

CHAPTER 17

Diseases of Muscle and Neuromuscular Junction

MYOPATHIES

Clinical Features

Myopathies are diseases that primarily affect the muscles and are usually characterized clinically by weakness, fatigue, or stiffness (myotonia). They are usually characterized by symmetrical proximal muscle weakness and wasting, normal sensation, and normal stretch reflexes. More than one-half of muscle bulk must be lost before functional weakness can be demonstrated on clinical examination. Achings or muscle cramps can be present. The patient's complaints usually localize the weakness to a certain group of muscles. The questions listed in Box 17-1 should be answered.

The neuromuscular examination (see Chapter 5) should give the examiner a good idea of muscle groups affected, acuteness or chronicity of disease, progression of disease, and inheritance pattern in familial myopathies.

BOX 17-1.

1. Is it an acute (days), subacute (weeks), or chronic (months to years) process?
 2. Is the weakness symmetrical, proximal, distal, or generalized?
 3. What muscles were affected first, and what has been the progression of the weakness? Relentlessly worse or fluctuating?
 4. Does exercise make the symptoms worse (fatigability in myasthenia), or do the symptoms improve with muscle activity (as in myotonias)?
 5. Are the ocular or bulbar muscles predominantly affected, as in myasthenic or mitochondrial disorders?
 6. Are the neck muscles involved?
 7. Is there difficulty chewing, swallowing, or breathing?
 8. Does exercise produce cramps or weakness? Is there an associated change in the color of the urine suggestive of myoglobinuria?
 9. Is there a family history? If so, what is the inheritance pattern? A pedigree of the family should be drawn.
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Laboratory Tests

Laboratory tests should be done in selected and methodical way, beginning with measurement of serum electrolytes (potassium, magnesium, and calcium) and enzymes. Electrolyte alterations can produce weakness or muscle irritability. The ischemic forearm exercise test to measure lactic acid combined with electromyography (EMG) is necessary in certain metabolic myopathies. The most reliable suspected serum muscle enzyme is creatine kinase (CK). Patients should avoid heavy exercise, injections, and muscle trauma before blood sampling for muscle enzymes. Serum CK isoenzymes evaluation (MM band) indicate skeletal muscle destruction. DNA studies are commercially available for Duchenne Becker, myotonic muscular dystrophy, and mitochondrial

disorders. Electrophysiologic studies such as EMG and nerve conduction velocities (NCV), should precede muscle biopsy. Electrophysiologic studies which can show those muscles which have active involvement can help to select the appropriate muscle for biopsy. In symmetrical myopathies, electrophysiologic studies can be done on one side and biopsy on other side to avoid needle tracks that produce artifactual alterations in biopsy sample. EMG demonstrates functional activity in the muscle. The muscle biopsy can confirm the clinical impression, differentiate denervation from primary myopathies, demonstrate metabolic diseases, and support diagnoses of inflammatory myopathies and detect mitochondrial disorders.

Inflammatory Myopathies

Inflammatory myopathies represent heterogeneous group of disorders characterized by different morphologic alterations of the muscle tissue with. The inflammatory myopathies can be acute in onset and rapidly progressive or can be insidious in onset and slowly progressive. They can be benign, transient and spontaneously remitting or respond to therapy (pyomyositis, parasitic and autoimmune forms), whereas others can be disabling, resistant to therapy, and even fatal. Immunodysfunction plays an important role in myositis.

Dermatomyositis and Polymyositis Syndromes

Dermatomyositis (DM) and polymyositis (PM) are the most common acquired inflammatory myopathies. Both share proximal and symmetrical involvement of muscles, elevation of muscle enzymes, response to immunosuppressive therapy. However, there are striking differences in the immunologic mechanism and in the pathologic changes besides the obvious skin involvement in dermatomyositis. Both diseases can occur at any age, and both occur predominantly in females. Most cases of DM occur between 5 and 14 years of age, and most cases of PM occur in the 50s and 60s. Both can be associated with connective tissue disorders, and predominantly the adult form of DM can be associated with malignancies (Table 17-1).

Childhood and juvenile dermatomyositis. It frequently has an insidious onset and rapid progression and lacks a precipitating factor. Facial erythema, fatigue, general malaise, and muscle weakness are the most frequent complaints.

Muscle weakness is a constant feature. It is usually proximal in distribution, involving shoulders and pelvic muscles. Neck muscles, predominantly flexors, are frequently affected. In half of the patients, weakness is associated with muscle pain and tenderness.

Dysphagia and dysphonia are frequent and indicate involvement of muscles of deglutition and phonation.

Skin involvement is variable according to the stage of the disease but consistently affects face and extensor surfaces on joints. Facial lesion affects predominantly sun-exposed areas and consists of erythematous rash in butterfly distribution over malar regions and lilac discoloration (heliotrope) and edema of periorbital surfaces. Rash extends to neck and upper thoracic areas. Erythematous discoloration affects extensor surfaces of elbows, knees, and knuckles (Gottron's sign). Scalp involvement includes diffuse scaly dermatosis with erythema, atrophy, and often nonscarring alopecia.

Periungual hyperemia and telangiectasis are frequent, seem to correlate with the disease activity, and may represent early signs of recurrence. Subcutaneous nodules and ulcerations

occur in severe disease or in partially treated patients. Subcutaneous calcification (calcinosis) is a late event and is frequently associated with joint contractures. Ulceration and perforation of gastrointestinal tract as result of vasculitis can be the cause of death. Cardiac involvement and restrictive pulmonary disease have been described.

Laboratory findings include elevation of sedimentation rate and elevation of CK. Elevation of CK, predominantly MM isoenzyme, and elevation of serum myoglobin occur in active disease and can be used along with the clinical improvement of weakness as guide for course of disease and response to therapy. EMG shows increased insertional activity, fibrillation potentials, and train of positive sharp as well as waves indicating abnormal spontaneous activity, be myopathic features (decrease in duration of motor unit potentials and short duration polyphasic motor units). Nerve conduction velocities are normal.

Pathology of muscle biopsy shows endothelial hyperplasia of intramuscular blood vessels and segmental perivascular and intravascular mononuclear cell infiltration. In biopsies, some intramuscular arteries and veins show deposition of IgG, complement (3 and 9) immune complexes. There is necrosis and decreased number of capillaries surrounding individual muscle fibers. This microvasculopathy is due to deposition of neoantigens of the C5b-9 complement membrane attack complex early in the disease. Small areas of infarction in center of fascicles and necrosis or atrophy of muscle fibers in periphery of fascicles (perifascicular atrophy) with little or no inflammatory reaction are prominent features. The vasculitis, perifascicular atrophy, and reduced capillary density are most important and specific histologic diagnostic features of the disease (Table 17-2).

