Part XXVII ■ Neuromuscular Disorders

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Chapter 606 ■ Evaluation and Investigation

The term **neuromuscular disease** defines disorders of the motor unit and excludes influences on muscular function from the brain, such as spasticity. The motor unit has four components: a motor neuron in the brainstem or ventral horn of the spinal cord; its axon that, together with other axons, forms the peripheral nerve; the neuromuscular junction; and all muscle fibers innervated by a single motor neuron. The size of the motor unit varies among different muscles and with the precision of muscular function required. In large muscles, such as the glutei and quadriceps femoris, hundreds of muscle fibers are innervated by a single motor neuron; in small finely tuned muscles, such as the stapedius or the extraocular muscles, a 1 : 1 ratio may prevail. The motor unit is influenced by suprasegmental or upper motor neuron control that alters properties of muscle tone, precision of movement, reciprocal inhibition of antagonistic muscles during movement, and sequencing of muscle contractions to achieve smooth, coordinated movements. Suprasegmental impulses also augment or inhibit the monosynaptic stretch reflex; the corticospinal tract is inhibitory upon this reflex.

Diseases of the motor unit are common in children. These neuromuscular diseases may be genetically determined, congenital or acquired, acute or chronic, and progressive or static. Because specific therapy is available for many diseases and because of genetic and prognostic implications, precise diagnosis is important; laboratory confirmation is required for most diseases because of overlapping clinical manifestations.

Many chromosomal loci have been identified with specific neuromuscular diseases as a result of genetic linkage studies and the isolation and cloning of a few specific genes. In some cases, such as Duchenne muscular dystrophy, the genetic defect has been shown to be a deletion of nucleotide sequences and is associated with a defective protein product, dystrophin; in other cases, such as myotonic muscular dystrophy, the genetic defect is an expansion or repetition, rather than a deletion, in a codon (a set of three consecutive nucleotide repeats that encodes for a single amino acid), with many copies of a particular codon, in this example also associated with abnormal mRNA. Some diseases present as autosomal dominant and autosomal recessive traits in different pedigrees; these distinct mendelian genotypes may result from different genetic mutations on different chromosomes (nemaline rod myopathy) or may be small differences in the same gene at the same chromosomal locus (myotonia congenita), despite many common phenotypic features and shared histopathologic findings in a muscle biopsy specimen. Among the several clinically defined mitochondrial myopathies, specific mtDNA deletions and tRNA point mutations are recognized. The inheritance patterns and chromosomal and mitochondrial loci of common neuromuscular diseases affecting infants and children are summarized in Table 607-1.

CLINICAL MANIFESTATIONS

Examination of the neuromuscular system includes an assessment of muscle bulk, tone, and strength. Tone and strength should not be confused: **Passive tone** is range of motion around a joint; **active tone** is physiologic resistance to movement. Head lag when an infant is pulled to a sitting position from supine is a sign of weakness, not of low tone. Hypotonia may be associated with normal strength or with weakness; enlarged muscles may be weak or strong; thin, wasted muscles may be weak or have unexpectedly normal strength. The distribution of these components is of diagnostic importance. In general, myopathies follow a proximal distribution of weakness and muscle wasting (with the notable exception of myotonic muscular dystrophy); neuropathies are generally distal in distribution (with the notable exception of juvenile spinal muscular atrophy) (Table 606-1). Involvement of the face, tongue, palate, and extraocular muscles provides an important distinction in the differential diagnosis. Tendon stretch reflexes are generally lost in neuropathies and in motor neuron diseases and are diminished but preserved in myopathies (see Table 606-1). A few specific clinical features are important in the diagnosis of some neuromuscular diseases. Fasciculations of muscle, which are often best seen in the tongue, are a sign of denervation. Sensory abnormalities indicate neuropathy. Fatigable weakness is characteristic of neuromuscular junctional disorders. Myotonia is specific for a few myopathies.

Some features do not distinguish myopathy from neuropathy. Muscle pain or myalgias are associated with acute disease of either myopathic or neurogenic origin. Both acute dermatomyositis and acute polyneuropathy (Guillain-Barré syndrome) are characterized by myalgias. Muscular dystrophies and spinal muscular atrophies are not associated with muscle pain. Myalgias also occur in several metabolic diseases of muscle and in ischemic myopathy. Contractures of muscles, whether present at birth or developing later in the course of an illness, occur in both myopathic and neurogenic diseases.

Infant boys who are weak in late fetal life and in the neonatal period often have undescended testes. The testes are actively pulled into the scrotum from the anterior abdominal wall by a pair of cords that consist of smooth and striated muscle called the gubernaculum. The gubernaculum is weakened in many congenital neuromuscular diseases, including spinal muscular atrophy, myotonic muscular dystrophy, and many congenital myopathies.

The thorax of infants with congenital neuromuscular disease often has a funnel shape, and the ribs are thin and radiolucent, due to intercostal muscle weakness during intrauterine growth. This phenomenon is characteristically found in infantile spinal muscular atrophy but also occurs in myotubular myopathy, neonatal myotonic dystrophy, and other disorders (Fig. 606-1). Because of the small muscle mass, birth weight may be low for gestational age.

Generalized hypotonia and motor developmental delay are the most common presenting manifestations of neuromuscular disease in infants and young children (Table 606-2). These features may also be expressions of neurologic disease, endocrine

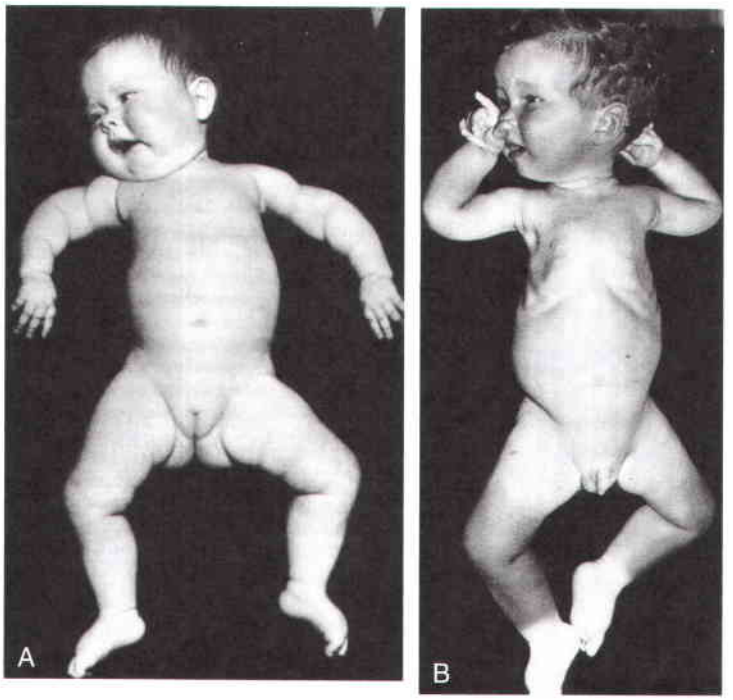

Figure 606-1. Type 1 spinal muscular atrophy (Werdnig-Hoffmann disease): characteristic postures in 6 wk old *(A)* and 1 yr old *(B)* infants with severe weakness and hypotonia from birth. Note the frog-leg posture of the lower limbs and internal rotation ("jug handle") *(A)* or external rotation *(B)* at the shoulders. Note also intercostal recession, especially evident in *B*, and normal facial expressions. (From Volpe J: *Neurology of the Newborn,* 4th ed. Philadelphia, WB Saunders, 2001, p 645.)

TABLE 606-1. Distinguishing Features of Disorders of the Motor System

	WEAKNESS*							
LOCUS OF LESION	FACE	ARMS	LEGS	PROXIMAL-DISTAL	DEEP TENDON REFLEXES	ELECTROMYOGRAPHY	MUSCLE BIOPSY	OTHER
Central	0	+	+	> or =	Normal or ↑	Normal	Normal	Seizures, hemiparesis, and delayed development
Anterior horn cell	Late	++++	++++	> or =	0	Fasciculations and fibrillations	Denervation pattern	Fasciculations (tongue)
Peripheral nerve	0	+++	+++	<	↓	Fibrillations	Denervation pattern	Sensory deficit, elevated cerebrospinal fluid protein, depressed nerve conduction velocity, abnormal nerve biopsy
Neuromuscular junction	+++	+++	+++	=	Normal	Decremental response (myasthenia); incremental response and BSAP (botulism)	Normal	Response to neostigmine or edrophonium (myasthenia); constipation and fixed pupils (botulism)
Muscle	Variable (+ to ++++)	++	+	>	↓	Short duration, small amplitude motor unit potentials and myopathic polyphasic potentials	Myopathic pattern†	Elevated muscle enzyme levels (variable)

*+ *to* ++++, Varying degrees of severity.
†May also show unique features, such as in central core disease, nemaline myopathy, myotubular myopathy, and congenital fiber type disproportion.
BSAP, brief duration, small amplitude, overly abundant motor unit potentials.
From Volpe J: *Neurology of the Newborn,* 4th ed. Philadelphia, WB Saunders, 2001, p 706.

TABLE 602-2. Pattern of Weakness and Localization in the Floppy Infant

ANATOMICAL REGION OF HYPOTONIA	CORRESPONDING DISORDERS	PATTERN OF WEAKNESS AND INVOLVEMENT
Central nervous system	Chromosomal disorders Inborn errors of metabolism Cerebral dysgenesis Cerebral, spinal cord trauma	Central hypotonia Axial hypotonia more prominent Hyperactive reflexes
Motor neuron Nerve	Spinal muscular atrophy Peripheral neuropathies	Generalized weakness; often spares the diaphragm, facial muscles, pelvis, and sphincters Distal muscle groups involved Weakness with wasting
Neuromuscular junction	Myasthenia syndromes Infantile botulism	Bulbar, oculomotor muscles exhibit greater degree of involvement
Muscle	Congenital myopathies Metabolic myopathies CMD Congenital myotonic dystrophy	Weakness is prominent Proximal musculature Hypoactive reflexes Joint contractures

CMD, congenital muscular dystrophy.
From Prasad AN, Prasad C: The floppy infant: Contribution of genetic and metabolic disorders. *Brain Dev* 2003; 27:457–476.

TABLE 606-3. Differential Diagnosis of Acute Flaccid Paralysis

BRAINSTEM STROKE

BRAINSTEM ENCEPHALITIS

ACUTE ANTERIOR POLIOMYELITIS
Caused by poliovirus
Caused by other neurotropic viruses

ACUTE MYELOPATHY
Space-occupying lesions
Acute transverse myelitis

PERIPHERAL NEUROPATHY
Guillain-Barré syndrome
Post–rabies vaccine neuropathy
Diphtheritic neuropathy
Heavy metals, biologic toxins, or drug intoxication
Acute intermittent porphyria
Vasculitic neuropathy
Critical illness neuropathy
Lymphomatous neuropathy

DISORDERS OF NEUROMUSCULAR TRANSMISSION
Myasthenia gravis
Biologic or industrial toxins

DISORDERS OF MUSCLE
Hypokalemia
Hypophosphatemia
Inflammatory myopathy
Acute rhabdomyolysis
Trichinosis
Periodic paralyses

From Hughes RAC, Camblath DR: Guillain-Barré syndrome. *Lancet* 2005; 366:1653–1666.

and systemic metabolic diseases, and Down syndrome, or they may be nonspecific neuromuscular expressions of malnutrition or chronic systemic illness. A prenatal history of decreased fetal movements and intrauterine growth retardation is often found in patients who are symptomatic at birth. Developmental disorders tend to be of slow onset and are progressive. Acute flaccid paralysis in older infants and children has a different differential diagnosis (Table 606-3).

LABORATORY FINDINGS

SERUM ENZYMES. Several lysosomal enzymes are released by damaged or degenerating muscle fibers and may be measured in serum. The most useful of these enzymes is the **creatine kinase (CK)**, which is found in only 3 organs and may be separated into corresponding isozymes: MM for skeletal muscle, MB for cardiac muscle, and BB for brain. Serum CK determination is by no means a universal screening test for neuromuscular disease because many diseases of the motor unit may not be associated with elevated enzymes. The CK level is characteristically elevated in certain diseases, such as Duchenne muscular dystrophy, and the magnitude of increase is characteristic for particular diseases.

MOLECULAR GENETIC MARKERS. Many DNA markers of hereditary myopathies and neuropathies are available from blood samples. If the clinical manifestations suggest a particular disease, these tests may provide a definitive diagnosis and not subject the child to more invasive procedures, such as muscle biopsy. Other molecular markers are available only in muscle biopsy tissue. Genetic blood tests, whether ordered individually or in "panels," are expensive and may be excluded from health insurance plans.

NERVE CONDUCTION VELOCITY (NCV). Motor and sensory nerve conduction may be measured electrophysiologically by using surface electrodes. Neuropathies of various types are detected by decreased conduction. The site of a traumatic nerve injury may also be localized. The nerve conduction at birth is about half of the mature value achieved by age 2 yr. Tables are available for normal values at various ages in infancy, including for preterm infants. Because the NCV study measures only the fastest conducting fibers in a nerve, 80% of the total nerve fibers must be involved before slowing in conduction is detected.

ELECTROMYOGRAPHY (EMG). EMG requires insertion of a needle into the belly of a muscle and recording the electric potentials in various states of contraction. It is less useful in pediatrics than in adult medicine, in part because of technical difficulties in recording these potentials in young children and in part because the best results require the patient's cooperation for full relaxation and maximal voluntary contraction of a muscle. Many children are too frightened to provide such cooperation. Characteristic EMG patterns distinguish denervation from myopathic involvement. The specific type of myopathy is not usually definitively diagnosed, but certain specialized myopathic conditions, such as myotonia, may be demonstrated. An EMG may transiently raise the serum CK level.

EMG combined with repetitive electrical stimulation of a motor nerve supplying a muscle to produce tetany is useful in demonstrating myasthenic decremental responses. Small muscles, such as the abductor digiti quinti of the hypothenar eminence, are used for such studies.

IMAGING OF MUSCLE. Imaging of muscle using ultrasonography, CT scans, and MRI are used in many neuromuscular diseases. While these methods are not always definitively diagnostic, in experienced hands, they provide a supplementary means of following the progression of disease over time. MRI is quite useful in identifying inflammatory myopathies of immune (dermatomyositis) or infectious (viral, bacterial, parasitic) origin. MRI is the study of choice to image the spinal cord or nerve roots and plexus (e.g., brachial).

MUSCLE BIOPSY. The muscle biopsy is the most important and specific diagnostic study of most neuromuscular disorders, if the definitive diagnosis of an hereditary disease is not provided by molecular genetic testing in blood. Not only are neurogenic and myopathic processes distinguished, but also the type of myopathy and specific enzymatic deficiencies may be determined. The vastus lateralis (quadriceps femoris) is the muscle that is most commonly sampled. The deltoid muscle should be avoided in most cases because it normally has a 60–80% predominance of type I fibers so that the distribution patterns of fiber types are difficult to recognize. Muscle biopsy is a simple outpatient procedure that may be performed under local anesthesia with or without femoral nerve block. Needle biopsies are preferred in some centers, but are not percutaneous and require an incision in the skin similar to open biopsy; numerous samples must be taken to conduct an adequate examination of the tissue, and they provide inferior specimens. The volume of tissue from a needle biopsy is usually not adequate for supplementary biochemical studies, such as mitochondrial respiratory chain enzymes; a small, clean, open biopsy is therefore advantageous.

Histochemical studies of frozen sections of the muscle are obligatory in all pediatric muscle biopsies because many congenital and metabolic myopathies cannot be diagnosed from paraffin sections using conventional histologic stains. Immunohistochemistry is a useful supplement in some cases, such as for demonstrating dystrophin in suspected Duchenne muscular dystrophy or merosin in congenital muscular dystrophy. A portion of the biopsy specimen should be fixed for potential electron microscopy, but ultrastructure has additional diagnostic value only in selected cases. Muscle biopsy sample interpretation is complex and should be performed by an experienced patholo-

gist. A portion of frozen muscle tissue should also be routinely saved for possible biochemical analysis (mitochondrial cytopathies, carnitine palmityltransferase, acid maltase).

NERVE BIOPSY. The most commonly sampled nerve is the sural nerve, a pure sensory nerve that supplies a small area of skin on the lateral surface of the foot. Whole or fascicular biopsy specimens of this nerve may be taken. When the sural nerve is severed behind the lateral malleolus of the ankle, regeneration of the nerve occurs in >90% of cases so that permanent sensory loss is not experienced. The sural nerve is often involved in many neuropathies whose clinical manifestations are predominantly motor.

Electron microscopy is performed on most nerve biopsy specimens because many morphologic alterations cannot be appreciated at the resolution of a light microscope. Teased fiber preparations are sometimes useful in demonstrating segmental demyelination, axonal swellings, and other specific abnormalities, but this time-consuming procedure is not done routinely. Special stains may be applied to ordinary frozen or paraffin sections of nerve biopsy material to demonstrate myelin, axoplasm, and metabolic products.

ELECTROCARDIOGRAPHY (ECG). Cardiac evaluation is important if myopathy is suspected because of involvement of the heart in muscular dystrophies and in inflammatory and metabolic myopathies. ECG often detects early cardiomyopathy or conduction defects that are clinically asymptomatic. At times, a more complete cardiac work-up, such as echocardiography and consultation with a pediatric cardiologist, may be indicated. Serial pulmonary function tests also should be performed in muscular dystrophies and in other chronic or progressive diseases of the motor unit.

Prasad AN, Prasad C: The floppy infant: Contribution of genetic and metabolic disorders. *Brain Dev* 2003;27:457–476.

Chapter 607 ■ Developmental Disorders of Muscle

A heterogeneous group of congenital neuromuscular disorders is sometimes known as the **congenital myopathies,** but in some of these disorders, the assumption that the pathogenesis is primarily myopathic is unjustified. Most congenital myopathies are nonprogressive conditions, but some patients show slow clinical deterioration accompanied by additional changes in their muscle biopsy specimen. Most of the diseases in the category of congenital myopathies are hereditary; others are sporadic. Although clinical features, including phenotype, may raise a strong suspicion of a congenital myopathy, the definitive diagnosis is determined by the histopathologic findings in the muscle biopsy specimen. In conditions for which the defective gene has been identified, the diagnosis may be established by the specific molecular genetic probe on lymphocytes. The morphologic and histochemical abnormalities differ considerably from those of the muscular dystrophies, spinal muscular atrophies, and neuropathies. Many are reminiscent of the embryologic development of muscle, thus suggesting possible defects in the genetic regulation of muscle development.

MYOGENIC REGULATORY GENES AND GENETIC LOCI OF INHERITED DISEASES OF MUSCLE (TABLE 607-1)

A family of four myogenic regulatory genes shares encoding transcription factors of "basic helix-loop-helix" (bHLH) proteins associated with common DNA nucleotide sequences. These genes direct the differentiation of striated muscle from any undifferentiated mesodermal cell. The earliest bHLH gene to program the differentiation of myoblasts is myogenic factor 5 *(Myf5)*. The second gene, *myogenin,* promotes fusion of myoblasts to form myotubes. *Herculin* (also known as *MYF6*) and *MYOD1* are the other two myogenic genes. *Myf5* cannot support myogenic differentiation without myogenin, *MyoD,* and *MYF6*. Each of these four genes can activate the expression of at least one other and, under certain circumstances, can autoactivate as well. The expression of *MYF5* and of *herculin* is transient in early ontogenesis but returns later in fetal life and persists into adult life. The human locus of the *MYOD1* gene is on chromosome 11, very near to the domain associated with embryonal rhabdomyosarcoma. The genes encoding *Myf5* and *herculin* are on chromosome 12 and that for *myogenin* is on chromosome 1. The myogenic genes are activated during muscle regeneration, recapitulating the developmental process; *MyoD* in particular is required for myogenic stem cell (satellite cell) activation in adult muscle. *PAX3* and *PAX7* genes also play an important role in myogenesis and interact with each of the four basic genes mentioned above. Another gene, *myostatin,* is a negative regulator of muscle development by preventing myocytes from differentiating. The precise role of the myogenic genes in developmental myopathies is not yet fully defined. Satellite cells in mature muscle that mediate regeneration have the same somitic origin as embryonic muscle progenitor cells.

607.1 • MYOTUBULAR MYOPATHY

The term **myotubular myopathy** implies a maturational arrest of fetal muscle during the myotubular stage of development at 8–15 wk of gestation. It is based on the morphologic appearance of myofibers: A row of central nuclei lies within a core of cytoplasm; contractile myofibrils form a cylinder around this core (Fig. 607-1). Many challenge this interpretation and use the more neutral term **centronuclear myopathy** when referring to this myopathy. This term is too nonspecific because internal nuclei occur in many unrelated myopathies.

PATHOGENESIS. Persistently high fetal concentrations of vimentin and desmin are demonstrated in myofibers of infants with myotubular myopathy, although not reproduced in cultured myocytes of patients. These intermediate filament proteins serve as cytoskeletal elements in fetal myotubes, attaching nuclei and mitochondria to the sarcolemmal membranes to preserve their central positions. As intracellular organization changes with maturation, the nuclei move to the periphery and mitochondria are redistributed between myofibrils. At the same time, vimentin and desmin diminish. Vimentin disappears altogether by term, and desmin remains only in trace amounts. Persistent fetal vimentin and desmin in muscle fibers may be one mechanism of "maturational arrest." A secondary myasthenia-like defect in neuromuscular transmission also occurs in some infants with myotubular myopathy. Myocytes of patients co-cultured with nerve in vitro develop normal innervation and mature normally, not reproducing the in vivo pathologic changes.

CLINICAL MANIFESTATIONS. Decreased fetal movements may occur in late gestation. Polyhydramnios is a common complica-

TABLE 607-1. Inheritance Patterns and Chromosomal or Mitochondrial Loci of Neuromuscular Diseases Affecting the Pediatric Age Group

DISEASE	TRANSMISSION	LOCUS
Duchenne/Becker muscular dystrophy	XR	Xp21.2
Emery-Dreifuss muscular dystrophy	XR	Xq28
Myotonic muscular dystrophy (Steinert)	AD	19q13
Facioscapulohumeral muscular dystrophy	AD	4q35
Limb-girdle muscular dystrophy	AD	5q
Limb-girdle muscular dystrophy	AR	15q
Congenital muscular dystrophy with merosin deficiency	AR	6q2
Congenital muscular dystrophy (Fukuyama)	AR	8q31–33
Myotubular myopathy	XR	Xq28
Myotubular myopathy	AR	Unknown
Nemaline rod myopathy (NEM1)	AD	1q21–q23
Nemaline rod myopathy (NEM2)	AR	2q21.2–q22
Nemaline rod myopathy (NEM3)	AD, AR	1q42.1
Nemaline rod myopathy (NEM4)	AD	9q13
Nemaline rod myopathy (NEM5)	AR	19q13
Congenital muscle fiber–type disproportion	AR, X-linked R	19p13.2, Xp23.12-p11.4, Xq13.1-q22.1; t(10; 17); sporadic
Central core disease	AD	19q13.1
Myotonia congenita (Thomsen)	AD	7q35
Myotonia congenita (Becker)	AR	7q35
Paramyotonia congenita	AD	17q13.1–13.3
Hyperkalemic periodic paralysis	AD	17q13.1–13.3
Hyperkalemic periodic paralysis	AD	1q31–q32
Glycogenosis II (Pompe; acid maltase deficiency)	AR	17q23
Glycogenosis V (McArdle; myophosphorylase deficiency)	AR	11q13
Glycogenosis VII (Tarui; phosphofructokinase deficiency)	AR	1cenq32
Glycogenosis IX (phosphoglycerate kinase deficiency)	XR	Xq13
Glycogenosis X (phosphoglycerate mutase deficiency)	AR	7p12–p13
Glycogenosis XI (lactate dehydrogenase deficiency)	AR	11p15.4
Muscle carnitine deficiency	AR	Unknown
Muscle carnitine palmityltransferase deficiency 2	AR	1p32
Spinal muscular atrophy (Werdnig-Hoffmann; Kugelberg-Welander)	AR	5q11–q13
Familial dysautonomia (Riley-Day)	AR	9q31–33
Hereditary motor-sensory neuropathy (Charcot-Marie-Tooth; Dejerine-Sottas)	AD	17p11.2
Hereditary motor-sensory neuropathy (axonal type)	AD	1p35–p36
Hereditary motor-sensory neuropathy (Charcot-Marie-Tooth-X)	XR	Xq13.1
Mitochondrial myopathy (Kearns-Sayre)	Maternal; sporadic	Single large mtDNA deletion
Mitochondrial myopathy (MERRF)	Maternal	tRNA point mutation at position 8344
Mitochondrial myopathy (MELAS)	Maternal	tRNA point mutation at positions 3243 and 3271

AD, autosomal dominant; AR, autosomal recessive; MELAS, mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes; MERRF, mitochondrial encephalomyopathy with ragged-red fibers; mtDNA, mitochondrial deoxyribonucleic acid; tRNA, transfer ribonucleic acid; XR, X-linked recessive.

tion because of pharyngeal weakness of the fetus and inability to swallow amniotic fluid. At birth, affected infants have a thin muscle mass involving axial, limb girdle, and distal muscles; severe generalized hypotonia; and diffuse weakness. Respiratory efforts may be ineffective, requiring ventilatory support. Gavage feeding may be required because of weakness of the muscles of sucking and deglutition. The testes are often undescended. Facial muscles may be weak, but infants do not have the characteristic facies of myotonic dystrophy. Ptosis may be a prominent feature. Ophthalmoplegia is observed in a few cases. The palate may be high. The tongue is thin, but fasciculations are not seen. Tendon stretch reflexes are weak or absent. Myotubular myopathy is not associated with cardiomyopathy; mature cardiac muscle fibers normally have central nuclei. Congenital anomalies of the central nervous system or of other systems are not associated.

Older children and adults may develop centronuclear myopathy with variable weakness. The relation of this disorder to the severe neonatal disease is uncertain.

LABORATORY FINDINGS. Serum levels of creatine kinase (CK) are normal. Electromyography (EMG) does not show evidence of denervation; results are usually normal or show minimal nonspecific myopathic features in early infancy. Nerve conduction velocity may be slow but is usually normal. The electrocardiogram (ECG) appears normal. Chest radiographs show no cardiomegaly; the ribs may be thin.

