplexy (a sudden loss of muscle tone usually lasting up to 30 minutes), temporary paralysis, and hallucinations. The hallucinations are associated with falling asleep or the transition from sleeping to waking.

NARCOTIC. Another term for opioid drugs that refers to their ability to produce drowsiness as well as relieve pain.

NASAL POLYPS. Drop-shaped overgrowths of the nasal membranes.

NECROSIS. Cellular or tissue death; skin necrosis may be caused by multiple, consecutive doses of radiation from fluoroscopic or x-ray procedures.

NEOPLASM. An abnormal growth of tissue or cells (a tumor) that may be either malignant (cancerous) or benign.

NERVE. Fibers that carry sensory information, movement stimuli, or both from the brain and spinal cord to other parts of the body and back again. Some nerves, including the vagus nerve, innervate distantly separated parts of the body.

NERVE CONDUCTION. The speed and strength of a signal being transmitted by nerve cells. Testing these factors can reveal the nature of nerve injury, such as damage to nerve cells or to the protective myelin sheath.

NERVE CONDUCTION STUDY. Testing that shows electrical impulse activity along nerves.

NERVE CONDUCTION VELOCITY. A recording of how well a nerve conducts electrical impulses.

NERVE IMPULSE. The electrochemical signal carried by an axon from one neuron to another neuron.

NERVE ROOT. Two groups of nerves that run from the spinal cord to join and form the spinal nerves.

NEURAL TUBE. A hollow column of ectodermal tissue that forms in early embryonic development and goes on to become the spinal cord and spinal column.

NEURAL TUBE DEFECT. A birth defect caused by abnormal closure or development of the neural tube, the embryonic structure that gives rise to the central nervous system.

NEURALGIA. Pain along the pathway of a nerve.

NEUROBLASTOMA. A malignant tumor of nerve cells that strikes children.

NEUROCUTANEOUS. Conditions involving unique manifestations of the skin, hair, teeth, and nervous system, usually with familial tendencies.

NEURODEGENERATIVE. Relating to the deterioration of nerve tissues.

NEURODEGENERATIVE DISEASE. A disease in which the nervous system progressively and irreversibly deteriorates.

NEUROFIBRILLARY TANGLES. Abnormal structures composed of twisted masses of protein fibers within nerve cells. They are found in the brains of persons with Alzheimer's disease.

NEUROFIBROMAS. Soft, rubbery, flesh-colored tumors made up of the fibrous substance that covers peripheral nerves.

NEUROFIBROMATOSIS. Also called von Recklinghausen's disease; a disease in which tumors grow on nerve cells throughout the body.

NEUROGENIC. Caused by or originating in the nerves.

NEUROGENIC PAIN. Pain originating in the nerves or nervous tissue and following the pathway of a nerve.

NEUROLEPTIC. Another name for the older type of antipsychotic medications, such as haloperidol and chlorpromazine, prescribed to treat psychotic conditions.

NEUROMUSCULAR. Involving both the muscles and the nerves that control them.

NEUROMUSCULAR DISEASE. Disease involving both the muscles and the nerves that control them.

NEUROMUSCULAR JUNCTION. The site at which nerve impulses are transmitted to muscles.

NEURON. A cell specialized to conduct and generate electrical impulses and to carry information from one part of the brain to another.

NEURONAL CEROID LIPOFUSCINOSES. A family of four progressive neurological disorders.

NEURONAL MIGRATION. A step of early brain development in which nerve cells travel over large distances to different parts of the brain.

NEUROPATHIC BLADDER. Improper or lack of bladder function, due to a nerve problem.

NEUROPATHY. A disease or abnormality of the peripheral nerves (the nerves outside the brain and spinal cord). Major symptoms include weakness, numbness, paralysis, or pain in the affected area.

NEUROSYPHILIS. This is the slowly progressive destruction of the brain and spinal cord due to untreated tertiary (late-stage) syphilis. It can be asymptomatic or cause different disorders like tabes dorsalis, general paresis, and meningovascular syphilis.

NEUROTOXIN. A poison that acts directly on the central nervous system.

NEUROTRANSMISSION. The process in which a neurotransmitter travels across the synapse to act on the target cell to either inhibit or excite it.

NEUROTRANSMITTER. A chemical messenger that transmits an impulse from one nerve cell to the next.

NOCICEPTOR. A specialized type of nerve cell that senses pain.

NOREPINEPHRINE. A hormone that controls blood pressure and heart rate. It is also a chemical found in the brain that is thought to play a role in attention deficit hyperactivity disorder (ADHD).

NUCLEUS PULPOSUS. Central core of a vertebrae.

NYSTAGMUS. An involuntary, rhythmic movement of the eyes.

O

OBSESSION. A persistent or recurrent thought, image, or impulse that is unwanted and distressing.

OBSTRUCTIVE SLEEP APNEA. The most common form of sleep apnea characterized by repeated episodes of upper airway obstruction during sleep.

OCCIPITAL LOBE. The back part of the brain that functions as a visual interpretation center.

OCCIPITAL NERVES. Two pairs of nerves that originate in the area of the second and third vertebrae of the neck. They are part of a network that innervate the neck, upper back, and head.

OCCLUSION. Blockage.

OLFACTORY. Pertaining to the sense of smell.

OPHTHALMIC ARTERY. The artery supplying the eye and adjacent structures with blood.

OPHTHALMOPARESIS. Paralysis of one or more of the muscles of the eye.

OPHTHALMOPLEGIA. Paralysis of the motor nerves of the eye, resulting in wandering or floating eye movements or drooping eyelids.

OPIOID. Any natural or synthetic substance that produces the same effects as an opiate, such as pain relief, sedation, constipation, and respiratory depression. Some opioids are produced by the human body (e.g., endorphins), while others are produced in the laboratory (e.g., methadone).

