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An Overview of Congenital Myopathies

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ABSTRACT

Purpose of Review: This article uses a case-based approach to highlight the clinical features as well as recent advances in molecular genetics, muscle imaging, and pathophysiology of the congenital myopathies.

Recent Findings: Congenital myopathies refer to a heterogeneous group of genetic neuromuscular disorders characterized by early-onset muscle weakness, hypotonia, and developmental delay. Congenital myopathies are further classified into core myopathies, centronuclear myopathies, nemaline myopathies, and congenital fiber-type disproportion based on the key pathologic features found in muscle biopsies. Genotype and phenotype correlations are hampered by the diverse clinical variability of the genes responsible for congenital myopathies, ranging from a severe neonatal course with early death to mildly affected adults with late-onset disease. An increasing number of genes have been identified, which, in turn, are associated with overlapping morphologic changes in the myofibers. Precise genetic diagnosis has important implications for disease management, including family counseling; avoidance of anesthetic-related muscle injury for at-risk individuals; monitoring for potential cardiac, respiratory, or orthopedic complications; as well as for participation in clinical trials or potential genetic therapies.

Summary: Collaboration with neuromuscular experts, geneticists, neuroradiologists, neuropathologists, and other specialists is needed to ensure accurate and timely diagnosis based on clinical and pathologic features. An integrated multidisciplinary model of care based on expert-guided standards will improve quality of care and optimize outcomes for patients and families with congenital myopathies.

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INTRODUCTION

Congenital myopathies refer to a genetically and clinically heterogeneous group of inherited skeletal muscle diseases associated with early infantile or childhood onset of motor weakness, hypotonia, and developmental delay, which have a static or slowly progressive course.¹ Variants of congenital myopathies with onset or progression of muscle weakness in adulthood have also been described. Pathologically, congenital myopathies have characteristic but not pathognomonic morphologic features such as the presence of focal myofibrillar disorganization, nuclear centralization, and pro-

tein aggregation.^{2,3} The three major groups of congenital myopathies include: (1) core myopathies, which have foci devoid of oxidative enzymes in myofibers⁴; (2) centronuclear or myotubular myopathies, which are defined by the presence of internally located myonuclei⁵; and (3) nemaline myopathies, which are marked by the presence of electron-dense nemaline bodies or rods within myofibers.⁶ Variants of nemaline myopathy include cap myopathy, zebra body myopathy, and core-rod myopathy. Other pathologic features of congenital myopathies include hyaline body or myosin storage myopathy, necklace fibers, radial sarcoplasmic strands,

and congenital fiber-type disproportion. The latter is defined by the presence of type 1 fiber hypotrophy with mean diameter being uniformly smaller than type 2 fibers by more than 35% to 40%, in the absence of other structural abnormalities and accompanied by clinical features consistent with congenital myopathies.⁷ Each of the pathologic features can be attributed to a number of genetic mutations; furthermore, the biopsy findings can be nonspecific or evolve over time.¹

To date, more than 20 genes have been associated with the congenital myopathies (refer to **Table 9-1** as well as to the useful websites section at the end of this article), and additional genes are being updated based on advances in molecular diagnostics.⁸ Emerging evidence suggests shared pathophysiologic pathways among the congenital myopathies, including defects in muscle membrane remodeling, impaired excitation-contraction coupling, mitochondrial dysfunction, abnormal myofibrillar force generation, and imbalance related to protein synthesis or degradation.²

EPIDEMIOLOGY

Congenital myopathies are rare disorders; the overall prevalence is estimated at 1 in 25,000 individuals.⁹ Previous point prevalence of congenital myopathies ranged from 1.37 per 100,000 of all age groups in northern England¹⁰ to 5 per 100,000 of the pediatric population in western Sweden.¹¹ The true prevalence is likely to be higher because of underrecognition of mildly affected individuals as well as a substantial proportion of cases with nonspecific histologic findings. Core myopathies including central core and multimicore myopathy are the most common histopathologic subtypes of congenital myopathies.¹² Mutations of the ryanodine receptor 1 (*RYR1*) gene are most often implicated as the cause of congenital myopathies,¹³ with a point prevalence of 1 in 90,000 of the pediatric population in the United

States, as reported by Amburgey and colleagues.¹⁴ In another study, the carrier frequency of *RYR1* mutation was estimated to be 1 in 2000 individuals in the Japanese population.¹⁵

Clinically, the diagnosis of congenital myopathies remains challenging because of the variable phenotypes. Significant heterogeneity exists even within family members affected by the same genetic mutation. In one large case series of congenital myopathies, approximately one-third of patients remained genetically unresolved.¹² The lack of molecular confirmation was in part related to the nonspecific clinical features (especially during the neonatal period), the genetic heterogeneity of congenital myopathies, as well as the large size of some involved genes, especially *TTN* and *NEB*.¹⁴ Recently, a targeted exome sequencing strategy in combination with muscle histology has been proposed to identify disease-causing mutations in myopathies of unknown causes. The sequencing includes coverage of each exon of known genes implicated in congenital myopathies to enable more precise genetic diagnosis.⁹

DIAGNOSTIC APPROACH

The history and neurologic examination are important first steps in the diagnostic approach. Careful review of the pregnancy, birth, growth and development, family history, and direct examination of the parents is essential to exclude other inherited neuromuscular disorders. In addition to muscle weakness and hypotonia, clues to the diagnosis of congenital myopathies include the early onset of symptoms, static or slow rate of disease progression, the presence of myopathic facies, ophthalmoplegia, or bulbar involvement, as well as associated signs such as muscle atrophy, hyporeflexia, spinal deformity, clubfoot, or other orthopedic complications. Systemic involvement may manifest as cardiomyopathy, malignant hyperthermia, or

KEY POINTS

- Congenital myopathies are characterized by early-onset muscle weakness, hypotonia, and developmental delay, which have a static or slowly progressive course.
- The three major types of congenital myopathies are core myopathies, centronuclear or myotubular myopathies, and nemaline myopathies.
- The pathologic features in congenital myopathies can be attributed to a number of genetic mutations; furthermore, the muscle biopsy findings can be nonspecific or change over time. A repeat muscle biopsy with muscle imaging guidance is sometimes necessary.
- More than 20 genes have been associated with congenital myopathies.
- A targeted exome sequencing strategy in combination with the clinical features and muscle histology can help identify disease-causing mutations in unspecified cases.

KEY POINTS

- In addition to muscle weakness and hypotonia, clues to the diagnosis of congenital myopathies include the early onset of symptoms, static or slow rate of disease progression, the presence of myopathic facies, ophthalmoplegia, or bulbar involvement, as well as associated signs such as muscle atrophy, hyporeflexia, spinal deformity, clubfoot, or other orthopedic complications.
- Infants with a prenatal onset of muscle weakness due to severe congenital myopathies often present with a history of reduced fetal movement and polyhydramnios.

TABLE 9-1 Genes and Mode of Inheritance Associated With Congenital Myopathies

- ▶ **Nemaline Myopathy**
 - TPM3* (autosomal dominant, autosomal recessive)
 - NEB* (autosomal recessive)
 - ACTA1* (autosomal dominant, autosomal recessive)
 - TPM2* (autosomal dominant)
 - TNNT1* (autosomal recessive)
 - KBTBD13* (autosomal recessive)
 - CFL2* (autosomal recessive)
 - KLHL40* (autosomal recessive)
 - KLHL41* (autosomal recessive)
 - LMOD3* (autosomal recessive)
- ▶ **Central Core Myopathy**
 - RYR1* (autosomal dominant, autosomal recessive)
 - SEPN1* (autosomal recessive)
 - ACTA1* (autosomal dominant)
 - TTN* (autosomal recessive)
- ▶ **Multiminicore Myopathy**
 - SEPN1* (autosomal recessive)
 - RYR1* (autosomal dominant, autosomal recessive)
 - MYH7* (autosomal dominant)
 - TTN* (autosomal recessive)
- ▶ **Core-rod Myopathy**
 - RYR1* (autosomal dominant, autosomal recessive)
 - NEB* (autosomal recessive)
 - KBTBD13* (autosomal dominant)
 - CFL2* (autosomal recessive)
- ▶ **Centronuclear Myopathy**
 - MTM1* (X-linked)
 - DNM2* (autosomal dominant)
 - BIN1* (autosomal recessive)
 - RYR1* (autosomal recessive)

TABLE 9-1 *Continued*

- TTN* (autosomal recessive)
- MTMR14* (autosomal recessive)
- CCDC78* (autosomal dominant)
- SPEG* (autosomal recessive)
- ▶ **Congenital Fiber-type Disproportion**
 - ACTA1* (autosomal dominant)
 - SEPN1* (autosomal recessive)
 - TPM3* (autosomal dominant)
 - TPM2* (autosomal dominant)
 - RYR1* (autosomal recessive)
 - MYH7* (autosomal dominant)
- ▶ **Myosin Storage Myopathy**
 - MYH7* (autosomal dominant)
- ▶ **Cap Myopathy**
 - TPM2* (autosomal dominant)
 - TPM3* (autosomal dominant)
 - ACTA1* (autosomal dominant)
- ▶ **Zebra Body Myopathy**
 - ACTA1* (autosomal dominant)
- ▶ **Distal Myopathy With No Rods**
 - NEB* (autosomal recessive)

respiratory insufficiency.¹ Sensation and intelligence are generally preserved. Infants with a prenatal onset of muscle weakness due to severe congenital myopathies often present with a history of reduced fetal movement and polyhydramnios. The consequence of fetal akinesia (or lack of movement in utero) includes craniofacial dysmorphism, multiple joint contractures (or arthrogyrosis), pulmonary hypoplasia, hip dysplasia, muscle atrophy, and profound generalized weakness. Severe hypotonia plus bulbar and respiratory insufficiency may necessitate invasive mechanical ventilation and gastrostomy tube feeding from birth.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