DIAGNOSIS. The muscle biopsy findings are diagnostic at birth, even in premature infants. More than 90% of muscle fibers are small and have centrally placed, large vesicular nuclei in a single row. Spaces between nuclei are filled with sarcoplasm containing mitochondria. Histochemical stains for oxidative enzymatic activity and glycogen reveal a central distribution as in fetal myotubes. The cylinder of myofibrils shows mature histochemical differentiation with adenosine triphosphatase stains. The connective tissue of muscle, spindles, blood vessels, intramuscular nerves, and motor end plates are mature. Ultrastructural features in neonatal myotubular myopathy, other than those that define the disease, are also mature. Vimentin and desmin show strong immunoreactivity in muscle fibers in myotubular myopathy and no demonstrable activity in normal term neonatal muscle. The molecular genetic marker in blood is available and is useful not only for confirming the diagnosis but also for early prenatal diagnosis.

GENETICS. X-linked recessive inheritance is the most frequent trait in this disease affecting boys. The mothers of affected infants are clinically asymptomatic, but their muscle biopsy specimen shows minor alterations. Genetic linkage on the X chromosome has been localized to the Xq28 site, a locus different from the Xp21 gene of Duchenne and Becker muscular dystrophies. A deletion in the responsible *MTM1* gene has been identified. It encodes a protein called myotubularin. This gene belongs to a

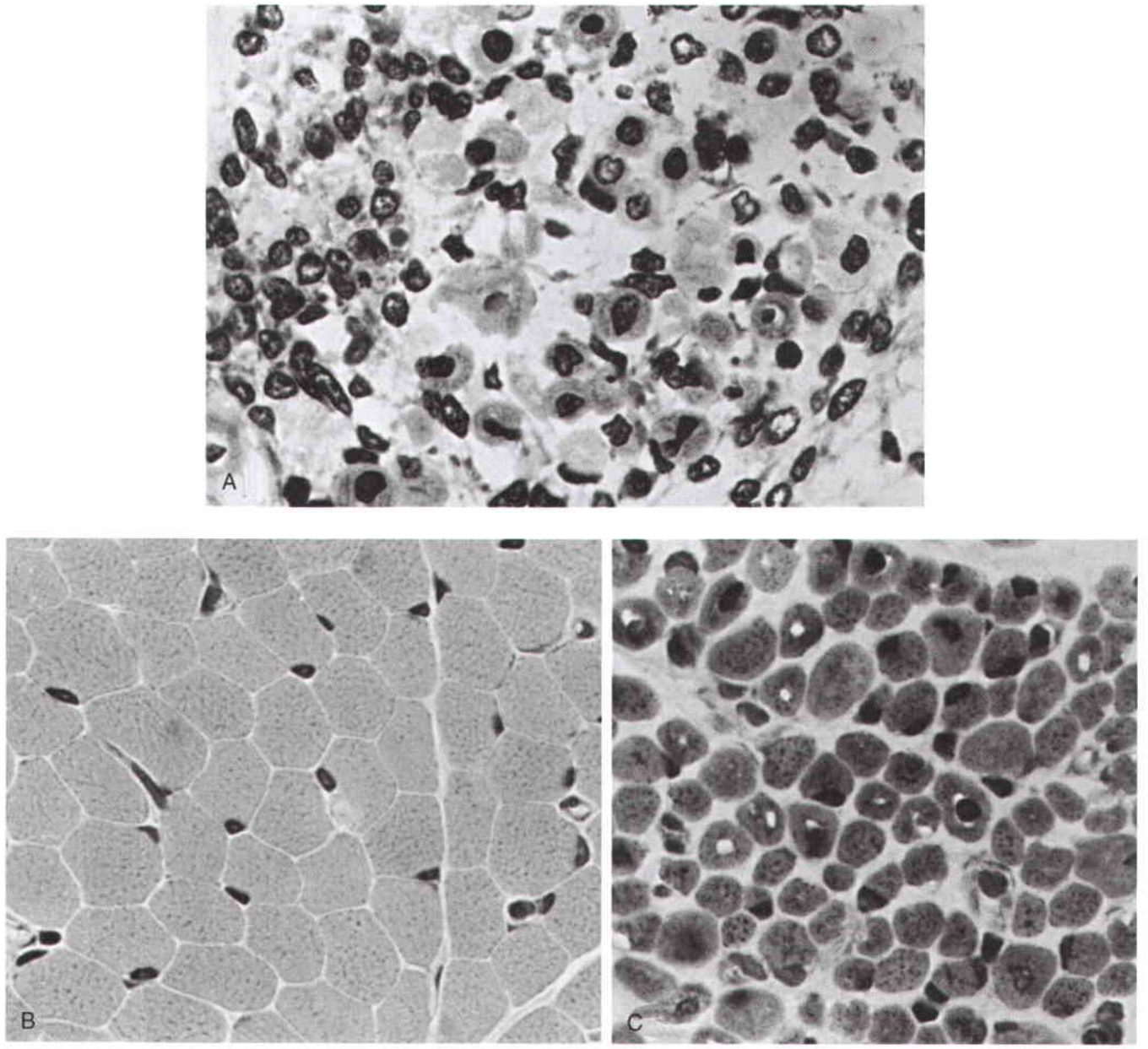

Figure 607-1. *A*, Cross section of muscle from a 14 wk old human fetus; *B*, normal full-term neonate; and *C*, term neonate with X-linked recessive myotubular myopathy. Myofibers have large central nuclei in the fetus and in myotubular myopathy, and nuclei are at the periphery of the muscle fiber in the term neonate as in the adult (hematoxylin and eosin, ×500).

family of similar genes encoding enzymatically active and inactive forms of phosphatidylinositol-3-phosphatases that form dimers. The pathogenesis is in the regulation of enzymatic activity and binding to other proteins induced by dimer interactions. Although only a single gene is involved, 5 distinct point mutations of the *MTM1* gene out of 242 known mutations account for only 27% of cases; many different alleles may produce the same clinical disease. Other, rarer, centronuclear myopathies also are known, some being autosomal dominant or recessive and affecting both sexes and others being sporadic and of unknown genetics. The recessive forms are sometimes divided into an early-onset form with or without ophthalmoplegia and a late-onset form without ophthalmoplegia. Autosomal dominant forms are usually mild and may not present clinically until adult life as diffuse, slowly progressive weakness and generalized muscular pseudohypertrophy.

TREATMENT. Only supportive and palliative treatment is available.

PROGNOSIS. About 75% of severely affected neonates die within the first few weeks or months of life. Survivors do not experience a progressive course but have major physical handicaps, rarely walk, and remain severely hypotonic.

607.2 • Congenital Muscle Fiber–Type Disproportion (CMFTD)

This condition occurs as an isolated congenital myopathy but also develops in association with various unrelated disorders that include nemaline rod disease, Krabbe disease (globoid cell

leukodystrophy) early in the course before expression of the neuropathy, cerebellar hypoplasia and certain other brain malformations, fetal alcohol syndrome, some glycogenoses, multiple sulfatase deficiency, Lowe syndrome, rigid spine myopathy, and some infantile cases of myotonic muscular dystrophy.

PATHOGENESIS. The association of CMFTD with cerebellar hypoplasia suggests that the pathogenesis may be an abnormal suprasegmental influence on the developing motor unit during the stage of histochemical differentiation of muscle between 20 and 28 wk of gestation. Muscle fiber types and growth are determined by innervation and are mutable even in adults. Although CMFTD does not actually correspond with any normal stage of development, it appears to be an embryologic disturbance of fiber type differentiation and growth.

CLINICAL MANIFESTATIONS. As an isolated condition not associated with other diseases, CMFTD is a nonprogressive disorder present at birth. Patients have generalized hypotonia and weakness, but the weakness is usually not severe and respiratory distress and dysphagia are rare. Contractures are present at birth in 25% of patients. Poor head control and developmental delay for gross motor skills are common in infancy. Walking is usually delayed until 18–24 mo but is eventually achieved. Because of the hypotonia, subluxation of the hips may occur. Muscle bulk is reduced. The muscle wasting and hypotonia are proportionately greater than the weakness, and the child may be stronger than expected during examination. Cardiomyopathy is a rare complication.

The facies of children with CMFTD often raise suspicion, especially if the child is referred for assessment of developmental delay and hypotonia. The head is dolichocephalic, and facial weakness is present. The palate is usually high arched. Thin muscles of the trunk and extremities give a thin, wasted appearance. The phenotype is very similar to that of nemaline myopathy, that also includes CMFTD as part of the pathological picture. Patients do not complain of myalgias. The clinical course is nonprogressive.

LABORATORY FINDINGS. Serum CK, ECG, EMG, and nerve conduction velocity results are normal in simple CMFTD. If other diseases are associated, laboratory investigation of those conditions discloses the specific features.

DIAGNOSIS. CMFTD is diagnosed by muscle biopsy that shows disproportion in both size and relative ratios of histochemical fiber types: Type I fibers are uniformly small, and type II fibers are hypertrophic; type I fibers are more numerous than type II fibers. Degeneration of myofibers and other primary myopathic features are absent. The biopsy is diagnostic at birth.

GENETICS. Many cases of simple CMFTD are sporadic, although autosomal recessive inheritance is well documented in some families and an autosomal dominant trait is suspected in others. The genetic basis is heterogeneous in hereditary forms; a mutation in the insulin receptor gene at 19p13.2 is reported. Translocation t(10;17) was seen in one family. X-linked transmission with linkage to Xp23.12-p11.4 and Xq13.1-q22.1 also is described. In 3 unrelated families with CMFTD, a heterozygous missense mutation of the skeletal muscle α-actin gene (ACTA1) was demonstrated, but this genetic defect probably represents a minority. In CMFTD associated with cerebellar hypoplasia, the genetic effect is on cerebellar development and the muscular expression is secondary.

TREATMENT. No drug therapy is available. Physiotherapy may be helpful for some patients in strengthening muscles that do not receive sufficient exercise in daily activities. Mild congenital contractures often respond well to gentle range of motion exercises and rarely require plaster casting or surgery.

607.3 • Nemaline Rod Myopathy

Nemaline rods (derived from the Greek *nema,* meaning "thread") are rod-shaped, inclusion-like abnormal structures within muscle fibers. They are difficult to demonstrate histologically with conventional hematoxylin-eosin stain but are easily seen with special stains. They are not foreign inclusion bodies but rather consist of excessive Z-band material with a similar ultrastructure (Fig. 607-2). Chemically, the rods are composed of actin, α-actinin, tropomyosin-3, and the protein nebulin. Nemaline rod formation may be an unusual reaction of muscle fibers to injury because these rod structures have rarely been found in other diseases. They are most abundant in the congenital myopathy known as nemaline rod disease. Most rods are within the myofibrils (cytoplasmic), but intranuclear rods are occasionally demonstrated by electron microscopy.

CLINICAL MANIFESTATIONS. Neonatal, infantile, and juvenile forms of the disease are known. The neonatal form is severe and usually fatal because of respiratory failure since birth. In the infantile form, generalized hypotonia and weakness, which can include bulbar-innervated and respiratory muscles, and a very thin muscle mass are characteristic (Fig. 607-3). The head is dolichocephalic, and the palate high arched or even cleft. Muscles of the jaw may be too weak to hold it closed (Fig. 607-4). Decreased fetal movements are reported by the mother, and neonates suffer from hypoxia and dysphagia; arthrogryposis may be present. Infants with severe neonatal and infantile nemaline myopathy have facies and phenotype that are nearly indistinguishable from that of neonatal myotonic dystrophy, but their mothers have normal facies. The juvenile form is the mildest and is not associated with respiratory failure, but the phenotype, including facial involvement, is similar.

LABORATORY FINDINGS. Serum CK level is normal or mildly elevated. The muscle biopsy is diagnostic. In addition to the characteristic nemaline rods, it also shows CMFTD or at least fiber type I predominance. In some patients, uniform type I fibers are seen with few or no type II fibers. Focal myofibrillar degeneration and an increase in lysosomal enzymes have been found in a few severe cases associated with progressive symptoms. Intranu-

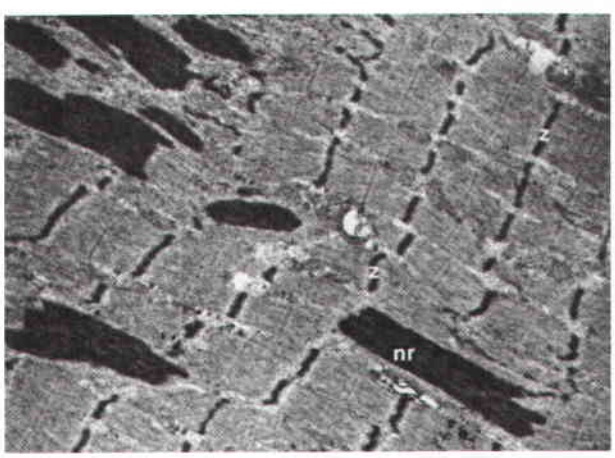

Figure 607-2. Electron micrograph of the muscle from a patient shown in Figure 607-4. Nemaline rods (nr) are seen within many myofibrils. They are identical in composition to the normal Z bands (z) (×6,000).

Figure 607-3. Back of a 13 yr old girl with juvenile form of nemaline rod disease. The paraspinal muscles are very thin, and winging of the scapulae is evident. The muscle mass of the extremities is also greatly reduced both proximally and distally.

clear nemaline rods correlate with the most severe clinical manifestations. They are demonstrated by electron microscopy.

GENETICS. Autosomal dominant and autosomal recessive forms of nemaline rod disease occur, and an X-linked dominant form in girls also may occur. Five genes are associated with this condition. One autosomal dominant nemaline rod myopathy (NEM1) has been mapped to the 1q21-23 locus; the responsible *TPM3* gene produces defective a-tropomyosin. Another genetic mutation (NEM2) at the 2q21.2-q22 locus produces *nebulin*, a large molecule also needed for Z-band integrity, and is transmitted as an autosomal recessive trait. NEM3 is due to a -actin defect and both autosomal dominant and recessive varieties occur at the same 1q42.1 locus. NEM4 is an autosomal dominantly inherited defect of ß-tropomyosin at 9q13. The α- and β-tropomyosin defects are rare and account for only 3% of patients with nemaline myopathy. NEM5 is an autosomal recessive troponin-T defect at 19q13, but has been found only in the Amish population.

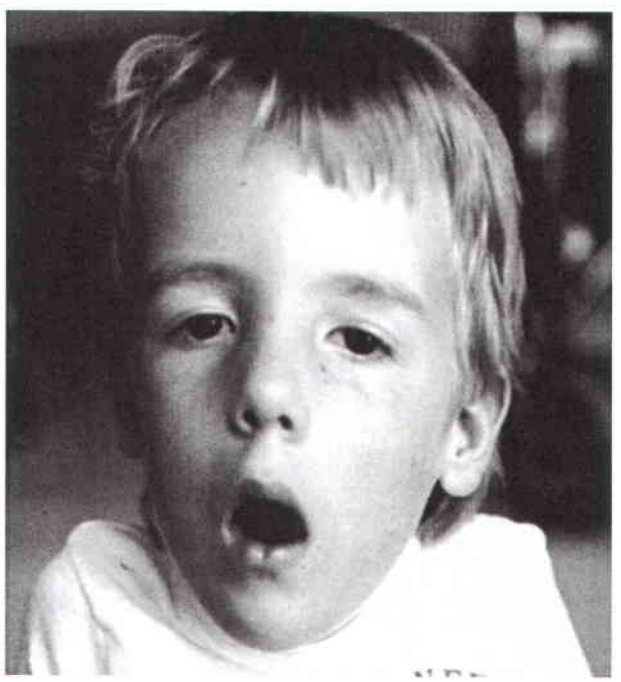

Figure 607-4. Infantile form of nemaline rod disease in a 6 yr old boy. Facial weakness and generalized muscle wasting are severe. The head is dolichocephalic. The mouth is usually open because the masseters are too weak to lift the mandible against gravity for more than a few seconds.

TREATMENT AND PROGNOSIS. Therapy is supportive. Survivors are confined to an electric wheelchair and are usually unable to overcome gravity. Both proximal and distal muscles are involved. Gastrostomy may be needed for chronic dysphagia. In the juvenile form, patients are ambulatory and are able to perform most tasks of daily living. Weakness is not usually progressive, but some patients have more difficulty over time or enter a phase of progressive weakness. Cardiomyopathy is an uncommon complication. Pneumonia occurs frequently.

607.4 • Central Core Disease and Minicore Myopathy

This disease is transmitted as either an autosomal dominant or recessive trait, both caused by the same abnormal gene at the 19q13.1 locus. The gene programs the ryanodine receptor *(RYR1),* a tetramere receptor to a nonvoltage-gated calcium channel in the sarcoplasmic reticulum. Mutations in this gene are also the cause of malignant hyperthermia. Infantile hypotonia, proximal weakness, muscle wasting, and involvement of facial muscles and neck flexors are the typical features in both the dominant and recessive forms. Contractures of the knees, hips, and other joints are common, and kyphoscoliosis and pes cavus frequently develop, even without much axial or distal muscle weakness. There is a high incidence of cardiac abnormalities. The course is nonprogressive, except for the contractures.

The disease is characterized pathologically by central cores within muscle fibers in which only amorphous, granular cytoplasm is found with an absence of myofibrils and organelles. Histochemical stains show a lack of enzymatic activities of all types within these cores. The serum CK value is normal in central core disease except during crises of malignant hyperthermia (see Chapter 610.2).

Central core disease is consistently associated with malignant hyperthermia, which may precede the diagnosis of central core disease. All patients should have special precautions with pretreatment by dantrolene before an anesthetic agent is administered. Salbutamol treatment in a few children with central core disease has demonstrated improved strength and forced vital capacity over a 6-mo period; this observation requires further documentation.

Variants of central cores, called *minicores* and *multicores,* are described in some families, but minicore myopathy is a different genetic disease. Cases with a similar mutation in the RYR1 gene are reported, but others have a defective selenoprotein-N *(SEPN1)* gene, the latter also implicated in rigid spine myopathy. Children with this disorder are hypotonic in early infancy and have a benign course but often develop progressive kyphoscoliosis or a rigid spine in adolescence. In one variant, external ophthalmoplegia also is present. Rare cases of minicore myopathy also show hypertrophic cardiomyopathy.

607.5 • Myofibrillar Myopathies

Most myofibrillar myopathies are not symptomatic in childhood, but occasionally older children and adolescents may show early symptoms of nonspecific proximal and distal weakness. An infantile form also occurs and may cause mild neonatal hypotonia and weakness with disproportionately severe dysphagia and respiratory insufficiency, at times leading to early death. It is nonprogressive, however, and some patients show improvement in later infancy and early childhood, acquiring the ability to swallow by 3 yr of age. Cardiomyopathy may be a complication in a minority. The diagnosis is by muscle biopsy: some sarcomeres of myofibers have disorganization or dissolution of myofibrils, adjacent to other areas of normal sarcomeres within the same fiber. These zones are associated with streaming of the Z bands and focally increased desmin intermediate filaments, myotilin, and α-B-crystallin. Immunocytochemical and ultrastructural study of the muscle biopsy tissue is required. Mutation in the desmin gene is implicated as the etiology. An associated mitochondrial defect is detected in some patients.

607.6 • Brain Malformations and Muscle Development

Infants with **cerebellar hypoplasia** are hypotonic and developmentally delayed, especially in gross motor skills. Muscle biopsy is sometimes performed to exclude a congenital myopathy. A biopsy specimen may show delayed maturation of muscle, fiber-type predominance, or CMFTD. Other malformations of the brain may also be associated with abnormal histochemical patterns, but supratentorial lesions are less likely than brainstem or cerebellar lesions to alter muscle development. Abnormal descending impulses along bulbospinal pathways probably alter discharge patterns of lower motor neurons that determine the histochemical differentiation of muscle at 20–28 wk of gestation. The corticospinal tract does not participate because it is not yet functional during this period of fetal life. In several congenital muscular dystrophies, including the Walker-Warburg syndrome, Fukuyama disease, and muscle-eye-brain disease of Santavuori, major cerebral malformations are present, such as pachygyria and lissencephaly.

607.7 • Amyoplasia

Congenital absence of individual muscles is common and is often asymmetric. A common aplasia is the *palmaris longus muscle* of the ventral forearm, which is absent in 30% of normal subjects and is fully compensated by other flexors of the wrist. Unilateral absence of a *sternocleidomastoid muscle* is one cause of congenital torticollis. Absence of one *pectoralis major muscle* is part of the Poland anomalad.

When innervation does not develop, such as in the lower limbs in severe cases of *myelomeningocele,* muscles may fail to develop. In *sacral agenesis,* the abnormal somites that fail to form bony vertebrae may also fail to form muscles from the same defective mesodermal plate, a disorder of induction resulting in segmental amyoplasia. Skeletal muscles of the extremities fail to differentiate from embryonic myomeres if the long bones do not form. Absence of 1 long bone, such as the radius, is associated with variable aplasia or hypoplasia of associated muscles, such as the *carpi flexor radialis.* End-stage neurogenic atrophy of muscle is sometimes called **amyoplasia,** but this use is semantically incorrect.

Generalized amyoplasia usually results in fetal death, and live-born neonates rarely survive. A mutation in 1 of the myogenic genes is the suspected etiology because of genetic knockout studies in mice, but it has not been proven in humans.

607.8 • Muscular Dysgenesis (Proteus Syndrome Myopathy)

The **Proteus syndrome** is a disturbance of cellular growth involving ectodermal and mesodermal tissues. The cause is unknown, but it is not a mendelian trait. It presents as asymmetric overgrowth of the extremities, verrucous cutaneous lesions, angiomas of various types, thickening of bones, hemimegalencephaly, and excessive growth of muscles without weakness. Histologically, the muscle is a unique *muscular dysgenesis.* Abnormal zones are adjacent to zones of normal muscle formation and do not follow anatomic boundaries. The disorder may be due to abnormal paracrine growth factors.

607.9 • Benign Congenital Hypotonia

Benign congenital hypotonia is not a disease but is a descriptive term for infants or children with nonprogressive hypotonia of unknown origin. The hypotonia is not usually associated with weakness or developmental delay, although some children acquire gross motor skills more slowly than normal. Tendon stretch reflexes are normal or hypoactive. There are no cranial nerve abnormalities, and intelligence is normal.

The **diagnosis** is one of exclusion after results of laboratory studies, including muscle biopsy and imaging of the brain with special attention to the cerebellum, are normal (Table 606-2). No known molecular genetic basis for this syndrome has been identified.

The **prognosis** is generally good; no specific therapy is required. Contractures do not develop. Hypotonia persists into adult life. The disorder is not always as "benign" as its name implies because a common complication is recurrent dislocation of joints, especially the shoulders. Excessive motility of the spine may result in stretch injury, compression, or vascular compromise of nerve roots or of the spinal cord. These are particular hazards for patients who perform gymnastics or who become circus performers because of agility of joints without weakness or pain.

607.10 • Arthrogryposis

Arthrogryposis multiplex congenita is not a disease but is a descriptive term that signifies numerous congenital contractures (see Chapter 681).

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Chapter 608 ■ Muscular Dystrophies

The term **dystrophy** means abnormal growth, derived from the Greek *trophe,* meaning "nourishment." A muscular dystrophy is distinguished from all other neuromuscular diseases by four obligatory criteria: It is a primary myopathy; it has a genetic basis; the course is progressive; degeneration and death of muscle fibers occur at some stage in the disease. This definition excludes neurogenic diseases such as spinal muscular atrophy, nonhereditary myopathies such as dermatomyositis, nonprogressive and non-necrotizing congenital myopathies such as congenital muscle fiber–type disproportion (CMFTD), and nonprogressive inherited metabolic myopathies. Some metabolic myopathies may fulfill the definition of a progressive muscular dystrophy but are not traditionally classified as dystrophies (muscle carnitine deficiency). All muscular dystrophies may eventually be reclassified as metabolic myopathies once the biochemical defects are better defined.

Muscular dystrophies are a group of unrelated diseases, each transmitted by a different genetic trait and each differing in its clinical course and expression. Some are severe diseases at birth that lead to early death; others follow very slow progressive courses over many decades, may be compatible with normal longevity, or may not even become symptomatic until late adult life. Some categories of dystrophies, such as limb-girdle muscular dystrophy, are not homogeneous diseases but rather syndromes encompassing several distinct myopathies. Relationships between the various muscular dystrophies are resolved by molecular genetics rather than by similarities or differences in clinical and histopathologic features.

608.1 • Duchenne and Becker Muscular Dystrophies

Duchenne muscular dystrophy is the most common hereditary neuromuscular disease affecting all races and ethnic groups. Its characteristic clinical features are progressive weakness, intellectual impairment, hypertrophy of the calves, and proliferation of connective tissue in muscle. The incidence is 1 : 3,600 liveborn infant boys. This disease is inherited as an X-linked recessive trait. The abnormal gene is at the Xp21 locus and is one of the largest genes. **Becker muscular dystrophy** is the same fundamental disease as Duchenne dystrophy, with a genetic defect at the same locus, but clinically it follows a milder and more protracted course.

CLINICAL MANIFESTATIONS. Infant boys are only rarely symptomatic at birth or in early infancy, although some are mildly hypotonic. Early gross motor skills, such as rolling over, sitting, and standing, are usually achieved at the appropriate ages or may be mildly delayed. Poor head control in infancy may be the 1st sign of weakness. Distinctive facies are not a feature because facial muscle weakness is a late event. Walking is often accomplished at the normal age of about 12 mo, but hip girdle weakness may be seen in subtle form as early as the 2nd yr. Toddlers may assume a lordotic posture when standing to compensate for gluteal weakness. An early Gowers sign is often evident by age 3 yr and is fully expressed by age 5 or 6 yr (see Fig. 591-2). A Trendelenburg gait, or hip waddle, appears at this time.

The length of time that a patient remains ambulatory varies greatly. Some patients are confined to a wheelchair by 7 yr of age; most patients continue to walk with increasing difficulty until age 10 yr without orthopedic intervention. With orthotic bracing, physiotherapy, and sometimes minor surgery (Achilles tendon lengthening), most are able to walk until age 12 yr. Ambulation is important not only for postponing the psychological depression that accompanies the loss of an aspect of personal independence but also because scoliosis usually does not become a major complication as long as a patient remains ambulatory, even for as little as 1 hr per day; scoliosis often becomes rapidly progressive after confinement to a wheelchair.

