Oculopharyngeal Muscular Dystrophy

This is a late-onset AD disorder typically of the fourth to fifth decade and is manifested by progressive ptosis, dysphagia, and limb weakness. Linkage of oculopharyngeal muscular dystrophy to 14q11.2-q13 has been reported in several French Canadian families (19). This disorder has been ultrastructurally characterized by the presence of filamentous inclusions in muscle nuclei (20).

MYOTONIC DISORDERS

Myotonia is an alteration of muscle relaxation characterized electromyographically by repetitive high-frequency discharges that wax and wane in frequency and amplitude and are not abolished by curarization or peripheral nerve block.

Myotonic Dystrophy

This is the most common form of adult muscular dystrophy, with an estimated incidence of 1 per 7,500. It is a multisystem disorder characterized by muscle weakness, wasting and myotonia, cardiomyopathy, cataract, baldness, and endocrine dysfunctions. The onset is usually in adolescence, and the course is slowly progressive, but one of the striking features of this disorder is the variability of phenotype both within and between families. EMG shows a combination of myotonic and myopathic features.

The inheritance pattern is AD with the affected gene locus on the long arm of chromosome 19. The disease is due to a variable trinucleotide repeat insert in the myotonic dystrophy gene consisting of 50 to several thousand CTG repeats (21). This mutation interrupts the 3′ untranslated region of a protein kinase gene that has been named myotonin protein kinase. The measurement of the (CTG)n repeat is considered an accurate diagnostic test (22). The muscle pathology is relatively distinct and consists of numerous central nuclei, sarcoplasmic masses, ring fibers, and variable type I fiber atrophy (23).

Congenital Myotonic Dystrophy

Affected infants manifest a clinical picture very different from that in adolescents; they show severe hypotonia, bilateral facial weakness with difficulty in sucking, and respiratory distress. The almost exclusively maternal transmission of congenital myotonic dystrophy has been attributed to genetic imprinting. An important negative feature is the absence of clinical and often electrical evidence of myotonia in these infants; however, clinical or electrical evidence of myotonia in the mother is a useful diagnostic clue. The most significant pathologic abnormality in the muscle biopsy is immaturity of muscle fibers. The fibers are of small caliber and have basophilic cytoplasm with internally placed nuclei, showing the histologic features of myotubes.

Myotonia Congenita

Myotonia congenita is an AD disorder due to mutations of the gene coding for the voltage-sensitive chloride channel of skeletal muscle (24). The symptoms are limited to myotonia, and muscle hypertrophy is common. Becker described an autosomal recessive (AR) form of congenital myotonia in which muscle hypertrophy is more pronounced than in the dominant form and weakness is often present. This form is also due to mutations of the voltage-sensitive chloride channel. Serum CK concentrations are normal in both forms of myotonia congenita, and EMG shows myotonic discharges but no myopathic features. Muscle biopsy findings are usually normal, except for lack of type IIB fibers.

Paramyotonia Congenita

The clinical hallmarks of this disorder are the temperature-sensitive nature of the myotonia and episodic paralysis. Transmission is AD, and the disorder is due to mutations of the gene coding for the voltage-sensitive sodium channel of the muscle fibers. Muscle biopsy shows no particular pathologic features (25).

Hypokalemic Periodic Paralysis

This condition is characterized by attacks of flaccid paralysis involving trunk and limb muscles, typically sparing respiratory and ocular muscles. Transmission is autosomal dominant, with a striking predominance of affected males, and the disorder is due to mutations in the voltage-dependent calcium channel of the muscle fibers (25). During attacks, muscle is inexcitable, and EMG shows electrical silence. Serum potassium concentrations are characteristically decreased, probably because of a shift of potassium into the muscle. Muscle biopsy taken during and between attacks show numerous vacuoles that may be empty or may contain granular or hyaline material. Another characteristic alteration that may be seen in period paralysis is the collection of structures referred to as tubular aggregates (Fig. 5).