Treatment consists of general supportive care including rest, passive physical therapy oriented toward preventing contractures, and immunosuppressive therapy. Prednisone, 2 mg/kg in divided daily doses, should be given for 1 month after disease is clinically and enzymatically inactive. Intravenous gamma globulin has been tried with great success. Cytoxan pulse therapy along with steroids speeds recovery and decreases side effects of steroids.

Polymyositis and Dermatomyositis of the Adult. The skin lesions of adult dermatomyositis are similar to those seen in the childhood type except for calcinosis. Also contractures and skin ulcers are rare in adult type'. Skin lesions in adults can be seen without muscle weakness and with normal CK for 2 or more years ("amyopathic dermatomyositis"). However, EMGs and muscle biopsies reveal muscle involvement. DM of the adult is more frequently associated with a occult tumor. The muscle biopsy, the immune mechanism, and treatment are similar for both childhood and adult DM. When associated with malignancy, eradication of tumor should be the priority.

Adult polymyositis has insidious onset and progresses over weeks or months. Weakness usually starts in hip muscles, exhibited by difficulty arising from sitting or squatting position and difficulty climbing stairs. At this time, patient notices difficulty combing hair or doing activities that requires raising arms above head. Neck flexor muscle weakness is prominent feature. Dysphagia and respiratory muscle weakness may occur. There is preservation of strength in distal muscles and in ocular and facial muscles. Muscle pain or tenderness is not prominent. Visceral involvement includes cardiac involvement and interstitial pneumonitis. Muscle biopsy and immune mechanisms in PM differ from those seen in DM. In PM muscle biopsy shows scattered necrotic and regenerating fibers. The prominent perimysial and endomysial inflammatory mononuclear infiltrate is predominantly composed of T cells, particularly activated

CD8, and macrophages. There is no perifascicular atrophy and capillary density is normal (see Table 17-2).

Therapy. The treatment is variable, and response is not always good. Prednisone, 60 to 80 mg daily, in divided doses until disease is stabilized or improved according to clinical findings and CK level is stabilized, followed by alternate-day doses of 60 to 80 mg for at least 6 months, is effective. Azathioprine (Imuran), 2 mg/kg/day, can be added to patients who are nonresponsive to steroids. Cyclophosphamide (Cytoxan) pulse therapy, once a month for 6 months, has been used with good results in some corticosteroid-resistant patients and can be the first line of therapy to avoid steroid side effects. Methotrexate, cyclosporine and cytoxan have also been utilized. Other therapeutic modalities include plasmapheresis, intravenous immunoglobulin and total body, low dose irradiation.

Polymyositis Associated with Connective Tissue Disorders. Some adult polymyositis patients have connective tissue disorder associated (rheumatoid arthritis, scleroderma, mixed connective tissue disorders, lupus erythematosus, poly-arteritis nodosa, or Sjögren's syndrome). Clinical features such as arthritis, sclerosis of skin, renal disease, multiple mononeuropathies, or salivary gland enlargement should suggest associated connective tissue disorder.

Viral Polymyositis. Viruses including influenza types A and B and Coxsackie virus have been associated with acute local or diffuse myositis similar clinically and morphologically to idiopathic form. The exact relationship between viral infection and myositis is still unknown, but possibility exists that viruses elicit and perpetuate the autoimmune response responsible for PM and DM.

Inclusion Body Myositis. Inclusion body myositis is a disease predominantly seen in males. Age of onset varies from adolescence to elderly, but disease rarely starts before age of 50. The disorder is relatively benign, has insidious onset, and runs slow course of several years duration characterized by progressive weakness. This is one of the rare exceptions where the myopathy may begin distally rather than proximally. Extensor muscles are more frequently involved than flexors. Muscle pain and association with other connective tissue disorders is rare. Dysphagia is unusual, and cardiac abnormalities have not been described. CK is mostly normal. EMG shows both myopathic and neurogenic patterns. Muscle biopsy shows endomysial inflammatory mononuclear exudate invading nonnecrotic muscle fibers. The main histologic differentiating feature is the presence of single or multiple vacuoles within muscle fibers that contain small basophilic granules in their lumen or against their wall ("lined" or "rimmed vacuoles"). There is increased number of capillaries around individual muscle fibers. The inclusions are masses of filaments found in nucleus or cytoplasm. The inclusions are congophilic and immunoreact for beta amyloid protein and ubiquitin. There are often atrophied angular fibers, which suggest denervation. Currently there is no effective therapy for the disease.

Dystrophic Myopathies

Muscular dystrophies are myopathies of undetermined causes, are usually hereditary, and characterized by weakness caused by progressive degeneration of muscles. The dystrophies are best classified according to inheritance pattern, age at onset, progression of the disease, and muscles affected (Table 17-3). This includes the dystrophinopathies (including the Duchenne and Becker forms of muscular dystrophy), the sarcoglycanopathies (including the limb-girdle

muscular dystrophy) and the channelopathies (including the periodic paralyses and myotonic syndromes). Abnormalities in the membrane ion channels (sodium, chloride, calcium, potassium) which are crucial to muscle excitation are defined as channelopathies and may cause myotonia and episodic weakness (periodic paralysis). The complex of muscle proteins including dystrophin, sarcoglycan proteins and laminin link the contractile proteins with extracellular support structures defects in these proteins can cause a diffuse array of muscular dystrophies including limb-girdle dystrophy.

Dystrophinopathies

These are a group of disorders produced by either absence of dystrophin protein encoded in X chromosome (Xp21). (Table 17-4). Dystrophin is subsarcolemmal cytoskeletal protein. Dystrophin is concentrated in transverse riblike rings, or costameres, on cytoplasmic side of sarcolemma and attaches myofibrils to sarcolemma. Dystrophin has tight membrane association via dystrophin-associated protein complex (DAP), and provides mechanical support for the muscle membrane. Absence of dystrophin produces weakness of muscle membrane that ruptures under mechanical stress.