The most helpful tools for the diagnostic workup of congenital myopathies are serum creatine kinase (CK), nerve conduction study and EMG, muscle imaging, muscle biopsy, and selective biochemical and genetic testing. Serum CK is usually normal or mildly elevated (less than five times the upper limit of normal) in congenital myopathies; significantly raised levels (more than 10 times the upper limit of normal) are suggestive of alternative diagnoses such as muscular dystrophies. Nerve conduction studies often yield normal motor and sensory responses, apart from reduced compound motor action potential (CMAP) amplitudes. EMG may reveal a myopathic recruitment pattern with occasionally nonspecific findings or neurogenic changes due to severe muscle atrophy. Increased jitter or significant electrodecremental responses can be seen in congenital myopathies associated with secondary neuromuscular junction defects, including cap myopathy due to mutations in the *TPM2* gene, centronuclear myopathies related to *DNM2* or X-linked *MTM1* mutations, and congenital fiber-type disproportion caused by *TPM3* and *RYR1* mutations.¹⁶

Muscle imaging using MRI or ultrasound provides additional noninvasive diagnostic clues as genetic myopathies are often associated with specific patterns of muscle involvement, particularly early in the course of the disease.¹ In contrast to CT, MRI provides excellent soft tissue contrast without the use of ionizing radiation and is frequently the modality of choice for skeletal muscle imaging, although sedation may be required in young children. Based on a relatively simple algorithm of an anterior versus posterior pattern of muscle involvement of the thighs followed by the same assessment of the lower legs, Wattjes and colleagues¹⁷ proposed the use of MRI to distinguish among the different subtypes of congenital myopathies (Figure 9-1). The differential diagnosis was further

expanded by Quijano-Roy and colleagues.¹⁸ Similar to MRI, muscle ultrasound performed by skilled clinicians can also be used to detect various types of congenital myopathies.¹ This technique is particularly useful as a screening tool in pediatric patients younger than 5 years of age and does not require sedation. In one study, muscle ultrasound was abnormal in 23 out of 25 patients (92%) with core myopathies, with a specificity of 26.3% and a positive predictive value of 62.2%.¹²

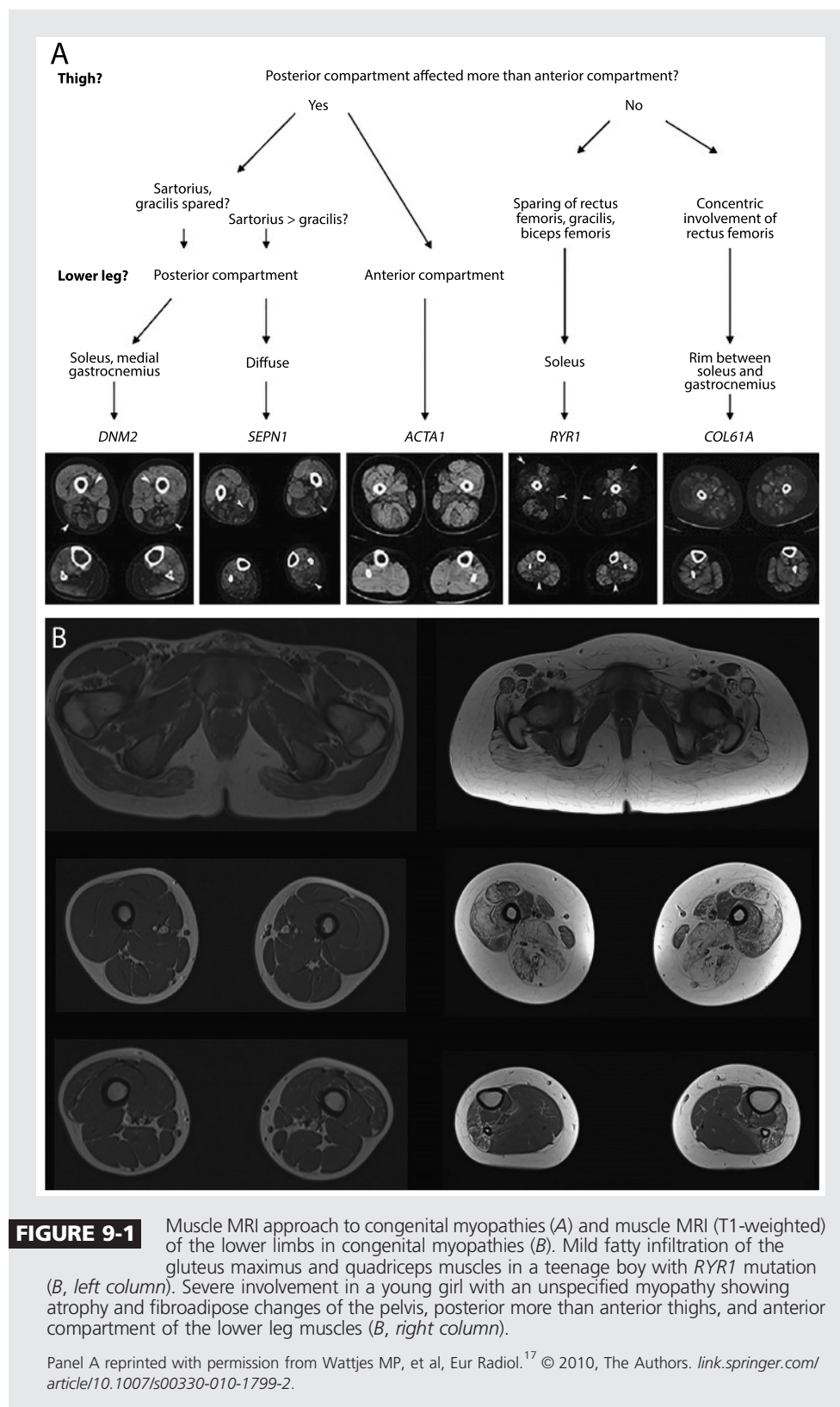
The differential diagnoses of hypotonia and severe generalized weakness in the newborn or early infancy period include congenital myopathies, congenital muscular dystrophies, congenital myotonic dystrophy, congenital myasthenic syndromes, myofibrillar myopathies, other myopathies, congenital neuropathies, spinal muscular atrophy, as well as genetic and metabolic conditions such as Prader-Willi syndrome or glycogen-storage disease.¹⁹ The presence of encephalopathy, microcephaly, or upper motor neuron signs such as increased tone, hyperreflexia, sustained clonus, and obligate extensor plantar responses may point to an alternative diagnosis such as hypoxic ischemic encephalopathy or other central nervous system disorders.

CORE MYOPATHIES

Core myopathies are characterized pathologically by the absence of oxidative enzyme activity in the central area of the myofiber due to mitochondrial depletion. Core myopathies are among the most common form of congenital myopathies^{12,13} and are further divided into central core and multiminicore myopathies. Pathologically, central cores are longitudinally extensive areas within the center of the myofiber that are devoid of mitochondrial enzymatic activity, whereas multiple smaller areas of reduced activity that affect shorter segments of the myofiber are characteristic of multiminicore myopathy.⁴ On electron microscopy, the cores represent areas of abnormal sarcomeric structure, including Z-band

KEY POINTS

- The most helpful tools for the diagnostic workup of congenital myopathies are serum creatine kinase, nerve conduction study and EMG, muscle imaging, muscle biopsy, and selective biochemical and genetic testing.
- Muscle imaging using MRI or ultrasound provides additional noninvasive diagnostic clues as genetic myopathies are often associated with specific patterns of muscle involvement, particularly early in the course of the disease.



streaming, complete myofibrillary disorganization, and accumulation of Z-band material. The abnormal regions are devoid of mitochondria, which correlate with the loss of mitochondrial enzymatic activity in histochemical (eg, NADH, succinate dehydrogenase [SDH], or cytochrome oxidase [COX]) stains.²⁰

Similar to other congenital myopathies, the pathologic features may evolve over time with earlier biopsies showing minimal changes or no abnormalities.

Core myopathies are mostly caused by autosomal dominant or recessive mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene on chromosome 19q13.1 or autosomal recessive mutations in the selenoprotein N 1 (*SEPN1*) gene on chromosome 1p36 that encodes an endoplasmic reticulum glycoprotein.⁴ Mutations in the skeletal muscle α -actin 1 (*ACTA1*) and titin (*TTN*) can also result in core myopathies.¹ Rarely, mutations of *RYR1* or *NEB* genes have been associated with a combination of rods and cores also known as core-rod myopathy.^{21,22} Type 1 fiber predominance, as well as an increase in internal nuclei, are also common pathologic findings in *RYR1*-related core myopathies.

