TABLE 462e-8 CONGENITAL MUSCULAR DYSTROPHIES[a]

Disease	Clinical Features	Laboratory Features	Abnormal Protein
Merosin deficiency	Onset at birth with hypotonia, joint contractures, delayed milestones, generalized muscle weakness Cerebral hypomyelination, less often cortical dysplasia Normal intelligence usually, some with MR (~6%) and seizures (~8%) Partial deficiency leads to milder phenotype (LGMD picture)	Serum CK 5–35× normal EMG myopathic NCS abnormal in some cases	Laminin α_2 chain
Fukutin-related protein deficiency[b]	Onset at birth or shortly after Hypotonia and feeding problems Weakness of proximal muscles, especially shoulder girdles Hypertrophy of leg muscles Joint contractures Cognition normal	Serum CK 10–50× normal EMG myopathic NCS normal	Fukutin-related protein
Fukuyama's congenital muscular dystrophy[b]	Onset at birth Hypotonia, joint contractures Generalized muscle weakness Hypertrophy of calf muscles Seizures, MR Cardiomyopathy	Serum CK 10–50× normal EMG myopathic NCS normal MRI shows hydrocephalus and periventricular and frontal hypomyelination	Fukutin
Muscle-eye-brain disease	Onset at birth, hypotonia Eye abnormalities include: progressive myopia, cataracts, and optic nerve, glaucoma, retinal pigmentary changes Progressive muscle weakness Joint contractures Seizures, MR	Serum CK 5–20× normal MRI shows hydrocephalus, cobblestone lissencephaly, corpus callosum and cerebellar hypoplasia, cerebral hypomyelination	*N*-Acetyl-glucosaminyl transferase (POMGnT1)
Walker-Warburg syndrome[b]	Onset at birth, hypotonia Generalized muscle weakness Joint contractures Microphthalmos, retinal dysplasia, buphthalmos, glaucoma, cataracts Seizures, MR	Serum CK 5–20× normal MRI shows cobblestone lissencephaly, hydrocephalus, encephalocele, absent corpus callosum	*O*-Mannoxyl-transferase-1 (POMT1)

[a]All are inherited as recessive traits. [b]There is phenotypic overlap between disorders related to defective glycosylation. In muscle, this is a consequence of altered glycosylation of dystroglycans; in brain/eye, other glycosylated proteins are involved. Clinically, Walker-Warburg syndrome is more severe, with death by 1 year.

Abbreviations: CK, creatine kinase; EMG, electromyography; LGMD, limb-girdle muscular dystrophy; MR, mental retardation; MRI, magnetic resonance imaging; NCS, nerve conduction studies.

Clinical Features The clinical expression of DM1 varies widely and involves many systems other than muscle. Affected patients have a typical "hatchet-faced" appearance due to temporalis, masseter, and facial muscle atrophy and weakness. Frontal baldness is also characteristic of the disease. Neck muscles, including flexors and sternocleidomastoids, and distal limb muscles are involved early. Weakness of wrist extensors, finger extensors, and intrinsic hand muscles impairs function. Ankle dorsiflexor weakness may cause footdrop. Proximal muscles remain stronger throughout the course, although preferential atrophy and weakness of quadriceps muscles occur in many patients. Palatal, pharyngeal, and tongue involvement produce a dysarthric speech, nasal voice, and swallowing problems. Some patients have diaphragm and intercostal muscle weakness, resulting in respiratory insufficiency.

Myotonia, which usually appears by age 5 years, is demonstrable by percussion of the thenar eminence, the tongue, and wrist extensor muscles. Myotonia causes a slow relaxation of hand grip after a forced voluntary closure. Advanced muscle wasting makes myotonia more difficult to detect.

Cardiac disturbances occur commonly in patients with DM1. ECG abnormalities include first-degree heart block and more extensive conduction system involvement. Complete heart block and sudden death can occur. Congestive heart failure occurs infrequently but may result from cor pulmonale secondary to respiratory failure. Mitral valve prolapse also occurs commonly. Other associated features include intellectual impairment, hypersomnia, posterior subcapsular cataracts, gonadal atrophy, insulin resistance, and decreased esophageal and colonic motility.

Congenital myotonic dystrophy is a more severe form of DM1 and occurs in ~25% of infants of affected mothers. It is characterized by severe facial and bulbar weakness, transient neonatal respiratory insufficiency, and mental retardation.

DM2, or PROMM, has a distinct pattern of muscle weakness affecting mainly proximal muscles. Other features of the disease overlap with DM1, including cataracts, testicular atrophy, insulin resistance, constipation, hypersomnia, and cognitive defects. Cardiac conduction defects occur but are less common, and the hatchet face and frontal baldness are less consistent features. A very striking difference is the failure to clearly identify a congenital form of DM2.

Laboratory Features The diagnosis of myotonic dystrophy can usually be made on the basis of clinical findings. Serum CK levels may be normal or mildly elevated. EMG evidence of myotonia is present in most cases of DM1 but may be more patchy in DM2. Muscle biopsy shows muscle atrophy, which selectively involves type 1 fibers in 50% of cases, and ringed fibers in DM1 but not in DM2. Typically, numerous internalized nuclei can be seen in individual muscle fibers as well as atrophic fibers with pyknotic nuclear clumps in both DM1 and DM2. Necrosis of muscle fibers and increased connective tissue, common in other muscular dystrophies, are less apparent in myotonic dystrophy.

DM1 and DM2 are both autosomal dominant disorders. New mutations do not appear to contribute to the pool of affected individuals. DM1 is transmitted by an intronic mutation consisting of an unstable expansion of a CTG trinucleotide repeat in a serine-threonine protein