Duchenne (Pseudohypertrophic) Muscular Dystrophy. This lethal disorder is the most common dystrophy. It is inherited through X-linked recessive gene that has high spontaneous mutation rate. This gene is located in band I of region 2 of short arm of X chromosome (Xp21). This gene encodes for dystrophin. Deletions or mutations in this gene are cause of absence of dystrophin in Duchenne patients. Most patients are boys, but the disease can be seen in girls who have Turner's (XO) syndrome. Also some female carriers can manifest some symptoms of the disease (manifesting carriers). In most patients with Duchenne's dystrophy there is delay in reaching motor developmental milestones, and most of these patients never learn to walk normally. Onset of symptoms is variable but usually begins before age 4, when it is noted that the child walks on his toes, becomes clumsy, falls frequently, and has difficulty rising from the floor. Characteristic findings include waddling gait, toe walking with external foot rotation, and difficulty going up stairs, running, and rising from sitting position. There is early neck muscle involvement. When child is examined early in the disease, there is abnormal posture when standing, with marked lumbar lordosis, protuberant abdomen, and overextended knees. These children have husky appearance with herculean features and enlarged rubbery calves mainly as a result of infiltration and replacement of muscle fibers by fat and connective tissue (pseudohypertrophy). The thighs and tongue can be enlarged. Pain in calf muscles can be triggered by exercise. When asked to get up from the floor or chair, patient uses his arms to push himself up (Gower's maneuver). The progression of the disease is variable but relentless. Most patients stop ambulating independently by 8 to 12 years of age. Shortening and contracture of Achilles tendons occur early, but contractures of other joints are accelerated by immobilization. At this stage, muscles become severely atrophic, and stretch reflexes are lost. Progressive kyphoscoliosis with severe deformity late in the disease causes restrictive pulmonary deficit that along with cardiac fibrosis is often the cause of death. Intellectual impairment of nonprogressive type is part of disease. Levels of serum muscle enzymes are elevated. Early in disease, CK value can be as high as 50 times normal. Enzyme elevations can precede clinical symptoms and decline as disease progresses. EMG shows myopathic features. Muscle biopsy changes vary with disease stage but consist of type I fiber predominance, variation in fiber size with degeneration and regeneration, rounding and splitting of the fibers, and central migration of nuclei. Fibrosis and fatty infiltration of muscle are frequent findings. Absence of dystrophin by

immunoblotting are diagnostic. Correct diagnosis is made by combined analysis of DNA, immunoblot, and immunostain methods. In new cases without family history of the disease, polymerase chain reaction (PCR) analysis identifies most deletional cases.

Treatment: Management of the patient includes intensive physical and occupational therapy and bracing to prolong ambulation and to delay the development of contractures and deformities.

Carrier detection: Carrier detection begins with pedigree analysis and manual muscle testing of a suspected carrier. An elevated CK can detect new cases in childhood, but CK gradually decreases with age and pregnancy. Once dystrophin mutation is discovered in affected child (proband), carrier status is easier to determine in the patient's sisters, mother, and aunts by DNA testing done on their blood cells. If proband shows no deletions, use of genetic markers can be offered. Finally carrier status can be determined by obtaining muscle biopsy from suspected carrier for immunoblotting and immunostaining. *Prenatal diagnosis:* Cells from amniocentesis or chorionic villus sampling can be obtained to look for DNA dystrophin mutations. Fetal muscle biopsy can be used when DNA dystrophin mutations have not been identified in the family.

Becker Dystrophy. This is a less severe form of dystrophinopathy with clinical features similar to Duchenne dystrophy and similar inheritance pattern. The abnormal gene (Xp21) is the same as for Duchenne dystrophy (allelic disorders), but the dystrophin is partially present or defective rather than absent. However, symptoms start later, weakness is less severe, and patient ambulates beyond twelfth year of life. Marked hypertrophy of calves is prominent feature. Skeletal deformities are not as prominent. Cardiac symptoms can occur.

Other Muscular Dystrophies

Congenital Muscular Dystrophy (CMD). CMD is autosomal recessive disorder (affects both boys and girls) seen at birth or infancy. The affected patients are floppy at birth and frequently have contractures. Intellectual functions are normal. Improvement in muscle strength is seen in the first few years, and some patients become able to walk. CK is elevated, and muscle biopsy shows severe dystrophic changes similar to those seen in Duchenne type. In CMD biopsy shows more fibrosis, less necrosis, and normal dystrophin immunofluorescence.

Limb-Girdle Dystrophy. This is a more heterogeneous disorder than previously considered. Some patients have severe muscle disease with early onset and others have mild disease with later onset. A defect in sarcoglycans causes severe form of disease and defects in other structural proteins (laminins, caveolins, calpains) cause other forms of limb-girdle dystrophies. Limb-girdle dystrophy is inherited through autosomal recessive gene. In some patients, disorder starts in childhood or adolescence, progression is slow, and patients are still able to ambulate into their 40s or 50s. In other patients the disease begins in the 40s but progresses faster. Weakness begins in hip, quadriceps, and hamstring muscles. Waddling gait, back-kneeing, and Gowers' sign are striking features. Shoulder girdle weakness can start early but is usually less striking than hip involvement. Early biceps involvement is followed by involvement of other muscles. Deltoid muscle weakness is also prominent. Neck muscles are affected, but facial and ocular muscles are spared. Usually there is no cardiac involvement or mental changes. Joint contractures are rare and late. Except for lordosis, skeletal deformities are rare. Serum CK level is elevated, and EMG shows myopathic low-amplitude polyphasic potentials. Muscle biopsy shows variation of muscle fiber size, evidence of degeneration and regeneration, splitting of fibers, and migration of nuclei

and should allow exclusion of denervation and inflammatory changes. Management should include physical therapy and bracing, encouraging ambulation.

Facioscapulohumeral Muscular Dystrophy (FSH). Facioscapulohumeral muscular dystrophy is inherited as autosomal dominant disorder with variable penetrance. Linkage to chromosome 4 (D4S 139 and D4S 163) has been found. In most cases weakness begins at end of first decade. Progression of disease is very slow, beginning usually in facial or scapular muscles. Muscle involvement can be asymmetrical. Inability to whistle, drink through a straw, or blow are early symptoms of facial weakness. Patients are unable to wrinkle their foreheads or close their eyes. They demonstrate Bell's phenomenon (upward movement of the eyeball seen through partially open lids), mimicking an infranuclear bilateral seventh nerve palsy. Mild facial weakness can be demonstrated by an inability to bury the eyelashes. Scapular weakness is usually early and severe with inability to raise arms above the head. There is drooping of shoulders and poor scapular fixation. Scapulae wings easily and displaced upward above shoulders. Deltoid muscles are strikingly preserved, characteristic differentiating this disorder from limb-girdle dystrophy. Preservation of the forearm muscles, which frequently become hypertrophic, causes a "Popeye" appearance. Hip weakness can also be early sign and is usually associated with lumbar lordosis and prominent abdominal protrusion. Serum CK level is usually mildly elevated. Muscle biopsy can show early and minimal myopathic features in spite of severe disability. Marked inflammatory changes as in polymyositis or denervation can be seen. Management includes genetic counseling, physical and occupational therapy, and bracing when needed.

Emery-Dreifuss Muscular Dystrophy. This is X-linked (Xq28) or autosomal dominant inherited disorder. Early onset of elbow and ankle contractures, even before there is a significant weakness, is the most prominent clinical feature. The intellectual functions are not impaired, and there can be cardiac involvement. Weakness affects first the triceps and biceps in upper limbs and anterior tibial and peroneal muscles in legs (humeroperoneal distribution) and CK is elevated, and muscle biopsy shows nonspecific dystrophic changes with normal dysrophin immunofluorescence.