OPPORTUNISTIC INFECTION. An infection in a person with an impaired immune system caused by an organism that does not usually cause disease in people with healthy immune systems.

OPSOCLONUS. Often called "dancing eyes," this symptom involves involuntary, quick darting movements of the eyes in all directions.

OPTIC NERVE. The bundle of nerve fibers that carry visual messages from the retina to the brain.

OPTIC NEURITIS. Inflammation of the optic nerve, often accompanied by vision loss.

OREXIN. Another name for hypocretin, a chemical secreted in the hypothalmus that regulates the sleep/wake cycle. Narcolepsy is sometimes described as an orexin deficiency syndrome.

ORGANELLE. A specialized structure within a cell, which is separated from the rest of the cell by a membrane composed of lipids and proteins, where chemical and metabolic functions take place.

ORGANIC BRAIN SYNDROME. A brain disorder that is caused by defective structure or abnormal functioning of the brain.

ORTHOSTATIC HYPOTENSION. A drop in blood pressure that causes faintness or dizziness and occurs when an individual rises to a standing position. Also known as postural hypotension.

ORTHOTIC DEVICE. An external device, such as a splint or a brace, that prevents or assists movement.Also called an orthosis.

OSSICLES. Tiny bones in the middle ear—the incus, malleus, and stapes—that convey sound impulses from the eardrum to the inner ear.

OSTEOPOROSIS. Literally meaning "porous bones," this condition occurs when bones lose an excessive amount of their protein and mineral content, particularly calcium. Over time, bone mass and strength are reduced leading to increased risk of fractures.

OTITIS MEDIA. Inflammation, usually with infection, of the middle ear.

OTOLARYNGOLOGIST. A physician who specializes in medical and surgical treatment of disorders of the ear, nose, throat, and larynx.

OTOLARYNGOLOGY. The branch of medicine that treats disorders of the ear, nose, and throat.

OTOLITH ORGANS. Organs in the vestibular apparatus that sense horizontal and vertical movements of the head.

OTOLOGY. The branch of medicine that specializes in medical or surgical treatment of ear disorders.

OTOSCLEROSIS. Abnormal bone development in the middle ear, resulting in progressive hearing loss.

P

PAIN MEDICINE. The medical specialty that deals with the study and prevention of pain, and with the evaluation, treatment, and rehabilitation of patients with acute or chronic pain.

PALLIDOTOMY. A surgical procedure that destroys a small part of a tiny structure within the brain called the globus pallidus internus. This structure is part of the basal ganglia, a part of the brain involved in the control of willed (voluntary) movement of the muscles.

PALPITATION. A heartbeat that is more pronounced, often felt physically.

PALSY. Uncontrollable tremors.

PANDEMIC. Widespread epidemic.

PANIC DISORDER. An anxiety disorder in which people have sudden and intense attacks of fear in certain situations. Symptoms such as shortness of breath, sweating, dizziness, chest pain, and extreme fear often accompany the attacks.

PAPILLEDEMA. Swelling of the optic disk inside the eye (the portion of the optic nerve that collects nerves from the light sensitive layer of the eye, the retina); often caused by increased pressure inside the head.

PARALYSIS. Loss of the ability to move one or more parts of the body voluntarily due to muscle or nerve damage.

PARANEOPLASTIC SYNDROME. A set of symptoms associated with cancer but not directly caused by the cancer.

PARAPARESIS. Weakness of the legs.

PARAPLEGIA. Loss of voluntary movement and sensation of both lower extremities.

PARASITE. An organism that lives and feeds in or on another organism (the host) and does nothing to benefit the host.

PARASYMPATHETIC NERVOUS SYSTEM. A branch of the autonomic nervous system that tends to induce secretion, increase the tone and contraction of smooth muscle, and cause dilation of blood vessels.

PARESIS. Partial or total loss of movement or sensation.

PARESTHESIA. An abnormal sensation often described as burning, tickling, tingling, or "pins and needles."

PARIETAL LOBE. One of two brain hemispheres responsible for associative processes.

PARKINSONIAN. Related to symptoms associated with Parkinson's disease, a nervous system disorder characterized by abnormal muscle movement of the tongue, face, and neck; inability to walk or move quickly; walking in a shuffling manner; restlessness; or tremors.

PARKINSONISM. A set of symptoms originally associated with Parkinson's 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.

PARTIAL SEIZURE. An episode of abnormal activity in a specific part of the brain that causes changes in attention, movement, or behavior.

PATHOGEN. A disease-causing organism.

PATHOPHYSIOLOGY. The changes in body functions associated with a disorder or disease.

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.

PENETRATING HEAD INJURY. Traumatic brain injury (TBI) in which an object pierces the skull and enters brain tissue.

PENICILLAMINE. A drug used to bind to and remove heavy metals (such as copper or lead) from the blood, to prevent kidney stones, and to treat rheumatoid arthritis. Brand names include Cuprimine and Depen.

PERCUTANEOUS ABLATION. Attempting to remove a foreign body by a method just above the skin, like using an ointment.

PERILYMPH. The fluid that lies between the membranous labyrinth of the inner ear and the bony labyrinth.

PERIPHERAL NERVES. Nerves outside the brain and spinal cord that provide the link between the body and the central nervous system.

PERIPHERAL NERVOUS SYSTEM. The part of the nervous system that is outside the brain and spinal cord. Sensory, motor, and autonomic nerves are included. PNS nerves link the central nervous system with sensory organs, muscles, blood vessels, and glands.

PERISTALSIS. Waves of involuntary muscle contraction and relaxation.

PERIUNGUAL FIBROMA. Small non-cancerous growth on the toe- or fingernail beds.