Core myopathies can present with variable phenotypes, ranging from mild to severe. In milder cases, affected individuals usually present with hypotonia, joint laxity, motor developmental delay, and weakness affecting the hip girdle or axial muscles. Marked clinical variability can occur within the same family with some individuals remaining asymptomatic aside from occasional muscle stiffness, exertional myalgia, or rhabdomyolysis as presenting symptoms.⁴ Orthopedic complications, as illustrated in **Case 9-1**, are common and include recurrent shoulder or patella dislocation and congenital hip dysplasia due to marked ligamentous laxity. Muscle ultrasound or MRI shows a striking pattern of muscle involvement in *RYR1*-related core myopathies. Unlike other congenital myopathies that predominantly affect the posterior thigh muscles, selective involvement of the

anterior and medial compartments of the thighs, including the quadriceps, is often seen in *RYR1*-related myopathies, even in relatively asymptomatic individuals. The rectus femoris and gracilis muscles are typically spared.¹

Most individuals with central core disease related to autosomal dominant *RYR1* mutations experience mild or moderate weakness with a static or slowly progressive course. As seen with the mother of the patient in **Case 9-1**, pregnancy can worsen the underlying muscle weakness.⁴ Furthermore, patients with central core myopathy, especially those with confirmed *RYR1* mutations, are at risk for developing malignant hyperthermia; both conditions are allelic disorders related to *RYR1* mutations that lead to impaired excitation-contraction coupling and abnormal calcium homeostasis.^{2,23} These patients need to be counseled regarding potentially fatal adverse reaction to volatile anesthetics or muscle relaxants, and wearing a medical alert bracelet is generally advisable in case of any unexpected emergency.

Prognosis for severe neonatal central core myopathy remains guarded (**Case 9-2**). The presence of marked joint laxity, generalized muscle weakness, and atrophy may preclude the possibility of independent ambulation and necessitate ongoing mechanical ventilation. Natural history studies suggested that early respiratory and nutritional support including gastrostomy feeding had a significant impact on overall survival and the clinical outcomes of neonatal central core myopathy.^{12,13} Depending on their dietary intake, patients should be encouraged to take vitamin D and calcium supplements to maximize bone health. Intermittent assessments of bone mineral density are indicated, especially for those with a history of fragility fractures or for those who have other risk factors for osteoporosis.

Multiminicore myopathy may present during infancy (**Case 9-3**) with feeding difficulties, axial hypotonia, progressive scoliosis with or without spinal rigidity,

KEY POINTS

- Individuals with core myopathies related to *RYR1* mutations are at risk for developing malignant hyperthermia and should be counseled regarding potential anesthesia-related muscle injury accordingly.
- Natural history studies suggest that early respiratory and nutritional support can have a positive impact on the overall survival and clinical outcomes of children with severe neonatal central core myopathy.

KEY POINT

■ Treatment for congenital myopathies remains symptomatic. Management of potential complications will require ongoing monitoring in a multidisciplinary setting with input from pediatric orthopedic, pulmonary, cardiology, and rehabilitation specialists.

Case 9-1

A 12-year-old girl presented with malignant hyperthermia intraoperatively during elective knee surgery. Her medical history was remarkable for recurrent shoulder dislocation. She sustained a fracture to the right lateral femoral condyle during a basketball game and was admitted for surgical repair, during which isoflurane was used as part of general anesthesia. Shortly after, she developed hyperthermia, tachycardia, increased carbon dioxide retention, and myoglobinuria. She responded to IV dantrolene, supplementary oxygen, and cessation of inhalational anesthetic.

Physical examination was normal apart from joint hypermobility, scapular winging, and mild symmetric proximal weakness (grade 4 out of 5). She had no known family history of malignant hyperthermia. However, her older brother had recurrent patellae subluxation with wasting of the quadriceps and pes cavus feet. The patient's mother had previously been diagnosed with congenital hip dysplasia and had walked with a cane since early adulthood because of slowly progressive hip girdle weakness; her muscle weakness had been aggravated by each subsequent pregnancy.

Investigations in the patient showed raised serum creatine kinase (CK) of 2232 IU/L approximately 12 hours postsurgery, which returned to normal after 2 days. EMG and muscle biopsy were deferred. Molecular genetic testing confirmed two heterozygous mutations of the *RYR1* gene. The first was a missense variant of unknown significance in exon 41. In addition, a second gene change was found in exon 103. This change had been previously reported as an autosomal dominant mutation in other patients with central core myopathy. The same heterozygous mutations were found in the patient's older brother, and her mother carried the dominant mutation involving exon 103.

Comment. This case illustrates the milder spectrum of central core myopathy as well as its important association with malignant hyperthermia; both conditions are allelic disorders related to *RYR1* mutations that lead to impaired excitation-contraction coupling and abnormal calcium homeostasis.^{2,23}

and early respiratory impairment that is often out of proportion to the degree of skeletal muscle weakness.⁴ Classic multiminiore myopathy is most often caused by autosomal recessive *SEPN1* mutations. To date, no cases of malignant hyperthermia due to *SEPN1*-related myopathies have been reported. Autosomal recessive *RYR1* mutations may also result in a similar clinical phenotype, except that ophthalmoplegia is more prominent in *RYR1*-related multiminiore myopathy.¹ Malignant hyperthermia is a potential risk for *RYR1*-related multiminiore myopathies. Genetic counseling including anesthetic precaution should be discussed. Rarely, mutations in the myosin heavy chain 7 (*MYH7*) or titin (*TTN*) genes have been found in multiminiore myop-

athies, especially when associated with cardiomyopathy. Minicores can also be seen in other conditions such as muscular dystrophies as well as collagen VI-related myopathies.¹

Treatment for core myopathies remains symptomatic. The frequent association with orthopedic complications such as congenital hip dislocation or scoliosis requires ongoing monitoring in a multidisciplinary setting with input from pediatric orthopedic and rehabilitation specialists. Judicious aerobic exercise such as cycling or swimming may help promote aerobic fitness. As respiratory impairment is another common complication, particularly in multiminiore myopathies, regular pulmonary function testing and polysomnography studies are necessary

Case 9-2

A 4-year-old boy presented for a follow-up visit in the pediatric neuromuscular clinic with progressive scoliosis. He had a history of arthrogryposis, bilateral hip dislocation, undescended testes, severe generalized weakness, hypotonia, developmental delay, scoliosis, and respiratory failure since birth. His mother's pregnancy had been remarkable for reduced fetal movements and polyhydramnios, and the patient's birth weight was only 1.9 kg (4.2 lb) at term. The patient had been intubated at birth because of low Apgar scores and required ongoing mechanical ventilation and gastrostomy tube feeding. The boy had learned to sit with support after age 1, had scooted on his bottom at 2.5 years of age, and had begun to speak in full sentences through his tracheostomy after his third birthday. Family history was unremarkable.

Physical examination at 1 year of age had revealed that the boy was small for his age and had generalized amyotrophy and alert interactive facies. He had no ptosis, and extraocular movements were full. He had very lax fingers and hands, prominent head lag, and severe scoliosis. His movements were limited because of generalized weakness, and he could only move his distal arms and legs with gravity assistance.

Initial investigations shortly after birth had been normal, including serum creatine kinase (CK), brain MRI, karyotype, and metabolic screening and genetic testing for spinal muscular atrophy, myotonic dystrophy type 1, and Prader-Willi syndrome. Nerve conduction study and EMG suggested a myopathic process. A neonatal muscle

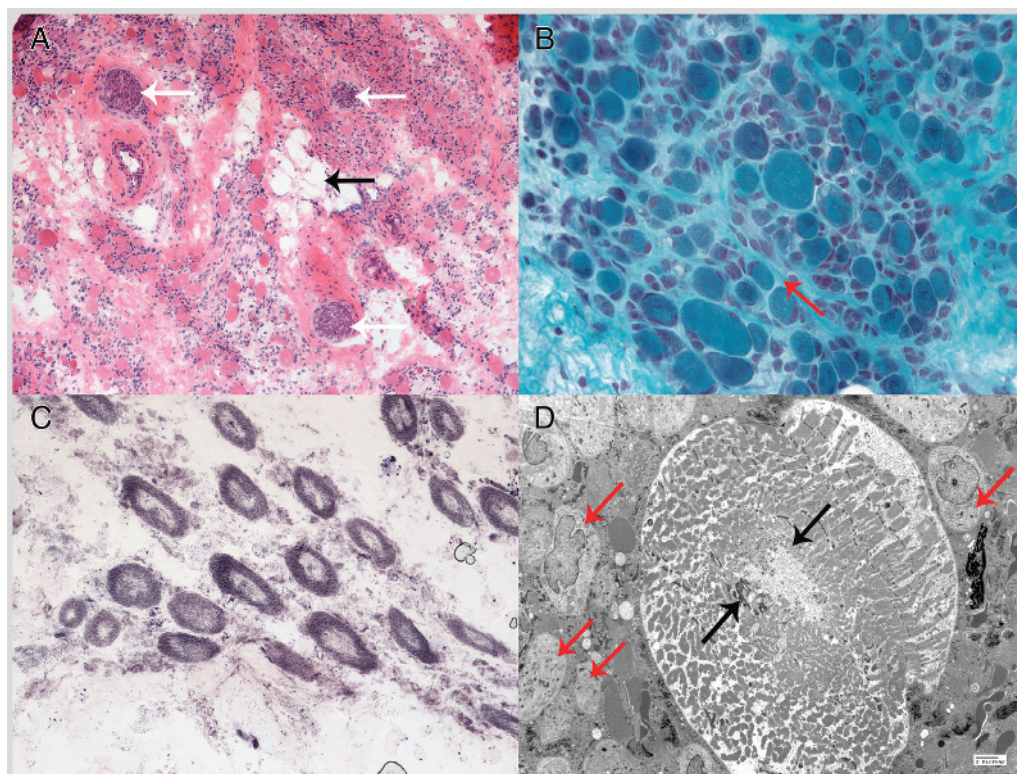


FIGURE 9-2

Neonatal muscle biopsy of the patient with central core myopathy in Case 9-2. *A*, In this hematoxylin and eosin (H&E) section, much of the muscle consists of tiny fibers intermixed with an occasional larger myofiber. Adipose replacement has formed (*black arrow*). Because of the extensive muscle atrophy, the intramuscular nerve twigs appear quite prominent (*white arrows*). *B*, At higher magnification in the Gomori trichrome stain section, a few near-normal myofibers are intermixed with many small and tiny fibers. Endomysial connective tissue is greatly increased (green staining material) (*red arrow*). *C*, In central cores, many of the large fibers contain central areas devoid of mitochondria (succinate dehydrogenase histochemistry). *D*, The electron micrograph shows one of the large fibers having a central core. In this fiber, the center of the core contains only some glycogen, while its rim is composed of disorganized or aggregated sarcomeric material (*black arrows*). Around the periphery of the large myofiber are many small, poorly formed myofibers (*red arrows*) that have a few scattered sarcomeric structures or aggregates.