Oculopharyngeal Muscular Dystrophy. Oculopharyngeal dystrophy is rare disease described in people of French-Canadian or Spanish-American origin. It is transmitted through autosomal dominant gene and is late in onset, usually in fifth decade. The disease begins with ptosis followed by pharyngeal weakness in the 40s or 50s. Inability to swallow can be prominent feature. The facial, neck, and hip girdle muscles can be involved. Serum CK level is mildly elevated. EMG shows myopathic features. Muscle biopsy reveals small angulated fibers and "rimmed vacuoles" within muscle fibers. Management includes genetic counseling, physical therapy, surgical correction of ptosis in severe cases, and gastrostomy in some cases.

Myotonic Disorders

Myotonia. This is an involuntary painless delay in relaxation of skeletal muscle after contraction, associated with spontaneous bursts of high-frequency and high-amplitude electrical discharges demonstrated on EMG (sounding like dive bomber effect). The patients usually describe symptoms as stiffness worse at onset of activity, improves with repeated muscle contraction, and worsens in cold weather. Myotonia can be elicited by voluntary contraction or by muscle percussion. This myotonia can be elicited by tapping thenar eminence causing adduction and flexion of thumb; tapping the tongue, producing temporary dimple in contracted muscle; or tapping radial side of forearm with hand flexed in pronation, producing extension of the hand with a very slow relaxation time. Myotonia should be differentiated from electrically

silent myoedema of hypothyroidism. Paramyotonia congenita (Eulenberg's disease) is rare familial type of myotonia in which patients exposed to cold suffer flaccid paralysis.

Myotonic Dystrophy. It is an autosomal dominant inherited disorder. Genetic linkage analysis has shown locus to be situated in central region of chromosome 19. The disorder is characterized by myotonia, muscle weakness that is usually late and distal in distribution, early cataracts, endocrine abnormalities, cardiac and central nervous system involvement. Age at onset is usually in late teens or early adulthood. The disease progression, severity of symptoms, and age of onset correlate with size of trinucleotide repeat (CTG) sequence in DNA. DNA analysis is the definitive diagnostic test for this condition. Anticipation of the disease, in which affected members of youngest generation have an earlier onset and more severe disability than those in the older generation, has been confirmed in disease and is explained by the progressive expansion of unstable DNA sequence. Myotonia is a predominant early symptom. This can be manifested by muscle stiffness, difficulty starting movements, or aching low back pain. The facial features are characterized by premature balding, marked temporal and masseter muscle atrophy and weakness ("hatchet face"), and inability to close thick and protuberant lips. There is mild ptosis and weakness of orbicularis oculi muscles manifested by inability to bury eyelashes on maximal effort. Neck muscles are atrophic and weak, mainly flexor group (sternocleidomastoid), and there is accentuation of normal cervical lordosis causing appearance of swan neck. Weakness in extremities, when present, is predominantly late and distal with atrophy and weakness of hand muscles and foot drop. Later on, there is quadriceps muscle weakness with recurvation of knee and weakness at hips. Voice becomes nasal, and speech is dysarthric and rapid. Smooth muscle involvement is frequent in gastrointestinal tract and can also involve urinary tract, uterus, and iris. Dysphagia, abdominal pain, and constipation are frequent complaints. Dilatation of esophagus and colon can occur. Mental changes are frequent and consist of low intelligence with a hostile and demanding personality. Hypersomnia is a frequent feature. Cardiac abnormalities caused by lesions in the conduction system are frequently detected and EKG shows of left bundle branch block and atrial flutter, which explains "sudden cardiac death" in these patients. Testicular or ovarian atrophy and abnormalities of carbohydrate metabolism (diabetes mellitus) are common. Low serum testosterone levels have been found in myotonic males. Eye abnormalities consist of cataract, retinal degeneration, and low intraocular pressure. There is no elevation of muscle enzymes. EMG detects myotonic discharges. Muscle biopsy is usually not necessary for the diagnosis but shows dystrophic changes, type I fiber hypotrophy with increase in number of central nuclei, and frequent ring fibers. Management consists of genetic counseling and symptomatic treatment. No treatment modifies disease progression. Phenytoin and acetazolamide reduce myotonic symptoms. Although quinine and procainamide improve myotonia, they can affect ventricular conduction and myocardial function in patients who may already have conduction defects. Tonocard (tocainide) does improve myotonia. Most patients are not as concerned about the myotonia as they are about the weakness. Cardiac pacemakers are useful in some patients. Cataract extraction should be done under local anesthesia because of the risk of complications of general anesthesia. Testosterone replacement has been used in male patients.

Congenital Myotonic Dystrophy. Congenital myotonic dystrophy is present at birth and is seen in children of either sex born of a mother who has overt or sub-clinical evidence of myotonic dystrophy. Characteristically the child is severely hypotonic at birth and has facial diplegia associated with open, triangular, tent-shaped mouth with high-arched palate. The children have difficulty sucking and swallowing. They have talipes and other joint contractures. No evidence

of myotonia is seen at birth, but floppiness improves with age only to be transformed into myotonia. Developmental motor milestones are delayed, and mental retardation is frequent.

Nondystrophic Myotonias

Myotonia Congenita. The other myotonic disorders are associated with abnormal ion channels (sodium, chloride, calcium, potassium) and the channelopathies include myotonic paralyses and periodic paralyses. The ion channel proteins control the electrical potential and the muscle action potential. The channelopathies are classified on molecular genetic basis. Myotonia congenita is rare non-progressive disease manifested by myotonia and inherited as autosomal dominant disorder (Thomsen's disease) or autosomal recessive (Becker myotonia). Both types share common clinical features, and both are linked to the same gene that encodes a chloride channel on chromosome 7. When the mutant gene is introduced, this abolishes the chloride current potential and impairs the functioning of the chloride channel. The disease can be seen at birth or in first two decades. Patients have muscle hypertrophy. There is no mental, cardiac, or endocrinologic abnormality. There is no baldness. Myotonia is pronounced at rest and improves with exercise. It is exacerbated by cold. EMG shows myotonic discharge but no myopathic features, and muscle tissue is normal when biopsed. Most patients myotonia respond to Tonocard (tocainamide) or mexiletine.

Paramyotonia Congenita and Periodic Paralyses. This rare group of disorders is usually hereditary and due to sodium channel deficiencies (channel-opathies). They have common periodicity of attacks of weakness that can last from minutes to several days. Weakness can be generalized or focal and is associated with hyporeflexia or areflexia. Paramyotonia congenita is characterized by paradoxical myotonia. Myotonia, which affects predominantly the face and upper limbs, appears with exercise, increases with continuous exercise, and is aggravated by cold exposure. Attacks of weakness can occur spontaneously or be precipitated by cold. The periodic paralyses are usually autosomal dominant inherited disorders. Paralysis is due to inexcitability of sarcolemma produced by sodium channel deficiencies. During weakness, there is shift of potassium, chloride, sodium, and water into muscle cells. Periodic paralyses are classified according to the serum potassium levels during the attacks and can be hypokalemic, hyperkalemic, or normokalemic. Prevention of the attacks can be achieved by avoiding precipitating factors and use of diuretics.