The relentless progression of **weakness** continues into the 2nd decade. The function of distal muscles is usually relatively well enough preserved, allowing the child to continue to use eating utensils, a pencil, and a computer keyboard. Respiratory muscle involvement is expressed as a weak and ineffective cough, frequent pulmonary infections, and decreasing respiratory reserve. Pharyngeal weakness may lead to episodes of aspiration, nasal regurgitation of liquids, and an airy or nasal voice quality. The function of the extraocular muscles remains well preserved. Incontinence due to anal and urethral sphincter weakness is an uncommon and very late event.

Contractures most often involve the ankles, knees, hips, and elbows. **Scoliosis** is common. The thoracic deformity further compromises pulmonary capacity and compresses the heart. Scoliosis usually progresses more rapidly after the child becomes nonambulatory and may be uncomfortable or painful. Enlargement of the calves (pseudohypertrophy) and wasting of thigh muscles are classic features. The enlargement is caused by hypertrophy of some muscle fibers, infiltration of muscle by fat, and proliferation of collagen. After the calves, the next most common site of muscular hypertrophy is the tongue, followed by muscles of the forearm. Fasciculations of the tongue do not occur. The voluntary sphincter muscles rarely become involved.

Unless ankle contractures are severe, ankle deep tendon reflexes remain well preserved until terminal stages. The knee deep tendon reflexes may be present until about 6 yr of age but are less brisk than the ankle jerks and are eventually lost. In the upper extremities, the brachioradialis reflex is usually stronger than the biceps or triceps brachii reflexes.

Cardiomyopathy, including persistent tachycardia and myocardiac failure, is seen in 50–80% of patients with this disease. The severity of cardiac involvement does not necessarily correlate with the degree of skeletal muscle weakness. Some patients die early of severe cardiomyopathy while still ambulatory; others in terminal stages of the disease have well-compensated cardiac function. Smooth muscle dysfunction, particularly of the gastrointestinal tract, is a minor, but often overlooked, feature.

Intellectual impairment occurs in all patients, although only 20–30% have an IQ <70. The majority has learning disabilities that still allow them to function in a regular classroom, particularly with remedial help. A few patients are profoundly mentally retarded, but there is no correlation with the severity of the myopathy. Epilepsy is slightly more common than in the general pediatric population. Dystrophin is expressed in brain and retina, as well as in striated and cardiac muscle, though the level, is lower in brain than in muscle. This distribution may explain some of the CNS manifestations. Abnormalities in cortical architecture and of dendritic arborization may be detected neuropathologically; cerebral atrophy is demonstrated by MRI late in the clinical course. The degenerative changes and fibrosis of muscle constitute a painless process. Myalgias and muscle spasms do not occur. Calcinosis of muscle is rare.

Death occurs usually at about 18–20 yr of age. The causes of death are respiratory failure in sleep, intractable heart failure, pneumonia, or occasionally aspiration and airway obstruction.

In **Becker muscular dystrophy,** boys remain ambulatory until late adolescence or early adult life. Calf pseudohypertrophy, cardiomyopathy, and elevated serum levels of creatine kinase (CK) are similar to those of patients with Duchenne dystrophy. Learning disabilities are less frequent. The onset of weakness is later in Becker than in Duchenne dystrophy. Death often occurs in the mid to late 20s; fewer than half of patients are still alive by age 40 yr; these survivors are severely disabled.

LABORATORY FINDINGS. The serum CK level is consistently greatly elevated in Duchenne muscular dystrophy, even in presymptomatic stages, including at birth. The usual serum concentration is 15,000–35,000 IU/L (normal <160 IU/L). A normal serum CK level is incompatible with the diagnosis of Duchenne dystrophy, although in terminal stages of the disease, the serum CK value may be considerably lower than it was a few years earlier because there is less muscle to degenerate. Other lysosomal enzymes present in muscle, such as aldolase and aspartate aminotransferase, are also increased but are less specific.

Cardiac assessment by echocardiography, electrocardiography (ECG), and radiography of the chest is essential and should be repeated periodically. After the diagnosis is established, patients should be referred to a pediatric cardiologist for long-term cardiac care.

Electromyography (EMG) shows characteristic myopathic features but is not specific for Duchenne muscular dystrophy. No evidence of denervation is found. Motor and sensory nerve conduction velocities are normal.

DIAGNOSIS. Blood polymerase chain reaction (PCR) for the dystrophin gene mutation is the primary test, if the clinical features and serum CK are consistent with the diagnosis. If the blood PCR is diagnostic, muscle biopsy may be deferred, but if it is normal and clinical suspicion is high, the more specific dystrophin immunocytochemistry performed on muscle biopsy sections detects the ⅓ of cases that do not show a PCR abnormality. Immunohistochemical staining of frozen sections of muscle biopsy tissue detects differences between the rod domain, the carboxyl-terminus (that attaches to the sarcolemma), and the amino-terminus (that attaches to the actin myofilaments) of the large dystrophin molecule, and may be prognostic of the clinical course as Duchenne or Becker disease. More severe weakness occurs with truncation of the dystrophin molecule at the carboxyl- than at the amino-terminus. Confirmation of the diagnosis by either blood PCR or muscle biopsy should be done in every case. Dystroglycans and other sarcolemmal regional proteins, such as merosin and sarcoglycans, also can be measured because they may be secondarily decreased.

The **muscle biopsy** is diagnostic and shows characteristic changes (Figs. 608-1 and 608-2). Myopathic changes include endomysial connective tissue proliferation, scattered degenerating and regenerating myofibers, foci of mononuclear inflammatory cell infiltrates as a reaction to muscle fiber necrosis, mild architectural changes in still functional muscle fibers, and many dense fibers. These hypercontracted fibers probably result from segmental necrosis at another level, allowing calcium to enter the site of breakdown of the sarcolemmal membrane and trigger a contraction of the whole length of the muscle fiber. Calcifications within myofibers are correlated with secondary β-dystroglycan deficiency.

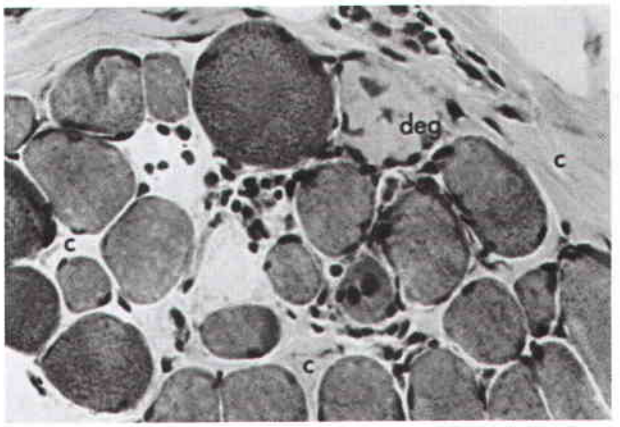

Figure 608-1. Muscle biopsy of a 4 yr old boy with Duchenne muscular dystrophy. Both atrophic and hypertrophic muscle fibers are seen, and some fibers are degenerating (deg). Connective tissue (c) between muscle fibers is increased (hematoxylin and eosin, ×400).

The decision about whether muscle biopsy should be performed to establish the diagnosis sometimes presents problems. If there is a family history of the disease, particularly in the case of an involved brother whose diagnosis has been confirmed, a patient with typical clinical features of Duchenne muscular dystrophy and high concentrations of serum CK probably does not need to undergo biopsy. The result of the PCR may also influence whether to perform a muscle biopsy. A first case in a family, even if the clinical features are typical, should have the diagnosis confirmed to ensure that another myopathy is not masquerading as Duchenne dystrophy. The most common muscles sampled are the vastus lateralis (quadriceps femoris) and the gastrocnemius.

GENETIC ETIOLOGY AND PATHOGENESIS. Despite the X-linked recessive inheritance in Duchenne muscular dystrophy, about 30% of patients are new mutations, and the mother is not a carrier. The female carrier state usually shows no muscle weakness or any clinical expression of the disease, but affected girls are occasionally encountered, usually having much milder weakness than boys. These symptomatic girls are explained by the Lyon hypothesis in which the normal X chromosome becomes inactivated and the one with the gene deletion is active (see Chapter 80). The full clinical picture of Duchenne dystrophy has occurred in several girls with Turner syndrome in whom the single X chromosome must have had the Xp21 gene deletion.

The asymptomatic carrier state of Duchenne dystrophy is associated with elevated serum CK values in 80% of cases. The level of increase is usually in the magnitude of hundreds or a few thousand but does not have the extreme values noted in affected males. Prepubertal girls who are carriers of the dystrophy also have increased serum CK values, with highest levels at 8–12 yr of age. Approximately 20% of carriers have normal serum CK values. If the mother of an affected boy has normal CK levels, it is unlikely that her daughter can be identified as a carrier by measuring CK. Muscle biopsy of suspected female carriers may detect

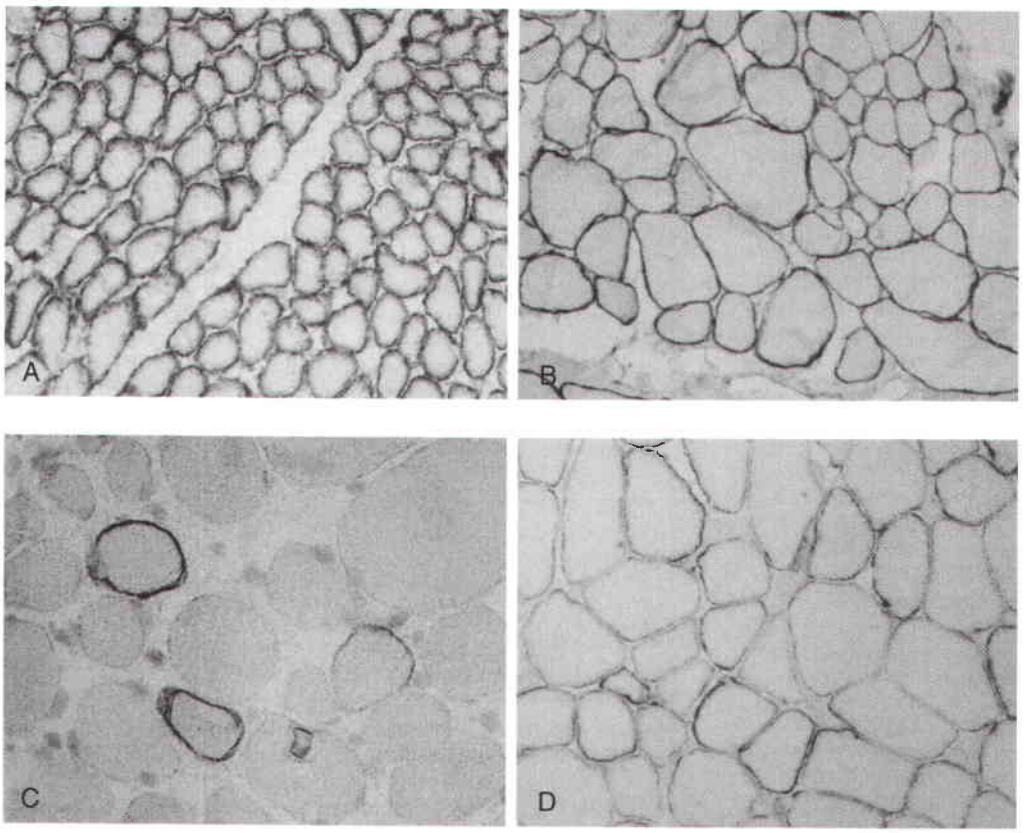

Figure 608-2. Dystrophin is demonstrated by immunohistochemical reactivity in the muscle biopsies of a normal term male neonate *(A)*, a 10 yr old boy with limb-girdle muscular dystrophy *(B)*, a 6 yr old boy with Duchenne muscular dystrophy *(C)*, and a 10 yr old boy with Becker muscular dystrophy *(D)*. In the normal condition and also in non–X-linked muscular dystrophies in which dystrophin is not affected, the sacrolemmal membrane of every fiber is strongly stained, including atrophic and hypertrophic fibers. In Duchenne dystrophy, most myofibers express no detectable dystrophin, but a few scattered fibers known as "revertant fibers" show near-normal immunoreactivity. In Becker muscular dystrophy, the abnormal dystrophin molecule is expressed as thin, pale-staining of the sarcolemma in which reactivity varies not only between myofibers but also along the circumference of individual fibers (×250).

an additional 10% in whom serum CK is not elevated; a specific genetic diagnosis using PCR on peripheral blood is definitive. Some female carriers may suffer cardiomyopathy without weakness of striated muscles.

A 427-kd cytoskeletal protein known as *dystrophin* is encoded by the gene at the Xp21.2 locus. This subsarcolemmal protein attaches to the sarcolemmal membrane overlying the A and M bands of the myofibrils and consists of 4 distinct regions or domains: the amino-terminus contains 250 amino acids and is related to the *N*-actin binding site of α-actinin; the second domain is the largest, with 2,800 amino acids, and contains many repeats, giving it a characteristic rod shape; a third cysteine-rich domain is related to the carboxyl terminus of α-actinin; and the final carboxyl-terminal domain of 400 amino acids is unique to dystrophin and to a dystrophin-related protein encoded by chromosome 6.

The molecular defects in the dystrophinopathies vary: intragenic deletions, duplications, or point mutations of nucleotides. About 65% of patients have deletions, and only 7% exhibit duplications. The site or size of the intragenic abnormality does not always correlate well with the phenotypic severity; in both Duchenne and Becker forms the mutations are mainly near the middle of the gene, involving deletions of exons 46-51. Phenotypic or clinical variations are explained by the alteration of the translational reading frame of mRNA, which results in unstable, truncated dystrophin molecules and severe, classic Duchenne dystrophy; mutations that preserve the reading frame still permit translation of coding sequences further downstream on the gene and produce a semifunctional dystrophin, expressed clinically as Becker muscular dystrophy. An even milder form of adult onset, formerly known as **quadriceps myopathy,** is also caused by an abnormal dystrophin molecule. The clinical spectrum of the dystrophinopathies not only includes the classic Duchenne and Becker forms but ranges from a severe neonatal muscular dystrophy to asymptomatic children with persistent elevation of serum CK levels >1,000 IU/L.

Analysis of the dystrophin protein requires a muscle biopsy and is demonstrated by Western blot analysis or in tissue sections by immunohistochemical methods using either fluorescence or light microscopy of antidystrophin antisera (see Fig. 608-2). In classic Duchenne dystrophy, levels of <3% of normal are found; in Becker muscular dystrophy, the molecular weight of dystrophin is reduced to 20–90% of normal in 80% of patients, but in 15% the dystrophin is of normal size but reduced in quantity, and 5% have an abnormally large protein caused by excessive duplications or repeats of codons. Selective immunoreactivity of different parts of the dystrophin molecule in sections of muscle biopsy material distinguishes the Duchenne and Becker forms (Fig. 608-3). The demonstration of deletions and duplications also can be made from blood samples by the more rapid PCR, which identifies as many as 98% of deletions by amplifying 18 exons but cannot detect duplications. The diagnosis can thus be confirmed at the molecular genetic level from either the muscle biopsy material or from peripheral blood, although as many as ⅓ of boys with Duchenne or Becker dystrophy have a false-normal blood PCR; all cases of dystrophinopathy are detected by muscle biopsy.

The same methods of DNA analysis from blood samples may be applied for carrier detection in female relatives at risk, such as sisters and cousins, and to determine whether the mother is a carrier or whether a new mutation occurred in the embryo. Prenatal diagnosis is possible as early as the 12th wk of gestation by sampling chorionic villi for DNA analysis by Southern blot or PCR and is confirmed in aborted fetuses with Duchenne dystrophy by immunohistochemistry for dystrophin in muscle.

TREATMENT There is neither a medical cure for this disease nor a method of slowing its progression. Much can be done to treat

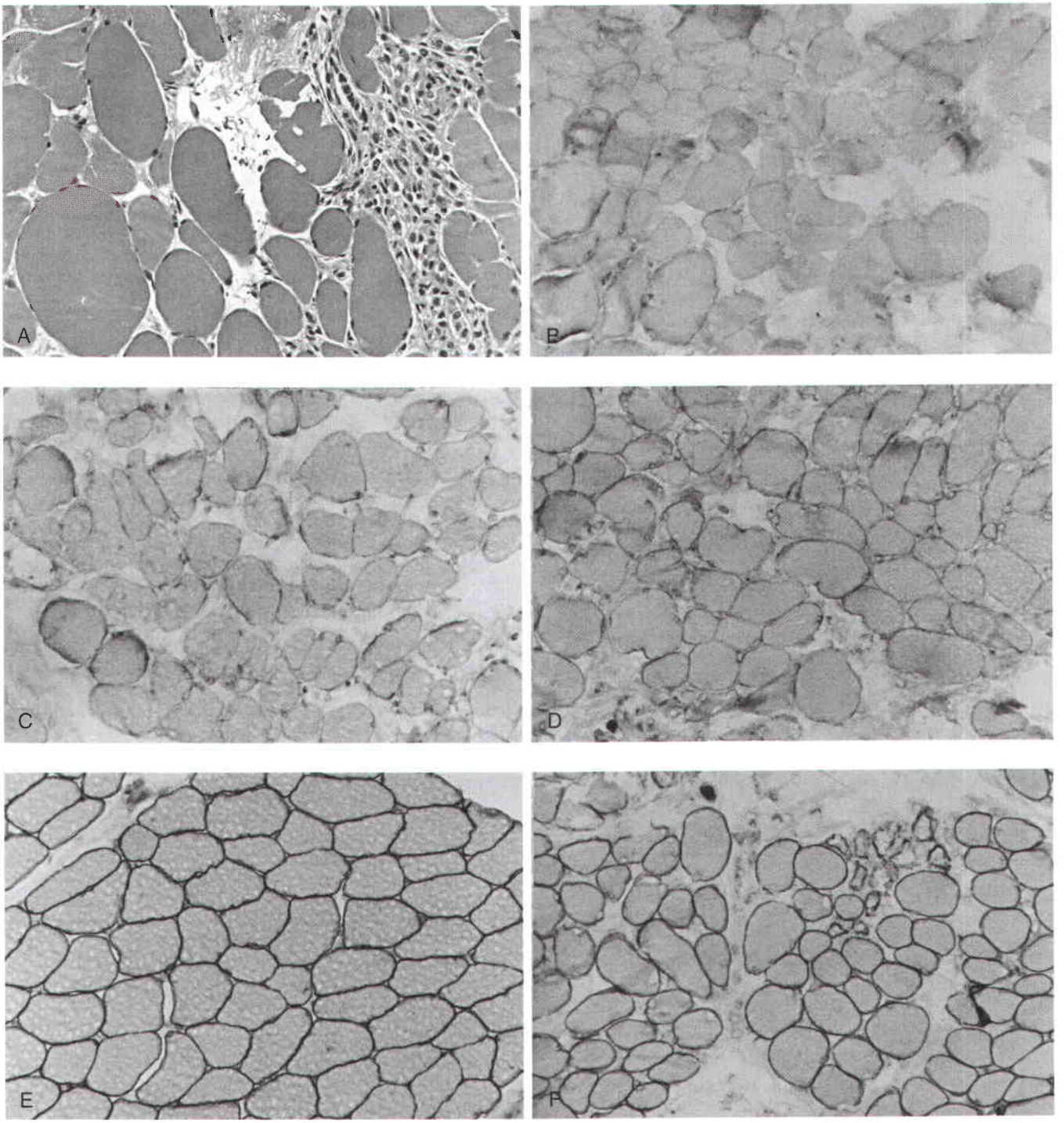

Figure 608-3. Quadriceps femoris muscle biopsy specimens from a 4 yr old boy with Becker muscular dystrophy. *A*, Myofibers vary greatly in size, with both atrophic and hypertrophic forms; at the right is a zone of degeneration and necrosis infiltrated by macrophages, similar to Duchenne muscular dystrophy (hematoxylin and eosin, ×250.) Immunoreactivity using antibodies against the dystrophin molecule in the rod domain *(B)*, carboxyl-terminus *(C)*, and amino-terminus *(D)* all show deficient but not totally absent dystrophin expression; most fibers of all sizes retain some dystrophin in parts of the sarcolemma but not around the entire circumference in cross section. Alternatively, the prominence of dystrophin is less, appearing weak, when compared with the simultaneously incubated normal control from another child of similar age *(E)*. *F*, Merosin expression is normal in this patient with Becker dystrophy, in both large and small myofibers, and is lacking only in frankly necrotic fibers. Compare with classic Duchenne muscular dystrophy illustrated in Figure 608-2C and with Figure 608-5.

complications and to improve the quality of life of affected children. **Cardiac decompensation** often responds initially well to digoxin. **Pulmonary infections** should be promptly treated. Patients should avoid contact with children who have obvious respiratory or other contagious illnesses. Immunizations for influenza virus and other routine vaccinations are indicated.

Preservation of a good **nutritional state** is important. Duchenne muscular dystrophy is not a vitamin deficiency disease, and excessive doses of vitamins should be avoided. Adequate calcium intake is important to minimize osteoporosis in boys confined to a wheelchair, and fluoride supplements may also be given, particularly if the local drinking water is not fluoridated. Because

sedentary children burn fewer calories than active children and because of depression as an additional factor, these children tend to eat excessively and gain weight. Obesity makes a patient with myopathy even less functional because part of the limited reserve muscle strength is dissipated in lifting the weight of excess subcutaneous adipose tissue. Dietary restrictions with supervision may be needed.

Physiotherapy delays but does not always prevent contractures. At times, contractures may actually be useful in functional rehabilitation. If contractures prevent extension of the elbow beyond 90 degrees and the muscles of the upper limb no longer are strong enough to overcome gravity, the elbow contractures are functionally beneficial in fixing an otherwise flail arm and in allowing the patient to eat and write. Surgical correction of the elbow contracture may be technically feasible, but the result may be deleterious. Physiotherapy contributes little to muscle strengthening because patients usually are already using their entire reserve for daily function, and exercise cannot further strengthen involved muscles. Excessive exercise may actually accelerate the process of muscle fiber degeneration.

Other treatment of human patients with Duchenne dystrophy involves the use of prednisone, prednisolone, deflazacort, or other steroids. Glucocorticoids decrease the rate of apoptosis or programmed cell death of myotubes during ontogenesis and may decelerate the myofiber necrosis in muscular dystrophy. Strength usually improves initially, but the long-term complications of chronic steroid therapy, including considerable weight gain and osteoporosis, may offset this advantage or even result in greater weakness than might have occurred in the natural course of the disease. Nevertheless, some cases of Duchenne dystrophy treated early with steroids appear to have an improved long-term prognosis as well as the short-term improvement and may help keep patients ambulatory for more years than expected if untreated. One protocol gives prednisone (0.75 mg/kg/day) for the first 10 days of each month to avoid chronic complications. Fluorinated steroids, such as dexamethasone or triamcinolone, should be avoided because they induce myopathy by altering the myotube abundance of ceramide.

608.2 • Emery-Dreifuss Muscular Dystrophy

Emery-Dreifuss muscular dystrophy, also known as **scapuloperoneal or scapulohumeral muscular dystrophy,** is a rare X-linked recessive dystrophy. The locus is on the long arm within the large Xq28 region that includes other mutations that cause myotubular myopathy, neonatal adrenoleukodystrophy, and the Bloch-Sulzberger type of incontinentia pigmenti; it is far from the gene for Duchenne muscular dystrophy on the short arm of the X chromosome. Another, rarer, form of Emery-Dreifuss dystrophy is transmitted as an autosomal dominant trait and is localized at 1q. This form may present quite late, in adolescence or early adult life, although the muscular and cardiac symptoms and signs are similar, and sudden death from ventricular fibrillation is a risk.

Clinical manifestations begin between 5 and 15 yr of age, but many patients survive to late adult life because of the slow progression of its course. Hypertrophy of muscles does not occur. Contractures of elbows and ankles develop early, and muscle becomes wasted in a scapulohumeroperoneal distribution. Facial weakness does not occur; this disease is thus distinguished clinically from autosomal dominant scapulohumeral and scapuloperoneal syndromes of neurogenic origin. Myotonia is absent. Intellectual function is normal. Cardiomyopathy is severe and is often the cause of death, more frequently from conduction defects and sudden ventricular fibrillation than from intractable myocardial failure. The serum CK value is only mildly elevated, further distinguishing this disease from other X-linked recessive muscular dystrophies.

Nonspecific myofiber necrosis and endomysial fibrosis are seen in the muscle biopsy. Many centronuclear fibers and selective histochemical type I muscle fiber atrophy may cause confusion with myotonic dystrophy. The defective gene in the X-linked form is called emerin and, unlike other dystrophies in which the defective gene is expressed at the sarcolemmal membrane, emerin is expressed at the inner nuclear membrane; this protein stabilizes the nuclear membrane against the mechanical stresses that occur during muscular contraction. Emerin may be demonstrated immunocytochemically in the muscle biopsy for definitive diagnosis. Emerin also may be tested as a genetic marker in blood. The defective protein in the autosomal dominant form is called lamin-A and lamin-C, proteins that constitute part of the nuclear lamina, a fibrous layer on the inner nuclear membrane. Several subtypes and different mutations are demonstrated.

Treatment should be supportive, with special attention to cardiac conduction defects, and may require medications or a pacemaker.

608.3 • Myotonic Muscular Dystrophy

Myotonic dystrophy (Steinert disease) is the second most common muscular dystrophy in North America, Europe, and Australia, having an incidence of 1 : 30,000 general population. It is inherited as an autosomal dominant trait. Classic myotonic dystrophy (DM1) is caused by a cytosine-thymine-guanine (CTG) trinucleotide expansion on chromosome 19q13.3 in the 3' untranslated region of DMPK, the gene that encodes a serine-threonine protein kinase. A second form (DM2) is associated with unstable CTG repeat expansion on chromosome 3q21 of an intron of the zinc finger 9 protein gene. Still a third, late form (DM3) is identified, at locus 15q21-q24.

Myotonic dystrophy is an example of a genetic defect causing dysfunction in multiple organ systems. Not only is striated muscle severely affected, but smooth muscle of the alimentary tract and uterus is also involved; cardiac function is altered; and patients have multiple and variable endocrinopathies, immunologic deficiencies, cataracts, dysmorphic facies, intellectual impairment, and other neurologic abnormalities.

CLINICAL MANIFESTATIONS. In the usual clinical course, **excluding the severe neonatal** form, infants may appear almost normal at birth, or facial wasting and hypotonia may already be early expressions of the disease. The facial appearance is characteristic, consisting of an inverted V-shaped upper lip, thin cheeks, and scalloped, concave temporalis muscles (Fig. 608-4). The head may be narrow, and the palate is high and arched because the weak temporal and pterygoid muscles in late fetal life do not exert sufficient lateral forces on the developing head and face.