Hyperkalemic Periodic Paralysis

Hyperkalemic periodic paralysis is transmitted as an AD trait. As in paramyotonia congenita, the disorder is due to a mutation resulting in a single amino acid change of voltage-sensitive sodium channels that alters the gating properties of the channel (25). Attacks are shorter than in the hypokalemic disorder and may be precipitated by rest after heavy exercise and by cold or fasting. Clinical or electrical evidence of myotonia is present in most
oxidative enzymes and phosphorylase (Fig. 6). The lesions are usually limited to type I fibers, and in most patients there is marked type I fiber predominance. By electron microscopy, the central cores can be divided into two types: structured cores, in which the architecture of the sarcomeres is preserved, and unstructured cores, in which the organization of the sarcomeres is lost. The ultrastructure of the cores shows streaming of the Z-disc, decreased numbers of mitochondria, and few glycogen granules within the core (Fig. 6). It is transmitted in an AD fashion, and the gene for both central core disease and malignant hyperthermia has been localized on chromosome 19q12-13. The protein encoded by this gene is the calcium release channel of the sarcoplasmic reticulum, and mutations of the gene have been found in families with malignant hyperthermia and central core disease (26).

Multicore (Minicores) Disease

This was originally described in two children with nonprogressive weakness at birth and delayed motor milestones. There were multiple small cores in each affected fiber, with abnormalities resembling those of unstruc-

MORPHOLOGICALLY DEFINED CONGENITAL MYOPATHIES

Congenital myopathies are defined as nonprogressive myopathies of the neonatal period with weakness and hypotonia of varying severity. They have been classified according to the pathologic features on histochemical study of frozen sections of muscle tissue. The following are brief descriptions of the most common congenital myopathies with incorporation of recent molecular pathology data when available.

Central Core Disease

In this disorder, well-circumscribed central areas or cores, usually extending along the entire length of the muscle fibers, show decreased staining with reactions for
Nemaline (Rod) Myopathy

This disorder is characterized by multiple “rod” structures in muscle fibers that are best revealed with the modified Gomori trichrome stain (Fig. 7). Both fiber types may be affected, but rods tend to be more abundant in type I fibers, and type I fiber predominance is common. The electron microscopy of the rods is similar to that of the Z-disks, from which they appear to originate (Fig. 7). The patients usually have dysmorphic features such as an elongated face, high arched palate, club foot, and kyphosis. It is usually transmitted as an AD trait, but AR cases have also been reported. Linkage studies assigned the gene for autosomal dominant nemaline myopathy to 1p13-25. When the gene for α-tropomyosin was assigned to the same region, it became a good candidate for nemaline myopathy, and Laing et al. (27) showed a point mutation in exon 1 of the gene that segregated with the expression of the disease in one family. Similar studies in other families with AD nemaline myopathy showed no mutation in different exons of the α-tropomyosin gene, suggesting the presence of genetic heterogeneity in the disease. In addition, AR nemaline myopathy did not show linkage to the α-tropomyosin locus, and linkage analysis mapped this form to chromosome 2q21 (28).

Myotubular (Centronuclear) Myopathy

The morphologic hallmark of this disorder is the presence of rows of central nuclei in both fiber types but predominantly in type I fibers (Fig. 8). Type I fiber preponderance and hypotrophy have also been described. The central nuclei are surrounded by areas of cytoplasm devoid of myofibrils and containing variably increased oxidative enzymes and decreased ATPase activity, a picture reminiscent of myotubes. Because of the similarity of these fibers to myotubes, it has been proposed that this disorder may be due to an arrest of normal muscle development. When type I hypotrophy is the predominant feature of the biopsy, the disorder is called type I fiber hypotrophy with central nuclei.

The most common mode of transmission is AR, but X-linked recessive transmission has been described in several families. Linkage studies of families with the X-linked form mapped the locus to Xq28, and recently, mutations in a gene coding for a tyrosine phosphatase have been reported in 12% of patients with myotubular myopathy. The putative protein, myotubulin, may play a role in the control of cell growth, proliferation, and differentiation (29).

REFERENCES

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girdle muscular dystrophy, LGMD 2F, is caused by a mutation in the t-