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biopsy (**Figure 9-2**) showed features of severe central core myopathy, including a few larger fibers that had central cores, many tiny myofibers, and extensive fibroadipose replacement. Gene testing at 3 months of age had confirmed a de novo dominant *RYR1* mutation involving exon 91.

He required bilateral orchidopexy and vertical expandable prosthetic titanium rib implantation for treatment of his scoliosis. He received intermittent IV bisphosphonate infusions due to a fragility fracture of the left humerus and generalized osteopenia seen on bone density x-rays.

Comment. This case illustrates the severe spectrum of central core myopathy with reduced fetal movements, pulmonary hypoplasia, arthrogryposis, congenital hip dislocation, and scoliosis due to profound muscle weakness. Extraocular movements are often spared in severe *RYR1*-related myopathies, which may serve to distinguish it from other severe forms of congenital myopathies with ophthalmoparesis, such as congenital nemaline or centronuclear myopathy secondary to *ACTA1*, *NEB*, *DNM2*, *MTM1*, or *KLHL40* mutations.⁴

to monitor for decline in respiratory function that might necessitate noninvasive positive-pressure ventilation.¹² Severe early-onset cases often require invasive mechanical ventilation.⁴ In addition, individuals with core myopathies unrelated to *RYR1* or *SEPN1* mutations will require periodic cardiac assessments to monitor for potential cardiac complications, especially in those with associated respiratory impairment. Results from a recent pilot study and case report suggested that albuterol, a β -2 agonist, may be helpful for the treatment of core myopathies^{24,25}; further recommendations must await confirmation from a larger prospective study. Similarly, *N*-acetylcysteine will be evaluated as part of a clinical trial regarding its role as antioxidant therapy for *RYR1*-related congenital myopathies.²⁶

CENTRONUCLEAR MYOPATHIES

Centronuclear myopathies refer to a heterogeneous group of genetic myopathies characterized pathologically by the presence of abundant, centrally located nuclei.²⁷ Early case reports were provided by Spiro and colleagues in 1966 and Sher and colleagues in 1967.²⁸

To date, 8 genes have been associated with centronuclear myopathies, including X-linked recessive mutations in *MTM1* encoding myotubularin 1; autosomal dominant mutations in *DNM2* encoding dynamin 2, the *BINI* gene encoding amphiphysin 2, and *CCDC78* gene encoding coiled-coil domain-containing protein 78; autosomal recessive

mutations in *BINI*, *MTMR14* encoding hJumpy, *RYR1* encoding the skeletal muscle ryanodine receptor, *TTN* encoding titin, and *SPEG* encoding striated muscle preferentially expressed protein kinase.^{1,29} The majority of mutations related to centronuclear myopathies to date (including *MTM1*, *DNM2*, *BINI*, and *MTMR14*) involve proteins being implicated in various aspects of membrane trafficking and remodeling relevant to endocytosis, vesicle transport, autophagy, and other essential cellular processes.^{2,27} *DNM2* is the most common cause of centronuclear myopathy and usually presents as a relatively mild form of autosomal dominant late-childhood or early-adult onset distal myopathy, and de novo mutations with a severe early-onset phenotype have also been described.²⁸

X-linked myotubular myopathy is caused by mutations of the *MTM1* gene, which encodes a 3'-phosphoinositides phosphatase called myotubularin 1. Affected neonates have the most severe phenotype of all centronuclear myopathies, including marked extraocular, facial, respiratory, and axial muscle weakness (**Case 9-4**). Most boys with X-linked myotubular myopathy die despite supportive treatment. Recently, pathologic recessive mutations of the gene encoding striated muscle preferentially expressed protein kinase (*SPEG*), an *MTM1*-interacting protein localized to the sarcoplasmic reticulum, were found to result in severe centronuclear myopathy with dilated cardiomyopathy.²⁹

Case 9-3

A 9-year-old boy presented with a history of hypotonia, developmental delay, exercise intolerance, shortness of breath, and progressive scoliosis that he had experienced since early childhood. He had been born after an uncomplicated pregnancy and birth. He had required aortopexy surgery during infancy for tracheomalacia, recurrent chest infections, and failure to thrive. His motor developmental milestones had been delayed. He had walked after 2 years of age and had continued to struggle with climbing stairs. Family history was unremarkable; he was an only child.

Physical examination revealed a tall boy with height, weight, and head circumference in approximately the 95th percentile. General examination was remarkable for a pear-shaped body habitus, high-arched palate, retrognathia, pectus excavatum, reduced muscle bulk in his anterior chest and upper arms, increased lumbar lordosis, rigid spine, severe scoliosis, and bilateral pes planus feet. He had mild ptosis and bifacial weakness. The patient's extraocular movements were spared. Motor examination revealed mild (grade 4 out of 5) proximal more than distal muscle weakness, with a positive Gowers sign. Reflexes were 2+ throughout with flexor plantar responses, and sensation and coordination were intact. Prior investigations at 7 years of age had included serum creatine kinase (CK), karyotype, comparative genomic hybridization microarray, metabolic screen, ECG, Holter monitoring, echocardiogram, nerve conduction study and EMG, and MRI brain and spine, all of which had been unremarkable. The initial quadriceps muscle biopsy performed at age 7 had shown mild type 2 myofiber atrophy, and a repeat biopsy of the paraspinal muscle (**Figure 9-3**) at age 9 showed type 2 myofiber atrophy but also showed frequent myofibers that had one to several sarcoplasmic cores devoid of mitochondrial enzymes,

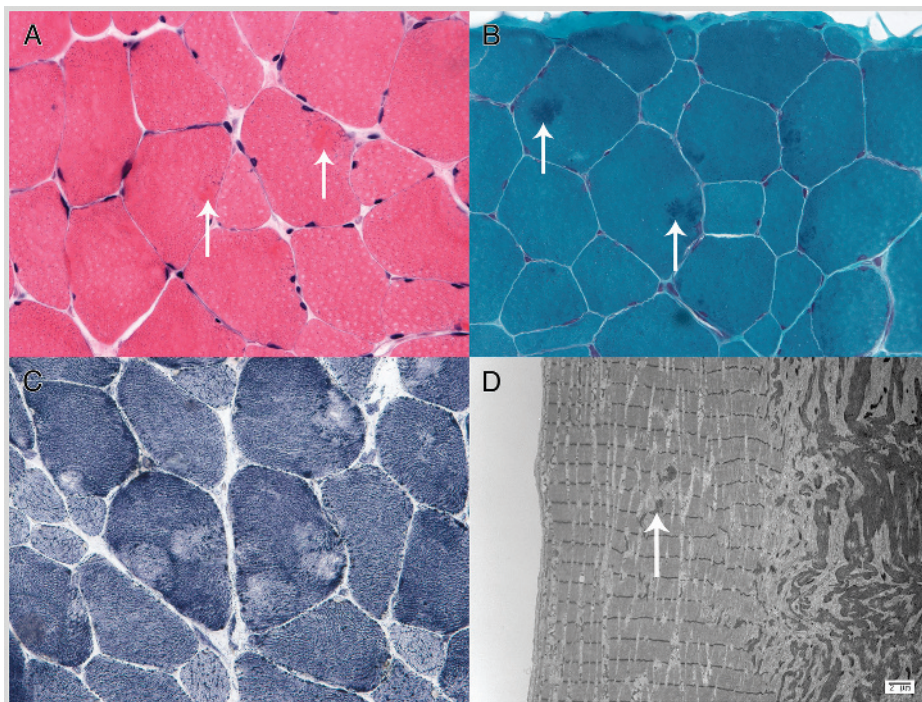


FIGURE 9-3 Muscle biopsy of the patient with multiminicore myopathy in Case 9-3. *A*, Hematoxylin and eosin (H&E) stain demonstrates some myofiber size variation. A few myofibers contain eosinophilic aggregates that have a light basophilic stippling around their edges (arrows). *B*, Gomori trichrome stain shows no significant endomysial connective tissue but does show various aggregates inside several of the fibers (arrows). *C*, On NADH histochemistry, many fibers contain one to several minicores that display reduced enzyme reactivity. *D*, Electron micrograph demonstrates a larger core on the right that has extensive sarcomeric disruption and Z-band material aggregation, as well as several much smaller areas of myofibrillary disarray (arrow).

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indicative of multimincore myopathy. Genetic testing for *RYR1* mutation was negative at age 9. He required noninvasive mechanical pressure support ventilation for progressive respiratory muscle weakness during adolescence.

