EMERY-DREIFUSS MUSCULAR DYSTROPHY

There are at least five genetically distinct forms of Emery-Dreifuss muscular dystrophy (EDMD). Emerin mutations are the most common cause of X-linked EDMD, although mutations in *FHL1* may also be associated with a similar phenotype, which is X-linked as well. Mutations involving the gene for lamin A/C are the most common cause of autosomal dominant EDMD (also known as LGMD1B) and are also a common cause of hereditary cardiomyopathy. Less commonly, autosomal dominant EDMD has been reported with mutations in nesprin-1, nesprin-2, and *TMEM43*.

Clinical Features Prominent contractures can be recognized in early childhood and teenage years, often preceding muscle weakness. The contractures persist throughout the course of the disease and are present at the elbows, ankles, and neck. Muscle weakness affects humeral and peroneal muscles at first and later spreads to a limb-girdle distribution. The cardiomyopathy is potentially life threatening and may result in sudden death. A spectrum of atrial rhythm and conduction defects includes atrial fibrillation and paralysis and atrioventricular heart block. Some patients have a dilated cardiomyopathy. Female carriers of the X-linked variant may have cardiac manifestations that become clinically significant.

Laboratory Features Serum CK may be elevated two- to tenfold. EMG is myopathic. Muscle biopsy usually shows nonspecific dystrophic features, although cases associated with *FHL1* mutations have features of myofibrillar myopathy. Immunohistochemistry reveals absent emerin staining of myonuclei in X-linked EDMD due to emerin mutations. ECGs demonstrate atrial and atrioventricular rhythm disturbances.

X-linked EDMD usually arises from defects in the emerin gene encoding a nuclear envelope protein. *FHL1* mutations are also a cause of X-linked scapuloperoneal dystrophy, but can also present with an X-linked form of EDMD. The autosomal dominant disease can be caused by mutations in the *LMNA* gene encoding lamin A and C; in the synaptic nuclear envelope protein 1 (*SYNE1*) or 2 (*SYNE2*) encoding nesprin-1 and nesprin-2, respectively; and most recently in *TMEM43* encoding LUMA. These proteins are essential components of the filamentous network underlying the inner nuclear membrane. Loss of structural integrity of the nuclear envelope from defects in emerin, lamin A/C, nesprin-1, nesprin-2, and LUMA accounts for overlapping phenotypes (Fig. 462e-7).

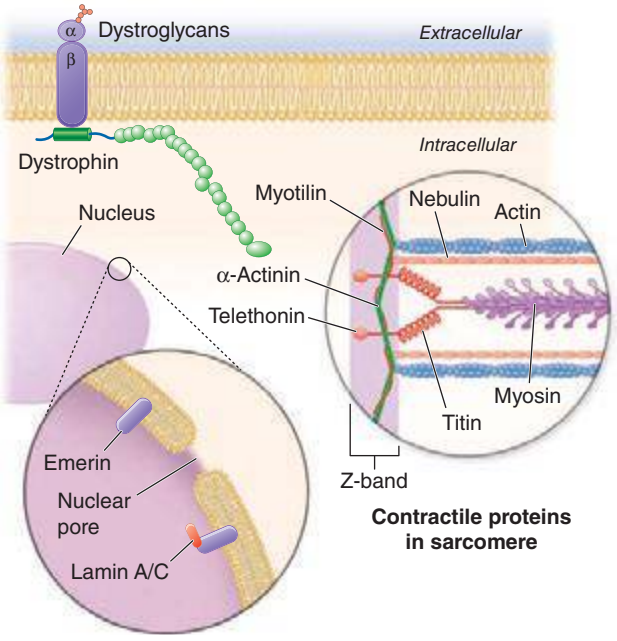

FIGURE 462e-7 Selected muscular dystrophy–associated proteins in the nuclear membrane and sarcomere. As shown in the exploded view, emerin and lamin A/C are constituents of the inner nuclear membrane. Several dystrophy-associated proteins are represented in the sarcomere including titin, nebulin, calpain, telethonin, actinin, and myotilin. The position of the dystrophin-dystroglycan complex is also illustrated.

TREATMENT EMERY-DREIFUSS MUSCULAR DYSTROPHY

Supportive care should be offered for neuromuscular disability, including ambulatory aids, if necessary. Stretching of contractures is difficult. Management of cardiomyopathy and arrhythmias (e.g., early use of a defibrillator or cardiac pacemaker) may be life saving.

CONGENITAL MUSCULAR DYSTROPHY (CMD)

This is not one entity but rather a group of disorders with varying degrees of muscle weakness, CNS impairment, and eye abnormalities.

Clinical Features As a group, CMDs present at birth or in the first few months of life with hypotonia and proximal or generalized muscle weakness. Calf muscle hypertrophy is seen in some patients. Facial muscles may be weak, but other cranial nerve–innervated muscles are spared (e.g., extraocular muscles are normal). Most patients have joint contractures of varying degrees at elbows, hips, knees, and ankles. Contractures present at birth are referred to as *arthrogryposis*. Respiratory failure may be seen in some cases.

The CNS is affected in some forms of CMD. In merosin and FKRP deficiency, cerebral hypomyelination may be seen by magnetic resonance imaging (MRI), although only a small number of patients have mental retardation and seizures. Three forms of congenital muscular dystrophy have severe brain impairment. These include Fukuyama's congenital muscular dystrophy (FCMD), muscle-eye-brain (MEB) disease, and Walker-Warburg syndrome (WWS). Patients are severely disabled in all three of these conditions. In MEB disease and WWS, but not in FCMD, ocular abnormalities impair vision. WWS is the most severe congenital muscular dystrophy, causing death by 1 year of age.

Laboratory Features Serum CK is markedly elevated in all of these conditions. The EMG is myopathic and muscle biopsies show nonspecific dystrophic features. Merosin, or laminin α_2 chain (a basal lamina protein), is deficient in surrounding muscle fibers in merosin deficiency. Skin biopsies can also demonstrate defects in laminin α_2 chain. In the other disorders (FKRP deficiency, FCMD, MEB disease, WWS), there is abnormal α-dystroglycan staining in muscle. In merosin deficiency, cerebral hypomyelination is common, and a host of brain malformations are seen in FCMD, MEB disease, and WWS.

All forms of CMD are inherited as autosomal recessive disorders. Chromosomal linkage and specific gene defects are presented in Table 462e-8. With the exception of merosin, the other gene defects affect posttranslational glycosylation of α-dystroglycan. This abnormality is thought to impair binding with merosin and leads to weakening of the dystrophin-glycoprotein complex, instability of the muscle membrane, and/or abnormalities in muscle contraction. CMDs with brain and eye phenotypes probably involve defective glycosylation of additional proteins, accounting for the more extensive phenotypes.

TREATMENT CONGENITAL MUSCULAR DYSTROPHY

There is no specific treatment for CMD. Proper wheelchair seating is important. Management of epilepsy and cardiac manifestations is necessary for some patients.

MYOTONIC DYSTROPHY

Myotonic dystrophy is also known as *dystrophia myotonica* (DM). The condition is composed of at least two clinical disorders with overlapping phenotypes and distinct molecular genetic defects: myotonic dystrophy type 1 (DM1), the classic disease originally described by Steinert, and myotonic dystrophy type 2 (DM2), also called *proximal myotonic myopathy* (PROMM).