PERIVENTRICULAR. Located around the brain's ventricles.

PERONEAL. Related to the legs.

PEROXISOME. A cellular organelle containing enzymes responsible for the breakdown of waste or other products.

PES CAVUS. A highly arched foot.

PHARYNGITIS. Inflammation of the throat, accompanied by dryness and pain. Pharyngitis caused by a streptococcal infection is the usual trigger of Sydenham's chorea.

PHARYNX. The part of the airway that is located at the back of the throat.

PHENOTYPE. The physical expression of an individual's genes.

PHENYLKETONURIA (PKU). A rare, inherited metabolic disorder in which the enzyme necessary to break down and use phenylalanine, an amino acid necessary for normal growth and development, is lacking. As a result, phenylalanine builds up in the body causing mental retardation and other neurological problems.

PHEOCHROMOCYTOMA. A tumor that originates from the adrenal gland's chromaffin cells, causing overproduction of catecholamines, powerful hormones that induce high blood pressure and other symptoms.

PHOBIA. An intense and irrational fear of a specific object, activity, or situation that leads to avoidance.

PHONEME. A discrete unit of a language that corresponds to a similar discrete unit of speech sound. It is the smallest meaningful segment of language; for example, the word "cat" has three phonemes, "kuh," "aah," and "tuh."

PHONICS. A system to teach reading by teaching the speech sounds associated with single letters, letter combinations, and syllables.

PHOTON. A light particle.

PIA MATER. The innermost of the three meninges covering the brain.

PICKWICKIAN SYNDROME. A distinctive form of obstructive sleep apnea associated with being overweight, having a large neck, fat buildup around the soft tissues of the neck, and loss of muscle tone with aging.

PITCH. The property of sound that is determined by the frequency of sound wave vibrations reaching the ear.

PITUITARY GLAND. The most important of the endocrine glands (glands that release hormones directly into the bloodstream), the pituitary is located at the base of the brain. Sometimes referred to as the "master gland," it regulates and controls the activities of other endocrine glands and many body processes including growth and reproductive function. Also called the hypophysis.

PLACEBO. A drug containing no active ingredients, such as a sugar pill, that may be used in clinical trials to compare the effects of a given treatment against no treatment.

PLAQUE. A deposit, usually of fatty material, on the inside wall of a blood vessel. Also refers to a small, round demyelinated area that develops in the brain and spinal cord of an individual with multiple sclerosis.

PLASMA CELL. A type of white blood cell that produces antibodies; derived from an antigen-specific B-cell.

PLASMAPHERESIS. A procedure in which harmful cells are removed from the blood plasma.

PNEUMOTHORAX. A condition in which air or gas is present in the chest cavity.

POLIO. A disease caused by the poliovirus that can result in muscle weakness and/or paralysis.

POLIOVIRUS. The virus responsible for the disease called polio.

POLYARTHRITIS. Inflammation of several joints at the same time.

POLYDACTYLY. The presence of extra fingers or toes.

POLYDIPSIA. Excessive thirst.

POLYMORPHISM. A difference in DNA sequence among individuals; genetic variation.

POLYNEUROPATHY. Peripheral neuropathy affecting multiple nerves.

POLYP. Piece of skin that pouches outward.

POLYSOMNOGRAM. A machine that is used to diagnose sleep disorders by measuring and recording a variety of body functions related to sleep, including heart rate, eye movements, brain waves, muscle activity, breathing, changes in blood oxygen concentration, and body position.

POLYURIA. Excessive production and excretion of urine.

POOR MUSCLE TONE. Muscles that are weak and floppy.

PORPHYRIA. A disorder in which porphyrins build up in the blood and urine.

PORPHYRIN. A type of pigment found in living things.

PORTAL HYPERTENSION. A condition caused by cirrhosis of the liver, characterized by impaired or reversed blood flow from the portal vein to the liver, an enlarged spleen, and dilated veins in the esophagus and stomach.

PORTAL VEIN THROMBOSIS. The development of a blood clot in the vein that brings blood into the liver. Untreated portal vein thrombosis causes portal hypertension.

POSITRON. One of the small particles that make up an atom. A positron has the same mass and amount of charge as an electron, but the positron has a positive charge.

POSTERIOR CIRCULATION. The blood supply to the back part of the brain, including the occipital lobe, cerebellum, and brain stem.

POSTERIOR FOSSA. Area at the base of the skull attached to the spinal cord.

POSTERIOR SUBCAPSULAR LENTICULAR OPACITY. A type of cataract in the eye.

POSTICTAL. The time period immediately following a seizure.

POSTURAL DRAINAGE. The use of positioning to drain secretions from the bronchial tubes and lungs into the trachea or windpipe.

POSTURAL HYPOTENSION. A drop in blood pressure that causes faintness or dizziness and occurs when an individual rises to a standing position. Also known as orthostatic hypotension.

PREGNANCY CATEGORY. A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but no human studies have been conducted, or, adverse effects have been shown in animal studies, but not in well-controlled human studies. Category C: No adequate human or animal studies, or adverse fetal effects in animal studies, but no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk. Risks outweigh any benefits.

PREMUTATION CARRIERS. Individuals who have the genetic protein repeats associated with a particular disorder, but not in sufficient numbers to cause the disorder.

The repeats may expand in these carriers' offspring, causing the disorder to occur.

PRENATAL TESTING. Testing for a disease such as a genetic condition in an unborn baby.

PRESBYCUSIS. Loss of hearing that gradually occurs because of age-related changes in the inner or middle ear.

PRESYNAPTIC. Before the synapse.

PRIMARY HEADACHE. A headache that is not caused by another disease or medical condition. Migraine headaches are one type of primary headache.