Weakness is mild in the first few years. Progressive wasting of distal muscles becomes increasingly evident, particularly involving intrinsic muscles of the hands. The thenar and hypothenar eminences are flattened, and the atrophic dorsal interossei leave deep grooves between the fingers. The dorsal forearm muscles and anterior compartment muscles of the lower legs also become wasted. The tongue is thin and atrophic. Wasting of the sternocleidomastoids gives the neck a long, thin, cylindric contour. Proximal muscles also eventually undergo atrophy, and scapular winging appears. Difficulty with climbing stairs and Gowers sign are progressive. Tendon stretch reflexes are usually preserved.

The distal distribution of muscle wasting in myotonic dystrophy is an exception to the general rule of myopathies having proximal and neuropathies having distal distribution patterns. The muscular atrophy and weakness in myotonic dystrophy are slowly progressive throughout childhood and adolescence and continue into adulthood. It is rare for patients with myotonic dys-

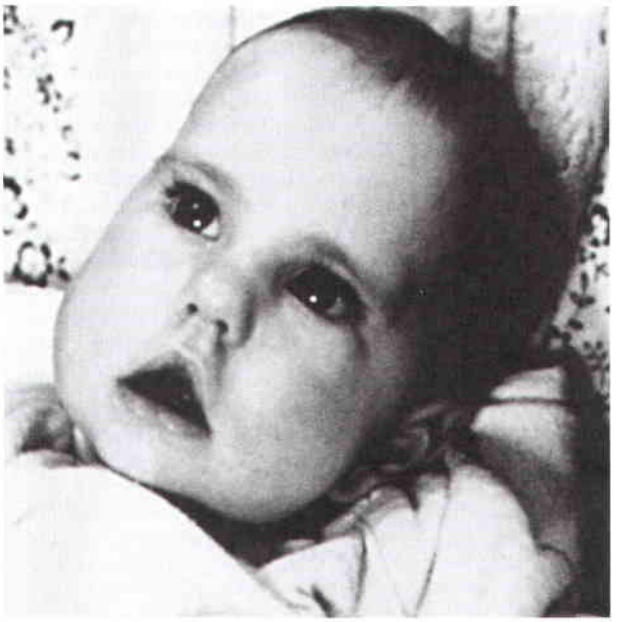

Figure 608-4. Facial weakness, inverted V-shaped upper lip, and loss of muscle mass in the temporal fossae are characteristic of myotonic muscular dystrophy, even in infancy, as seen in this 8 mo old girl.

trophy to lose the ability to walk even in late adult life, although splints or bracing may be required to stabilize the ankles.

Myotonia, a characteristic feature shared by few other myopathies, does not occur in infancy and is usually not clinically or even electromyographically evident until about age 5 yr. Exceptional patients develop it as early as age 3 yr. Myotonia is a very slow relaxation of muscle after contraction, regardless of whether that contraction was voluntary or was induced by a stretch reflex or electrical stimulation. During physical examination, myotonia may be demonstrated by asking the patient to make tight fists and then to quickly open the hands. It may be induced by striking the thenar eminence with a rubber percussion hammer, and it may be detected by watching the involuntary drawing of the thumb across the palm. Myotonia may also be demonstrated in the tongue by pressing the edge of a wooden tongue blade against its dorsal surface and by observing a deep furrow that disappears slowly. The severity of myotonia does not necessarily parallel the degree of weakness, and the weakest muscles often have only minimal myotonia. Myotonia is not a painful muscle spasm. Myalgias do not occur in myotonic dystrophy.

The **speech** of patients with myotonic dystrophy is often articulated poorly and is slurred because of the involvement of the muscles of the face, tongue, and pharynx. Difficulties with swallowing sometimes occur. Aspiration pneumonia is a risk in severely involved children. Incomplete external ophthalmoplegia may sometimes result from extraocular muscle weakness.

Smooth muscle involvement of the **gastrointestinal tract** results in slow gastric emptying, poor peristalsis, and constipation. Some patients have encopresis associated with anal sphincter weakness. Women with myotonic dystrophy may have ineffective or abnormal uterine contractions during labor and delivery.

Cardiac involvement is usually manifested as heart block in the Purkinje conduction system and arrhythmias rather than as cardiomyopathy, unlike most other muscular dystrophies.

Endocrine abnormalities involve many glands and appear at any time during the course of the disease so that re-evaluation of endocrine status must be done annually. Hypothyroidism is common; hyperthyroidism may occur rarely. Adrenocortical insufficiency may lead to an addisonian crisis even in infancy. Diabetes mellitus is common in patients with myotonic dystrophy; some children have a disorder of insulin release rather than defective insulin production. Onset of puberty may be precocious or, more often, delayed. Testicular atrophy and testosterone deficiency are common in adults and are responsible for a high incidence of male infertility. Ovarian atrophy is rare. Frontal baldness is also characteristic in males and often begins in adolescence.

Immunologic deficiencies are common in myotonic dystrophy. The plasma IgG level is often low.

Cataracts occur frequently in myotonic dystrophy. They may be congenital, or they may begin at any time during childhood or adult life. Early cataracts are detected only by slit-lamp examination; periodic examination by an ophthalmologist is recommended. Visual evoked potentials are often abnormal in children with myotonic dystrophy and are unrelated to cataracts. They are not usually accompanied by visual impairment.

About ½ of the patients with myotonic dystrophy are **intellectually impaired,** but severe mental retardation is unusual. The remainder is of average or occasionally above average intelligence. Epilepsy is not common. Cognitive impairment and mental retardation may be due to accumulations of mutant *DMPK* mRNA and aberrant alternative splicing in cerebral cortical neurons.

A severe **congenital form** of myotonic dystrophy appears in a minority of involved infants born to mothers with myotonic dystrophy. All patients with this severe congenital disease to date have had the DM1 form. Clubfoot deformities alone or more extensive congenital contractures of many joints may involve all extremities and even the cervical spine. Generalized hypotonia and weakness are present at birth. Facial wasting is prominent. Infants may require gavage feeding or ventilator support for respiratory muscle weakness or apnea. Those requiring ventilation for <30 days often survive while those with prolonged ventilation have an infant mortality of 25%. Children ventilated for <30 days have better motor, language, and daily activity skills than those requiring prolonged ventilation. One or both leaves of the diaphragm may be nonfunctional. The abdomen becomes distended with gas in the stomach and intestine because of poor peristalsis from smooth muscle weakness. The distention further compromises respiration. Inability to empty the rectum may compound the problem.

LABORATORY FINDINGS. The classic myotonic electromyogram is not found in infancy but may appear in toddlers or during the early school years. The levels of serum CK and other serum enzymes from muscle may be normal or only mildly elevated in the hundreds (never the thousands).

ECG should be performed annually in early childhood. Ultrasound imaging of the abdomen may be indicated in affected infants to determine diaphragmatic function. Radiographs of the chest and abdomen and contrast studies of gastrointestinal motility may be needed.

Endocrine assessment should be undertaken to determine thyroid and adrenal cortical function and to verify carbohydrate metabolism (glucose tolerance test). Immunoglobulins should be examined, and, if needed, more extensive immunologic studies should be performed.

DIAGNOSIS. The primary diagnostic test is a DNA analysis of blood to demonstrate the abnormal expansion of the CTG repeat. Prenatal diagnosis also is feasible. The muscle biopsy specimen in older children shows many muscle fibers with central nuclei and selective atrophy of histochemical type I fibers, but degenerating fibers are usually few and widely scattered, and there is little or no fibrosis of muscle. Intrafusal fibers of muscle spindles are also abnormal. In young children with the common form of the disease, the biopsy specimen may even appear normal or may at

least not show myofiber necroses, which is a striking contrast with Duchenne muscular dystrophy. In the severe neonatal form of myotonic dystrophy, the muscle biopsy reveals maturational arrest in various stages of development in some and congenital muscle fiber-type disproportion in others. It is likely that the sarcolemmal membrane of muscle fibers not only has abnormal properties of electrical polarization but is also incapable of responding to trophic influences of the motor neuron. Muscle biopsy is not usually required for diagnosis, which in typical cases can be based on the clinical manifestations.

GENETICS. The genetic defect in myotonic muscular dystrophy is on chromosome 19 at the 19q13 locus. It consists of an expansion of the *DM* gene that encodes a serine-threonine kinase *(DMPK)*, with numerous repeats of the CTG codon. Expansions range from 50 to >2,000, with the normal alleles of this gene ranging in size from 5 to 37; the larger the expansion is, the more severe the clinical expression, with the largest expansions seen in the severe neonatal form. Rarely, the disease is associated with no detectable repeats, perhaps a spontaneous correction of a previous expansion but a phenomenon still incompletely understood. Another myotonic dystrophy (PROMM) is a clinical entity linked to at least 2 different chromosomal loci than classic myotonic dystrophy but 1 that shares a common unique pathogenesis in being mediated by a mutant mRNA. Defects in RNA splicing explain the insulin resistance in myotonic dystrophies as well as the myotonia.

Both clinical and genetic expression may vary between siblings or between an affected parent and child. In the severe neonatal form of the disease, the mother is the transmitting parent in 94% of cases, a fact not explained by increased male infertility alone. Genetic analysis reveals that such infants usually have many more repeats of the CTG codon than do patients with the more classic form of the disease. Myotonic dystrophy often exhibits a pattern of **anticipation** in which each successive generation has a tendency to be more severely involved than the previous generation.

TREATMENT. There is no specific medical treatment, but the cardiac, endocrine, gastrointestinal, and ocular complications can often be treated. Physiotherapy and orthopedic treatment of contractures in the neonatal form of the disease may be beneficial.

Myotonia may be diminished, and function may be restored by drugs that raise the depolarization threshold of muscle membranes, such as mexiletine, phenytoin, carbamazepine, procainamide, and quinidine sulfate. These drugs also have cardiotropic effects; thus, cardiac evaluation is important before prescribing them. Phenytoin and carbamazepine are used in doses similar to their use as anticonvulsants (see Chapter 593.4); serum concentrations of 40–80 µmol/L for phenytoin and 35–50 µmol/L for carbamazepine should be maintained. If a patient's disability is caused mainly by weakness rather than by myotonia, these drugs will be of no value.

OTHER MYOTONIC SYNDROMES. Most patients with myotonia have myotonic dystrophy. Myotonia is not specific for this disease and occurs in several rarer conditions.

Myotonic chondrodystrophy (Schwartz-Jampel disease) is a rare congenital disease characterized by generalized muscle hypertrophy and weakness. Dysmorphic phenotypical features and the radiographic appearance of long bones are reminiscent of Morquio disease (see Chapter 88), but abnormal mucopolysaccharides are not found. Dwarfism, joint abnormalities, and blepharophimosis are present. Several patients have been the products of consanguinity, suggesting autosomal recessive inheritance. The muscle protein perlecan, encoded by the *SJS1* gene, a large heparan sulfate proteoglycan of basement membranes and cartilage, is defective in some cases of Schwartz-Jampel disease and explains both the muscular hyperexcitability and the chondrodysplasia.

EMG reveals continuous electrical activity in muscle fibers closely resembling or identical to myotonia. Muscle biopsy reveals nonspecific myopathic features, which are minimal in some cases and pronounced in others. The sarcotubular system is dilated.

Myotonia congenita (Thomsen disease) is a channelopathy (Table 608-1) and is characterized by weakness and generalized muscular hypertrophy so that affected children resemble bodybuilders. Myotonia is prominent and may develop at age 2–3 yr, earlier than in myotonic dystrophy. The disease is clinically stable and is apparently not progressive for many years. Muscle biopsy specimens show minimal pathologic changes, and the EMG demonstrates myotonia. Various families are described as showing either autosomal dominant (Thomsen disease) or reces-

TABLE 608-1. Channelopathies and Related Disorders

DISORDER	PATTERN OF CLINICAL FEATURES	INHERITANCE	CHROMOSOME	GENE
Chloride channelopathies				
Myotonia congenita				
Thomsen's disease	Myotonia	Autosomal dominant	7q35	*CLC1*
Becker's disease	Myotonia and weakness	Autosomal recessive	7q35	*CLC1*
Sodium channelopathies				
Paramyotonia congenita	Paramyotonia	Autosomal dominant	17q13.1–13.3	*SCNA4A*
Hyperkalemic periodic paralysis	Periodic paralysis with myotonia and paramyotonia	Autosomal dominant	17q13.1–13.3	*CNA4A*
Hypokalemic periodic paralysis	Periodic paralysis	Autosomal dominant	17q13.1–13.3	*SCNA4A*
Potassium-aggravated myotonias				
Myotonia fluctuans	Myotonia	Autosomal dominant	17q13.1–13.3	*SCNA4A*
Myotonia permanens	Myotonia	Autosomal dominant	17q13.1–13.3	*SCNA4A*
Acetaxolamide-responsive myotonia	Myotonia	Autosomal dominant	17q13.1–13.3	*SCNA4A*
Calcium channelopathies				
Hypokalemic periodic paralysis	Periodic paralysis	Autosomal dominant	1q31–32	Dihydropyridine receptor
Schwartz-Jampel syndrome (chondrodystrophic myotonia)	Myotonia; dysmorphic	Autosomal recessive	1q34.1–36.1	Perlecan
Rippling muscle disease	Muscle mounding/stiffness	Autosomal dominant	1q41	Caveolin-3
Anderson's syndrome	Periodic paralysis, cardiac arrhythmia, distinctive facies	Autosomal dominant	17q23	KCNJ2-Kir2.1
Brody's disease	Delayed relaxation, no EMG myotonia	Autosomal recessive	16p12	Calcium ATPase
Malignant hyperthermia	Anesthetic-induced delayed relaxation	Autosomal dominant	19q13.1	Ryanodine receptor

ATPase, adenosine triphosphatase; EMG, electromyogram.
From Goldman L, Ausiello D: *Cecil Textbook of Medicine*, 22nd ed. Philadelphia, WB Saunders, 2004, p. 2392.

sive (Becker disease, not to be confused with Becker/Duchenne muscular dystrophy) inheritance. Rarely, myotonic dystrophy and myotonia congenita coexist in the same family. Both the autosomal dominant and autosomal recessive forms of myotonia congenita have been mapped to the same 7q35 locus. This gene is important for the integrity of chloride channels of the sarcolemmal and T-tubular membranes.

Paramyotonia is a temperature-related myotonia that is aggravated by cold and alleviated by warm external temperatures. Patients have difficulty when swimming in cold water or if they are dressed inadequately in cold weather. *Paramyotonia congenita* (Eulenburg disease) is a defect in a gene at the 17q13.1-13.3 locus, the identical locus identified in hyperkalemic periodic paralysis. By contrast with myotonia congenita, paramyotonia is a disorder of the voltage-gated sodium channel due to a mutation in the α subunit. Myotonic dystrophy also is a sodium channelopathy (see Table 608-1).

In sodium channelopathies, exercise produces increasing myotonia, whereas in chloride channelopathies, exercise reduces the myotonia. This is easily tested during examination by asking patients to close the eyes forcefully and open them repeatedly; it becomes progressively more difficult in sodium channel disorders and progressively easier in chloride channel disorders.

608.4 • Limb-Girdle Muscular Dystrophies

This term encompasses a group of progressive hereditary myopathies that mainly affect muscles of the hip and shoulder girdles. Distal muscles also eventually become atrophic and weak. Hypertrophy of the calves and ankle contractures develop in some forms, causing potential confusion with Becker muscular dystrophy. Sixteen genetic forms of limb-girdle dystrophy are now described, each at a different chromosomal locus and expressing different protein defects. Some include diseases classified with other traditional groups, such as the lamin-A/C defects of the nuclear membrane (see Emery-Dreifuss muscular dystrophy, above), and some forms of congenital muscular dystrophy.

The initial **clinical manifestations** rarely appear before middle or late childhood or may be delayed until early adult life. Low back pain may be a presenting complaint because of the lordotic posture resulting from gluteal muscle weakness. Confinement to a wheelchair usually becomes obligatory at about 30 yr of age. The rate of progression varies from 1 pedigree to another but is uniform within a kindred. Although weakness of neck flexors and extensors is universal, facial, lingual, and other bulbar-innervated muscles are rarely involved. As weakness and muscle wasting progress, tendon stretch reflexes become diminished. Cardiac involvement is unusual. Intellectual function is generally normal. The clinical **differential diagnosis** of limb-girdle muscular dystrophy includes juvenile spinal muscular atrophy (Kugelberg-Welander disease), myasthenia gravis, and metabolic myopathies.

Most cases of limb-girdle muscular dystrophy are of autosomal recessive inheritance, but some families express an autosomal dominant trait. The latter often follows a benign course with little functional impairment.

The EMG and muscle biopsy show confirmatory evidence of muscular dystrophy, but none of the findings is specific enough to make the definitive **diagnosis** without additional clinical criteria. In some cases, adhalen, a dystrophin-related glycoprotein of the sarcolemma, is deficient; this specific defect may be demonstrated in the muscle biopsy by immunocytochemistry. Increased serum CK level is usual, but the magnitude of elevation varies among families. The ECG is usually unaltered.

In one autosomal dominant form of limb-girdle muscular dystrophy, a genetic defect has been localized to the long arm of chromosome 5. In the autosomal recessive disease, it is on the long arm of chromosome 15. A mutated dystrophin-associated protein in the sarcoglycan complex (sarcoglycanopathy) is responsible for some cases of autosomal recessive limb-girdle muscular dystrophy. Adhalen is α-sarcoglycan; other limb-girdle dystrophies due to deficiencies in β-, γ-, and δ-sarcoglycan also occur. In normal smooth muscle, α-sarcoglycan is replaced by ε-sarcoglycan and the others are the same.

Another group of limb-girdle dystrophies are caused by allelic mutations of the dysferlin *(DYSF)* gene, another gene expressing a protein essential to structural integrity of the sarcolemma, though not associated with the dystrophin-glycoprotein complex. *DYSF* interacts with caveolin-3 or calpain-3, and *DYSF* deficiency may be secondary to defects in these other gene products. Autosomal recessive (Miyoshi myopathy) and autosomal dominant traits are documented. Both are slowly progressive myopathies with onset in adolescence or young adult life and may affect distal as well as proximal muscles. Cardiomyopathy is rare. Chronically elevated serum CK in the thousands is found in dysferlinopathies. Ultrastructure shows a thickened basal lamina over defects in the sarcolemma and replacement of the sarcolemma by multiple layers of small vesicles. Regenerating myofibers outnumber degenerating myofibers. These disorders were formerly called *hyperCKemia* and *rippling muscle disease,* the latter sometimes confused with myotonia.

608.5 • Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy, also known as **Landouzy-Dejerine disease,** is probably not a single disease entity but a group of diseases with similar clinical manifestations. Autosomal dominance is the rule; genetic anticipation is often found within several generations of a family, the succeeding more severely involved at an earlier age than the preceding. The frequency is 1 : 20,000. The genetic mechanism in autosomal dominant facioscapulohumeral dystrophy involves integral deletions of a 3.3-kb tandem repeat (D4Z4) in the subtelomeric region at the 4q35 locus. A closely homologous 3.3-kb repeat array at the subtelomeric locus 10q26, with chromosomal translocation or sequence conversion between these two regions, possibly predisposes to the DNA rearrangement causing facioscapulohumeral dystrophy.

CLINICAL MANIFESTATIONS. Facioscapulohumeral dystrophy shows the earliest and most severe weakness in facial and shoulder girdle muscles. The facial weakness differs from that of myotonic dystrophy; rather than an inverted V-shaped upper lip, the mouth in facioscapulohumeral dystrophy is rounded and appears puckered because the upper and lower lips protrude. Inability to close the eyes completely in sleep is a common expression of upper facial weakness; some patients have extraocular muscle weakness, although ophthalmoplegia is rarely complete. Facioscapulohumeral dystrophy has been associated with Möbius syndrome on rare occasions. Pharyngeal and tongue weakness may be absent and is never as severe as the facial involvement. Hearing loss, which may be subclinical, and retinal vasculopathy (indistinguishable from Coats disease) are associated features, particularly in severe cases of facioscapulohumeral dystrophy with early childhood onset.

Scapular winging is prominent, often even in infants. Flattening or even concavity of the deltoid contour is seen, and the biceps and triceps brachii muscles are wasted and weak. Muscles of the hip girdles and thighs also eventually lose strength and undergo atrophy, and Gowers sign and a Trendelenburg gait appear. Contractures are rare. Finger and wrist weakness occasionally is the first symptom. Weakness of the anterior tibial and peroneal muscles may lead to footdrop; this complication usually occurs only in advanced cases with severe weakness. Lumbar lordosis

and kyphoscoliosis are common complications of axial muscle involvement. Calf pseudohypertrophy is not a feature.

Facioscapulohumeral muscular dystrophy may also be a mild disease causing minimal disability. Clinical manifestations may not be expressed in childhood and are delayed into middle adult life. Unlike most other muscular dystrophies, asymmetry of weakness is common.

LABORATORY FINDINGS. Serum levels of CK and other enzymes vary greatly, ranging from normal or near normal to elevations of several thousand. ECG should be performed, although the anticipated findings are usually normal. EMG reveals nonspecific myopathic muscle potentials. Diagnostic molecular testing in both individual cases and within families is indicated for prediction.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS. Muscle biopsy distinguishes more than one form of facioscapulohumeral dystrophy, consistent with clinical evidence that several distinct diseases are embraced by the term *FSH dystrophy.* Muscle biopsy and EMG also distinguish the primary myopathy from a neurogenic disease with a similar distribution of muscular involvement. The general histopathologic findings in the muscle biopsy material are extensive proliferation of connective tissue between muscle fibers, extreme variation in fiber size with many hypertrophic as well as atrophic myofibers, and scattered degenerating and regenerating fibers. An "inflammatory" type of facioscapulohumeral muscular dystrophy is also distinguished, characterized by extensive lymphocytic infiltrates within muscle fascicles. Despite the resemblance of this form to inflammatory myopathies, such as polymyositis, there is no evidence of autoimmune disease, and steroids and immunosuppressive drugs do not alter the clinical course. A precise histopathologic diagnosis has important therapeutic implications. Mononuclear cell "inflammation" in a muscle biopsy sample of infants younger than 2 yr is usually facioscapulohumeral dystrophy.

TREATMENT. Physiotherapy is of no value in regaining strength or in retarding progressive weakness or muscle wasting. Footdrop and scoliosis may be treated by orthopedic measures. Cosmetic improvement of the facial muscles of expression may be achieved by reconstructive surgery, which grafts a fascia lata to the zygomatic muscle and to the zygomatic head of the quadratus labiae superioris muscle.

608.6 • CONGENITAL MUSCULAR DYSTROPHY

The term congenital muscular dystrophy is misleading because all muscular dystrophies are genetically determined. It is used to encompass several distinct diseases with a common characteristic of severe involvement at birth but that ironically usually follow a benign clinical course. Autosomal recessive inheritance is the rule.

CLINICAL MANIFESTATIONS. Infants often have contractures or arthrogryposis at birth and are diffusely hypotonic. The muscle mass is thin in the trunk and extremities. Head control is poor. Facial muscles may be mildly involved, but ophthalmoplegia, pharyngeal weakness, and weak sucking are not common. A minority has severe dysphagia and requires gavage or gastrostomy. Tendon stretch reflexes may be hypoactive or absent. Arthrogryposis is common in all forms of congenital muscular dystrophy (see Chapter 607.9). Congenital contractures of the elbows have a high association with the Ullrich type of congenital muscular dystrophy, due to a defect in one or more of the three collagen VI genes, each at a different locus.

The Fukuyama type of congenital muscular dystrophy is the 2nd most common muscular dystrophy in Japan (after Duchenne dystrophy); it has also been reported in children of Dutch, German, Scandinavian, and Turkish ethnic backgrounds. In the Fukuyama variety, severe cardiomyopathy and malformations of the brain usually accompany the skeletal muscle involvement. Signs and symptoms related to these organs are prominent: cardiomegaly and heart failure, mental retardation, seizures, microcephaly, and failure to thrive. The genetic defect in Fukuyama congenital muscular dystrophy has been identified at the 8q31-33 locus in Japanese patients.

Neurologic disease may accompany forms of congenital muscular dystrophy other than Fukuyama disease. Mental and neurologic status are the most variable features; an apparently normal brain and normal intelligence do not preclude the diagnosis if other manifestations indicate this myopathy. The cerebral malformations that occur are not consistently of one type and vary from severe dysplasias (holoprosencephaly, lissencephaly) to milder conditions (agenesis of the corpus callosum, focal heterotopia of the cerebral cortex and subcortical white matter, cerebellar hypoplasia). Congenital muscular dystrophy is a consistent association with cerebral dysgenesis in the **Walker-Warburg syndrome** and **in muscle-eye-brain disease of Santavuori.** The neuropathologic findings are those of neuroblast migratory abnormalities in the cerebral cortex, cerebellum, and brainstem. Mutations in genes of O-mannosylation of a-dystroglycan, essential for neuroblast migration in the fetal brain, have been demonstrated: *POMT1* and *POMGnT1.* Another separate form of congenital muscular dystrophy is characterized by microcephaly and mental retardation.

LABORATORY FINDINGS. Serum CK level is usually moderately elevated from several hundred to many thousand IU/L; only marginal increases are sometimes found. EMG shows nonspecific myopathic features. Investigation of all forms of congenital muscular dystrophy should include cardiac assessment and an imaging study of the brain. Muscle biopsy is essential for the diagnosis.

DIAGNOSIS. Muscle biopsy is diagnostic in the neonatal period or thereafter. An extensive proliferation of endomysial collagen envelops individual muscle fibers even at birth, also causing them to be rounded in cross-sectional contour by acting as a rigid sleeve, especially during contraction. The perimysial connective tissue and fat are also increased, and the fascicular organization of the muscle may be disrupted by the fibrosis. Tissue cultures of intramuscular fibroblasts exhibit increased collagen synthesis, but the structure of the collagen is normal. Muscle fibers vary in diameter, and many show central nuclei, myofibrillar splitting, and other cytoarchitectural alterations. Scattered degenerating and regenerating fibers are seen. No inflammation or abnormal inclusions are found.