Muscle Cramps and Stiffness

Muscle cramps are intermittent painful muscle contractions, which may last seconds to minutes. They may develop during or after exercise ceases. They may occur at night involving feet and toe. EMG shows short-lived periodic bursts of motor unit potentials, which may appear irregularly. If the muscle is stretched, this usually terminates the cramp. Quinine is effective in controlling cramps. Cramps may occur in pregnancy, endocrine disease or renal failure. If neurological exam is normal the cramps are usually benign. Muscle stiffness is a more sustained continuous muscle contraction, which is present at rest. Slow moving with clawing of the fingers, toe walking and stiffness of proximal and axial muscles may occur (neuromyotonia). This disorder may be treated with drugs, which influence sodium channel (phenytoin, carbamazepine).

Congenital Myopathies

Congenital myopathies are heterogeneous hereditary disorders. Although they are called congenital and frequently appear early in life as floppiness or delayed motor development, muscle weakness can appear later or even in adulthood. Improvement of weakness can occur in cases seen in infancy. The earlier age of onset, worse motor deficit will be. The muscle mass is constantly small, and there can be associated dysmorphic features such as elongated face, scoliosis, pigeon chest, and hip and foot deformities. When disease manifests in adulthood, muscle weakness is slowly progressive, usually self-limited, and very rarely leads to a wheelchair-bound or bedridden state. Serum muscle enzymes and EMG are usually normal.

Central Core Disease and Malignant Hyperthermia

Central core disease (CCD) and malignant hyperthermia are autosomal dominant allelic disorders caused by missense mutations in the ryanodine receptor gene (sarcoplasmic reticulum calcium release channel) mapped to chromosome 19 (19q13.1). Patients with CCD have a high risk of malignant hyperthermia (MH) during general anesthesia. However, not all patients who have MH have CCD. Malignant hyperthermia is produced by potent volatile anesthetic agents or succinylcholine used during surgery. These agents produce increased oxygen and lactate production resulting in exaggerated heat production, muscle rigidity, and cellular permeability. The syndrome is most likely produced by inability of muscle cells to control calcium concentration as result of mutation in ryanodine receptor gene. CCD is manifested by early childhood hypotonia and proximal muscle weakness. CK is usually normal, and EMG not specific. Muscle biopsy shows characteristic cores in muscle fibers devoid of mitochondrial enzymatic activity. There is no treatment for CCD. Malignant hyperthermia can be prevented by avoiding use of precipitating agents. Treatment of acute episodes consist of (1) immediate discontinuation of precipitating agent; (2) use of dantrolene 2 mg/kg intravenously each 5 minutes to reach a total of 10 mg/kg; (3) rapid intravenous infusion of 2 to 4 mEq/kg of sodium bicarbonate; and (4) aggressive cooling if the temperature is above 40.6° C. Subsequent treatment is based on arterial blood gases and acid-base values.

Nemaline Myopathy

Nemaline myopathy is a genetically heterogeneous disorder transmitted by autosomal dominant or recessive inheritance. Symptoms appear in neonatal period with severe hypotonia, facial diplegia, and joint contractures. This type of myopathy carries poor prognosis. When symptoms appear in childhood, weakness is slow or nonprogressive and is associated with skeletal deformities and dysmorphic facial features. Adult onset type has variable weakness, and patients have Marfan-like phenotypic features. CK is normal, and EMG is nonspecific. The diagnostic histologic features in the muscle biopsy consist of subsarcolemmal nemaline rods in small muscle fibers. No treatment currently is available.

Centronuclear (Myotubular) Myopathy

Centronuclear (myotubular) myopathy can appear in either of two forms, neonatal or late onset form. The neonatal X-linked form is characterized by severe weakness, dysmorphic facial features, and skeletal abnormalities. Ptosis and limitation of ocular movements are frequent. The late onset form appears before third decade. Ptosis and limb weakness are less marked than in neonatal form. No linkage has been described yet. Characteristic histologic features consist of

presence of round muscle fibers, type I fiber predominance, and central nuclei in 30% to 95% of the fibers. In neonatal X-linked form, numerous small fibers with central nuclei resemble myotubes.

Other Congenital Myopathies

Congenital fiber-type disproportion. EMG shows myopathic potentials but no muscle membrane instability. At birth these children are hypotonic and have diffuse weakness. Achilles tendon contractures and hip dislocation are common. Muscle biopsy shows marked disproportion between size of type 2 and type 1 fibers (atrophic and predominant). Myofibrillar myopathy is characterized by biopsy evidence of myofibrillar disruption and desmin (protein) muscle fiber accumulation. Patients develop weakness and cardiac muscle disorder between ages 25 and 45.

Metabolic Myopathies

Metabolic myopathies are rare familial muscle diseases in which an enzymatic defect, endocrine dysfunction, or metabolic abnormality is associated with transitory or permanent muscle weakness as part of a multisystem disease or primary muscle disorder. Disturbances in the biochemical pathways that support aerobic metabolism that involves adenosine triphosphate (ATP) in muscle will result in exercise intolerance, muscle weakness and fatigue. Disorders of carbohydrate and lipid biochemistry and mitochondrial metabolism lead to abnormalities of muscle metabolism. When muscle metabolism is abnormal, levels of ATP are reduced and muscle injury occurs. Muscle pain develops and then muscle becomes tender and swollen. There is muscle breakdown with release of myoglobin into the blood and then into the urine (myoglobinuria) and this may result in acute renal tubular necrosis.

Diseases of Carbohydrate Metabolism

At least seven different enzymatic defects of glycogen metabolism have been described. Only a few affect muscles, and only two are discussed here.

Acid Maltase Deficiency. Pompe's disease (glycogenosis type II) is a rare disease due to acid maltase (1,4-glucosidase) deficiency and is inherited as autosomal recessive disorder. Acid maltase is a lysosomal alpha-glucosidase that releases glucose from maltose, glycogen, and oligosaccharides. The gene that codes for acid maltase has been mapped to region 2 of long arm of chromosome 17 (17q 21-23 or 17q 23-25). In infantile or classic form, disease appears as severe hypotonia with cardiorespiratory problems. There is associated visceromegaly including enlarged heart, liver, and spleen. Muscle weakness is due to accumulation of intracytoplasmic glycogen. It is usually fatal in infancy. The childhood type starts later, does not usually involve the heart, causes proximal muscle weakness that is difficult to differentiate from limb-girdle or Duchenne's dystrophy, and is frequently associated with mental changes. Adult form appears after age of 20 with very slowly progressive proximal muscle weakness. In some adult cases, respiratory failure is first manifestation. Muscle is characterized by vacuolar degeneration, in which accumulated glycogen can be detected. Biochemical analysis of the muscle shows the enzyme defect. Enzyme replacement has not modified the course of the disease.