PRIMARY TUMOR. Abnormal growths that originated in the location where they were diagnosed.

PRION. A protein particle lacking nucleic acid and thought to be the cause of certain infectious diseases of the central nervous system, such as Creutzfeldt-Jakob disease.

PRODROMAL. Symptomatic of the approaching onset of an attack or a disease.

PRODROME. A symptom or group of symptoms that appears shortly before an acute attack of illness. The term comes from a Greek word that means "running ahead of."

PROGRESSIVE SUPRANUCLEAR PALSY. A rare disease that gradually destroys nerve cells in the parts of the brain that control eye movements, breathing, and muscle coordination. The loss of nerve cells causes palsy, or paralysis, that slowly gets worse as the disease progresses. The palsy affects ability to move the eyes, relax the muscles, and control balance.

PROJECTILE VOMITING. Forceful vomiting that is not preceded by nausea. It is usually associated with increased pressure inside the head.

PRONATION. The motion of the forearm to turn the palm downwards.

PROPHYLACTIC. Treatment given to protect against or ward off disease. Many doctors give antibiotics to patients who have been bitten by ticks as a prophylactic measure against Lyme disease.

PROPHYLAXIS. A measure taken to prevent disease or an acute attack of a chronic disorder. Migraine prophylaxis refers to medications taken to reduce the frequency of migraine attacks.

PROPRIOCEPTION. The ability to sense the location, position, orientation, and movement of the body and its parts.

PROSENCEPHALON. The part of the brain that develops from the front portion of the neural tube.

PROSTAGLANDINS. A group of hormone-like molecules that exert local effects on a variety of processes including fluid balance, blood flow, and gastrointestinal function. They may be responsible for the production of some types of pain and inflammation.

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.

PROXIMAL MUSCLES. Muscles closest to the center of the body, such as muscles used in breathing and sitting upright.

PSYCHOMETRIC. The development, administration, and interpretation of tests to measure mental or psychological abilities. Psychometric tests convert an individual's psychological traits and attributes into a numerical estimation or evaluation.

PSYCHOMOTOR. Movement produced by action of the mind or will.

PSYCHOMOTOR RETARDATION. Slowing of movement and speech.

PSYCHOSIS. A severe mental disorder characterized by loss of contact with reality. Hallucinations are associated with such psychotic disorders as schizophrenia and brief psychotic disorder.

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.

PTOSIS. Drooping of the upper eyelid.

PUTAMEN. Structure in the brain that is connected to the caudate nucleus and a component of the corpus striatum.

Q

QI. The Chinese term for energy, life force, or vital force.

QUADRIPARESIS. Partial or incomplete paralysis of all four limbs.

QUADRIPLEGIA. Permanent paralysis of the trunk, lower and upper limbs. It is caused by injury or disease affecting the spinal cord at the neck level.

R

RADICULONEURITIS. Inflammation of a spinal nerve.

RADICULONEUROPATHY. Disease of the nerve roots and nerves.

RADIOISOTOPE. One of two or more atoms with the same number of protons but a different number of neutrons with a nuclear composition. In nuclear scanning, radioactive isotopes are used as a diagnostic agent.

RADIOLOGIST. A physician who specializes in imaging techniques such as x rays, CT scans, MRI scans, and certain scans using radioactive isotopes.

RADIOTHERAPY. The use of x rays or other radioactive substances to treat disease.

REBOUND HEADACHE. A type of primary headache caused by overuse of migraine medications or pain relievers. It is also known as analgesic abuse headache.

RECEPTOR. A structure located on the outside of a cell's membrane that causes the cell to attach to specific molecules; the molecules are then internalized, taken inside the cell, and they either activate or inhibit certain cellular functions.

RECESSIVE GENE. A type of gene that is not expressed as a trait unless inherited by both parents.

RECOMBINANT DNA. DNA that has been altered by joining genetic material from two different sources. It usually involves putting a gene from one organism into the genome of a different organism.

RECOMBINANT HUMAN GROWTH HORMONE. A synthetic form of growth hormone that can be given to a patient to help skeletal growth.

RELEASE HALLUCINATIONS. Hallucinations that develop after partial loss of sight or hearing, and represent images or sounds formed from memory traces rather than present sensory input. They are called "release" hallucinations because they would ordinarily be blocked by incoming sensory data.

RENAL CELL CARCINOMA. A type of kidney cancer.

RESONATOR. As used in regard to the human speech mechanism, it is the cavity extending from the vocal folds to the lips, which selectively amplifies and modifies the energies produced during speech and voice production. It is synonymous with the term vocal tract.

RESTLESS LEGS SYNDROME. A condition that causes an annoying feeling of tiredness, uneasiness, and itching deep within the muscle of the leg. It is accompanied by twitching and sometimes pain. The only relief is in walking or moving the legs.

RETICULAR ACTIVATING SYSTEM. A network of structures, including the brain stem, medulla, and thalamus, and nerve pathways, which function together to produce and maintain arousal.

RETINA. The inner, light-sensitive layer of the eye containing rods and cones. The retina transforms the image it receives into electrical signals that are sent to the brain via the optic nerve.

RETINAL ACHROMIC PATCH. Small area of the retina that is lighter than the area around it.

RETINITIS PIGMENTOSA. A family of genetically linked retinal diseases that causes progressive deterioration of peripheral vision and eventually blindness.

RETROCOLLIS. Muscular spasms that affect the neck muscles located in the back.

RETROGRADE AMNESIA. A form of amnesia, or memory loss, in which the memories lost are those that occurred before a traumatic injury.

RETROVIRUS. A family of ribonucleic acid (RNA) viruses containing a reverse transcriptase enzyme that allows the viruses' genetic information to become part of the genetic information of the host cell upon replication. Human immunodeficiency virus (HIV) is a retrovirus.