Immunocytochemical reactivity for merosin (α_2 chain of laminin) at the sarcolemmal region is absent in about 40% of cases and normally expressed in the others (Figs. 608-5 and 608-6). Merosin is a protein that binds the sarcolemmal membrane of the myofiber to the basal lamina or basement membrane. Its defect is a mutation of the *LAMA2* gene at the 6q22-q23 locus. Merosin also is expressed in brain and in Schwann cells. The presence or absence of merosin does not always correlate with the severity of the myopathy or predict its course, but cases with merosin deficiency tend to have more severe cerebral involvement and myopathy. Adhalen (α-dystroglycan) may be secondarily reduced in some cases. Collagen VI is selectively reduced or absent in Ullrich disease.

TREATMENT. Only supportive therapy is available.

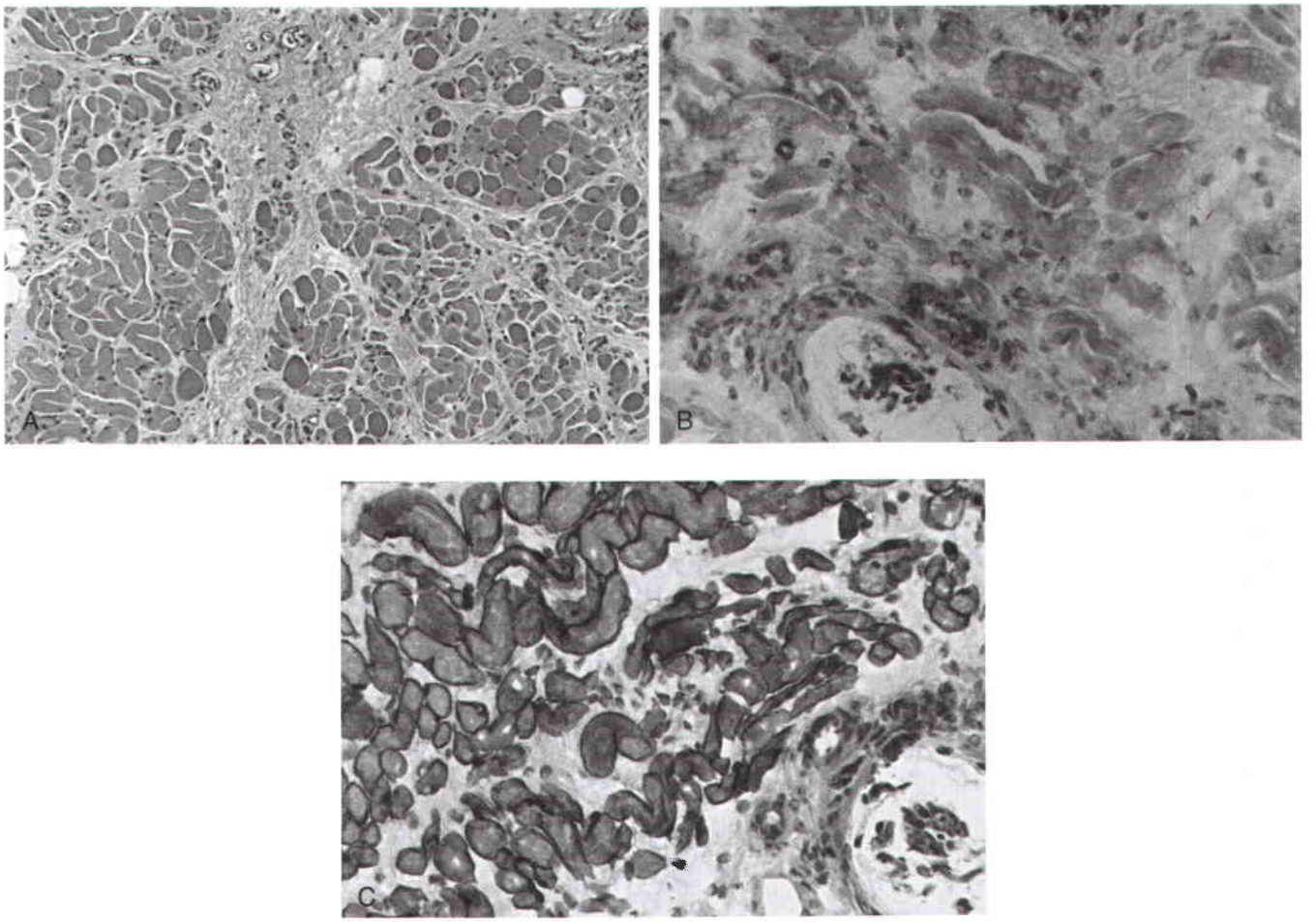

Figure 608-5. Quadriceps femoris muscle biopsy of a 6 mo old girl with congenital muscular dystrophy associated with merosin (α_2-laminin) deficiency. *A*, Histologically, the muscle is infiltrated by a great proliferation of collagenous connective tissue; myofibers vary in diameter, but necrotic fibers are rare. *B*, Immunocytochemical reactivity for merosin (α_2-laminin) is absent in all fibers, including the intrafusal myofibers of a muscle spindle seen at bottom. *C*, Dystrophin expression (rod domain) is normal. Compare with Figures 608-2, 608-3, and 608-6.

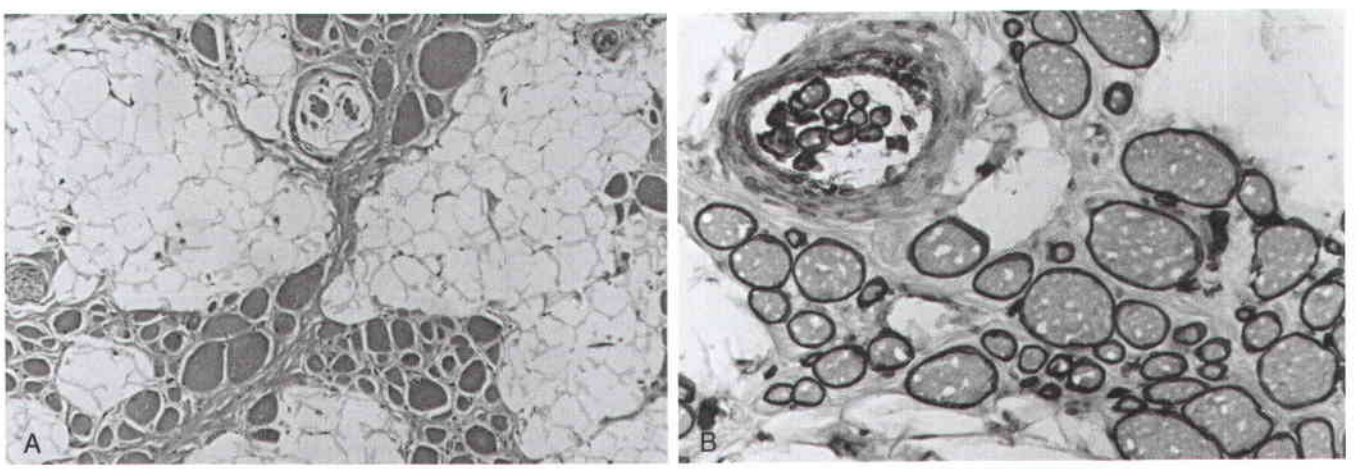

Figure 608-6. Quadriceps femoris muscle biopsy specimen of a 2 yr old girl with congenital muscular dystrophy. *A*, The fascicular architecture of the muscle is severely disrupted, and muscle is replaced by fat and connective tissue; the remaining small groups of myofibers of variable size are seen, including a muscle spindle at top. *B*, Merosin expression is normal in both extrafusal fibers of all sizes and in intrafusal spindle fibers. The severity of the myopathy does not relate to the presence or absence of merosin in congenital muscular dystrophy. Compare with Figure 608-5.

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Chapter 609 ■ Endocrine and Toxic Myopathies

THYROID MYOPATHIES (SEE ALSO PART XXV, SECTION 2.)

Thyrotoxicosis causes proximal weakness and wasting accompanied by myopathic electromyographic changes. Thyroxine binds to myofibrils and, if in excess, impairs contractile function. *Hyperthyroidism* may also induce myasthenia gravis and hypokalemic periodic paralysis.

Hypothyroidism, whether congenital or acquired, consistently produces hypotonia and a proximal distribution of weakness. Although muscle wasting is most characteristic, one form of cretinism, the Kocher-Debré-Sémélaigne syndrome, is characterized by generalized pseudohypertrophy of weak muscles. Infants may have a Herculean appearance reminiscent of myotonia congenita. The serum creatine kinase (CK) level is elevated in hypothyroid myopathy and returns to normal after thyroid replacement therapy.

Results of muscle biopsy in hypothyroidism reveal acute myopathic changes, including myofiber necrosis and sometimes central cores. In hyperthyroidism, the muscle biopsy specimen shows only mild, nonspecific myopathic changes without necrosis of myofibers.

Both the clinical and pathologic features of hyperthyroid myopathy and hypothyroid myopathy resolve after appropriate treatment of the thyroid disorder. Many of the systemic symptoms of hyperthyroidism, including myopathic weakness and ophthalmoparesis, improve with the administration of ß blockers.

Hyperparathyroidism (see Chapter 574). Most patients with primary hyperparathyroidism develop weakness, fatigability, fas-

TABLE 609-1. Toxic Myopathies

Inflammatory
Cimetidine
D-Penicillamine
Procainamide
L-Tryptoplan
L-Dopa

Noninflammatory Necrotizing or Vacuolar
Cholesterol-lowering agents
Chloroquine
Colchicine
Emetine
ε-Aminocaproic acid
Labetalol
Cyclosporine and tacrolimus
Isoretinoic acid (vitamin A analogue)
Vincristine
Alcohol

Rhabdomyolysis and Myoglobinuria
Cholesterol-lowering drugs
Alcohol
Heroin
Amphetamine
Toluene
Cocaine
ε-Aminocaproic acid
Pentazocine
Phencyclidine

Malignant Hyperthermia
Halothane
Ethylene
Diethyl ether
Methoxyflurane
Ethyl chloride
Trichloroethylene
Gallamine
Succinylcholine

Mitochondrial
Zidovudine

Myotonia
2,4-*d*-Chlorophenoxyacetic acid
Anthracene-9-carboxycyclic acid
Cholesterol-lowering drugs
Chloroquine
Cyclosporine

Myosin Loss
Nondepolarizing neuromuscular blocking agents
Intravenous glucocorticoids

From Goldman L, Ausiello D: *Cecil Textbook of Medicine,* 22nd ed, 2004, Saunders, Philadelphia, p. 2399.

ciculations, and muscle wasting that are reversible after removal of the parathyroid adenoma. The serum CK and muscle biopsy remain normal, but the electromyography may show nonspecific myopathic features. A minority of patients develop myotonia that could be confused with myotonic dystrophy.

STEROID-INDUCED MYOPATHY

Both natural Cushing disease and iatrogenic Cushing syndrome due to exogenous corticosteroid administration may cause painless, symmetrical, progressive proximal weakness, increased serum CK levels, and a myopathic electromyogram and muscle biopsy specimen (see Chapter 578). Myosin filaments may be selectively lost. The 9α-fluorinated steroids, such as dexamethasone, betamethasone, and triamcinolone, are the most likely to produce *steroid myopathy*. Dexamethasone alters the abundance of ceramides in myotubes in developing muscle. In patients with dermatomyositis or other myopathies treated with steroids, it is sometimes difficult to distinguish refractoriness of the disease from steroid-induced weakness, especially after long-term steroid administration. All patients who have been taking steroids for long periods develop reversible type II myofiber atrophy; this is a *steroid effect* but is not steroid myopathy unless it progresses to become a necrotizing myopathy. At greatest risk in the pediatric age group are children requiring long-term steroid therapy for asthma, rheumatoid arthritis, dermatomyositis, lupus, and other autoimmune or inflammatory diseases, and in the treatment of leukemia and other hematologic diseases. In addition to steroids, acute or chronic toxic myopathies may occur from other drugs (Table 609-1).

Hyperaldosteronism (Conn syndrome) is accompanied by episodic and reversible weakness similar to that of periodic paralysis. The proximal myopathy may become irreversible in chronic cases. Elevated CK levels and even myoglobinuria sometimes occur during acute attacks.

Chronic growth hormone excess (sometimes illicitly by adolescent athletes) or in acromegaly produces atrophy of some myofibers and hypertrophy of others, and scattered myofiber degeneration. Despite augmented protein synthesis induced by growth hormone, it impairs myofibrillar ATPase activity and reduces sarcolemmal excitability, with a result of diminished, rather than increased, strength to correspond to the larger muscle mass.

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Chapter 610 ■ Metabolic Myopathies

The differential diagnosis of metabolic myopathies is noted in Table 610-1.

610.1 • PERIODIC PARALYSES (POTASSIUM-RELATED)

Episodic, reversible weakness or paralysis known as **periodic paralysis** is associated with transient alterations in serum potassium levels, usually hypokalemia but occasionally hyperkalemia. All familial forms of periodic paralysis are caused by mutations in genes encoding voltage-gated ion channels in muscle: sodium, calcium, and potassium (Table 608-1). During attacks, myofibers are electrically inexcitable, although the contractile apparatus can respond normally to calcium. The disorder is inherited as an autosomal dominant trait. It is precipitated in some patients by a heavy carbohydrate meal, insulin, adrenaline including that induced by emotional stress, hyperaldosteronism or hyperthyroidism, administration of amphotericin B, or ingestion of licorice. The defective genes are at the 17q13.1-13.3 locus in **hyperkalemic periodic paralysis,** the same as in paramyotonia congenita, and at the 1q31-32 locus in **hypokalemic periodic paralysis.**

Attacks often begin in infancy and the disease is nearly always symptomatic by 10 yr of age, affecting both sexes equally. In childhood, periodic paralysis is an episodic event; patients are unable to move after awakening and gradually recover muscle strength during the next few minutes or hours. Muscles that remain active in sleep, such as the diaphragm and cardiac muscle, are not affected. Patients are normal between attacks, but in adult life the attacks become more frequent, and the disorder causes progressive myopathy with permanent weakness even between attacks. The usual frequency of attacks in childhood is once a week.

Alterations in serum potassium level occur only during acute episodes and are accompanied by T-wave changes in the electrocardiogram. Hypokalemia may be due to alterations in calcium gradients. The creatine kinase (CK) level may be mildly elevated at those times. Plasma phosphate levels often decrease during symptomatic periods. Muscle biopsy findings are often normal

TABLE 610-1. Metabolic and Mitochondrial Myopathies

GLYCOGEN METABOLISM DEFICIENCIES
Type II α-1,4 Glucosidase (acid maltase)
Type III Debranching
Type IV Branching
Type V Phosphorylase (McArdle disease)*
Type VII Phosphofructokinase (Tarui disease)*
Type VIII Phosphorylase B kinase*
Type IX Phosphoglycerate kinase*
Type X Phosphoglycerate mutase*
Type XI Lactate dehydrogenase*
LIPID METABOLISM DEFICIENCIES
Carnitine palmitoyl transferase*
Primary systemic/muscle carnitine deficiency
Secondary carnitine deficiency
β-Oxidation defects
Medications (valproic acid)
PURINE METABOLISM DEFICIENCIES
Myoadenylate deaminase deficiency*
MITOCHONDRIAL MYOPATHIES
Pyruvate dehydrogenase complex deficiencies (including Leigh syndrome)
Progressive external ophthalmoplegia
Autosomal dominant with multiple mitochondrial DNA deletions
Adenine nucleotide translocator 1
TWINKLE
Polymerase gamma
Kearns-Sayre syndrome
Mitochondrial encephalopathy with lactic acidosis and strokelike episodes
Myoclonic epilepsy and ragged red fibers
Mitochondrial neurogastrointestinal encephalomyopathy
Mitochondrial depletion syndrome
Leigh syndrome and neuropathy, ataxia, retinitis pigmentosa
Succinate dehydrogenase deficiency*

*Deficiency can produce exercise intolerance and myoglobinuria.
From Goldman L, Ausiello D. *Cecil Textbook of Medicine*, 22nd ed. Philadelphia, WB Saunders, 2004, p. 2392.

between attacks, but during an attack a vacuolar myopathy is demonstrated. Pathologic changes in the periodic paralyses are similar whether the disease is due to a sodium or potassium channel defect, suggesting that they may result from the recurrent paralytic state rather than the specific channelopathy. The vacuoles are dilated sarcoplasmic reticulum and invaginations of the extracellular space into the cytoplasm, and they may be filled with glycogen. Hypoglycemia does not occur.

TREATMENT. Paralytic attacks of hypokalemic periodic paralysis are best treated by the oral administration of potassium or even fruit juices that contains potassium. A low sodium intake and the administration of acetazolamide, 125–250 mg bid or tid in school-age children, often is effective in abolishing attacks or at least reducing their frequency and severity. Spironolactone, in a dose of 100–200 mg/day PO in school-aged children may be beneficial as well.

610.2 • MALIGNANT HYPERTHERMIA

(See also Chapters 76 and 607.4.)

This syndrome is usually inherited as an autosomal dominant trait. It occurs in all patients with central core disease but is not limited to that particular myopathy. The gene is at the 19q13.1 locus in both central core disease and malignant hyperthermia without this specific myopathy. At least 15 separate mutations in this gene are associated with malignant hyperthermia. The gene programs the ryanodine receptor, a tetrameric calcium release channel in the sarcoplasmic reticulum, in apposition to the voltage-gated calcium channel of the transverse tubule. It occurs rarely in Duchenne and other muscular dystrophies, in various other myopathies, and in an isolated syndrome not associated with other muscle disease. Affected children sometimes have peculiar facies. All ages are affected, including premature infants whose mothers underwent general anesthesia for cesarean section.

Acute episodes are precipitated by exposure to general anesthetics and occasionally to local anesthetic drugs. Patients suddenly develop extreme fever, rigidity of muscles, and metabolic and respiratory acidosis; the serum CK level rises to as high as 35,000 IU/L. Myoglobinuria may result in tubular necrosis and acute renal failure.

The muscle biopsy specimen obtained during an episode of malignant hyperthermia or shortly afterward shows widely scattered necrosis of muscle fibers known as rhabdomyolysis. Between attacks, the muscle biopsy specimen is normal unless there is an underlying chronic myopathy.

It is important to recognize patients at risk of malignant hyperthermia because the attacks may be prevented by administering dantrolene sodium before an anesthetic is given. Identification of patients at risk, such as siblings, is done by the caffeine contracture test: A portion of fresh muscle biopsy tissue in a saline bath is attached to a strain gauge and exposed to caffeine and other drugs; an abnormal spasm is diagnostic. The syndrome receptor also may be demonstrated by immunochemistry in frozen sections of the muscle biopsy. The gene defect of the ryanodine receptor is present in 50% of patients; gene testing is available only for this genetic group. This receptor also may be seen in the muscle biopsy by immunoreactivity. Another candidate gene is at the 1q31 locus.

Apart from the genetic disorder of malignant hyperthermia, some drugs may induce acute rhabdomyolysis with myoglobinuria and potential renal failure, but this usually occurs in patients who are predisposed by some other metabolic disease. Valproic acid, for example, may induce this process in children with mitochondrial cytopathies or with carnitine palmitoyltransferase deficiency.

610.3 • GLYCOGENOSES

(See also Chapter 87.1.)

Glycogenosis I (von Gierke disease) is not a true myopathy because the deficient liver enzyme glucose-6-phosphatase is not normally present in muscle. Nevertheless, children with this disease are hypotonic and mildly weak for unknown reasons.

Glycogenosis II (Pompe disease) is an autosomal recessively inherited deficiency of the glycolytic lysosomal enzyme acid maltase. Of the 12 known glycogenoses, type II is the only one with a defective lysosomal enzyme. The defective gene is at locus 17q23. Two forms are described. The infantile form is a severe generalized myopathy and cardiomyopathy. Patients have cardiomegaly and hepatomegaly and are diffusely hypotonic and weak. The serum CK level is greatly elevated. A muscle biopsy specimen reveals a vacuolar myopathy with abnormal lysosomal enzymatic activities such as acid and alkaline phosphatases. Death in infancy or early childhood is usual.

The late childhood or adult form is a much milder myopathy without cardiac or hepatic enlargement. It may not become clinically expressed until later childhood or early adult life but may be symptomatic as myopathic weakness and hypotonia even in early infancy. Even in late adult-onset acid maltase deficiency, more than ½ of the patients report difficulties with muscle strength dating from childhood.

The serum CK level is greatly elevated, and the muscle biopsy findings are diagnostic even in the presymptomatic stage. The diagnosis of glycogenosis II is confirmed by quantitative assay of acid maltase activity in muscle or liver biopsy specimens. A rare KM variant of the milder form of acid maltase deficiency may show muscle acid maltase activity in the low normal range with only intermittent decreases to subnormal values, but the muscle biopsy findings are similar although milder. In another form, **Danon disease,** transmitted as an X-linked recessive trait at the Xq24 locus, the primary deficiency is lysosomal membrane protein-2 (LAMP2) and results in hypertrophic cardiomyopathy, proximal myopathy, and mental retardation.

Glycogenosis III (Cori-Forbes disease), deficiency of debrancher enzyme (amylo-1,6-glucosidase), is more common than is usually diagnosed, and is generally the least severe. Hypotonia, weakness, hepatomegaly, and fasting hypoglycemia in infancy are common, but these features often resolve spontaneously, and patients become asymptomatic in childhood and adult life. Others experience slowly progressive distal muscle wasting, hepatic cirrhosis, recurrent hypoglycemia, and heart failure. This more serious chronic course is particularly seen in the Inuit population (Eskimos). Minor myopathic findings including vacuolation of muscle fibers are found in the muscle biopsy specimen.

Glycogenosis IV (Andersen disease) is a deficiency of brancher enzyme, resulting in the formation of an abnormal glycogen molecule, amylopectin, in the liver, reticuloendothelial cells, and skeletal and cardiac muscle. Hypotonia, generalized weakness, muscle wasting, and contractures are the usual signs of myopathic involvement. Most patients die before age 4 yr because of hepatic or cardiac failure. A few children without neuromuscular manifestations have been described.

Glycogenosis V (McArdle disease) is due to muscle phosphorylase deficiency inherited as an autosomal recessive trait at locus 11q13. Exercise intolerance is the cardinal clinical feature. Physical exertion results in cramps, weakness, and myoglobinuria, but strength is normal between attacks. The serum CK level is elevated only during exercise. A characteristic clinical feature is lack of the normal rise in serum lactate level during ischemic exercise because of inability to convert pyruvate to lactate under anaerobic conditions in vivo. Myophosphorylase deficiency may be demonstrated histochemically and biochemically in the muscle biopsy tissue. Some patients have a defect in adenosine monophosphate–dependent muscle phosphorylase-b-kinase, a

phosphorylase enzyme activator. Muscle phosphorylase deficiency was the first neuromuscular disease to be diagnosed by MR spectroscopy, that shows that intramuscular pH does not decrease with exercise and there is no depletion of ATPase, but the phosphocreatine concentration falls excessively. This noninvasive technique may be useful in some patients if the radiologist is experienced with the disease.

A rare **neonatal form of myophosphorylase deficiency** causes feeding difficulties in early infancy, may be severe enough to result in neonatal death, or may follow a course of slowly progressive weakness resembling a muscular dystrophy.

The long-term prognosis is good. Patients must learn to moderate their physical activities, but they do not develop severe chronic myopathic handicaps or cardiac involvement.

Glycogenosis VII (Tarui disease) is muscle phosphofructokinase deficiency. Although this disease is more rare than glycogenosis V, the symptoms of exercise intolerance, clinical course, and inability to convert pyruvate to lactate are identical. The distinction is made by biochemical study of the muscle biopsy specimen. It is transmitted as an autosomal recessive trait at the 1cenq32 locus.

610.4 • Mitochondrial Myopathies

(See also Chapters 87.4 and 598.2.)

Several diseases involving muscle, brain, and other organs are associated with structural and functional abnormalities of mitochondria, producing defects in aerobic cellular metabolism, the electron transport chain, and the Krebs cycle. The structural aberrations are best demonstrated by electron microscopy of the muscle biopsy sample, revealing abnormally shaped cristae and fusion of cristae to form paracrystalline structures. Histochemical study of the muscle biopsy specimen reveals abnormal clumping of oxidative enzymatic activity, scattered myofibers with loss of cytochrome-c oxidase activity, sometimes increased neutral lipids because of impaired lipid metabolism, and ragged red muscle fibers with accumulations of membranous material beneath the muscle fiber membrane, best demonstrated by special stains. These characteristic histochemical and ultrastructural changes are most consistently seen with point mutation in mitochondrial transfer RNA. The large mitochondrial DNA (mtDNA) deletions of 5 or 7.4 kb (the single mitochondrial chromosome has 16.5 kb) are associated with defects in mitochondrial respiratory oxidative enzyme complexes, if as few as 2% of the mitochondria are affected, but minimal or no morphologic or histochemical changes may be noted in the muscle biopsy specimen, even by electron microscopy; hence, the quantitative biochemical studies of the muscle tissue are needed to confirm the diagnosis. Because most of the subunits of the respiratory chain complexes are encoded by nuclear DNA (nDNA) rather than mtDNA, mendelian autosomal inheritance is possible rather than maternal transmission as with pure mtDNA point mutations.

Several distinct mitochondrial diseases that primarily affect striated muscle or muscle and brain are identified. These can be divided into the ragged red fiber diseases (Kearns-Sayre, MELAS [mitochondrial encephalopathy, lactic acidosis, and strokelike symptoms] syndrome, MERRF [myoclonic epilepsy and ragged red fibers] syndrome, progressive external ophthalmoplegia syndromes) that are associated with a combined defect in respiratory chain complexes I and IV, and non–ragged fiber diseases (Leigh encephalopathy, Leber hereditary optic atrophy) that involve complex I or IV alone or, in children, the common combination of defective complexes III and V. ***Kearns-Sayre syndrome*** is characterized by the triad of progressive external ophthalmoplegia, pigmentary degeneration of the retina, and onset before age 20 yr. Heart block, cerebellar deficits, and high cerebrospinal fluid protein content are often associated. Visual evoked potentials are abnormal. Patients usually do not experience weakness of the trunk or extremities or dysphagia. Most cases are sporadic.

Chronic progressive external ophthalmoplegia may be isolated or accompanied by limb muscle weakness, dysphagia, and dysarthria. A few patients described as having *ophthalmoplegia plus* have additional central nervous system involvement. Autosomal dominant inheritance is found in some pedigrees, but most cases are sporadic.

MERRF and ***MELAS syndromes*** are other mitochondrial disorders affecting children. The latter is characterized by stunted growth, episodic vomiting, seizures, and recurrent cerebral insults causing hemiparesis, hemianopia or even cortical blindness, and dementia. The disease behaves as a degenerative disorder, and children die within a few years.