McArdle's Disease. McArdle's disease (glycogenosis type V), nonlysosomal glycogenosis, is rare disease produced by deficiency of myophosphorylase. This enzyme initiates glycogen breakdown. Myophosphorylase along with debrancher enzyme degrades glycogen completely into glucose-1-phosphate and glucose. Deficiency of myophosphorylase produces accumulation

of subsarcolemmal glycogen. The disease has autosomal recessive inheritance. Six mutations that cause the disease have been identified in the gene that encodes the enzyme localized on chromosome 11. The disease is more frequently seen in males, varies in intensity, and is manifested early by fatigability followed by muscle cramps precipitated by exercise. The amount of exercise needed to produce cramps seems to shorten with progression. Exercise can trigger myoglobinuria. Diagnosis should be confirmed by a muscle biopsy demonstrating subsarcolemmal vacuoles, glycogen accumulation, and lack of myophosphorylase. Treatment consists of decreasing activity, warming muscles before activity, or the second wind effect. Oral loading with glucose or fructose has produced inconsistent effects.

Diseases of Lipid Metabolism

Diseases of lipid metabolism are rare. They cause accumulation of excessive lipid seen on muscle biopsy. They can be caused by defective transport of fatty acids substrates into mitochondria, defects in beta oxidation of fatty acids, defects in the respiratory chain, and defects in use of endogenous triglycerides. Histologic diagnosis is not always certain because some defects of lipid metabolism do not result in lipid storage myopathy. Ischemia and obesity increase muscle fiber lipid content, and diseases of lipid metabolism affect heart, liver, and other organs.

Carnitine Deficiency. Lipids are important source of skeletal muscle energy during fasting or prolonged exercise. Diet provides 75% of body carnitine requirements; the rest is endogenously synthesized. Carnitine deficiency is believed to be produced by defective transport in tissues. It has two forms, one with progressive cardiomyopathy and other with episodes of hypoketotic hypoglycemia. In both cases there is consistent muscle weakness and excess of lipid in skeletal muscle. Myoglobinuria can occur. There are normal or slightly decreased serum concentrations of carnitine. Muscle biopsy shows vacuolar myopathy with accumulation of lipids. Biochemical analysis of muscle demonstrates low skeletal muscle carnitine. The patients have a dramatic response to 2 to 6 g of oral L-carnitine daily supplementation, with improvement of cardiac and skeletal muscle function.

Carnitine Palmitoyltransferase Deficiency. This is a rare disease with an autosomal recessive X-linked inheritance. Myoglobinuria not preceded by muscle cramps is hallmark of late onset form, which becomes symptomatic in second or third decade. Myoglobinuria is precipitated by fasting or exercise. Biochemical studies of muscle demonstrate decreased carnitine palmitoyltransferase. Therapy consists of high-carbohydrate, low-fat diet and regulation of exercise to reduce number of attacks. In infantile form hepatic failure and nonketotic hypoglycemic coma occur. The response to treatment of this form is not as good as in adult form.

Mitochondrial Myopathies

Mitochondrial myopathies are a clinically, biochemically, and genetically heterogeneous group of disorders that affect multiple systems, including skeletal muscles, and are characterized by nonspecific structural abnormalities of affected tissue mitochondria. There are several defects in respiratory chain function. Disorders in mitochondrial function results in multisystem failure (brain, heart, kidney, skeletal muscle); however some patients may have only skeletal muscle involvement and they may have fatigue and exercise intolerance only. Diagnosis needs to be confirmed by biopsy, biochemical analysis of skeletal muscle, and determination of

mitochondrial DNA (mtDNA) deletions or mutations. With exercise there is increased need for oxidative metabolism to generate ATP; however if this is not possible due to mitochondrial defect, anaerobic metabolism is turned on and lactic acid production increases. Increased serum lactate is evidence of mitochondrial dysfunction. Magnetic resonance spectroscopy may show ATP and lactate levels. In this disorder, serum lactate is elevated and magnetic resonance spectroscopy shows marked brain lactic acid peak. In mitochondrial myopathies muscle histologic abnormalities consist of presence of ragged-red fibers, seen with the modified Gomori's trichrome stain. Transmission electron microscopy of muscle can show mitochondria abnormalities, including presence of crystalline or par crystalline mitochondrial inclusions ("parking lot" appearance), or excessive accumulation of glycogen or lipid droplets. Three distinctive clinical encephalomyopathies will be described. The first, *Kearns-Sayre syndrome*, is characterized by onset before age 15, progressive external ophthalmoplegia, pigmentary degeneration of retina, heart block, cerebellar dysfunction, and variable limb weakness. Elevated CSF protein and peripheral neuropathies have also been described. Spongy degeneration of brain has been found. However, chronic progressive external ophthalmoplegia and proximal muscle weakness can be the early or only manifestations of late-onset mitochondrial myopathies. Muscle biopsy confirms diagnosis by showing ragged red fibers. *Myoclonus epilepsy with ragged-red fibers (MERRF)* is a familial disorder characterized by myoclonus, ataxia, weakness, generalized seizures. A syndrome that includes *mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)* appears early in life with episodic vomiting, seizures, and recurrent strokes. Treatment of mitochondrial disorders include coenzyme Q, riboflavin, vitamin C but efficacy is unproven. Treatment of lactic acidosis is beneficial.

Corticosteroid Myopathy

Corticosteroid myopathy is one complication of prolonged high-dose Corticosteroid therapy, usually appearing after months or years of therapy. Although fluorinated corticosteroids are more frequently implicated, any Corticosteroid can produce same effect. Corticosteroids produce muscle protein catabolism. This is enhanced by disuse or during sepsis. The myopathy appears as proximal shoulder and hip girdle muscle weakness. CK level is usually normal or slightly elevated. Muscle biopsy reveals nonspecific type II fiber atrophy. Acute quadriplegic myopathy has recently been described in patients who had received large doses of intramuscular or intravenous doses of glucocorticoid. Most of these patients had also received neuromuscular blockade agents and mechanical ventilation. The treatment consists of discontinuing the steroids.