REYE SYNDROME. A serious, life-threatening illness in children, usually developing after a bout of flu or chicken pox, and often associated with the use of aspirin. Symptoms include uncontrollable vomiting, often with lethargy, memory loss, disorientation, or delirium. Swelling of the brain may cause seizures, coma, and in severe cases, death.

RHABDOMYOLYSIS. Breakdown of muscle fibers resulting in release of muscle contents into the blood.

RHABDOMYOMA. Non-cancerous growth in the heart muscle.

RHABDOMYOSARCOMA. A tumor of the tendons, muscles, or connective tissue.

RHEUMATIC FEVER. Fever following a throat infection with group A Streptococcus, typically affecting children and young adults.

RHINITIS. Inflammation and swelling of the nasal membranes.

RHIZOTOMY. Surgery to relieve pain by cutting the nerve root near its point of entry to the spinal cord.

RNA. Ribonucleic acid, a nucleic acid that transmits messages in the DNA to other elements in the cell.

RODENTICIDES. Chemical that kills rodents

ROTE LEARNING. Learning by means of repetition and memorization, usually without significant understanding of the concepts involved.

S

SACCULAR ANEURYSM. A type of aneurysm that resembles a small sack of blood attached to the outer surface of a blood vessel by a thin neck.

SACROILIAC JOINT. The joint between the triangular bone below the spine (sacrum) and the hip bone (ilium).

SACRUM. An area in the lower back, below the lumbar region.

SCAPULA. The bone also known as the shoulder blade.

SCHIZOPHRENIA. A severe mental illness in which a person has difficulty distinguishing what is real from what is not real. It is often characterized by hallucinations, delusions, and withdrawal from people and social activities.

SCHWANN CELL. A type of supportive cell in the nervous system that makes up the myelin sheath around nerve fibers, providing both insulation and increasing the speed of nerve conduction.

SCIATIC NERVE. The nerve controlling the muscles of the back of the knee and lower leg, and providing sensation to the back of the thigh, part of the lower leg, and the sole of the foot.

SCIATICA. A common form of nerve pain related to compression of fibers from one or more of the lower spinal nerve roots, characterized by burning low back pain radiating to the buttock and back of the leg to below the knee or even to the foot.

SCLERA. The tough white membrane that forms the outer layer of the eyeball.

SCOLIOSIS. An asymmetric curvature of the spine to one side.

SECONDARY HEADACHE. A headache that is caused by another disease or disorder.

SEDATIVE. A medication that has a calming effect and may be used to treat nervousness or restlessness. Sometimes used as a synonym for hypnotic.

SEIZURE. A sudden attack, spasm, or convulsion produced by an abnormal electrical discharge of neurons in the brain.

SEMICIRCULAR CANALS. A set of three fluid-filled loops in the inner ear that are important for balance.

SENSORIUM. The place in the brain where external expressions are localized and processed before being perceived.

SENSORY. Related to the senses, or the ability to feel.

SENSORY NERVES. Sensory or afferent nerves carry impulses of sensation from the periphery or outward parts of the body to the brain. Sensations include feelings, impressions, and awareness of the state of the body.

SEPSIS. A severe systemic infection in which bacteria have entered the bloodstream or body tissues.

SEPTUM PELLUCIDUM. Two-layered thin wall separating the right and the left anterior horn of lateral ventricle.

SEQUENCING. Genetic testing in which the entire sequence of deoxyribonucleic acid (DNA) bases that make up a gene is studied, in an effort to find a mutation.

SEROTONIN. A widely distributed neurotransmitter that is found in blood platelets, the lining of the digestive tract, and the brain, and that works in combination with norepinephrine. It causes very powerful contractions of smooth muscle and is associated with mood, attention, emotions, and sleep. Low levels of serotonin are associated with depression.

SEROTONIN SYNDROME. A potentially fatal drug interaction caused by combining drugs that raise the level of serotonin in the patient's nervous system to dangerously high levels. The symptoms of serotonin syndrome include shivering, overreactive reflexes, nausea, low-grade fever, sweating, delirium, mental confusion, and coma.

SERUM. The fluid part of the blood that remains after blood cells, platelets, and fibrogen have been removed. Also called blood serum.

SHAGREEN PATCHES. Patches of skin with the consistency of an orange peel.

SHAKEN BABY SYNDROME. A severe form of traumatic brain injury (TBI) resulting from shaking an infant or small child forcibly enough to cause the brain to jar against the skull.

SHINGLES. A disease caused by an infection with the herpes zoster virus, the same virus that causes chicken pox. Symptoms of shingles include pain and blisters along one nerve, usually on the face, chest, stomach, or back.

SKILLED NURSING FACILITY. An inpatient facility that provides 24-hour nursing services to individuals in need of extended care.

SKIN TAG. Abnormal outward pouching of skin, with a varying size.

SKULL. All of the bones of the head.

SLEEP APNEA. A condition in which a person temporarily stops breathing during sleep.

SLEEP PARALYSIS. An abnormal episode of sleep in which the patient cannot move for a few minutes, usually occurring while falling asleep or waking up. Sleep paralysis is often found in patients with narcolepsy.

SOMATIC EDUCATION. A term used in both Hellerwork and the Feldenkrais method to describe the integration of bodywork with self-awareness, intelligence, and imagination.

SOMATOFORM DISORDERS. A group of psychiatric disorders in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) classification that are characterized by external physical symptoms or complaints related to psychological problems rather than organic illness.

SOUND WAVES. Changes in air pressure that produce an oscillating wave that transmits sound.

SPASM. Sudden involuntary muscle movement or contraction.