Comment. This case illustrates the challenge of carrying out an initial muscle biopsy in a patient with congenital myopathy as the muscle biopsy will occasionally only show nonspecific changes. The typical histopathologic findings of core myopathies in some cases may evolve over time and can be absent when the biopsy is performed at an early age. A repeat muscle biopsy with muscle imaging (MRI or ultrasound) guidance is sometimes necessary. Genetic testing is required for confirmation of diagnosis and counseling.

KEY POINT

■ Defects in neuromuscular transmission have recently been recognized as one of the pathogenic mechanisms among subtypes of congenital myopathies. Anticholinesterase therapy may be beneficial in some cases.

Individuals with late-onset *MTM1* mutations are clinically distinct from the severe neonatal-onset X-linked myotubular myopathy (Case 9-5). Generally, symptoms are milder and well compensated for during childhood with progression of motor dysfunction, exercise intolerance, and fatigable weakness developing after the first 2 decades of life.⁵ As seen in Case 9-5, hemiatrophy and asymmetric weakness have been described in women with late-onset *MTM1*-related myopathy.³²

Autosomal recessive centronuclear myopathies caused by *BINI* mutations are generally very rare.³³ Affected individuals usually present as an intermediate form of disease between the severe neonatal-onset X-linked *MTM1* and the autosomal dominant late-childhood-onset *DNM2* forms of centronuclear myopathy.³⁴ Marked fiber size disproportion between type 1 and type 2 fibers are commonly seen in *DNM2*-related centronuclear myopathies, whereas fiber diameters are more uniform in *BINI*-related mutations. Similarly, *RYR1*-related centronuclear myopathies have variable degrees of muscle weakness, are associated with prominent myofibrillar disarray in the muscle biopsies, and are usually inherited as autosomal recessive disorders.¹ Muscle biopsies from patients with centronuclear myopathies and occasionally other severe forms of congenital myopathies can have a variable degree of endomysial fibrosis and adipose tissue replacement.³⁵ These findings sometimes have led to a diagnosis of muscular dystrophy, despite the lack of frank muscle necrosis. The presence of ptosis and ophthalmoplegia on clinical examination should help to dis-

tinguish centronuclear myopathy from congenital muscular dystrophy.¹

Individuals with centronuclear myopathies can present with myasthenic features with positive response to anticholinesterase therapy or evidence of impaired neuromuscular transmission based on electrophysiologic (repetitive stimulation or single-fiber) studies (Case 9-5). Indeed, defects in neuromuscular transmission have recently been recognized as one of the pathogenic mechanisms among subtypes of congenital myopathies, particularly in cases related to *MTM1*, *BINI*, *DNM2*, *TPM2*, *TPM3*, and *RYR1* mutations.^{2,16} The use of pyridostigmine, an acetylcholinesterase inhibitor, can sometimes be associated with significant clinical improvement.

NEMALINE MYOPATHIES

Shy and colleagues³⁶ first described an infant girl with early-onset hypotonia and muscle weakness, and the term *nemaline myopathy* was coined because of the presence of threadlike (the prefix *nema* refers to thread) or rodlike structures found in her muscle biopsy. The clinical spectrum is wide, ranging from a severe congenital form to mild adult-onset nemaline myopathy. Prominent axial and limb-girdle weakness occurs initially, followed by progression to involve the distal muscles.³⁷ A distal or a predominantly lower-extremity pattern of weakness has also been described.⁶

Currently, 10 genes have been associated with nemaline myopathy, including dominant mutations of skeletal muscle α -actin 1 (*ACTA1*) or recessive mutations of nebulin (*NEB*) genes.¹ Other mutations include muscle-specific

Case 9-4

A term 37-week gestational age infant boy was born to a 28-year-old woman by cesarean delivery because of fetal tachycardia. The infant's birth weight was 2.76 kg (6 lb). Because of significant hypotonia and poor respiratory effort, the infant was intubated at birth and then switched to continuous positive airway pressure by nasal prong the next day. He was fed by nasogastric tube from birth because of poor feeding. Family history was unremarkable; his parents had no evidence of muscle wasting, myotonia, or fatigable weakness.

Physical examination revealed a severely hypotonic infant with tachypnea, moderate indrawing, and pectus excavatum. His head circumference was normal. He had a myopathic face with bilateral ptosis, limited extraocular movements, inverted V-shaped upper lip, high-arched palate, and reduced facial movements. No cataracts or tongue fasciculations were noted. His cry and gag were weak. Motor examination revealed paucity of spontaneous movements due to generalized weakness. Deep tendon reflexes were 1+ in both knees and absent elsewhere. Primitive reflexes including rooting, suck, Moro, and grasp were absent.

Laboratory investigations including complete blood count, serum electrolytes, lactate, thyroid functions, blood and urine cultures, and a screen for toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex (TORCH) were negative. Serum creatine kinase (CK) was 198 IU/L. Karyotype was 46 XX, and molecular genetic testing for spinal muscular atrophy, myotonic dystrophy type 1, and facioscapulohumeral muscular dystrophy were negative. Metabolic screens, including plasma amino acids, urine organic acids, liver function tests, acylcarnitine profile, and very-long-chain fatty acids, were negative. In addition, his brain MRI, EEG, and echocardiogram were normal. Nerve conduction studies and EMG revealed small-amplitude polyphasic motor units with occasional fibrillation potentials. Muscle biopsy of the right vastus lateralis at 2 weeks of age showed normal muscle fascicular architecture without fiber necrosis, regeneration, or proliferation of connective tissue. ATPase showed mild (60%) predominance of type 2 fibers with normal glycogen, lipid, and oxidative enzymatic activities. Trichrome stain revealed no ragged red fibers. A repeat muscle biopsy at 3 months of age showed type 1 fiber predominance with preserved fascicular architecture. One-half of the myofibers had a single internal nucleus with surrounding pale-staining core (**Figure 9-4**). The infant died at 6 months of age because of aspiration pneumonia. An autopsy was declined.

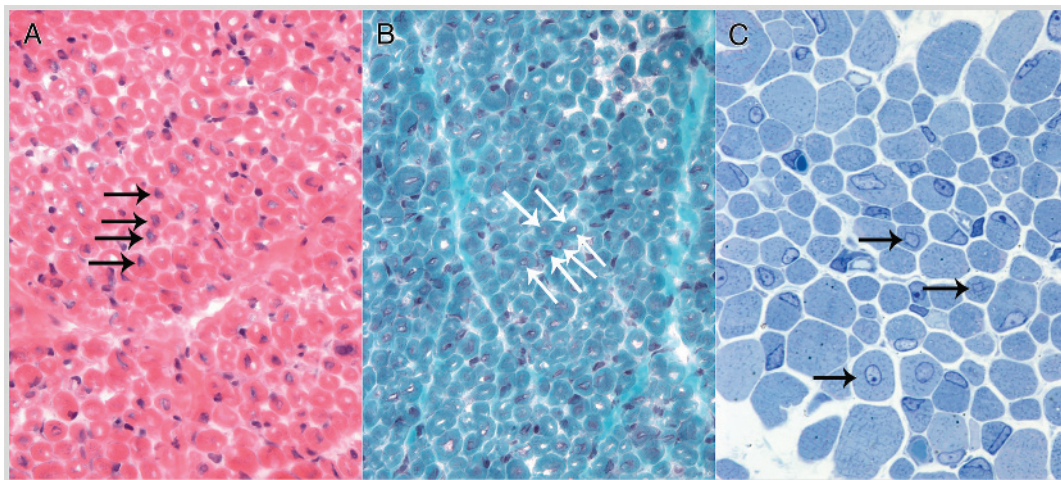


FIGURE 9-4 Muscle biopsy of patient with neonatal centronuclear myopathy in Case 9-4. Both the hematoxylin and eosin (H&E) (A, 40X) and Gomori trichrome stains (B, 40X) at high magnification from the biopsy at 3 months of age contained many internalized nuclei (several identified with *black* or *white* arrows). Neither showed myofiber necrosis or degeneration. Internalized nuclei were significantly less frequent in the biopsy at 2 weeks of age (toluidine blue plastic section, 100X) (C, *black* arrows).

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Comment: Severe neonatal centronuclear myopathy in a male infant is often caused by mutations of the *MTM1* gene. *MTM1* gene testing was not done in this case as it had not been available at that time. Rarely, skewed X inactivation of *MTM1* as well as de novo dominant mutations of *DNM2* can result in a severe neonatal phenotype in females. As congenital myotonic dystrophy type 1 is also associated with prominent central nuclei in muscle biopsies,³⁰ clinical examination of the mother and *DMPK* genetic testing should be considered to exclude this diagnosis.

cofilin 2 (*CFL2*), troponin T1 slow skeletal type (*TNNT1*), β -tropomyosin 2 (*TPM2*), α -tropomyosin 3 (*TPM3*), kelch-like family member 40 (*KLHL40*), kelch-like family member 41 (*KLHL41*), and muscle-specific ubiquitin ligase (*KBTBD13*) genes. *KBTBD13* can cause both core-rod myopathy and nemaline myopathy.¹ Recently, recessive mutations of leiomodin 3 (*LMOD3*) were found to be associated with a severe and often fatal form of congenital nemaline myopathy.³⁸ Mutations associated with nemaline myopathies are distributed worldwide, apart from troponin T1 slow skeletal type (*TNNT1*), which is responsible for a distinct form of nemaline myopathy among the Old Order Amish families.³⁹ Genetic confirmation of nemaline myopathies is often complicated by the large number of genes involved as well as the large size of the nebulin (*NEB*) gene.