Other "degenerative" diseases of the central nervous system that also involve myopathy with mitochondrial abnormalities include **Leigh subacute necrotizing encephalopathy** (see Chapter 87.4) and **cerebrohepatorenal (Zellweger) disease** (see Chapter 86.2). Another recognized mitochondrial myopathy is **cytochrome-c oxidase deficiency. Oculopharyngeal muscular dystrophy** is also fundamentally a mitochondrial myopathy. ***Mitochondrial depletion syndrome of early infancy*** is characterized by severely decreased oxidative enzymatic activities in all 5 of the complexes; in addition to diffuse muscle weakness, neonates and young infants may show multisystemic involvement, with failure of liver, kidney, and heart functions; encephalopathy; and sometimes bullous skin lesions or generalized edema. Many other rare diseases with only a few case reports are suspected of being mitochondrial disorders. It is also now recognized that secondary mitochondrial defects occur in a wide range of non-mitochondrial diseases, including inflammatory autoimmune myopathies, and some cerebral malformations, and also may be induced by certain drugs and toxins, so that interpretation of mitochondrial abnormalities as primary defects must be approached with caution.

mtDNA is distinct from the DNA of the cell nucleus and is inherited exclusively from the mother; mitochondria are present in the cytoplasm of the ovum but not in the head of the sperm, the only part that enters the ovum at fertilization. The rate of mutation of mtDNA is 10 times higher than that of nDNA. The mitochondrial respiratory enzyme complexes each have subunits encoded either in mtDNA or nDNA. Complex II (succinate dehydrogenase, a Krebs cycle enzyme) has 4 subunits, all encoded in nDNA; complex III (ubiquinol or cytochrome-b oxidase) has 9 subunits, only 1 of which is encoded by mtDNA and 8 of which are programmed by nDNA; complex IV (cytochrome-c oxidase) has 13 subunits, only 3 of which are encoded by mtDNA. For this reason, mitochondrial diseases of muscle may be transmitted as autosomal recessive traits rather than by strict maternal transmission, even though all mitochondria are inherited from the mother.

In Kearns-Sayre syndrome, a single large mtDNA deletion has been identified, but other genetic variants are known; in MERRF and MELAS syndromes of mitochondrial myopathy, point mutations occur in transfer RNA (see Table 607-1).

There is no effective treatment of mitochondrial cytopathies, but various "cocktails" are often used empirically to try to overcome the metabolic deficits. These include oral carnitine supplements, riboflavin, coenzyme Q_{10}, ascorbic acid (vitamin C), vitamin E, and other antioxidants. Although some anecdotal reports are encouraging, no controlled studies that prove efficacy have been published.

610.5 • Lipid Myopathies

(See Chapter 86.4.)

Considered as metabolic organs, skeletal muscles are the most important sites in the body for long-chain fatty acid metabolism

because of their large mass and their rich density of mitochondria where fatty acids are metabolized. Hereditary disorders of lipid metabolism that cause progressive myopathy are an important, relatively common, and often treatable group of muscle diseases. Increased lipid within myofibers is seen in the muscle biopsy of some, but not all, mitochondrial myopathies and is a constant, rather than an unpredictable, feature of specific diseases. Among the ragged red fiber diseases, Kearns-Sayre syndrome always shows increased neutral lipid, whereas MERRF and MELAS syndromes do not, a useful diagnostic marker for the pathologist.

Muscle carnitine deficiency is an autosomal recessive disease involving deficient transport of dietary carnitine across the intestinal mucosa. Carnitine is acquired from dietary sources but is also synthesized in the liver and kidneys from lysine and methionine; it is the obligatory carrier of long- and medium-chain fatty acids into muscle mitochondria.

The clinical course may be one of sudden exacerbations of weakness or may resemble a progressive muscular dystrophy with generalized proximal myopathy and sometimes facial, pharyngeal, and cardiac involvement. Symptoms usually begin in late childhood or adolescence or may be delayed until adult life. Progression is slow but may end in death.

Serum CK level is mildly elevated. Muscle biopsy material shows vacuoles filled with lipid within muscle fibers in addition to nonspecific changes suggestive of a muscular dystrophy. Mitochondria may appear normal or abnormal. Carnitine measured in muscle biopsy tissue is reduced, but the serum carnitine level is normal.

Treatment stops the progression of the disease and may even restore lost strength if the disease is not too advanced. It consists of special diets low in long-chain fatty acids. Steroids may enhance fatty acid transport. Specific therapy with L-carnitine taken orally in large doses overcomes the intestinal barrier in some patients. Some patients also improve when given supplementary riboflavin, and other patients seem to improve with propranolol.

Systemic carnitine deficiency is a disease of impaired renal and hepatic synthesis of carnitine rather than a primary myopathy. Patients with this autosomal recessive disease experience progressive proximal myopathy and show muscle biopsy changes similar to those of muscle carnitine deficiency; however, the onset of weakness is earlier and may be evident at birth. Endocardial fibroelastosis also may occur. Episodes of acute hepatic encephalopathy resembling Reye syndrome may occur. Hypoglycemia and metabolic acidosis complicate acute episodes.

The concentration of carnitine is reduced in serum as well as in muscle and liver. A similar clinical syndrome may be a complication of renal Fanconi syndrome because of excessive urinary loss of carnitine or loss during chronic hemodialysis.

Treatment with L-carnitine improves the maintenance of blood glucose and serum carnitine levels but does not reverse the ketosis or acidosis or improve exercise capacity.

Muscle carnitine palmitoyltransferase (CPT) deficiency presents as episodes of rhabdomyolysis, coma, and elevated serum CK level that may be indistinguishable from Reye syndrome. CPT transfers long-chain fatty acid acyl coenzyme A residues to carnitine on the outer mitochondrial membrane for transport into the mitochondria. Exercise intolerance and myoglobinuria resemble glycogenoses V and VII. The degree of exercise that triggers an attack varies among individuals, ranging from casual walking to strenuous exercise. Myoglobinuria is an inconstant feature. Fasting hypoglycemia may occur. Some patients present only in late adolescence or adult life with myalgias. Genetic transmission is autosomal recessive, due to a defect on chromosome 1 at the 1p32 locus. Administration of valproic acid may precipitate acute rhabdomyolysis with myoglobinuria in patients with CPT deficiency; it should be avoided in the treatment of seizures or migraine if they occur.

610.6 • Vitamin E Deficiency Myopathy

Deficiency of vitamin E (α-tocopherol, an antioxidant also important in mitochondrial superoxide generation) in experimental animals produces a progressive myopathy closely resembling a muscular dystrophy. Myopathy and neuropathy are recognized in humans who lack adequate intake of this antioxidant. Patients with chronic malabsorption, those undergoing long-term dialysis, and premature infants who do not receive vitamin E supplements are particularly vulnerable. Treatment with high doses of vitamin E may reverse the deficiency. Myopathy due to chronic hypervitaminosis E also occurs.

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Chapter 611 ■ Disorders of Neuromuscular Transmission and of Motor Neurons

611.1 • Myasthenia Gravis

This chronic disease is characterized by rapid fatigability of striated muscle. The most frequent cause is an immune-mediated neuromuscular blockade. The release of acetylcholine (ACh) into the synaptic cleft by the axonal terminal is normal, but the postsynaptic muscle membrane or *motor end plate* is less responsive than normal. A decreased number of available ACh receptors is due to circulating receptor-binding antibodies in most cases of acquired myasthenia. The disease is generally nonhereditary and is an autoimmune disorder. A rare familial myasthenia gravis is probably an autosomal recessive trait and is not associated with plasma anti-ACh antibodies. One familial form is a deficiency of motor end plate ACh, designated AChE. Infants born to myasthenic mothers may have a transient neonatal myasthenic syn-

TABLE 611-1. Clinical, Pathologic, and Neurophysiologic Characteristics of Various Congenital Myasthenic Syndromes

	LEMS	CMS-EA	END PLATE ACHE DEFICIENCY	SLOW CHANNEL SYNDROMES	FAST CHANNEL SYNDROME	ACH RECEPTOR DEFICIENCY
Mode of inheritance	AR-sporadic	AR	AR	AD	AR	AR
Gene location		17 pter	3p24.2 (for type 1c)	2q24–q32, 17p11–p12 & 17p13	17p13	17p13
Gene product		FIM	COLQ	CHRNA, CHRNB1 & CHRNE	CHRNE	CHRNE
Pathogenesis/defect	autoimmune	presynaptic	synaptic	postsynaptic	postsynaptic	postsynaptic
Contractures	–	+	–	–	–	–
Tendon reflexes	–	+	±	±	±	±
Early manifestations	+	+	+	Variable	–	Variable
Episodic crises	±	+	–	–	–	–
Response to Ach inhibitors	–	+	–	–	+	+
Response to 3,4-DAP	Sometimes	–	–	–	Mild response	+
Response to quinidine	–	–	–	+	–	–
Low-frequency RS	Decrement	Decrement	Decrement	Decrement	Decrement	Decrement
High-frequency RS	Increment	Decrement	Decrement	Decrement	Decrement	Decrement
Repetitive CMAP	–	–	+	+	–	–
Low-amplitude baseline CMAP	+	–	–	–	–	–
Small MUP in electromyography	–	–	+	+	+	+
Muscle biopsy	Normal	Normal	Abnormal	Abnormal	Normal	Abnormal

ACHE, acetycholinesterase; AD, autosomal dominant; AR, Autosomal recessive; CHRNA, acetylcholine receptor α subunit; CHRNB1, acetylcholine receptor β subunit; CHRNE, acetylcholine receptor e subunit; CMAP, compound muscle action potential; CMS-EA, congenital myasthenic syndrome with episodic apnea; COLQ, collagen Q; 3,4-DAP, 3,4-diaminopyridine; FIM, familial infantile myasthenia; LEMS, Lambert-Eaton myasthenic syndrome; MUP, motor unit potential; RS, repetitive stimulation; +, present; –, absent; ±, equivocal.

From Zafeiriou DI, Pitt M, de Sousa C: Clinical and neurophysiological characteristics of congenital myasthenic syndromes presenting in early infancy. *Brain Dev* 2004; 26:47–52.

drome secondary to placentally transferred anti-ACh receptor antibodies, distinct from congenital myasthenia gravis (Table 611-1).

CLINICAL MANIFESTATIONS. Three clinical varieties are distinguished in childhood: juvenile myasthenia gravis in late infancy and childhood, congenital myasthenia, and transient neonatal myasthenia. In the juvenile form, ptosis and some degree of extraocular muscle weakness are the earliest and most constant signs. Older children may complain of diplopia, and young children may hold open their eyes with their fingers or thumbs if the ptosis is severe enough to obstruct vision. The pupillary responses to light are preserved. Dysphagia and facial weakness are also common, and in early infancy, feeding difficulties are often the cardinal sign of myasthenia. Poor head control because of weakness of the neck flexors is also prominent. Involvement may be limited to bulbar-innervated muscles, but the disease is systemic and weakness involves limb-girdle muscles and distal muscles of the hands in most cases. Fasciculations of muscle, myalgias, and sensory symptoms do not occur. Tendon stretch reflexes may be diminished but rarely are lost.

Rapid fatigue of muscles is a characteristic feature of myasthenia gravis that distinguishes it from most other neuromuscular diseases. Ptosis increases progressively as patients are asked to sustain an upward gaze for 30–90 sec. Holding the head up from the surface of the examining table while lying supine is very difficult, and gravity cannot be overcome for more than a few seconds. Repetitive opening and closing of the fists produces rapid fatigue of hand muscles, and patients cannot elevate their arms for more than 1–2 min because of fatigue of the deltoids. Patients are more symptomatic late in the day or when tired. Dysphagia may interfere with eating, and the muscles of the jaw soon tire when an affected child chews.

If untreated, myasthenia gravis is usually progressive and may become life threatening because of respiratory muscle involvement and the risk of aspiration, particularly at times when the child is otherwise unwell with an upper respiratory tract infection. Familial myasthenia gravis usually is not progressive.

Infants born to myasthenic mothers may have respiratory insufficiency, inability to suck or swallow, and generalized hypotonia and weakness. They may show little spontaneous motor activity for several days to weeks. Some require ventilatory support and feeding by gavage during this period. After the abnormal antibodies disappear from the blood and muscle tissue, the infants regain normal strength and are not at increased risk of developing myasthenia gravis in later childhood. This syndrome of *transient neonatal myasthenia gravis* is to be distinguished from a rare and often hereditary **congenital myasthenia gravis** not related to maternal myasthenia that is nearly always a permanent disorder without spontaneous remission (see Table 611-1).

Three **presynaptic congenital myasthenic syndromes** are recognized, all as autosomal recessive traits; some of these have anti-MuSK antibodies. These children exhibit weakness of extraocular, pharyngeal, and respiratory muscles and later show shoulder girdle weakness as well. Episodic **apnea** is a problem in congenital myasthenia gravis. Another synaptic form is caused by absence or marked deficiency of AChE in the synaptic basal lamina, and postsynaptic forms of congenital myasthenia are caused by mutations in ACh receptor subunit genes that alter the synaptic response to ACh. An abnormality of the ACh receptor channels appearing as high conductance and excessively fast closure may be the result of a point mutation in a subunit of the receptor affecting a single amino acid residue. Children with congenital myasthenia gravis do not experience myasthenic crises and rarely exhibit elevations of anti-ACh antibodies in plasma.

Myasthenia gravis is occasionally associated with hypothyroidism, usually due to **Hashimoto thyroiditis.** Other collagen vascular diseases may also be associated. Thymomas, noted in some adults, rarely coexist with myasthenia gravis in children; nor do carcinomas of the lung occur, which produce a unique form of myasthenia in adults, **Eaton-Lambert syndrome.** Postinfectious myasthenia gravis in children is transitory and usually follows a varicella-zoster infection in 2–5 wk as an immune response.

LABORATORY FINDINGS AND DIAGNOSIS. Myasthenia gravis is 1 of the few neuromuscular diseases in which electromyography (EMG) is more specifically diagnostic than a muscle biopsy. A decremental response is seen in response to repetitive nerve stimulation; the muscle potentials diminish rapidly in amplitude until the muscle becomes refractory to further stimulation. Motor nerve conduction velocity remains normal. This unique EMG pattern is the electrophysiologic correlate of the fatigable weakness observed clinically and is reversed after a cholinesterase inhibitor is administered. A myasthenic decrement may be absent

or difficult to demonstrate in muscles that are not involved clinically. This feature may be confusing in early cases or in patients showing only weakness of extraocular muscles. Microelectrode studies of end plate potentials and currents reveal whether the transmission defect is presynaptic or postsynaptic. Special electrophysiologic studies are required in the classification of congenital myasthenic syndromes and involve the estimation of the number of ACh receptors per end plate and in vitro study of end plate function. These special studies and patch-clamp recordings of kinetic properties of channels are performed on special biopsy samples of intercostal muscle strips that include both origin and insertion of the muscle but are only performed in specialized centers. If myasthenia is limited to the extraocular muscles, levator palpebrae and pharyngeal muscles, evoked-potential EMG of the muscles of the extremities and spine, diagnostic in the generalized disease, usually is normal.

Anti-ACh antibodies should be assayed in the plasma but are inconsistently demonstrated. About ⅓ of affected adolescents show elevations, but anti-ACh receptor antibodies are only occasionally demonstrated in the plasma of prepubertal children. Many juvenile myasthenics who show no anti-ACh antibodies in serum have instead antibodies against the receptor tyrosine kinase (MuSK), which also is localized at the neuromuscular junction and appears essential to fetal development of this junction. Many cases of congenital myasthenia gravis are due not to a refractory postsynaptic membrane at the neuromuscular junction as in juvenile and adult myasthenia, but rather failure to synthesize or release ACh at the presynaptic membrane. In some cases, the gene that mediates the enzyme choline acetyltransferase for the synthesis of ACh is mutated. In others, there is a defect in the quantal release of vesicles containing ACh. The treatment of such patients with cholinesterase inhibitors is futile.

Other serologic tests of autoimmune disease, such as antinuclear antibodies and abnormal immune complexes, should also be sought. If these are positive, more extensive autoimmune disease involving vasculitis or tissues other than muscle is likely. A thyroid profile should always be examined. The serum creatine kinase (CK) level is normal in myasthenia gravis.

The heart is not involved, and electrocardiographic findings remain normal. Radiographs of the chest often reveal an enlarged thymus, but the hypertrophy is not a thymoma. It may be further defined by tomography or by CT scanning of the anterior mediastinum.

The role of conventional muscle biopsy in myasthenia gravis is limited. It is not required in most cases, but about 17% of patients show inflammatory changes sometimes called *lymphorrhages* that are interpreted by some physicians as a mixed myasthenia-polymyositis immune disorder. Muscle biopsy tissue in myasthenia gravis shows nonspecific type II muscle fiber atrophy, similar to that seen with disuse atrophy, steroid effects on muscle, polymyalgia rheumatica, and many other conditions. The ultrastructure of motor end plates shows simplification of the membrane folds; the ACh receptors are located in these postsynaptic folds, as shown by bungarotoxin (snake venom), which binds specifically to the ACh receptors.

A **clinical test for myasthenia gravis** is administration of a short-acting cholinesterase inhibitor, usually edrophonium chloride. Ptosis and ophthalmoplegia improve within a few seconds, and fatigability of other muscles decreases.

RECOMMENDATIONS ON THE USE OF CHOLINESTERASE INHIBITORS AS A DIAGNOSTIC TEST FOR MYASTHENIA GRAVIS IN INFANTS AND CHILDREN

FOR CHILDREN 2 YR OF AGE OR OLDER

1. Child should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, or inability of cervical muscles to support head; nonspecific generalized weakness without cranial nerve motor deficits is not a criterion.
2. An intravenous infusion should be started to enable the administration of medications in the event of an adverse reaction.
3. Electrocardiographic monitoring during test is recommended.
4. A dose of atropine sulfate (0.01 mg/kg) should be available in a syringe, ready for IV administration at the bedside during the edrophonium test, to block acute muscarinic effects of the cholinesterase inhibitor (mainly abdominal cramps and/or sudden diarrhea from increased peristalsis, profuse bronchotracheal secretions that may obstruct the airway, or, rarely, cardiac arrhythmias, if needed. Some physicians pretreat all patients with atropine before administering edrophonium, but this is not recommended unless there is a history of reaction to tests. Remember that atropine may cause the pupils to be dilated and fixed for as long as 14 days after a single dose, and the pupillary effects of homatropine may last 4–7 days.
5. Edrophonium chloride (Tensilon) is administered intravenously. Initially, a test dose of 0.04 mg/kg is given to ensure that the patient does not have an allergic reaction or is otherwise very sensitive to muscarinic side effects. If this test dose is well tolerated, the diagnostic dose administered is 0.1–0.2 mg/kg (maximum single dose is 10 mg regardless of weight; in children weighing <30 kg, 2 mg is the maximum dose; a typical dose for a 3–5 yr old child is 5 mg). These same doses may be given intramuscularly or subcutaneously, but these routes are not recommended because the results are much more variable due to unpredictable absorption, and the test may be ambiguous or falsely negative.
6. Effects should be seen within 10 sec and disappear within 120 sec; weakness is measured (e.g., distance between upper and lower eyelids before and after administration, degree of external ophthalmoplegia, ability to swallow a sip of water).
7. Long-acting cholinesterase inhibitors, such as pyridostigmine (Mestinon) are generally not as useful for the acute assessment of myasthenic weakness. The prostigmine test may be used (as outlined later) but may not be as definitively diagnostic as the edrophonium test.

FOR INFANTS YOUNGER THAN 2 YR OF AGE

1. Infants ideally should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, and inability of cervical muscles to support head; nonspecific generalized weakness without cranial nerve motor deficits is less easy to assess results but may be a criterion at times.
2. An IV infusion should be started as a rapid route for medications in the event of an adverse effect of the test medication.
3. Electrocardiographic monitoring is recommended during test.
4. Pretreatment with atropine sulfate to block the muscarinic effects of the test medication is not recommended but should be available at the bedside in a prepared syringe. If needed, it should be administered intravenously in a dose of 0.1 mg/kg.
5. Edrophonium is not recommended for use in infants; its effect is too brief for objective assessment and an increased incidence of acute cardiac arrhythmias is reported in infants, especially neonates, with this drug.
6. Prostigmine methylsulfate (Neostigmine) is administered intramuscularly at a dose of 0.04 mg/kg; if the result is negative or equivocal, another dose of 0.04 mg/kg may be administered 4 hr after the first dose (a typical dose is 0.5–1.5 mg). The peak effect is seen in 20–40 min. Intravenous prostigmine is contraindicated because of risk of cardiac arrhythmias, including fatal ventricular fibrillation, especially in young infants.
7. Long-acting cholinesterase inhibitors administered orally, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness because onset and duration are less predictable.

Where should test be performed? The setting may be the emergency department, hospital ward, or, at times, a physician's office; the important issue is preparation for potential complications such as cardiac arrhythmia or cholinergic crisis, as previously outlined.

TREATMENT. Some patients with mild myasthenia gravis require no treatment. **Cholinesterase-inhibiting drugs** are the primary therapeutic agents. Neostigmine methylsulfate (0.04 mg/kg) may be given intramuscularly every 4–6 hr, but most patients tolerate oral neostigmine bromide, 0.4 mg/kg every 4–6 hr. If dysphagia is a major problem, the drug should be given about 30 min before meals to improve swallowing. Pyridostigmine is an alternative; the dose required is about 4 times greater than that of neostigmine, but it may be slightly longer acting. Overdoses of cholinesterase inhibitors produce cholinergic crises; atropine blocks the muscarinic effects but does not block the nicotinic effects that produce additional skeletal muscle weakness. In the rare familial myasthenia gravis caused by absence of end plate

AChE, cholinesterase inhibitors are not helpful and often cause increased weakness; these patients can be treated with ephedrine or diaminopyridine, both of which increase ACh release from terminal axons.

Because of the autoimmune basis of the disease, long-term **steroid treatment** with prednisone may be effective. **Thymectomy** should be considered and may provide a cure. Thymectomy is most effective in patients with high titers of anti-ACh receptor antibodies in the plasma and who are symptomatic for <2 yr. Thymectomy is ineffective in congenital and familial forms of myasthenia gravis. Treatment of hypothyroidism usually abolishes an associated myasthenia without the use of cholinesterase inhibitors or steroids.

Plasmapheresis is effective treatment in some children, particularly those who do not respond to steroids, but plasma exchange therapy may provide only temporary remission. **Intravenous immunoglobulin** (IVIG) is sometimes beneficial and might be tried before plasmapheresis because it is less invasive. Both plasmapheresis and IVIG appear to be most effective in patients with high circulating levels of anti-ACh receptor antibodies. Refractory patients may respond to rituximab, a monoclonal antibody to the B-cell CD20 antigen.

Neonates with transient maternally transmitted myasthenia gravis require cholinesterase inhibitors for only a few days or occasionally for a few weeks, especially to allow feeding. No other treatment is usually necessary.

COMPLICATIONS. Children with myasthenia gravis do not tolerate neuromuscular blocking drugs, such as succinylcholine and pancuronium, and may be paralyzed for weeks after a single dose. An anesthesiologist should carefully review myasthenic patients who require a surgical anesthetic. Also, certain antibiotics may potentiate myasthenia and should be avoided; these include the aminoglycosides (gentamicin and others).

PROGNOSIS. This is difficult to predict. Some patients undergo spontaneous remission after a period of months or years; others have a permanent disease extending into adult life. Immunosuppression, thymectomy, and treatment of associated hypothyroidism may provide a cure.

OTHER CAUSES OF NEUROMUSCULAR BLOCKADE. **Organophosphate chemicals,** commonly used as insecticides, may cause a myasthenia-like syndrome in children exposed to these toxins (see Chapter 58).

Botulism results from ingestion of food containing the toxin of *Clostridium botulinum,* a gram-positive, spore-bearing, anaerobic bacillus (see Chapter 207). Honey is a frequent source of contamination. The incubation period is short, only a few hours, and symptoms begin with nausea, vomiting, and diarrhea. Cranial nerve involvement soon follows, with diplopia, dysphagia, weak suck, facial weakness, and absent gag reflex. Generalized hypotonia and weakness then develop and may progress to respiratory failure. Neuromuscular blockade is documented by EMG with repetitive nerve stimulation. Respiratory support may be required for days or weeks until the toxin is cleared from the body. No specific antitoxin is available. Guanidine, 35 mg/kg/24 hr, may be effective for extraocular and limb muscle weakness but not for respiratory muscle involvement.

Tick paralysis is a disorder of ACh release from axonal terminals due to a neurotoxin that blocks depolarization. It also affects large myelinated motor and sensory nerve fibers. This toxin is produced by the wood tick or dog tick, insects common in the Appalachian and Rocky Mountains of North America. The tick embeds its head into the skin, usually the scalp, and neurotoxin production is maximal about 5–6 days later. Motor symptoms include weakness, loss of coordination, and sometimes an ascending paralysis resembling Guillain-Barré syndrome. Tendon reflexes are lost. Sensory symptoms of tingling paresthesias may occur in the face and extremities. The diagnosis is confirmed by EMG and nerve conduction studies and by identifying the tick. The tick must be removed completely, and the buried head not left beneath the skin. Patients then recover completely within hours or days.

611.2 • Spinal Muscular Atrophies

Spinal muscular atrophies (SMAs) are degenerative diseases of motor neurons that begin in fetal life and continue to be progressive in infancy and childhood. The progressive denervation of muscle is compensated in part by reinnervation from an adjacent motor unit, but giant motor units are thus created with subsequent atrophy of muscle fibers when the reinnervating motor neuron eventually becomes involved. Upper motor neurons remain normal.

SMA is classified into a severe infantile form, also known as **Werdnig-Hoffmann disease** or SMA type 1; a late infantile and more slowly progressive form, SMA type 2; and a more chronic or juvenile form, also called **Kugelberg-Welander disease,** or SMA type 3. A severe fetal form that is usually lethal in the perinatal period has been described as SMA type 0. These distinctions are clinical and are based on age at onset, severity of weakness, and clinical course; muscle biopsy does not distinguish types 1 and 2, although type 3 shows a more adult than perinatal pattern of denervation/reinnervation. The type 0 may show biopsy features more similar to myotubular myopathy because of maturational arrest; scattered myotubes and other immature fetal fibers also are demonstrated in the muscle biopsies of patients with types 1 and 2, but do not predominate. About 25% of patients are type 1, 50% type 2, and 25% type 3; type 0 is rare and accounts for <1%. Some patients are transitional between types 1 and 2 or between types 2 and 3 in terms of clinical function. A variant of SMA, **Fazio-Londe disease,** is a progressive bulbar palsy resulting from motor neuron degeneration more in the brainstem than the spinal cord.