SPASTIC. Refers to a condition in which the muscles are rigid, posture may be abnormal, and fine motor control is impaired.

SPASTIC QUADRIPLEGIA. Inability to use and control movements of the arms and legs.

SPASTICITY. Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

SPEECH SYNTHESIZER. A computerized device that accepts input, interprets data, and produces audible language.

SPHENOID. A bone of the skull.

SPHENOIDAL ELECTRODES. Fine wire electrodes that are implanted under the cheek bones, used to measure temporal seizures.

SPHINCTER. A band of muscle that encircles an opening in the body, allowing the opening to open and close (anal sphincter, esophageal sphincter).

SPIKE WAVE DISCHARGE. Characteristic abnormal wave pattern in the electroencephalogram that is a hallmark of an area that has the potential of generating a seizure.

SPINA BIFIDA. A birth defect (a congenital malformation) in which part of the vertebrae fail to develop completely so that a portion of the spinal cord, which is normally protected within the vertebral column, is exposed. People with spina bifida can suffer from bladder and bowel incontinence, cognitive (learning) problems, and limited mobility.

SPINA BIFIDA OCCULTA. A relatively mild form of spina bifida in which the defect is not visible from the surface. This condition is most often asymptomatic.

SPINAL CORD. The part of the central nervous system that extends from the base of the skull and runs through the vertebral column in the back. It acts as a relay to convey information between the brain and the periphery.

SPINAL DEGENERATION. Wear and tear on the intervertebral discs, which can narrow the spinal canal and cause back stiffness and pain.

SPINAL FUSION. A surgical procedure that stabilizes the spine and prevents painful movements, but with resulting loss of flexibility.

SPINAL STENOSIS. A congenital narrowing of the spinal canal.

SPIROCHETE. A bacterium shaped like a loosely coiled spiral. The organism that causes Lyme disease is a spirochete.

SPONDYLITIS. Inflammation of the spinal joints, characterized by chronic back pain and stiffness.

SPONDYLOLISTHESIS. A more extreme form of spondylosis, with slippage of one vertebra relative to its neighbor.

SPONDYLOSIS. A condition in which one or more of the vertebral joints in the spine becomes stiff or fixed in one position.

SPORE. A dormant form assumed by some bacteria, such as anthrax, that enable the bacterium to survive high temperatures, dryness, and lack of nourishment for long periods of time. Under proper conditions, the spore may revert to the actively multiplying form of the bacteria. Also refers to the small, thick-walled reproductive structure of a fungus.

STATUS EPILEPTICUS. A serious condition involving continuous seizures with no conscious intervals.

STATUS MIGRAINOSUS. The medical term for an acute migraine headache that lasts 72 hours or longer.

STENOSIS. A condition in which an opening or passageway in the body is narrowed or constricted.

STERNOCLEIDOMASTOID MUSCLE. A muscle located in front of the neck that functions to turn the head from side to side.

STEROID. A class of drugs resembling normal body substances that often help control inflammation in the body tissues.

STIMULANT. Any chemical or drug that has excitatory actions in the central nervous system.

STORAGE DISEASES. Diseases in which too much of a substance (usually fats, glycogen, or certain enzymes) builds up in specific cells of the body and causes metabolic or tissue disorders.

STRABISMUS. Deviation of one eye from parallelism with the other.

STRESS. A physical and psychological response that results from being exposed to a demand or pressure.

STRIATUM. Area located deep within the brain.

STRIDOR. A high-pitched sound made when breathing, caused by the narrowing of the airway.

STROKE. Interruption of blood flow to a part of the brain with consequent brain damage. A stroke may be caused by a blood clot or by hemorrhage due to a burst blood vessel. Also known as a cerebrovascular accident.

STRUCTURAL INTEGRATION. The term used to describe the method and philosophy of life associated with Rolfing. Its fundamental concept is the vertical line.

STUTTERING. A disorder characterized by speech that has more dysfluencies (involuntary hesitations and repetitions) than is considered average.

SUBARACHNOID. The space underneath the layer of meningeal membrane called the arachnoid.

SUBARACHNOID HEMORRHAGE. A cause of some strokes in which arteries on the surface of the brain begin bleeding.

SUBARACHNOID SPACE. The space between two membranes surrounding the spinal cord and brain, the arachnoid and pia mater.

SUBCORTICAL. The neural centers located below (inferior to) the cerebral cortex.

SUBDURAL ELECTRODES. Strip electrodes that are placed under dura mater (the outermost, toughest, and most fibrous of the three membranes [meninges] covering the brain and spinal cord). They are used to locate foci of epileptic seizures prior to epilepsy surgery.

SUBDURAL HEMATOMA. A localized accumulation of blood, sometimes mixed with spinal fluid, in the space between the middle (arachnoid) and outer (dura mater) membranes covering the brain. It is caused by an injury to the head that tears blood vessels.

SUBEPENDYMAL GIANT CELL ASTROCYTOMA. Specific type of cancerous brain tumor found in tuberous sclerosis.

SUBSTANTIA NIGRA. One of the movement control centers of the brain. It can become depleted of a specific neurotransmitter, dopamine, and cause symptoms of Parkinson's disease.

SULFONAMIDES. A group of antibiotics used to treat a wide range of bacterial infections.

SUPERIOR OBLIQUE MUSCLE. One of six extraocular muscles concerned with eye movement. The superior oblique muscle pushes the eye down, turns it inward and rotates it outward.

SYLVIAN FISSURE. The lateral fold separating the brain hemisphere into the frontal and temporal lobes.

SYMPATHETIC NERVOUS SYSTEM. A branch of the autonomic nervous system that regulates involuntary reactions to stress such as increased heart and breathing rates, blood vessel contraction, and reduction in digestive secretions.