Pathologically, nemaline rods appear as dark red staining inclusions with the Gomori trichrome stain. The major constituents of rods include α -actinin, tropomyosin, and Z-disk-related proteins such as actin, myotilin, and nebulin, which are all components of the sarcomere. The presence of intranuclear nemaline bodies, as opposed to the more common sarcoplasmic location, is exclusive to *ACTA1* mutations and can be associated with a more severe disease phenotype.⁶

A mutation involving the *NEB* gene is generally the most common cause of nemaline myopathies. The disease is clinically variable. Severe cases presenting in the neonatal period (classic form) usually have significant facial, respiratory,

axial, and generalized muscle weakness.⁴⁰ Most patients with *NEB* mutations have predominant proximal weakness; however, distal-predominant involvement also has been observed, particularly in late-onset cases.⁴¹

In addition to nemaline rods, mutations in the skeletal muscle α -actin gene (*ACTA1*) are associated with other pathologic features, including cap myopathy, intranuclear rod myopathy, and congenital fiber-type disproportion. The clinical phenotypes are also variable, ranging from severe neonatal onset (with hypotonia, generalized weakness, and early death), late childhood (Case 9-6), or early-adult presentation with slowly progressive proximal weakness.⁴⁰ Rarely, childhood-onset muscle stiffness and hypertonia has been described as the result of an *ACTA1* mutation.⁴² Similarly, mutations in the *TPM2* gene can cause cap myopathy and congenital arthrogryposis in addition to nemaline myopathy.¹ The clinical phenotypes of *TPM2* and *TPM3* mutations are quite variable, including early-onset hypotonia, motor developmental delay, as well as slowly progressive proximal- or distal-predominant muscle weakness.⁴³

Treatment for nemaline myopathy remains largely symptomatic, including range of motion exercise, use of orthotics for footdrop, positive-pressure mechanical ventilation, and nasogastric tube feeding for nutritional support. Regular low-impact aerobic exercise may help to maintain cardiovascular fitness. Tyrosine has been reported as a potentially beneficial supplement for nemaline myopathy⁴⁴; however, the mechanism of action of tyrosine in

Case 9-5

A 34-year-old woman presented with progressive limb-girdle weakness as well as left arm and face hemiatrophy. At birth, she had been floppy with a weak suck reflex and had required brief nasogastric tube feeding. She had walked at 14 months but was unable to jump or climb stairs without assistance. Over time, she had repeated falls and eventually became partially wheelchair dependent in her early twenties. Review of systems was notable for increased tendency to choke with liquids, myalgia, shortness of breath on exertion, and fluctuating ptosis. Physical examination revealed mild bilateral ptosis with left more than right facial weakness, high-arched palate, micrognathia, scoliosis, and scapular winging. Motor examination revealed moderate asymmetric muscle weakness. She had atrophy of her thenar and hypothenar muscles, which was worse on the left side. She had prominent calves with mild contractures in her heel cords, elbows, shoulders, and long finger flexors bilaterally. Gait examination showed bilateral footdrop.

The patient's serum creatine kinase (CK) was 105 IU/L. Genetic testing for myotonic dystrophy types 1 and 2 (*DMPK* and *CNBP*) were both negative. ECG and echocardiogram were normal. Pulmonary function testing showed a reduced forced vital capacity of 67% predicted. Her first muscle biopsy at 8 years of age had shown many central nuclei, frequent rounded fibers, increased connective tissue, type 1 fiber predominance, and some

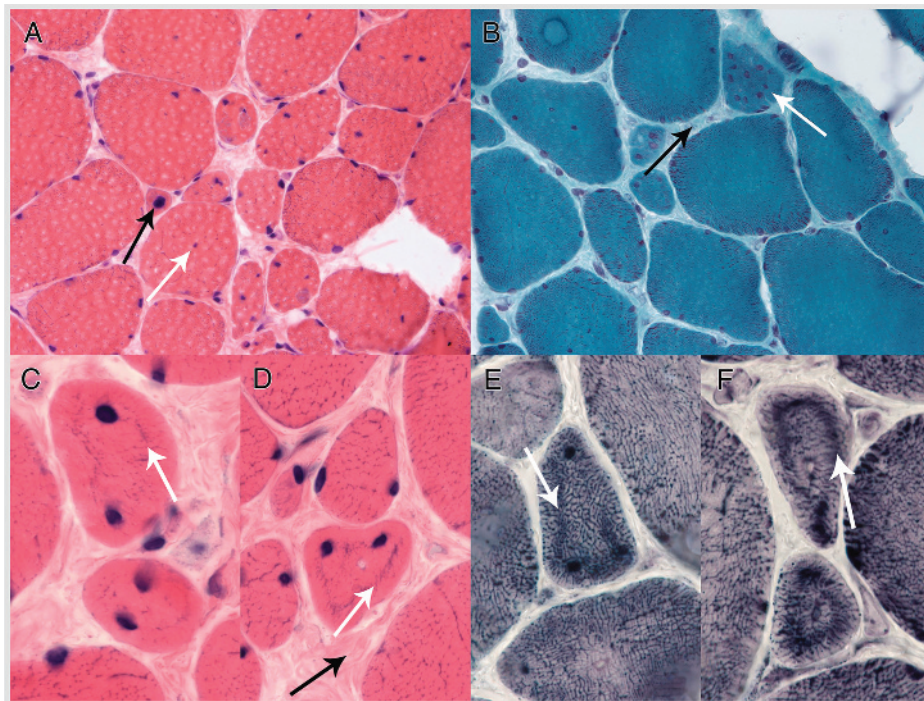


FIGURE 9-5 Muscle biopsy of the patient with myotubular myopathy in Case 9-5. In this adult version of myotubular myopathy, the hematoxylin and eosin stain (H&E) (A) shows moderate to marked variation in myofiber size and increased internalized nuclei. Only a few fibers have central nuclei (A, white arrow) or central nuclear clumps (A, black arrow). The Gomori trichrome stain (B) has similar features, including some fibers with abundant internalized nuclei (B, white arrow) and also emphasizes the increased endomysial connective tissue (B, black arrow). Different necklace fibers on H&E stain (C, D) and NADH histochemistry (E, F) are illustrated. H&E stains also demonstrate the increased connective tissue (D, black arrow). Necklace fibers have internalized nuclei that are often equidistant from the sarcolemma and often have a gossamer string that connects them together (C–F, white arrows). The gossamer string is basophilic in H&E stains (D, white arrow) and has increased NADH activity in NADH histochemistry (E, F, white arrows). Some fibers have been cut in a plane that misses the nuclei and shows only the string (F, white arrow).

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ring fibers. A repeat biopsy at 24 years of age (**Figure 9-5**) had shown many internalized nuclei and frequent necklace fibers without necrosis. Genetic testing confirmed a heterozygous mutation of part of the *MTM1* gene. Treatment with pyridostigmine led to symptomatic improvement in her motor function and endurance.

Comment. The presence of necklace fibers in the second muscle biopsy plus the abundance of central myonuclei in the first muscle biopsy were helpful diagnostic clues in this case. Necklace fibers refer to a subsarcolemmal zone of nuclei linked by obliquely oriented small myofibrils associated with a higher density of mitochondria and sarcoplasmic reticulum, which have been described in sporadic late-onset cases of *MTM1*- or *DNM2*-related centronuclear myopathies.³¹

KEY POINT

- Congenital myopathy with fiber-type disproportion is defined by significant type 1 fiber hypotrophy in the absence of other structural abnormalities.

nemaline myopathies remains unclear. Other experimental therapies for nemaline myopathies involving muscle stem cells, antisense oligonucleotides, and gene replacement will depend on the underlying genetic mutations and ongoing research.⁴⁵

CONGENITAL FIBER-TYPE DISPROPORTION

Brooke and Engel⁴⁶ first coined the term congenital fiber-type disproportion in 1973 to describe the presence of discordant fiber size, with type 1 fibers being smaller by 12% or more in muscle biopsies from 14 patients. However, a mild degree of fiber size disproportion is nonspecific and can be observed in a variety of conditions, including diseases of the central nervous system, metabolic disorders, spinal muscular atrophy, and muscular dystrophies. For example, mutations in *SEPNI*, lamin A/C (*LMNA*), collagen type VI alpha 1 (*COL6A1*), and *DMPK*, as well as other congenital myopathies, can be associated with a predominance of small type 1 fibers. The diagnosis of congenital fiber-type disproportion is reserved for cases of congenital myopathy with type 1 fibers being consistently smaller in diameter than type 2 fibers by more than 35% to 40% in the absence of other histopathologic abnormalities.⁷ The presence of rods, cores, abundant central nuclei, or other structural features of congenital myopathies indicates an alternative diagnosis other than congenital fiber-type disproportion.