ETIOLOGY. The cause of SMA is a pathologic continuation of a process of programmed cell death that is normal in embryonic life. A surplus of motor neuroblasts and other neurons is generated from primitive neuroectoderm, but only about ½ survive and mature to become neurons; the excess cells have a limited life cycle and degenerate. If the process that arrests physiologic cell death fails to intervene by a certain stage, neuronal death may continue in late fetal life and postnatally. The survivor motor neuron gene *(SMN)* arrests apoptosis (programmed cell death) of motor neuroblasts. Unlike most genes that are highly conserved in evolution, *SMN* is a uniquely mammalian gene.

CLINICAL MANIFESTATIONS. The cardinal features of **SMA type 1** are severe hypotonia (Fig. 611-1); generalized weakness; thin muscle mass; absent tendon stretch reflexes; involvement of the tongue, face, and jaw muscles; and sparing of extraocular muscles and sphincters. Diaphragmatic involvement is late. Infants who are symptomatic at birth may have respiratory distress and are unable to feed. Congenital contractures, ranging from simple clubfoot to generalized arthrogryposis, occur in about 10% of severely involved neonates. Infants lie flaccid with little movement, unable to overcome gravity (Fig. 606-1). They lack head control. More than ⅔ die by 2 yr of age, and many die early in infancy.

In **type 2 SMA,** affected infants are usually able to suck and swallow and respiration is adequate in early infancy. These infants show progressive weakness, but many survive into the school years or beyond, although confined to an electric wheelchair and severely handicapped. Nasal speech and problems with

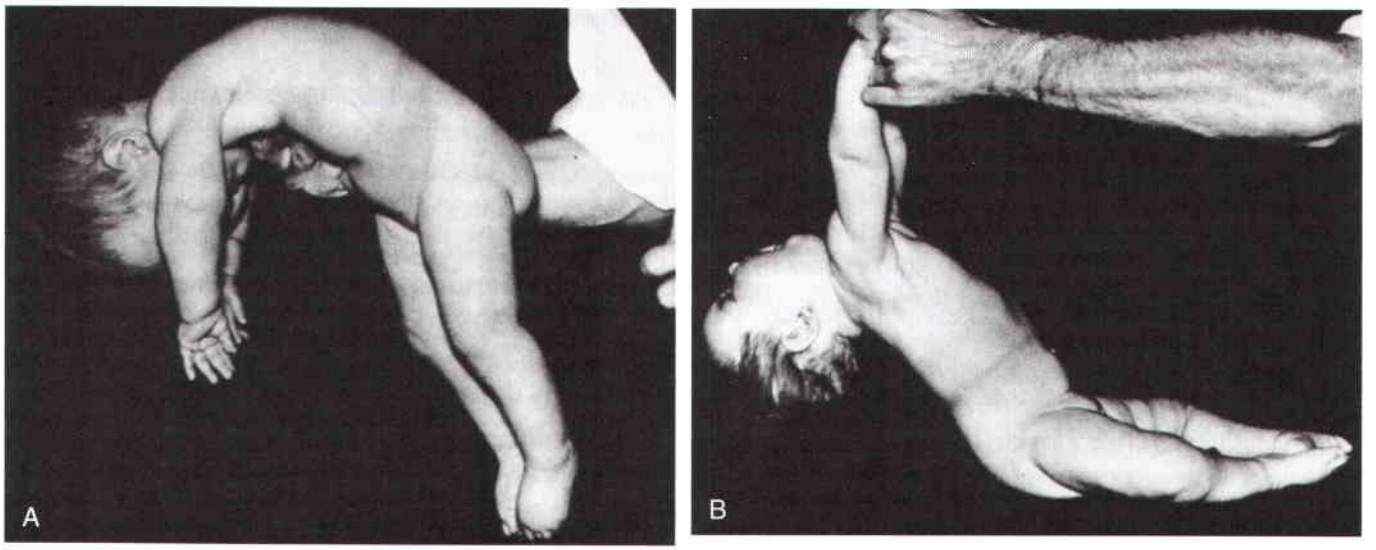

Figure 611-1. Type 1 spinal muscular atrophy (Werdnig-Hoffmann disease). Clinical manifestations of weakness of limb and axial musculature in a 6 wk old infant with severe weakness and hypotonia from birth. Note the marked weakness of the limbs and trunk on ventral suspension *(A)* and of neck on pull to sit *(B)*. (From Volpe J: *Neurology of the Newborn*, 4th ed. Philadelphia, WB Saunders, 2001, p. 644.)

deglutition develop later. Scoliosis becomes a major complication in many patients with long survival.

Kugelberg-Welander disease is the mildest **SMA (type 3)**, and patients may appear normal in infancy. The progressive weakness is proximal in distribution, particularly involving shoulder girdle muscles. Patients are ambulatory. Symptoms of bulbar muscle weakness are rare. About 25% of patients with this form of SMA have muscular hypertrophy rather than atrophy, and it may easily be confused with a muscular dystrophy. Longevity may extend well into middle adult life. Fasciculations are a specific clinical sign of denervation of muscle. In thin children, they may be seen in the deltoid, biceps brachii, and occasionally the quadriceps femoris muscles, but the continuous, involuntary, wormlike movements may be masked by a thick pad of subcutaneous fat. Fasciculations are best observed in the tongue, where almost no subcutaneous connective tissue separates the muscular layer from the epithelium. If the intrinsic lingual muscles are contracted, such as in crying or when the tongue protrudes, fasciculations are more difficult to see than when the tongue is relaxed.

The outstretched fingers of children with SMA often show a characteristic tremor owing to fasciculations and weakness. It should not be confused with a cerebellar tremor. Myalgias are not a feature of SMA.

The heart is not involved in SMA. Intelligence is normal, and children often appear brighter than their normal peers because the effort they cannot put into physical activities is redirected to intellectual development, and they are often exposed to adult speech more than to juvenile language because of the social repercussions of the disease.

LABORATORY FINDINGS. The serum CK level may be normal but more commonly is mildly elevated in the hundreds. A CK level of several thousand is rare. Results of motor nerve conduction studies are normal, except for mild slowing in terminal stages of the disease, an important feature distinguishing SMA from peripheral neuropathy. EMG shows fibrillation potentials and other signs of denervation of muscle.

DIAGNOSIS. The simplest, most definitive diagnostic test is a molecular genetic marker in blood for the *SMN* gene. Muscle biopsy reveals a characteristic pattern of perinatal denervation that is unlike that of mature muscle. Groups of giant type I fibers are mixed with fascicles of severely atrophic fibers of both histochemical types (Fig. 611-2). Scattered immature myofibers resembling myotubes also are demonstrated. In juvenile SMA, the pattern may be more similar to adult muscle that has undergone many cycles of denervation and reinnervation. Neurogenic changes in muscle also may be demonstrated by EMG, but the results are less definitive than by muscle biopsy in infancy. Sural nerve biopsy sometimes shows mild sensory neuropathic changes, and sensory nerve conduction velocity may be slowed; hypertrophy of unmyelinated axons also is seen. At autopsy, mild degenerative changes are seen in sensory neurons of dorsal root ganglia and in somatosensory nuclei of the thalamus, but these alterations are not perceived clinically as sensory loss or paresthesias. The most pronounced neuropathologic lesions are the extensive neuronal degeneration and gliosis in the ventral horns of the spinal cord and brainstem motor nuclei, especially the hypoglossal nucleus.

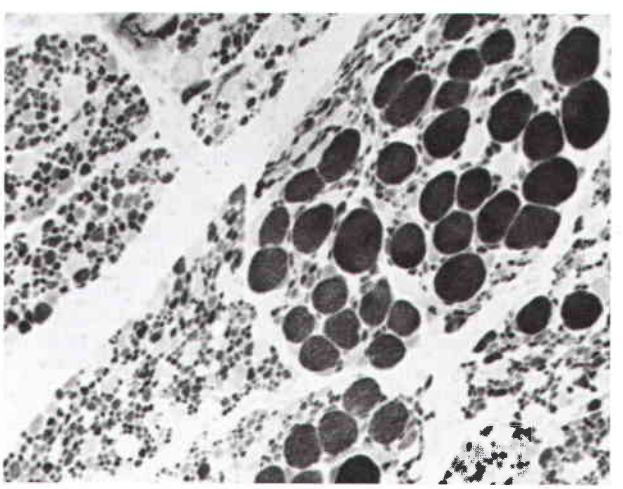

Figure 611-2. Muscle biopsy of neonate with infantile spinal muscular atrophy. Groups of giant type I (darkly stained) fibers are seen within muscle fascicles of severely atrophic fibers of both histochemical types. This is the characteristic pattern of perinatal denervation of muscle. Myofibrillar ATPase, preincubated at pH 4.6 (×400).

GENETICS. Molecular genetic diagnosis by DNA probes in blood samples or in muscle biopsy or chorionic villi tissues is available not only for diagnosis of suspected cases but also for prenatal diagnosis. Most cases are inherited as an autosomal recessive trait. The incidence of SMA is 10–15 per 100,000 live births, affecting all ethnic groups; it is the 2nd most common neuromuscular disease, following Duchenne muscular dystrophy. The incidence of heterozygosity for autosomal recessive SMA is 1 : 50. The genetic locus for all 3 of the common forms of SMA is on chromosome 5, a deletion at the 5q11-q13 locus, indicating that they are variants of the same disease rather than different diseases. The affected *SMN* gene contains 8 exons that span 20 kb, telomeric and centromeric exons that differ only by 5 bp and produce a transcript encoding 294 amino acids. Another gene, the *neuronal apoptosis inhibitory gene (NAIP),* is located next to the *SMN* gene and in many cases there is an inverted duplication with 2 copies, telomeric and centromeric, of both genes; isolated mutations or deletions of *NAIP* do not produce clinical SMA and generate a mostly nonfunctional isoform lacking the carboxy-terminus amino acids encoded by exon 7. Milder forms of SMA have more than 2 copies of *SMN2*, and in late-onset patients with homozygous deletion of the *SMN1* gene, there are 4 copies of *SMN2*. An additional gene mapped to 11q13-q21 in SMA may help explain early respiratory failure in some patients.

Infrequent families with autosomal dominant inheritance are described, and a rare X-linked recessive form occurs. Carrier testing by dose analysis is available.

TREATMENT. No medical treatment is able to delay the progression. Supportive therapy includes orthopedic care with particular attention to scoliosis and joint contractures, mild physiotherapy, and mechanical aids for assisting the child to eat and to be as functionally independent as possible. Most children learn to use a computer keyboard with great skill but cannot use a pencil easily.

611.3 • Other Motor Neuron Diseases

Motor neuron diseases other than SMA are rare in children. *Poliomyelitis* used to be a major cause of chronic disability, but since the routine use of polio vaccine, this viral infection is now rare (see Chapter 246). Other enteroviruses, such as *Coxsackie* and *Echo* viruses, or the live polio vaccine virus may also cause an acute infection of motor neurons with symptoms and signs similar to poliomyelitis, although usually milder. Specific polymerase chain reaction tests and viral cultures of cerebrospinal fluid are diagnostic. Motor neuron infection with the West Nile virus also occurs.

A **juvenile form of amyotrophic lateral sclerosis** is rare. Upper motor neuron loss as well as lower motor neuron loss is evident clinically, unlike SMA. The course is progressive and is ultimately fatal.

Pena-Shokeir and **Marden-Walker syndromes** are progressive motor neuron degenerations associated with severe arthrogryposis and congenital anomalies of many organ systems. **Pontocerebellar hypoplasias** are progressive degenerative diseases of the central nervous system that begin in fetal life; one form also involves motor neuron degeneration resembling an SMA, but the *SMN* gene or chromosome 5 is normal.

Motor neurons become involved in several metabolic diseases of the nervous system, such as gangliosidosis (Tay-Sachs disease), ceroid lipofuscinosis (Batten disease), and glycogenosis II (Pompe disease), but the signs of denervation may be minor or obscured by the more prominent involvement of other parts of the central nervous system or of muscle.

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Chapter 612 ■ Hereditary Motor-Sensory Neuropathies

The hereditary motor-sensory neuropathies (HMSNs) are a group of progressive diseases of peripheral nerves. Motor components generally dominate the clinical picture, but sensory and autonomic involvement is expressed later.

612.1 • Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease; HMSN Type I)

This disease is the most common genetically determined neuropathy and has an overall prevalence of 3.8/100,000. It is transmitted as an autosomal dominant trait with 83% expressivity; the 17p11.2 locus is the site of the abnormal gene. Autosomal

recessive transmission also is described, but is rarer. The gene product is peripheral myelin protein P22 (PMP22). A much rarer X-linked HMSN type I results from a defect at the Xq13.1 locus, causing mutations in the gap junction protein connexin-32.

CLINICAL MANIFESTATIONS. Most patients are asymptomatic until late childhood or early adolescence, but young children sometimes manifest gait disturbance as early as the 2nd yr. The peroneal and tibial nerves are the earliest and most severely affected. Children with the disorder are often described as being clumsy, falling easily, or tripping over their own feet. The onset of symptoms may be delayed until after the 5th decade.

Muscles of the anterior compartment of the lower legs become wasted, and the legs have a characteristic stork-like contour. The muscular atrophy is accompanied by progressive weakness of dorsiflexion of the ankle and eventual footdrop. The process is bilateral but may be slightly asymmetric. Pes cavus deformities invariably develop due to denervation of intrinsic foot muscles, further destabilizing the gait. Atrophy of muscles of the forearms and hands is usually not as severe as that of the lower extremities, but in advanced cases contractures of the wrists and fingers produce a claw hand. Proximal muscle weakness is a late manifestation and is usually mild. Axial muscles are not involved.

The disease is slowly progressive throughout life, but patients occasionally show accelerated deterioration of function over a few years. Most patients remain ambulatory and have normal longevity, although orthotic appliances are required to stabilize the ankles.

Sensory involvement mainly affects large myelinated nerve fibers that convey proprioceptive information and vibratory sense, but the threshold for pain and temperature may also increase. Some children complain of tingling or burning sensations of the feet, but pain is rare. Because the muscle mass is reduced, the nerves are more vulnerable to trauma or compression. Autonomic manifestations may be expressed as poor vasomotor control with blotching or pallor of the skin of the feet and inappropriately cold feet.

Nerves often become palpably enlarged. Tendon stretch reflexes are lost distally. Cranial nerves are not affected. Sphincter control remains well preserved. Autonomic neuropathy does not affect the heart, gastrointestinal tract, or bladder. Intelligence is normal. A unique point mutation in *PMP22* causes progressive auditory nerve deafness in addition, but this is usually later in onset than the peripheral neuropathy.

Davidenkow syndrome is a variant of HMSN type I with a scapuloperoneal distribution.

LABORATORY FINDINGS AND DIAGNOSIS. Motor and sensory nerve conduction velocities are greatly reduced, sometimes as slow as 20% of normal conduction time. In new cases without a family history, both parents should be examined, and nerve conduction studies should be performed.

Electromyography (EMG) and muscle biopsy are not usually required for diagnosis, but they show evidence of many cycles of denervation and reinnervation. Serum creatine kinase level is normal. Cerebrospinal fluid (CSF) protein may be elevated, but no cells appear in the CSF.

Sural nerve biopsy is diagnostic. Large- and medium-sized myelinated fibers are reduced in number, collagen is increased, and characteristic **onion bulb formations** of proliferated Schwann cell cytoplasm surround axons. This pathologic finding is called **interstitial hypertrophic neuropathy.** Extensive segmental demyelination and remyelination also occur.

The definitive molecular genetic diagnosis may be made in blood.

TREATMENT. Stabilization of the ankles is a primary concern. In early stages, stiff boots that extend to the mid-calf often suffice, particularly when patients walk on uneven surfaces such as ice and snow or stones. As the dorsiflexors of the ankles weaken further, lightweight plastic splints may be custom made to extend beneath the foot and around the back of the ankle. They are worn inside the socks and are not visible, reducing self-consciousness. External short-leg braces may be required when footdrop becomes complete. Surgical fusion of the ankle may be considered in some cases.

The leg should be protected from traumatic injury. In advanced cases, compression neuropathy during sleep may be prevented by placing soft pillows beneath or between the lower legs. Burning paresthesias of the feet are not common but are often abolished by phenytoin or carbamazepine. No medical treatment is available to arrest or slow the progression.

612.2 • Peroneal Muscular Atrophy (Axonal Type)

This disease is clinically similar to HMSN type I, but the rate of progression is slower and the disability is less. EMG shows denervation of muscle. Sural nerve biopsy reveals axonal degeneration rather than the demyelination and whorls of Schwann cell processes typical in type I. The locus is on chromosome 1 at 1p35-p36; this is a different disease than HMSN type I, although both are transmitted as autosomal dominant traits.

612.3 • Dejerine-Sottas Disease (HMSN Type III)

This interstitial hypertrophic neuropathy of autosomal dominant transmission is similar to HMSN type I but is more severe. Symptoms develop in early infancy and are rapidly progressive. Pupillary abnormalities, such as lack of reaction to light and *Argyll Robertson pupil,* are common. Kyphoscoliosis and pes cavus deformities complicate about 35% of cases. Nerves become palpably enlarged at an early age.

The onion-bulb formations seen in the sural nerve biopsy specimen are more pronounced. Hypomyelination also occurs.

The genetic locus of 17p11.2 is identical to that of HMSN type I or Charcot-Marie-Tooth disease. The clinical and pathologic differences may be phenotypical variants of the same disease, analogous to the situation in Duchenne and Becker muscular dystrophies. An autosomal recessive form of Dejerine-Sottas disease is also described but is incompletely documented.

612.4 • Roussy-Lévy Syndrome

This syndrome is defined as a combination of HMSN type I and cerebellar deficit resembling Friedreich ataxia, but it does not have cardiomyopathy.

612.5 • Refsum Disease

(See Chapter 86.2.)

This rare disease is due to an enzymatic block in β-oxidation of phytanic acid to pristanic acid. Phytanic acid is a branched-chain fatty acid that is derived mainly from dietary sources: spinach, nuts, and coffee. Levels of phytanic acid are greatly elevated in plasma, CSF, and brain tissue. The CSF shows an albuminocytologic dissociation with a protein concentration of 100–600 mg/dL.

Clinical onset is usually between 4 and 7 yr of age, with intermittent motor and sensory neuropathy. Ataxia, progressive neurosensory hearing loss, retinitis pigmentosa and loss of night vision, ichthyosis, and liver dysfunction also develop in various degrees. Motor and sensory nerve conduction velocities are delayed. Treatment is by dietary management and periodic plasma exchange.

612.6 • Fabry Disease

(See Chapter 86.4.)

This rare X-linked recessive trait results in storage of ceramide trihexose because of deficiency of the enzyme ceramide trihexosidase, which cleaves the terminal galactose from ceramide trihexose (ceramide-glucose-galactose-galactose), resulting in tissue accumulation of this trihexose lipid in central nervous system (CNS) neurons, Schwann cells and perineurial cells, ganglion cells of the myenteric plexus, skin, kidneys, blood vessel endothelial and smooth muscle cells, heart, sweat glands, cornea, and bone marrow. It is due to a missense mutation disrupting the crystallographic structure of α-galactosidase A.

CLINICAL MANIFESTATIONS. The presentation is in late childhood or adolescence, with recurrent episodes of burning pain and paresthesias of the feet and lower legs so severe that patients are unable to walk. These episodes are often precipitated by fever or by physical activity. Objective sensory and motor deficits are not demonstrated on neurologic examination, and reflexes are preserved. Characteristic skin lesions are seen in the perineal region, scrotum, buttocks, and periumbilical zone as flat or raised red-black telangiectases known as **angiokeratoma corporis diffusum.** Hypohidrosis may be present. Corneal opacities, cataracts, and necrosis of the femoral heads are inconstant features. The disease is progressive. Hypertension and renal failure are usually delayed until early adult life. Recurrent strokes result from vascular wall involvement. Death often occurs in the 5th decade owing to cerebral infarction or renal insufficiency, but a significant morbidity already occurs in childhood despite the absence of major organ failure.

LABORATORY FINDINGS. Motor and sensory nerve conduction velocities are normal to only mildly slow, showing preservation of large myelinated nerve fibers. CSF protein is normal. Proteinuria is present early in the course.

Pathologic features are usually first detected in skin or sural nerve biopsy specimens. Crystalline glycosphingolipids appear as *zebra bodies* in lysosomes of endothelial cells, in smooth myocytes of arterioles, and in Schwann cells, best demonstrated by electron microscopy. Nerves show a selective loss of small myelinated fibers and relative preservation of large and medium-sized axons, contrasting to most axonal neuropathies in which large myelinated fibers are most involved.

Assay for the deficient enzyme may be performed from skin fibroblasts, leukocytes, and other tissues. This test permits detection of the asymptomatic female carrier state and provides a reliable means of prenatal diagnosis.

TREATMENT. See Chapter 86.4 for specific therapy of Fabry disease. Medical therapy of painful neuropathies includes management of the initiating disease and therapy directed to the neuropathic pain independent of etiology. Pain may be burning or associated with paresthesias, hyperalgesia (abnormal response to noxious stomach), or allodynia (induced by non-noxious stimuli) (see Chapter 77). Neuropathic pain is often successfully managed by tricyclic antidepressants; selective serotonin reuptake inhibitors are less effective. Anticonvulsants (carbamazepine, phenytoin, gabapentin, lamotrigine) are also effective as are narcotic and non-narcotic analgesic agents.

612.7 • Giant Axonal Neuropathy

This rare autosomal recessive disease with onset in early childhood is a progressive mixed peripheral neuropathy and degeneration of central white matter, similar to the leukodystrophies. Ataxia and nystagmus are accompanied by signs of progressive peripheral neuropathy. Many affected children have frizzy hair, which microscopically shows variation in diameter of the shaft and twisting, similar to Menkes disease, or may appear normal. Focal axonal enlargements are seen in both the peripheral nervous system and the CNS, but the myelin sheath is intact. The disease is a general proliferation of intermediate filaments, including neurofilaments in axons, glial filaments (i.e., Rosenthal fibers) in brain, cytokeratin in hair, and vimentin in Schwann cells and fibroblasts. Nonsense and missense mutations or deletions occur in the *GAN* gene, with allelic heterogeneity, at 16q24. These mutations are responsible for defective synthesis of the protein gygaxonin, a member of the cytoskeletal BTB/kelch superfamily, crucial to linkage between intermediate proteins and the cell membrane. MRI shows white matter lesions of the brain similar to leukodystrophies, and magnetic resonance spectroscopy (MRS) demonstrates increased ratios of choline/creatine and myoinositol/creatine, with a normally preserved ratio of *N*-acetyl aspartate/creatine, indicating demyelination and glial proliferation without axonal loss. Gygaxonin is expressed in a wide variety of neuronal cell types and is localized to the Golgi apparatus and endoplasmic reticulum.

The diagnosis is established by microscopic examination of scalp hair and by MRI and MRS of the brain; it is confirmed by sural nerve biopsy and/or by genetic studies, if available, of the *GAN* gene.

612.8 • Congenital Hypomyelinating Neuropathy

This disorder is a lack of normal myelination of motor and sensory peripheral nerves but not of CNS white matter. It is not a degeneration or loss of previously formed myelin, thus differentiating it from a leukodystrophy. Schwann cells are preserved, and axons are normal. Cases in siblings suggest autosomal recessive inheritance. Mutations in the *MTMR2, PMP22, EGR2,* and *MPZ* genes have been demonstrated in various children with this neuropathy; hence, it is a syndrome rather than a single disease.

The condition is present from birth; hypotonia and developmental delay are the hallmark clinical findings. Many patients present clinically as having congenital insensitivity to pain. Cranial nerves are inconsistently involved, and respiratory distress and dysphagia are rare complications. Tendon reflexes are absent. Arthrogryposis is present at birth in at least ½ of the cases. It is uncertain whether the condition is progressive; myelination of nerves proceeds at a slow rate and remains incomplete. Motor and sensory nerve conduction velocities are slow. The diagnosis is confirmed by sural nerve biopsy, which shows lack of myelination of large and small fibers and sometimes interstitial hypertrophic reactive changes. Muscle biopsy may show mild neurogenic atrophy but not the characteristic alterations of spinal muscular atrophy. No inflammation is demonstrated in muscle or nerve. Treatment is supportive.

612.9 • Tomaculous Neuropathy

This hereditary neuropathy is characterized by redundant overproduction of myelin around each axon in an irregular segmen-

tal fashion so that tomaculous (i.e., sausage-shaped) bulges occur in the individual myelinated nerve fibers. The nerves are particularly prone to pressure palsies, and patients present with recurrent mononeuropathies secondary to minor trauma. It is transmitted as an autosomal dominant trait, and the locus has been identified at 17p11.2. Sural nerve biopsy is diagnostic, but special "teased fiber" preparations should be made to demonstrate the myelin abnormalities most clearly. The genetic defect is a deletion of exons in the *PMP22* gene. Treatment is supportive.

612.10 • LEUKODYSTROPHIES

Several hereditary degenerative diseases of white matter of the CNS also cause peripheral neuropathy. The most important are Krabbe disease (globoid cell leukodystrophy), metachromatic leukodystrophy, and adrenoleukodystrophy (see Chapter 86).

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Chapter 613 ■ Toxic Neuropathies

Many chemicals (organophosphates), toxins, and drugs are capable of causing peripheral neuropathy (Table 613-1). Heavy metals are well-known neurotoxins. Lead poisoning, especially if chronic, causes mainly a motor neuropathy selectively involving large nerves, such as the common peroneal, radial, and median nerves, a condition known as **mononeuritis multiplex** (see Chapter 709). Arsenic produces painful burning paresthesias and motor polyneuropathy. Exposure to industrial and agricultural chemicals is a less common cause of toxic neuropathy in children than in adults, but insecticides are neurotoxins for both insects and humans, and, if used as sprays in closed spaces, they may be inhaled and induce lethargy, vomiting, seizures, and neuropathy, particularly with recurrent or long-term exposure. Working adolescents and children in developing countries are also at risk. Puffer fish poisoning, usually by ingestion of even cooked fish meat contaminated with the venom, produces Guillain-Barré syndrome.