DISEASES OF THE NEUROMUSCULAR JUNCTION

Myasthenic Disorders

Acquired autoimmune myasthenia gravis is a disorder of neuromuscular transmission that is due to acetyl-choline receptor (AChR) deficiency at the myoneural junction. The disease is manifested by abnormal and objective (pathologic) fatigability and weakness after repeated or sustained muscle activity with recovery of strength after rest or anticholinesterase medication. The disease is more frequent in young females but there is a second peak in elderly patients,

especially in males. The disease invariably involves most frequently used muscles such as eyelids, extraocular and bulbar muscles. Ptosis or diplopia as result of involvement of one or more extraocular muscles is seen in most myasthenics. Eye muscle involvement is frequently asymmetrical and can resemble internuclear ophthalmoplegia. Although disease is initially purely ocular, it remains confined to ocular muscles in less than 15% of patients after 1 year of onset. Bulbar muscles affected include those of mastication, deglutition, and phonation. Speech becomes nasal, and jaw can hang on so loosely that the patient must hold it up by using the hands. Facial expression and facial mobility are lost, and smile can become a snarl. In advanced cases weakness can become generalized and involve intercostal and diaphragmatic muscles, impairing respiratory function. In spite of severe weakness, atrophy of muscle is unusual. The progression of the disease is variable. There are rare spontaneous remissions. There is some association of myasthenia gravis with other autoimmune diseases including hyperthyroidism, lupus erythematosus, rheumatoid arthritis, and polymyositis. Diagnosis is made by history and clinical findings and by demonstrating fatigability if clinical signs are not obvious. When the patient looks upward forcibly and for prolonged period of time, there is a progressive eyelid droop. Counting rapidly and loudly brings progressively nasal quality to the speech. Walking or running can demonstrate extremity weakness. This weakness should improve after rest. When objective signs are present or are precipitated by the examiner, edrophonium chloride (Tensilon) improves weakness. Tensilon test is an important diagnostic test. The test is performed by intravenous injection of edrophonium chloride, 2 to 10 mg (0.2-1.0 ml). After 2 mg (0.2 ml) infusion the patient is observed for a response or cholinergic sign (tearing or fasciculations of eyelids); then the rest of injection can be given very slowly. The response, in affected patients, appears in 10 to 30 seconds, and positive effect (improved muscle strength) lasts no more than 5 minutes. Atropine should be available to counteract unfavorable cholinergic side effects including cardiac rhythm disturbances. Edrophonium chloride is a fast acting anticholinesterase that reduces the hydrolysis of acetylcholine, making acetylcholine available in larger quantities and for a longer period of time at the neuromuscular junction.

The next step in the diagnosis consists of the repetitive nerve stimulation test. Repeated supramaximal nerve stimulation at rate of 3 Hz while recording from muscles innervated by the nerve produces more than 10% decremental response in myasthenic patients. Single fiber EMG shows abnormal response (jitter) in myasthenic patients. Antibodies to acetylcholine receptor have been found in the serum of 87% to 93% of myasthenic patients and are highly specific. The titer of antibodies does not correlate with disease severity. Moreover, antibodies can be absent in some patients with ocular myasthenia. Antibodies to striated muscle have also been found in myasthenia gravis but are less specific. The thymus is frequently abnormal and shows germinal hyperplasia (thymitis). A thymoma is present in some myasthenic patients. Tissue typing has shown that young female myasthenics (under age 40) have a high prevalence of HLA A1, B8 or DRw3, or both, and these patients have higher acetylcholine receptor antibody titers, have a higher incidence of associated autoimmune disorders, have no thymoma, and respond faster and better to thymectomy. Older (over age 40) myasthenic patients without thymoma are frequently males; have a higher prevalence of HLA A3, B7 or DRw2, or both; and have low titers of acetylcholine receptor antibodies. In patients with MG and thymoma there is no sex or HLA association, AChR antibody titers are high, and may have striated muscle antibodies.

Pathogenesis. There is good evidence that the antibodies to AChR are important in causing myasthenia gravis. These polyclonal antibodies recognize one immunogenic region of AChR. There is also electron microscopic evidence of damage of postsynaptic folds with

deposition of IgG, C3, and C9. Antiidiotypic antibodies have been found in some of myasthenics, and these antibodies seem to regulate immune response to acetylcholine receptor antibodies and affect clinical expression. There is a high prevalence of thymic abnormalities in myasthenic patients, and there is often a favorable response after thymectomy. All myasthenic patients must have chest radiogram (including oblique views) and chest CT. The normal thymus gland contains myoid cells. Some incompletely characterized thymus cells express AChR molecules. The hyperplastic thymus of myasthenic patients contains increased number of B cells, and thymocytes of MG patients secrete anti-AChR antibodies.

Treatment is directed toward improving the symptoms and immunosuppressing the patient. Symptomatic treatment consists of use of anti-cholinesterase drugs, mainly pyridostigmine (Mestinon). The dosage varies according to individual patient response and severity of weakness. The use of pyridostigmine should be as required by patient's symptoms. In bulbar involvement, 60 mg should be given 30 to 45 minutes before each meal to avoid aspiration. Most patients learn when they need the Mestinon and when to take it. When dosage reaches more than eight tablets a day, patient should be put on immunosuppressive medication. Plasmapheresis reduces antibodies and produces dramatic but temporary improvement of symptoms. It is indicated in myasthenic crisis and should be used along with other therapeutic measures. It can also be used intermittently as adjuvant in patients who are not responding well to immunosuppression. Intravenous gamma globulin has also been used with mixed results and should be used along with immunosuppressive treatment. Immunosuppressive measures include transsternal thymectomy with complete removal of the thymus. This is particularly important when there is a thymoma. Complete remission is more likely if thymectomy is done early in the disease. The best response is achieved in young females without a thymoma. High doses of prednisone (60 to 80 mg on alternate days) can be used, but treatment should be initiated with smaller (20 mg) doses that are gradually increased by 10 mg every third dose to avoid exacerbation of weakness. After optimal results have been obtained, dosage should be continued for at least 6 months and then gradually reduced over a period of 12 to 16 months. Response to corticosteroids is quite dramatic. Undesirable secondary effects of high-dose corticosteroids can appear in some patients and should be carefully monitored and managed. Azathioprine (Imuran) in a dosage of 2.5 mg/kg/day can help bring about a remission and reduce antibodies. Results are better in males who do not have HLA-B8 and who have high titers of antibodies. Careful observation is necessary. Imuran is usually added to the therapy of patients who are not responding well to prednisone. Therapy should be individualized. It is important to remember that myasthenic patients can suffer worsening of symptoms during pregnancy, menstruation, and hyperthyroid states. Drugs that are contraindicated in myasthenics include antibiotics of the amino glycoside group that inhibit release of acetylcholine such as gentamicin, kanamycin, neomycin, polymyxin, and streptomycin and antiarrhythmic drugs such as quinine (including tonic water), quinidine, procainamide, lidocaine, beta-adrenergic blockers, and phenytoin (Dilantin) (Box 17-2).

Transient neonatal myasthenia is a transient (1 to 6 weeks) form of myasthenia seen in approximately 15% of newborns born to mothers with myasthenia gravis and is due to transplacental passage of antibodies to acetylcholine receptors. Symptoms improve with spontaneous or therapeutic reduction of antibodies (plasmapheresis).