Currently, at least five different genes have been associated with congenital

fiber-type disproportion. Most affected individuals have a static or slowly progressive course of generalized muscle weakness (**Case 9-7**), consistent with the clinical features of congenital myopathies as well as variable degrees of hypotonia, respiratory insufficiency, facial diplegia, dysphagia, and ophthalmoparesis. Ophthalmoparesis can also be seen in *RYR1*-related myopathy with fiber-type disproportion. The most common genetic causes in descending order of frequency are slow α -tropomyosin 3 (*TPM3*), ryanodine receptor 1 (*RYR1*), skeletal muscle α -actin 1 (*ACTA1*), myosin heavy chain 7 (*MYH7*), β -tropomyosin 2 (*TPM2*), and selenoprotein N 1 (*SEPNI*) mutations, which are all inherited as either autosomal dominant or recessive disorders.¹ An unspecified X-linked form of congenital fiber-type disproportion has been described, but the genetic cause remains unclear.⁴⁷ In addition to congenital fiber-type disproportion, mutations in the *MYH7* gene can present with myosin storage or hyaline body myopathy, multiminicore myopathy, early childhood-onset Laing distal myopathy, as well as hereditary cardiomyopathies.^{48,49}

Detection of specific genetic mutations resulting in congenital fiber-type disproportion can help with ongoing disease monitoring and genetic counseling. For example, pulmonary function testing is particularly important in patients with *TPM3* mutations. Muscle weakness generally follows a relatively stable or slowly progressive course during childhood and adolescence. In general, scoliosis and joint contractures (apart from mild Achilles tendon contractures)

Case 9-6

An 11-year-old girl presented with gross motor delay, proximal muscle weakness, and recurrent myalgia involving her calves, hamstrings, and biceps. She was the product of a normal term pregnancy. As an infant, the girl had rolled at 6 months, sat up at 9 months, pulled up to stand at 15 months, and walked independently at 20 months. Her parents described her as a “clumsy” child as she tripped easily. She also struggled with climbing steps and could do so only with support. Physical examination revealed a slender young girl with a high-arched palate, mild bilateral ptosis, and small hands and feet. Her weight was in the 10th percentile, and her height and head circumference were in the 50th percentile for her age. Cranial nerve examination showed mild bifacial weakness. She had reduced muscle bulk as well as mild symmetric proximal more than distal muscle weakness. Truncally, she rolled to one side to get up and used a one-handed Gowers sign to get up from the floor. She had no scoliosis, scapular winging, or spinal rigidity. Apart from mild heel cord tightness, she had no fixed contractures. Deep tendon reflexes were 2+ and symmetric throughout with flexor plantar responses, and sensation and coordination were intact. Investigations including serum creatine kinase (CK), pulmonary function tests, ECG, and echocardiogram were normal. Muscle biopsy (**Figure 9-6**) showed single and clustered rodlike structures in the Gomori trichrome stain that had ultrastructural parallel and perpendicular striations typical of nemaline rods.

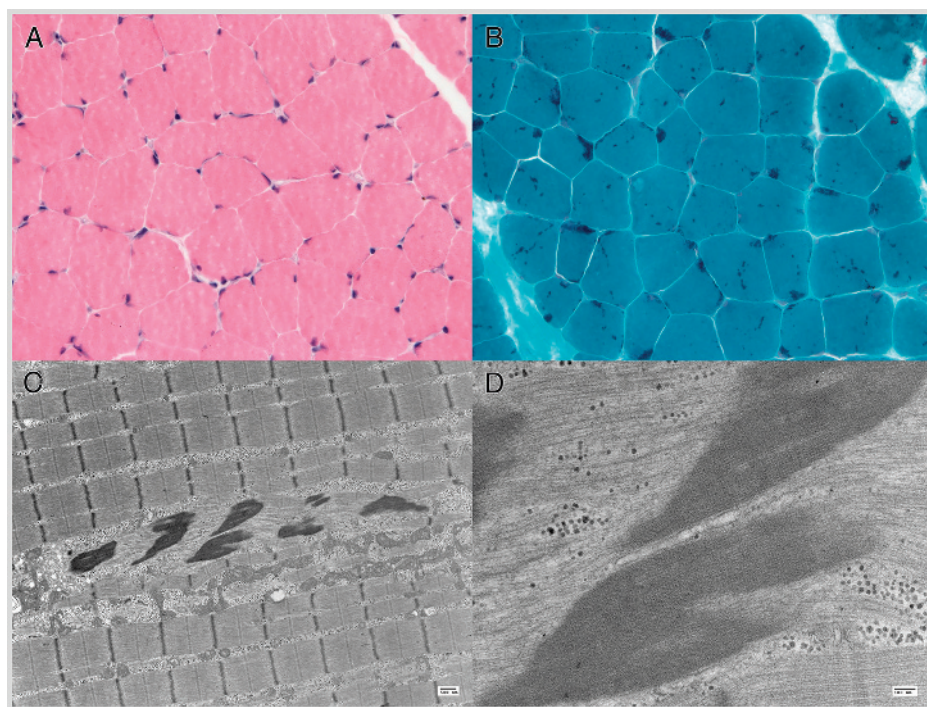


FIGURE 9-6

Muscle biopsy of patient with nemaline myopathy in **Case 9-6**. *A*, The muscle in the hematoxylin and eosin (H&E) stain has mild variation in myofiber size. *B*, In contrast, the Gomori trichrome stain reveals numerous clumps of darkly staining nemaline rods both within the sarcoplasm and clumped into aggregates at some myofiber corners or edges. *C, D*, Ultrastructurally, these nemaline aggregates consists of bands of dark material that are interconnected by thin filaments. *D*, At higher magnification, the dark material is oriented parallel to the thin filaments but also has a distinct periodicity that is perpendicular to the filaments. This pattern is characteristic of nemaline.

Comment. This case illustrates a patient with a mild form of nemaline myopathy. Muscle imaging (MRI or ultrasound) may also help with the differential diagnosis. In mild cases, relative sparing of the thigh with early involvement of the tibialis anterior can be seen.¹⁸ More severe cases are associated with diffuse changes in the lower limbs with relative sparing of the gastrocnemius muscles.¹

are relatively uncommon, and cardiac abnormalities are rare. Cardiac surveillance every 2 to 3 years is indicated for patients with *MYH7*- or *TPM2*-related myopathies or unconfirmed molecular diagnosis. Physical therapy and regular aerobic exercise such as cycling and swimming should be encouraged as much as possible. Nocturnal noninvasive ventilation, gastrostomy tube feeding, and scoliosis surgery may be required for those with a more severe or progressive disease.

GUIDELINES

As congenital myopathies are relatively uncommon, many clinicians may not be familiar with the management of affected individuals. Fortunately, a panel of experts convened in 2010 and created a guideline in order to optimize care and improve outcomes for congenital myopathies.³ A patient and family version of the guideline is available through the Cure CMD (congenital muscular dystrophy) website (see the useful website section at the end of this article). The guideline focuses on five major management areas: diagnostics/genetics, neuro-

logy, pulmonary, orthopedics/rehabilitation, and gastroenterology/nutrition. Neurologic care includes the provision of key information related to the diagnosis, prognosis, treatment plan, genetic counseling, as well as family support and community resources. The risk of malignant hyperthermia secondary to *RYR1*-related myopathies as well as the early and disproportionate degree of respiratory involvement in *SEPN1*-related myopathies should be discussed with the patient and family. Follow-up care and anticipatory guidance are best provided using an integrated multidisciplinary approach in collaboration with orthopedic surgeons, physiatrists, pulmonologists, cardiologists, gastroenterologists, psychologists, pediatricians/internists, as well as physical therapists, occupational therapists, respiratory therapists, speech-language pathologists, nurses, and social workers. Each visit should include a careful review of systems, including growth and development for pediatric patients, as well as a thorough physical examination with focus on potential complications such as respiratory insufficiency, feeding

Case 9-7

A 2-month-old boy presented with hypotonia and generalized weakness since birth. He had been born after a normal term pregnancy, apart from reduced fetal movements in utero. He required resuscitation for transient tachypnea, had increased difficulty breathing, and had feeding difficulty that necessitated nasogastric tube feeding. Family history was negative, and both parents were healthy with no evidence of neuromuscular disease.

Physical examination revealed normal growth parameters for his age. He was mildly tachypneic at rest with alert facies and a paucity of spontaneous movements of all four limbs. Cranial nerves II through XII were intact apart from weak cry and reduced facial expression. He had no tongue fasciculations. Truncally, he was significantly hypotonic with head lag on pull to sit, and he slipped through the examiner's hands when held by the axilla on vertical suspension. Motor examination revealed hyperextensible joints, scapular winging, and reduced bulk. He had near antigravity strength (grade 2) in his elbows, with no antigravity movements in his proximal upper and lower limbs. Primitive reflexes including Moro, Galant, and atonic neck response could not be elicited. Deep tendon reflexes were absent in all four extremities. The rest of his general examination was normal.

Serum creatine kinase (CK) was 80 IU/L, and brain MRI was normal. Metabolic screen and gene mutation analysis for spinal muscular atrophy, myotonic dystrophy type 1, and Prader-Willi syndrome were negative. Nerve conduction study and EMG suggested a myopathic process. Muscle biopsy of the right vastus lateralis revealed a predominance of moderately small type 1 myofibers intermixed with occasional normally sized type 2 fibers, in contrast to relatively homogenous sizes of type 1 and 2 fibers seen in a normal muscle biopsy (**Figure 9-7**). In the absence of other structural abnormalities, such as rods or cores, the findings were indicative of congenital muscle fiber-type disproportion.