Antimetabolic and immunosuppressive drugs, such as vincristine, cisplatin, and paclitaxel, produce polyneuropathies as complications of chemotherapy for neoplasms. This "iatrogenic" cause is the most frequent etiology of toxic neuropathies in children. It is usually an axonal degeneration rather than primary demyelination, unlike autoimmune neuropathies.

Chronic uremia is associated with toxic neuropathy and myopathy. The neuropathy is caused by excessive levels of circulating parathyroid hormone. Reduction in serum parathyroid hormone levels is accompanied by clinical improvement and a return to normal of nerve conduction velocity.

Biologic neurotoxins are associated with tick paralysis, diphtheria, botulism, and the variants of paralytic shellfish poisoning. Lyme disease, West Nile virus, leprosy, herpes viruses (Bell palsy), and rabies also produce peripheral nerve– or anterior horn cell–induced weakness or paralysis. Various inborn errors of metabolism are also associated with peripheral neuropathy from metabolite toxicity or deficiencies (See Part X and Table 613-1).

TABLE 613-1. Toxic and Metabolic Neuropathies

METALS

Arsenic (insecticide, herbicide)
Lead (paint, batteries, pottery)
Mercury (metallic, vapor)
Thallium (rodenticides)

OCCUPATIONAL/INDUSTRY

Acrylamide (grouting, flocculation)
Carbon disulfide (solvent)
Cyanide
Dichlorophenoxyacetate
Dimethylaminopropionitrite
Ethylene oxide (gas sterilization)
Hexacarbons (glue, solvents)
Organophosphates (insecticides, petroleum additive)
Polychlorinated biphenyls
Tetrachlorbiphenyl
Trichloroethylene

DRUGS

Amiodarone
Chloramphenicol
Chloroquine
Cisplatin
Colchicine
Dapsone
Ethambutol
Ethanol
Gold
Hydralazine
Isoniazid
Metronidazole
Nitrofurantoin
Nucleosides (antiretroviral agents ddC, ddI, d4T)
Penicillamine
Pentamidine
Phenytoin
Pyridoxine (excessive)
Stilbamidine
Suramin
Thalidomide
Vincristine

METABOLIC DISORDERS

Fabry disease
Krabbe disease
Leukodystrophies
Porphyria
Tangier disease
Tyrosinemia
Uremia

Chapter 614 ■ Autonomic Neuropathies

Involvement of small, lightly or unmyelinated autonomic nerve fibers may be seen in many peripheral neuropathies; the autonomic manifestations are usually mild or subclinical. Certain autonomic neuropathies are more symptomatic and demonstrate varying degrees of involvement of the autonomic nervous system regulation of the cardiovascular, gastrointestinal, genitourinary, thermoregulatory, sudomotor, and pupillomotor systems.

The differential diagnosis is noted in Table 614-1. Autonomic nervous system functional tests are noted in Table 614-2. The general treatment of acquired autonomic dysfunction includes treating the primary disorder (systemic lupus erythematosus, diabetes) and long-term management of specific organ system manifestations (Table 614-3). Acute fluctuations of autonomic symptoms may be seen in Guillain-Barré syndrome. Rapid fluctuations of hypertension or tachycardia changing to hypotension or bradycardia should be managed carefully and with very short-acting medications.

TABLE 614-1. Autonomic Neuropathies

GUILLAIN-BARRÉ SYNDROME (GBS) (CHAPTER 615)

Non-GBS Autoimmunity
Paraneoplastic (type I antineuronal nuclear antibody)
Lambert-Eaton syndrome
Antibodies to neuronal nicotinc acetylcholine receptors
Antibodies to P/Q type calcium channels
Other autoantibodies
Systemic lupus erythematosus

Hereditary
Type I autosomal dominant
Type II autosomal recessive (Morvan disease)
Type III autosomal recessive (Riley-Day)
Type IV autosomal recessive (congenital insensitivity to pain with anhidrosis)
Type V absence of pain

Metabolic
Fabry disease
Diabetes mellitus
Tangier disease
Porphyria

Infectious
HIV
Chagas' disease
Botulism
Leprosy
Diphtheria

Other
Triple A (Allgrove) syndrome
Navajo Indian neuropathy
Multiple endocrine neoplasia type 2b

Toxins (see Table 613-1)

TABLE 614-2. Autonomic Function Testing

Both sympathetic and parasympathetic divisions of the autonomic nervous system are involved in all tests of autonomic function

CARDIAC PARASYMPATHETIC NERVOUS SYSTEM FUNCTION
Heart rate variability with deep respiration (respiratory sinus arrhythmia); time-domain and frequency-domain assessments
Heart rate response to Valsalva maneuver
Heart rate response to standing

SYMPATHETIC ADRENERGIC FUNCTION
Blood pressure response to upright posture (standing or tilt table)
Blood pressure response to Valsalva maneuver
Microneurography

SYMPATHETIC CHOLINERGIC FUNCTION
Thermoregulatory sweat testing
Quantitative sudomotor-axon reflex test
Sweat imprint methods
Sympathetic skin response

From Freeman R: Autonomic peripheral neuropathy. *Lancet* 2005;365:1259–1270.

TABLE 614-3. Management of Autonomic Neuropathies

PROBLEM	TREATMENT
Orthostatic hypotension	Volume and salt supplements Fluorohydrocortisone (mineralocorticoid) Midodrine (α-agonist)
Gastroparesis	Prokinetic agents (metaclopramide, domperidone, erythromycin)
Hypomotility	Fiber, laxatives
Urinary dysfunction	Timed voiding; bladder catheterization
Hyperhidrosis	Anticholinergic agents (glycopyrrolate, propanthdine) Intracutaneous botulism toxin

614.1 • Familial Dysautonomia

Familial dysautonomia (Riley-Day syndrome) is an autosomal recessive disorder that is common in Eastern European Jews, among whom the incidence is 1/10,000–20,000, and the carrier state is estimated to be 1%. It is rare in other ethnic groups. The defective gene is at the 9q31-q33 locus. The familial dysautonomia gene is identified as *IKBKAP,* with aberrant splicing and a truncated protein. This and other autonomic neuropathies are often regarded as **neurocristopathies** because the abnormal target tissues are largely derived from neural crest.

PATHOLOGY. This disease of the peripheral nervous system is characterized pathologically by a reduced number of small unmyelinated nerve fibers that carry pain, temperature, and taste sensations and that mediate autonomic functions. Large myelinated afferent nerve fibers that relay impulses from muscle spindles and Golgi tendon organs also are deficient. The degree of demonstrable anatomic change in peripheral and especially autonomic nerves is variable. Fungiform papillae of the tongue (taste buds) are absent or reduced in number. The number of parasympathetic ganglion cells in the myenteric plexuses is reduced. There is terminal vessel hyperperfusion in tissues, despite an overall hypoperfusion of organs and extremities.

CLINICAL MANIFESTATIONS. The disease is expressed in infancy by poor sucking and swallowing. Aspiration pneumonia may occur. Feeding difficulties remain a major symptom throughout childhood. Vomiting crises may occur. Episodic somnolence may occur in infants. Excessive sweating and blotchy erythema of the skin are common, especially at mealtime or when the child is excited. Infants are vulnerable to heatstroke. Episodic hyperhidrosis is due to chemical hypersensitivity of the remaining reduced number of sudomotor axons rather than of the sweat gland secretory cells. Breath-holding spells followed by syncope are common in the 1st 5 yr. As affected children become older, insensitivity to pain becomes evident and traumatic injuries are frequent. Corneal ulcerations are common. Newly erupting teeth cause tongue ulcerations. Walking is delayed or clumsy or appears ataxic because of poor sensory feedback from muscle spindles. The ataxia is probably related more to deficient muscle spindle feedback and to vestibular nerve dysfunction than to cerebellar involvement. Tendon stretch reflexes are absent. Scoliosis is a serious complication in the majority of patients and usually is

progressive. Overflow tearing with crying does not normally develop until 2–3 mo of age but fails to develop after that time or is severely reduced in children with familial dysautonomia. There is an increased incidence of urinary incontinence. Bradycardia and other cardiac arrhythmias may occur, and some patients require a cardiac pacemaker.

About 40% of patients have generalized major motor seizures, some of which are associated with acute hypoxia during breath holding, some with extreme fevers, but most without an apparent precipitating event. Body temperature is poorly controlled; both hypothermia and extreme fevers occur. Intellectual function is usually impaired but is unrelated to epilepsy. Puberty is often delayed, especially in girls. Understature may occur, but growth velocity can be accelerated by treatment with growth hormone. Speech is often slurred or nasal.

After 3 yr of age, autonomic crises begin, usually with attacks of cyclic vomiting lasting 24–72 hr or even several days. Retching and vomiting occur every 15–20 min and are associated with hypertension, profuse sweating, blotching of the skin, apprehension, and irritability. Prominent gastric distention may occur, causing abdominal pain and even respiratory distress. Hematemesis may complicate pernicious vomiting.

Allgrove syndrome is a clinical variant, involving alacrima, achalasia, autonomic dysfunction with orthostatic hypotension and altered heart rate variability, and sensorimotor polyneuropathy, usually presenting in adolescence. Cholinergic dysfunction may be demonstrated.

LABORATORY FINDINGS. Electrocardiography discloses prolonged correcting QT intervals with lack of appropriate shortening with exercise, a reflection of the aberration in autonomic regulation of cardiac conduction. Chest radiographs show atelectasis and pulmonary changes resembling cystic fibrosis. Urinary vanillylmandelic acid level is decreased, and homovanillic acid level is increased. Plasma level of dopamine β-hydroxylase (the enzyme that converts dopamine to epinephrine) is diminished. Sural nerve biopsy shows a decreased number of unmyelinated fibers. Electroencephalography is useful for evaluating seizures.

DIAGNOSIS. Slow IV infusion of norepinephrine produces an exaggerated pressor response. The hypotensive response to infusion of methacholine is increased. Intradermal injection of 1 : 1,000 histamine phosphate fails to produce a normal axon flare, and local pain is absent or diminished. Because the skin of a normal infant reacts more intensely to histamine, a 1 : 10,000 dilution should be used. Instillation of 2.5% methacholine into the conjunctival sac produces miosis in patients with familial dysautonomia and no detectable effect on a normal pupil; this is a nonspecific sign of parasympathetic denervation due to any cause. Methacholine is applied to only 1 eye in this test, with the other eye serving as a control; the pupils are compared at 5-min intervals for 20 min. The genetic marker in blood will be available for definitive diagnostic testing.

TREATMENT. Symptomatic treatment includes special attention to the respiratory and gastrointestinal systems, methylcellulose eyedrops or topical ocular lubricants to replace tears and prevent corneal ulceration, orthopedic management of scoliosis and joint problems, and appropriate anticonvulsants for epilepsy. Chlorpromazine is an effective antiemetic and may be given as rectal suppositories during autonomic crises. It also reduces apprehension and lowers the blood pressure. Dehydration and electrolyte disturbances should be anticipated. Bethanechol may be an alternative drug for cyclic vomiting. It is also useful for enuresis, another common complication, and augments tear production. Protection from injuries is important because of the lack of pain as a protective mechanism. Scoliosis often requires surgical treatment. Antiepileptic drugs may be required. A cardiac pacemaker may be required by some children. Blood pressure monitoring may be important in some cases. A promising genetic approach to treatment, although not standard therapy at this time, is the use of a polyphenol to regulate the expression of *IKBKAP* transcripts.

PROGNOSIS. Most patients die in childhood, usually of chronic pulmonary failure or aspiration.

614.2 • Other Autonomic Neuropathies

MYENTERIC PLEXUS NEUROPATHIES. *Aganglionic megacolon (Hirschsprung disease)* is a failure of embryonic development of parasympathetic neurons in the submucosal and myenteric plexuses of segments of the colon and rectum. Nerves between the longitudinal and circular layers of smooth muscle of the gut wall are hypertrophic; ganglion cells are absent (see Chapter 329).

CONGENITAL INSENSITIVITY TO PAIN AND ANHIDROSIS. This hereditary disorder of uncertain genetic transmission affects boys much more frequently than girls and presents in early infancy. Patients have episodes of high fever related to warm environmental temperatures because they do not perspire. Frequent burns and traumatic injuries result from apparent lack of pain perception. Intelligence is normal. Nerve biopsy reveals an almost total absence of unmyelinated nerve fibers that convey impulses of pain, temperature, and autonomic functions. Some cases of hypomyelinating neuropathy present clinically as congenital insensitivity to pain (see Chapter 612.8). The sympathetic skin response as an electrophysiologic study is a reliable diagnostic test in cases associated with a mutation at the TrKA receptor for nerve growth factor.

REFLEX SYMPATHETIC DYSTROPHY. This disorder is a form of local causalgia, usually involving a hand or foot but not corresponding to the anatomic distribution of a peripheral nerve (see Chapter 167.2). A continuous burning pain and hyperesthesia are associated with vasomotor instability in the affected zone, resulting in increased skin temperature, erythema, and edema due to vasodilatation and hyperhidrosis. In the chronic state, atrophy of skin appendages, cool and clammy skin, and disuse atrophy of underlying muscle and bone occur. More than 1 extremity is occasionally involved. The pain is disabling and is exacerbated by the movement of an associated joint, although no objective signs of arthritis are seen; immobilization provides some relief. The most common preceding event is local trauma in the form of a contusion, laceration, sprain, or fracture that occurred days or weeks earlier.

Several theories of pathogenesis have been proposed to explain this phenomenon. The most widely accepted is reflexive overactivity of autonomic nerves in response to injury, and regional sympathetic blockade often affords temporary relief. Physiotherapy also is helpful. Some cases resolve spontaneously after weeks or months, but others continue to be symptomatic and require sympathectomy. A psychogenic component is suspected in some cases but is difficult to prove.

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Chapter 615 ■ Guillain-Barré Syndrome

Guillain-Barré syndrome is a postinfectious polyneuropathy involving mainly motor but sometimes also sensory and autonomic nerves. This syndrome affects people of all ages and is not hereditary. The disorder closely resembles experimental allergic polyneuritis in animals. Most patients have a demyelinating neuropathy, but primarily axonal degeneration is documented in some cases.

CLINICAL MANIFESTATIONS. The paralysis usually follows a nonspecific viral infection by about 10 days. The original infection may have caused only gastrointestinal (especially *Campylobacter jejuni,* but also *Helicobacter pylori)* or respiratory tract (especially *Mycoplasma pneumoniae*) symptoms. West Nile virus also may cause Guillain-Barré–like syndrome, but more frequently causes motor neuron disease similar to poliomyelitis. Guillain-Barré syndrome is reported following administration of vaccines against rabies, influenza poliomyelitis (oral), and possibly the conjugated meningococcal vaccine.

Weakness begins usually in the lower extremities and progressively involves the trunk, the upper limbs, and finally the bulbar muscles, a pattern known as **Landry ascending paralysis.** Proximal and distal muscles are involved relatively symmetrically, but asymmetry is found in 9% of patients. The onset is gradual and progresses over days or weeks. Particularly in cases with an abrupt onset, tenderness on palpation and pain in muscles is common in the initial stages. Affected children are irritable. Weakness may progress to inability or refusal to walk and later to flaccid tetraplegia. Paresthesias occur in some cases. The differential diagnosis of acute weakness is noted in Table 606-3.

Bulbar involvement occurs in about half of cases. Respiratory insufficiency may result. Dysphagia and facial weakness are often impending signs of respiratory failure. They interfere with eating and increase the risk of aspiration. The facial nerves may be involved. Some young patients may exhibit symptoms of viral meningitis or meningoencephalitis. Extraocular muscle involvement is rare, but in an uncommon variant, oculomotor and other cranial neuropathies are severe early in the course. **Miller-Fisher syndrome** consists of acute external ophthalmoplegia, ataxia, and areflexia. Papilledema is found in some cases, although visual impairment is not clinically evident. Urinary incontinence or retention of urine is a complication in about 20% of cases but is usually transient. Miller-Fisher syndrome overlaps with Bickerstaff brainstem encephalitis, which also shares many features with Guillain-Barré syndrome with lower motor neuron involvement and may indeed be the same basic disease.

Tendon reflexes are lost, usually early in the course, but are sometimes preserved until later. This variability may cause confusion when attempting early diagnosis. The autonomic nervous system may also be involved in some cases. Lability of blood pressure and cardiac rate, postural hypotension, episodes of profound bradycardia, and occasional asystole occur. Cardiovascular monitoring is important. A few patients require insertion of a temporary venous cardiac pacemaker.

Chronic relapsing polyradiculoneuropathy (sometimes called chronic inflammatory demyelinating polyradiculoneuropathy) or ***chronic unremitting polyradiculoneuropathy*** are chronic varieties of Guillain-Barré syndrome that recur intermittently or do not improve for a period of months or years. About 7% of children with Guillain-Barré syndrome suffer an acute relapse. Patients are usually severely weak and may have a flaccid tetraplegia with or without bulbar and respiratory muscle involvement.

Congenital Guillain-Barré syndrome is described rarely, presenting as generalized hypotonia, weakness, and areflexia in an affected neonate, fulfilling all electrophysiologic and cerebrospinal fluid (CSF) criteria, and in the absence of maternal neuromuscular disease. Treatment may not be required, and there is gradual improvement over the first few months and no evidence of residual disease by 1 yr of age. In one case, the mother had ulcerative colitis treated with prednisone and mesalamine from the 7th mo until delivery at term.

LABORATORY FINDINGS AND DIAGNOSIS. CSF studies are essential for diagnosis. The CSF protein is elevated to more than twice the upper limit of normal, glucose level is normal, and there is no pleocytosis. Fewer than 10 white blood cells/mm^3 are found. The results of bacterial cultures are negative, and viral cultures rarely isolate specific viruses. The dissociation between high CSF protein and a lack of cellular response in a patient with an acute or subacute polyneuropathy is diagnostic of Guillain-Barré syndrome.

Motor nerve conduction velocities are greatly reduced, and sensory nerve conduction time is often slow. Electromyography shows evidence of acute denervation of muscle. Serum creatine kinase (CK) level may be mildly elevated or normal. Antiganglioside antibodies, mainly against GM1 and GD1, are sometimes elevated in the serum in Guillain-Barré syndrome, particularly in cases with primarily axonal rather than demyelinating neuropathy, and suggest that they may play a role in disease propagation and/or recovery in some cases (Table 615-1). Muscle biopsy is not usually required for diagnosis; specimens appear normal in early stages and show evidence of denervation atrophy in chronic stages. Sural nerve biopsy tissue shows segmental demyelination, focal inflammation, and wallerian degeneration but also is usually not required for diagnosis.

Serologic testing for *Campylobacter* and *Helicobacter* infections helps establish the cause if results are positive but does not alter the course of treatment. Results of stool cultures are rarely positive because the infection is self-limited and only occurs for about 3 days, and the neuropathy follows the acute gastroenteritis.

TREATMENT. Patients in early stages of this acute disease should be admitted to the hospital for observation because the ascending paralysis may rapidly involve respiratory muscles during the next 24 hr. Patients with slow progression may simply be observed for stabilization and spontaneous remission without

TABLE 615-1. Classification of Guillain-Barré Syndrome and Related Disorders and Typical Antiganglioside Antibodies by Pathology

	ANTIBODIES
Acute inflammatory demyelinating polyradiculoneuropathy	Unknown
Acute motor and sensory axonal neuropathy	GM1, GM1b, GD1a
Acute motor axonal neuropathy	GM1, GM1b, GD1a, GalNac-GD1a
Acute sensory neuronopathy	GD1b
Acute pandysautonomia	
Regional variants	
Fisher syndrome	GQ1b, GT1a
Oropharyngeal	GT1a
Overlap	
Fisher/Guillain-Barré overlap syndrome	GQ1b, GM1, GM1b, GD1a, GalNac-GD1a

From Hughes RAC: Treatment of Guillain-Barré syndrome with corticosteroids: Lack of benefit? *Lancet* 2004;363:181–182.

treatment. Rapidly progressive ascending paralysis is treated with intravenous immunoglobulin (IVIG), administered for 2, 3, or 5 days. A commonly recommended protocol is IVIG 0.4 gm/kg/day for 5 consecutive days. Plasmapheresis, and/or immunosuppressive drugs are alternatives, if IVIG is ineffective. Steroids are not effective. Combined administration of immunoglobulin and interferon is effective in some patients. Supportive care, such as respiratory support, prevention of decubiti in children with flaccid tetraplegia, and treatment of secondary bacterial infections, is important.

Chronic relapsing polyradiculoneuropathy or unremitting chronic neuropathy is also treated with IVIG. Plasma exchange, sometimes requiring as many as 10 exchanges daily, is an alternative. Remission in these cases may be sustained, but relapses may occur within days, weeks, or even after many months; relapses usually respond to another course of plasmapheresis. Steroid and immunosuppressive drugs are another alternative, but their effectiveness is less predictable. High-dose pulsed methylprednisolone given intravenously is successful in some cases. The prognosis in chronic forms of the Guillain-Barré syndrome is more guarded than in the acute form, and many patients are left with major residual handicaps.

Even if *Campylobacter jejuni* infection is documented by stool culture or serologic tests, treatment of the infection is not necessary because it is self-limited, and the use of antibiotics does not alter the course of the polyneuropathy.

For the treatment of chronic neuropathic pain following Guillain-Barré syndrome, gabapentin is more effective than carbamazepine, and the requirement for fentanyl is reduced.

PROGNOSIS. The clinical course is usually benign, and spontaneous recovery begins within 2–3 wk. Most patients regain full muscular strength, although some are left with residual weakness. The tendon reflexes are usually the last function to recover. Improvement usually follows a gradient inverse to the direction of involvement, with recovery of bulbar function first and lower extremity weakness resolving last. Bulbar and respiratory muscle involvement may lead to death if the syndrome is not recognized and treated. Although prognosis is generally good with the majority of children recovering completely, three clinical features are predictive of poor outcome with sequelae: cranial nerve involvement, intubation, and maximum disability at the time of presentation. An electrophysiologic feature of conduction block is predictive of good outcome. Long-term follow-up studies of patients who recover from an attack of Guillain-Barré syndrome reveal that many do have some permanent axonal loss, with or without residual clinical signs of chronic neuropathy. Easy fatigue is one of the most common chronic symptoms, but it is not the rapid fatigability of muscles in myasthenia gravis. Among patients with the axonal form of Guillain-Barré syndrome, most who had slow recovery over the first 6 mo could eventually walk, although some required years to recover. EMG and NCV electrophysiologic studies do not necessarily predict the long-term outcome.

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Chapter 616 ■ Bell Palsy

Bell palsy is an acute unilateral facial nerve palsy that is not associated with other cranial neuropathies or brainstem dysfunction. It is a common disorder at all ages from infancy through adolescence and usually develops abruptly about 2 wk after a systemic viral infection. The preceding infection is due to the herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, Lyme disease, mumps virus, *Mycoplasma* (Table 616-1). Active or reac-

TABLE 616-1. Etiologies of Acute Peripheral Facial Palsy

COMMON
Herpes simplex virus type 1*
Varicella-zoster virus*
LESS COMMON INFECTIONS
Otitis media ± cholesteatoma
Lyme disease
Epstein-Barr virus
Cytomegalovirus
Mumps
Human herpesvirus 6
Intranasal influenza vaccine
Mycoplasma
OTHER LESS COMMON CONDITIONS
Trauma
Tumor
Hypertension
Guillain-Barré syndrome
Sarcoidosis
Melkersson-Rosenthal syndrome†
Ribavirin
Interferon

*Implicated in idiopathic Bell palsy.
†Noncaseating granulomas with facial (lips, eyelids) edema, recurrent alternating facial paralysis, family history, migraines, or headaches.

tivation of herpes simplex or varicella-zoster virus may be the most common cause of Bell palsy. The disease may occasionally be a postinfectious allergic or immune demyelinating facial neuritis. It also may be a focal toxic or inflammatory neuropathy and has been associated with ribavirin and interferon-α therapy for hepatitis C.

CLINICAL MANIFESTATIONS. The upper and lower portions of the face are paretic, and the corner of the mouth droops. Patients are unable to close the eye on the involved side and may develop an exposure keratitis at night. Taste on the anterior ⅔ of the tongue is lost on the involved side in about ½ of cases; this finding helps to establish the anatomic limits of the lesion as being proximal or distal to the chorda tympani branch of the facial nerve. Numbness and paresthesias do not usually occur, but ipsilateral numbness of the face is reported in a few cases and probably is due to viral (especially herpes) or postviral immunologic impairment of the trigeminal and the facial nerved. Several grading systems have been devised for Bell palsy: the Sunnybrook, House-Brackmann, and Yanagihara systems.

TREATMENT. Oral prednisone (1 mg/kg/day for 1 wk, then a 1-wk taper) started within the first 3–5 days results in improved outcome. Because of the recovery of herpes simplex virus in the neural fluid of the 7th nerve, some also recommend adding oral acyclovir or valacyclovir to the prednisone therapy. Surgical decompression of the facial canal, theoretically to provide more space for the swollen facial nerve, is not of value. Physiotherapy to the facial muscles is recommended in some chronic cases with poor recovery, but the efficacy of this treatment is uncertain. Protection of the cornea with methylcellulose eyedrops or an ocular lubricant is especially important at night. Some plastic surgeons use botulinum toxin to treat chronic unilateral ptosis, but this has little application in pediatric patients.

PROGNOSIS. The prognosis is excellent. More than 85% of cases recover spontaneously with no residual facial weakness; another 10% have mild facial weakness as a sequela; only 5% are left with permanent severe facial weakness. In patients who do not recover within a few weeks (chronic), electrophysiologic examination of the facial nerve helps to determine the degree of neuropathy and regeneration. In chronic cases, other causes of facial neuropathy should be considered, including facial nerve tumors such as schwannomas and neurofibromas, infiltration of the facial nerve by leukemic cells or by a rhabdomyosarcoma of the middle ear, brainstem infarcts or tumors, and traumatic injury of the facial nerve.

FACIAL PALSY AT BIRTH. This is usually a compression neuropathy from forceps application during delivery and recovers spontaneously in a few days or weeks in most cases. ***Congenital absence of the depressor angularis oris muscle*** causes facial asymmetry, especially when an affected infant cries. It is not a facial nerve lesion but is a cosmetic defect that does not interfere with feeding. Infants with ***Möbius syndrome*** may have bilateral or, less commonly, unilateral facial palsy; this syndrome is usually caused by symmetric calcified infarcts in the tegmentum of the pons and medulla oblongata during mid-gestation or late fetal life, although it rarely may be a developmental anomaly of the brainstem.

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