SYMPATHETIC SKIN RESPONSE. Minute change of palmar and plantar electrical potential.

SYNAPSE. A junction between two neurons. At a synapse the neurons are separated by a tiny gap called the synaptic cleft.

SYNCOPE. A loss of consciousness over a short period of time, caused by a temporary lack of oxygen in the brain.

SYNDROME. A group of symptoms that together characterize a disease or disorder.

SYPHILIS. Sexually transmitted disease caused by a corkscrew shaped bacterium called *Treponema pallidum.* It is characterized by three clinical stages, namely primary, secondary, and tertiary or late syphilis.

SYRINGOMYELIA. Excessive fluid in the spinal cord.

SYRINX. Abnormal fluid-filled cavities within the spinal cord.

T

TACHYCARDIA. Elevated heart rate.

TACHYPNEA. Elevated breathing rate.

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."

TEMPORAL LOBE. A large lobe of each hemisphere of the brain that is located on the side of the head, nearest the ears. It contains a sensory area associated with hearing.

TENDON REFLEX. This is a simple circuit that consists of a stimulus, like a sharp tap delivered to a tendon, and the response, muscle contraction. It is used to test the integrity of the nervous system.

TERATOGEN. A substance that has been demonstrated to cause physical defects in the developing human embryo.

TERATOGENIC. Able to cause birth defects.

TETANUS. Denotes continuous, involuntary contraction of voluntary muscles due to repetitive stimuli from nerve endings. It can occur due to infection with a bacterium called *Clostridium tetani.*

THALAMOTOMY. A surgical procedure that destroys part of a large oval area of gray matter within the brain that acts as a relay center for nerve impulses. The thalamus is an essential part of the nerve pathway that controls intentional movement. By destroying tissue at a particular spot on the thalamus, the surgeon can interrupt the nerve signals that cause tremor.

THALAMUS. A pair of oval masses of gray matter within the brain that relay sensory impulses from the spinal cord to the cerebrum.

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).

THERMOGRAPHY. A test using infrared sensing devices to measure differences in temperature in body regions thought to be the source of pain.

THORACIC. Referring to the area of the torso commonly called the chest. There are 12 thoracic vertebrae.

THROMBOSIS. The formation of a blood clot in a vein or artery that may obstruct local blood flow or may dislodge, travel downstream, and obstruct blood flow at a remote location. The clot or thrombus may lead to infarction, or death of tissue, due to a blocked blood supply.

THROMBUS. A blood clot, which may form at the site of an atherosclerotic plaque and block the artery.

THYMOMA. A tumor that originates in the thymus, a small gland located in the upper chest just below the neck, that produces hormones necessary for the development of certain components of the immune system.

THYROTOXICOSIS. The most common form of hyperthyroidism, characterized by bulging eyes, rapid heart rate, and other symptoms. Also called Graves' disease.

THYROXINE. Hormone produced by the thyroid gland.

TIC. A brief and intermittent involuntary movement or sound.

TINNITUS. A noise, ranging from faint ringing or thumping to roaring, that originates in the ear not in the environment.

TONIC. A type of seizure characterized by episodes of stiffening in all the limbs for up to one or two minutes.

TOPICAL. For application to the surface of the skin.

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.

TOURETTE SYNDROME. An abnormal condition that causes uncontrollable facial grimaces and tics and arm and shoulder movements. Tourette syndrome is perhaps best known for uncontrollable vocal tics that include grunts, shouts, and use of obscene language (coprolalia).

TRACHEOSTOMY. A surgical procedure that makes an opening in the windpipe to bypass the obstructed airway.

TRACTION. Spinal stretching using weights applied to the spine, once thought to decrease pressure on the nerve roots but now seldom used.

TRANSCRIPTION FACTOR. A protein that acts to regulate the expression of genes.

TRANSIENT ISCHEMIC ATTACK (TIA). A brief interruption of the blood supply to part of the brain, it causes a temporary impairment of vision, speech, or movement. Usually the episode lasts for just a few moments, but it may be a warning sign for a full-scale stroke.

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY. A term that refers to a group of diseases, including kuru, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, and new variant Creutzfeldt-Jakob disease. These diseases share a common origin as prion diseases, caused by abnormal proteins that accumulate within the brain and destroy brain tissue, leaving spongy holes.

TRANSVERSE MYELITIS. A neurologic syndrome caused by inflammation of the spinal cord.

TRAPEZIUS. Muscle of the upper back that rotates the shoulder blade, raises the shoulder, and flexes the arm.

TREMOR. Involuntary shakiness or trembling.

TREMOR CONTROL THERAPY. A method for controlling tremor by self-administered shocks to the part of the brain that controls intentional movement (thalamus). An electrode attached to an insulated lead wire is implanted in the brain; the battery power source is implanted under the skin of the chest, and an extension wire is tunneled under the skin to connect the battery to the lead. The patient turns on the power source to deliver the electrical impulse and interrupt the tremor.

TRICEPS. Muscle of the back of the upper arm, primarily responsible for extending the elbow.

TRIGEMINAL NERVE. The main sensory nerve of the face and motor nerve for chewing muscles.

TRIGEMINAL NEURALGIA. Brief episodes of severe shooting pain on one side of the face caused by inflammation of the root of the trigeminal nerve. Also referred to as tic douloureux.

TRIGGER FINGER. An overuse disorder of the hand in which one or more fingers tend to lock or "trigger" when the patient tries to extend the finger.

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.

TRIPTANS. Also known as serotonin agonists or 5-hydroxytryptamine receptor agonists, triptans are a class of drugs that are used in the treatment of migraine headaches.

TRISOMY. An abnormality in chromosomal development. In a trisomy syndrome, an extra chromosome is present so that the individual has three of a particular chromosome instead of the normal pair. An extra chromosome 18 (trisomy 18) causes mental retardation.