BOX 17-2. Drugs Reportedly Inducing or Exacerbating Myasthenic Weakness

Antibiotics Contraindicated in MG

Inhibition of presynaptic release of Ach

Gentamicin	Streptomycin
Neomycin	Kanamycin
Tobramycin	Erythromycin

Depression of postjunctional sensitivity

Bacitracin	Netilmicin
Clindamycin	Polymyxin B
Colistin	Tetracycline (rare)
Lincomycin	Ampicillin* (rare)
Neomycin	*Ca ⁺⁺ reverses weakness

Other Medications

D-penicillamine	Phenytoin
Verapamil	Beta-blockers
Quinine	Chloroquinequinidine
Procainamide	Chlorpromazine
Lithium	K-wasting diuretics
Curare	Gallamine
Pancuronium	Ether

Clinical Myasthenic Syndromes

Congenital Myasthenic Syndromes

Congenital myasthenia is a familial heterogeneous disorder of nonimmune causes that is possibly inherited as autosomal recessive gene. It is seen predominantly in male children. The disease appears in newborn period in infants of nonmyasthenic mothers. Although symptoms are similar to those of myasthenia gravis, they do not respond well to anticholinesterase therapy or thymectomy, and there is no increase of antibodies to acetylcholine receptors. The symptoms do not seem to progress. Although the pathogenesis in this disorder is not clear, both presynaptic and postsynaptic defects have been described, including defect in acetylcholine synthesis or packaging, congenital end-plate acetylcholinesterase deficiency, slow channel syndrome, and congenital end-plate acetylcholine receptor deficiency.

Drug-Induced Myasthenia

Drug-induced myasthenia appears in patients with rheumatoid arthritis who have been treated with penicillamine for several months. It does not usually occur in patients receiving penicillamine for Wilson's disease. The symptoms and antibodies to acetylcholine receptors are the same as in myasthenia gravis, and symptoms improve when AChR antibody titers decrease after discontinuation of the drug.

Eaton-Lambert Syndrome

This is an acquired autoimmune myasthenic syndrome produced by autoantibodies that deplete the voltage sensitive calcium channels (VSCCs) of the motor nerve terminal (presynaptic). It is frequently but not always associated with the presence of a malignant tumor, usually a small (oat) cell carcinoma, and rarely with other tumors. The syndrome is more frequent in males and is characterized by fatigability and weakness, predominantly of limb-girdle musculature and less prominently of ocular and bulbar muscles, and is associated with areflexia. Strength improves and reflexes reappear after maximal voluntary contraction. There is no increase of acetylcholine receptor antibodies. The diagnosis is confirmed by electromyography. Stimulation of a nerve at or above 10 cps evokes incremental responses of the muscle. The response to the anticholinesterase edrophonium (Tensilon) is positive but not as dramatic as in myasthenia gravis. The discovery of the malignancy can be delayed by several years after diagnosis of the syndrome. Therapy consists of eradication of the tumor when present and administration of guanidine (15 mg/kg/day) to increase the release of acetylcholine from nerve terminals. Symptoms also respond to plasmapheresis and immunosuppressive therapy.

Botulism

Botulism is a disease of neuromuscular transmission produced by the exotoxin of *Clostridium botulinum*, an anaerobic microorganism that can contaminate improperly prepared canned or bottled foods. The toxin interferes with the release of acetylcholine and produces acute and progressive weakness within 72 hours. There is ocular, bulbar, and generalized muscle weakness with loss of stretch reflexes and no sensory abnormalities. Botulism, unlike myasthenia gravis or Guillain-Barré syndrome, causes dilated unreactive pupils. Treatment consists of cardiorespiratory support and administration of antiserum, 10,000 U intravenously, followed by intramuscular doses of 50,000 U daily, until strength improves. Guanidine has been beneficial in some cases.

Tick Paralysis

Tick paralysis is ascending paralysis probably produced by neurotoxin liberated by female tick (*Dermacentor andersoni* or *D. variabilis*). Although mode and site of action of toxin are not known, there are reductions in motor nerve conduction velocities and myoneural junction abnormalities. The disease causes ascending paralysis with bulbar involvement, areflexia, and facial weakness but no pupillary abnormalities. Symptoms improve soon after the engorged tick is removed.

SUMMARY

Disorders of muscle (myopathies) are characterized by proximal muscle weakness and wasting. Muscle enzymes including CK and aldolase are elevated as a result of muscle destruction. Electromyography confirms abnormal function of muscle fiber, and specific pathologic feature of myopathy can be determined by muscle biopsy. Disorders of neuromuscular junction are manifested by abnormal fatigue and weakness after sustained muscle activity with recovery of strength after period of rest. Myasthenia gravis is most characteristic disorder of neuromuscular junction transmission. The eye muscle can be initially involved. This can result in ptosis and diplopia. Diagnosis of myasthenia gravis can be established by improvement in strength

following intravenous injection of edrophonium (Tensilon) and demonstration of serum antibodies to the acetylcholine receptor.

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Tables

TABLE 17-1. Inflammatory Myopathies Clinical Features

	Age	Site of Weakness	Calcinosis	Malignancy	CK
DM	5-14	Prox. limbs & neck muscles	Frequent	No association	Elevated
	40-50	Prox. limbs & neck muscles	Rare	Found in 10-20%	Elevated
PM	40-60	Prox. limb & neck muscles	Absent	Rare	Elevated
IBM	After 50	Prox. & distal limbs	Absent	No association	Normal

DM, Dermatomyositis; PM, polymyositis; IBM, inclusion body myositis.

TABLE 17-2. Inflammatory Myopathies Histopathology

	Arteries and Arteholes	Capillaries	Muscle Fascicles
DM	Vasculitis, immune complex	Decreased	Perifascicular atrophy, necrosis, & microinfarcts
PM	Perivascular inflammation	Normal	Single fiber necrosis, T cells around normal fibers
I.B.M.	Normal	Increased	Atrophic fibers, rimmed vacuoles, inclusions

TABLE 17-3. Muscular Dystrophies

Type	Inherit	Onset	Progression	Intellect and Others
Congenital	A-R	Birth	Early improvement	Normal intellect
			Later slow progression	
Limb girdle	A-R	Teens	Normal life span	Normal intellect
FSH	A-D	Variable	Slow	Normal intellect
Emery-Dreifuss	X Linked	First decade	Slow	Cardiac involvement
	AD			
Oculopharyngeal	A-D	>Fourth decade	Slow	Normal intellect

FSH, Facioscapulohumeral muscular dystrophy.

TABLE 17-4. Dystrophinopathies Xp21

Duchenne	Becker	Manifesting Carrier
2-5	5-12yrs	Second decade
Fatal in 20s	Slow progression	Slow progression
Cardiac involvement	Cardiac involvement	No cardiac involvement
Intellectual deficit	Color blind	Normal intellect
Absent dystrophin	Decreased or abnormal dystrophin	Patchy dystrophin