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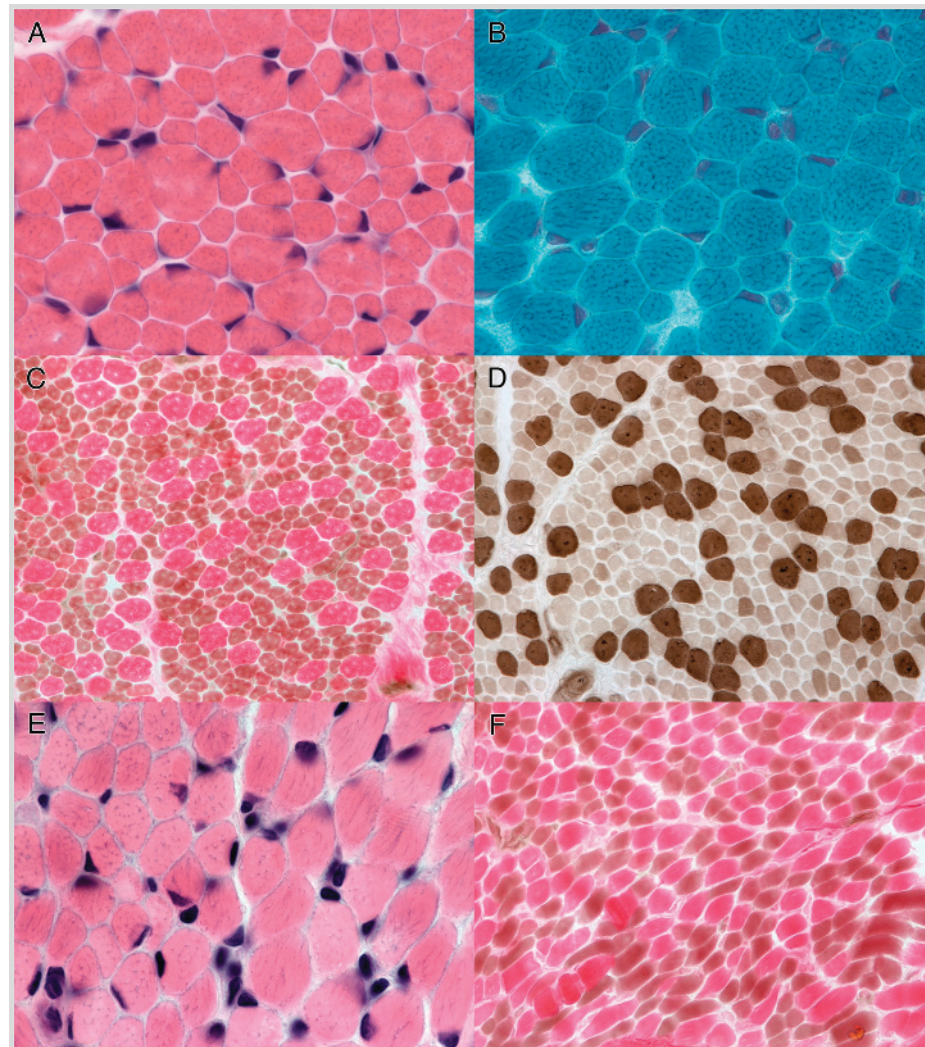


FIGURE 9-7 Muscle biopsy of the patient in **Case 9-7** with congenital fiber-type disproportion and normal control. The only anomaly in the muscle from this infant, performed at 5 months of age, on either hematoxylin and eosin (H&E) (*A*) or Gomori trichrome stains (*B*) is the presence of two distinct populations of myofibers based on their size. No other aggregated material, nemaline rods, or cores are present. The larger population of normally sized myofibers are all of type 2 (ATPase histochemistry, pH 4.3 in *panel C* and pH 10.4 in *panel D*). The type 1 fibers are more than 30% smaller in diameter and much smaller in area than the type 2 myofibers. Compared to *panels A–D* that show congenital fiber-type disproportion, *panel E* and *panel F* illustrate a more normal muscle from a 7-month-old infant that lacks the two distinct populations of myofiber sizes, although it does have some fiber size variation (*panel E*, with the same magnification as in *panel A*). The pH 4.3 ATPase histochemistry (*panel F*, with the same magnification as in *panel C*) demonstrates that the fiber size variation is not selective for either type 1 (darker at this pH) or type 2 (red from the counterstain used at this pH) myofibers.

Comment. This case illustrates the natural history of congenital myopathy with fiber-type disproportion. Over time, the patient's gross motor delay slowly improved. He sat at 1 year, walked independently at 2 years, and climbed stairs at 3 years of age. He continued to struggle with jumping, hopping, and running due to proximal muscle weakness. At the last examination at age 8, he had good functional ability despite pes planus gait and hyperextensible joints.

difficulty, or scoliosis. Optimal weight, diet, physical activity, range-of-motion exercises, calcium and vitamin D supplementation to promote bone health, up-to-date immunizations, education, and career planning should be addressed. Specific issues related to congenital myopathies include: (1) screening for potential ocular, cardiac, and respiratory involvement; (2) management of respiratory and orthopedic complications; (3) monitoring for motor deterioration due to disease progression; and (4) family counseling regarding avoidance of anesthesia-induced muscle injury, and perioperative management, as carefully summarized by Wang and colleagues.³ A formal video fluoroscopic swallowing study may be indicated for infants with feeding concerns or failure to thrive. Baseline and follow-up ECG and echocardiography should also be considered for all individuals with unspecified congenital myopathies. The presence of cardiomyopathy may suggest specific genes such as *MYH7*, *TTN*, *SPEG*, or, rarely, *ACTA1* mutations.

Respiratory complications beyond the infancy period are uncommon; they are more likely to occur in congenital myopathy-related mutations involving *MTM1*, *SEPN1*, *ACTA1*, *TPM3*, *NEB*, and *DNM2*. Close monitoring of respiratory function is required to detect early respiratory insufficiency. The use of mechanical or manual cough-assisted devices, lung volume recruitment exercises, as well as airway clearance techniques should be offered as prophylactic respiratory care strategies for affected individuals in addition to noninvasive positive-pressure ventilation as indicated based on pulmonary function tests, overnight pulse oximetry, and polysomnography. Pain and fatigue are common patient-reported symptoms but may be underrecognized by clinicians. Beyond identifying the cause (such as skeletal fracture or secondary neuromuscular junction transmission defects) and excluding treatable conditions (such as sleep-disordered breathing or nutritional or hormonal

deficiency), appropriate use of mobility devices and physical therapist-guided exercise programs should improve patients' overall function and endurance.

Severity of disease in the neonatal or early infantile period correlates with increased mortality during the first year of life. Clear genotype-phenotype correlations among the severe congenital myopathies (related to *ACTA1*, *KLHL40*, or X-linked *MTM1*) will help provide anticipatory guidance for subsequent pregnancies. The exception to this appears to be neonates with severe weakness and *RYR1* mutations, most of whom survived and improved clinically in the study by Colombo and colleagues,¹³ thus suggesting a more benign course for congenital *RYR1*-related myopathies.

Maggi and colleagues¹² found that while the majority (93.4%) of 66 patients with congenital myopathies in their series remained stable or improved, progression of muscle weakness was experienced by a subset (6.6%) of affected individuals. Colombo and colleagues¹³ further found that eight out of 89 patients (9%) who lost ambulation were often late walkers, thus the loss of independent ambulation may reflect the additional burden of increased growth on already substantially compromised muscle function. Furthermore, one-half of all 17 patients with scoliosis in their natural history study were ambulant at the time of surgery. The development of scoliosis may be more related to the disproportionate axial weakness rather than change in the ambulatory function.¹³

NEW EMERGING THERAPIES

Beyond recognizing the association of myasthenic syndrome and centronuclear myopathies, modulation of the neuromuscular junction represents a potential disease-modifying option for the treatment of other types of congenital myopathies. Larger prospective clinical trials are needed to determine the role of antioxidants (such as *N*-acetylcysteine) as adjunctive treatment. Research using

animal or zebra fish models of disease provides insight into pathogenesis as well as important proof of concept regarding further therapeutic trials for congenital myopathies.⁵⁰ For example, a single intravascular administration of a recombinant adeno-associated virus (AAV) serotype 8 vector expressing the *MTM1* gene rescued the muscle pathology and dramatically improved the survival of *MTM1*-deficient mice and dogs, thus laying the groundwork for future AAV-mediated gene therapy trials for X-linked myotubular myopathy.⁵¹ Similar to other neuromuscular disorders, the treatment of the congenital myopathies will likely require multiple strategies addressing the underlying disease processes, including gene therapy, enzyme replacement, upregulation of compensatory genes or proteins, antiapoptosis approaches, myostatin modulators, muscle troponin activators, or other regulators of calcium homeostasis.² Advances in basic science research offer a glimmer of hope that new emerging therapies may soon become available for many subtypes of congenital myopathies.

CONCLUSION

Genetic advances have identified a growing list of more than 20 genes responsible for congenital myopathies. Each gene can be associated with multiple histopathologic abnormalities in the myofibers that may change over time; at the same time, each distinct pathologic feature can be caused by multiple different genes. The clinical phenotypes related to the congenital myopathies are highly diverse. Accurate diagnosis requires a systematic approach, incorporating clues from the history, physical examination, nerve conduction study and EMG, and ancillary studies such as muscle imaging to help select the appropriate site for muscle biopsy as well as targeted next-generation gene sequencing. Guidelines are available to help clinicians, patients, and their families

navigate through treatment options for congenital myopathies. Those with secondary neuromuscular junction defects may benefit from anticholinesterase therapy or other strategies to enhance synaptic function. Recent advances in the understanding of molecular genetics and shared pathophysiologic mechanisms should help identify novel therapeutic options for congenital myopathies.

USEFUL WEBSITES

The Care of Congenital Myopathies: A Guide for Families

www.curecmd.org/wp-content/uploads/resources/cm-guide-view.pdf

Genetics Home Reference

ghr.nlm.nih.gov

Leiden Open Variation database

www.lovd.nl

Online Mendelian Inheritance of Man

www.omim.org

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KEY POINT

- Recent advances in the understanding of molecular genetics and shared pathophysiologic mechanisms should help identify novel therapeutic options for congenital myopathies.

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