TSUBO. In shiatsu, a center of high energy located along one of the body's meridians. Stimulation of the tsubos during a shiatsu treatment is thought to rebalance the flow of vital energy in the body.

TUBEROUS SCLEROSIS. A genetic condition that affects many organ systems including the brain, skin, heart, eyes, and lungs. Benign (non-cancerous) growths or tumors called hamartomas form in various parts of the body, disrupting their normal function.

TUBERS. Firm growths in the brain, named for their resemblance in shape to potato stems.

TUMOR. An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

TUMORIGENESIS. Formation of tumors.

U

ULNAR NERVE. The nerve that supplies some of the forearm muscles, the elbow joint, and many of the short muscles of the hand.

ULTRASONOGRAPHY. A medical test in which sound waves are directed against internal structures in the body. As sound waves bounce off the internal structure, they create an image on a video screen. Ultrasonography is often used to diagnose fetal abnormalities, gallstones, heart defects, and tumors. Also called ultrasound imaging.

UNILATERAL. Refers to one side of the body or only one organ in a pair.

URINARY INCONTINENCE. Lacking the ability to control urinary excretion.

UVEITIS. Inflammation of all or part the uvea. The uvea is a continuous layer of tissue that consists of the iris, the ciliary body, and the choroid. The uvea lies between the retina and sclera.

V

VAGINISMUS. An involuntary spasm of the muscles surrounding the vagina, making penetration painful or impossible.

VAGUS NERVE. Tenth cranial nerve and an important part of the autonomic nervous system, influencing motor functions in the larynx, diaphragm, stomach, and heart, and sensory functions in the ears and tongue.

VALSALVA MANEUVER. A strain against a closed airway combined with muscle tightening, such as happens when a person holds his or her breath and tries to move a heavy object. Most people perform this maneuver several times a day without adverse consequences, but it can be dangerous for anyone with cardiovascular disease. Pilots perform this maneuver to prevent black-outs during high-performance flying.

VASCULAR. Related to the blood vessels.

VASCULITIS. Inflammation of the walls of the blood vessels.

VASOCONSTRICTIVE. Causing a blood vessel to become narrower, thus decreasing blood flow.

VASODILATOR. Any drug that relaxes blood vessel walls.

VASOMOTOR. Referring to the regulation of the diameter of blood vessels.

VECTOR. A carrier organism (such as a fly or mosquito) that serves to deliver a virus (or other agent of infection) to a host. Also refers to a retrovirus that had been modified and is used to introduce specific genes into the genome of an organism.

VENTRAL. Pertaining in direction to the front or lower surface of an organ.

VENTRICLES. In neurology, the four fluid-filled chambers, or cavities, found in the two cerebral hemispheres of

the brain, at the center of the brain, and between the brain stem and cerebellum. They are linked by channels, or ducts, allowing cerebral fluid to circulate through them.

VENTRICULOPERITONEAL SHUNT. A tube equipped with a low-pressure valve, one end of which is inserted into a cerebral ventricle, the other end of which is routed into the peritoneum, or abdominal cavity.

VENTRICULOSTOMY. Surgery that drains cerebrospinal fluid from the brain to treat hydrocephalus or increased intracranial pressure.

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.

VERTEBRAE. Singular, vertebra. The individual bones of the spinal column that are stacked on top of each other. There is a hole in the center of each bone through which the spinal cord passes.

VERTEX PRESENTATION. Head presentation during delivery.

VERTIGO. A feeling of dizziness together with a sensation of movement and a feeling of rotating in space.

VESICLE. A small, raised lesion filled with clear fluid.

VESTIBULAR. A term that refers to the organs of balance.

VESTIBULAR SYSTEM. The sensory system located in the inner ear that allows the body to maintain balance.

VIRUS. A small infectious agent consisting of a core of genetic material (DNA or RNA) surrounded by a shell of protein. A virus needs a living cell to reproduce.

VISCERAL. Generally related to the digestive, respiratory, urogenital, or endocrine organs.

VISUAL FIELD. A field of vision that is visible without eye movement.

VITAMINS. Small compounds required for metabolism that must be supplied by diet, microorganisms in the gut (vitamin K), or sunlight (UV light converts pre-vitamin D to vitamin D).

VOLUNTARY MUSCLE. A muscle under conscious control; contrasted with smooth muscle and heart muscle which are not under voluntary control.

W

WESTERN BLOT. A sensitive laboratory blood test for specific antibodies; useful in confirming the diagnosis of AIDS.

WHITE MATTER. A substance, composed primarily of myelin fibers, found in the brain and nervous system that protects nerves and allows messages to be sent to and from the brain and various parts of the body. Also called white substance.

WHITE MATTER RADIAL MIGRATION LINE. White lines seen on a brain scan, signifying abnormal movement of neurons (brain cells) at that area.

WITHDRAWAL SYMPTOMS. A group of physical or mental symptoms that may occur when a person suddenly stops using a drug upon which he or she has become dependent.

WOODS LAMP. Lamp that uses ultraviolet light, making subtle skin changes more obvious.

WRAPAROUND. A relatively new form of mental health service delivery that strives to accommodate all family members based on self-defined needs, flexibly incorporating both formal and informal community services.

X

X INACTIVATION. The process in which each cell in a girl's body selects at random and turns off one of its two X chromosomes. X inactivation is one reason why some patients with Rett syndrome (RS) have more severe symptoms than others.

X RAY. Electromagnetic radiation of very short wavelength and very high energy.

Y

YIN AND YANG. In traditional Chinese medicine and philosophy, a pair of opposing forces whose harmonious balance in the body is necessary for good health.

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