Congenital Muscular Dystrophy and Congenital Myopathy

By Russell J. Butterfield, MD, PhD, FAAN

Address correspondence to
Dr Russell J. Butterfield,
Departments of Pediatrics and
Neurology, University of Utah
School of Medicine, 15 N 2030 E,
Salt Lake City, UT 84112, *russell.
butterfield@hsc.utah.edu*.

ABSTRACT

PURPOSE OF REVIEW: Congenital muscular dystrophies and congenital myopathies are a heterogeneous group of disorders resulting in hypotonia, muscle weakness, and dystrophic or myopathic features on muscle biopsy. This article summarizes the clinical and genetic aspects of these disorders.

RECENT FINDINGS: Historically, diagnoses of congenital muscular dystrophy and congenital myopathy have been made by clinical features and histopathology; however, recent advances in genetics have changed diagnostic practice by relying more heavily on genetic findings. This article reviews the clinical and genetic features of the most common congenital muscular dystrophies including laminin subunit alpha 2 (LAMA2)–related (merosin deficient), collagen VI–related, and α-dystroglycan–related congenital muscular dystrophies and reviews the most common congenital myopathies including nemaline rod, core, and centronuclear myopathies. With the increasing accessibility of genetic testing, the number of genes found to be associated with these disorders has increased dramatically. A wide spectrum of severity and onset (from birth to adulthood) exist across all subtypes. Progression and other features are variable depending on the subtype and severity of the specific genetic mutation.

SUMMARY: Congenital muscular dystrophy and congenital myopathy are increasingly recognized disorders. A growing appreciation for the breadth of phenotypic variability and overlap between established subtypes has challenged long-standing phenotypic and histopathologic classifications of these disorders but has driven a greater understanding of pathogenesis and opened the door to the development of novel treatments.

INTRODUCTION

Congenital muscular dystrophies and congenital myopathies are a heterogeneous group of disorders resulting in hypotonia, progressive muscle weakness, and dystrophic or myopathic features on muscle biopsy. In most cases, congenital muscular dystrophies result from disruption of components of the muscle extracellular matrix and its interaction with the sarcolemmal membrane. In contrast, congenital myopathies are caused by abnormalities of the contractile

matrix, or structures supporting efficient excitation-contraction coupling, including the T tubules, sarcoplasmic reticulum, and other supporting structures.

Historically, congenital muscular dystrophies and congenital myopathies have been diagnosed based on clinical features and histopathology; however, with the increasing accessibility of genetic diagnosis has come an increasing appreciation for the breadth of phenotypic variability and overlap between established congenital muscular dystrophy subtypes and congenital myopathy subtypes. By definition, weakness in patients with congenital myopathy and congenital muscular dystrophy is present from birth or becomes apparent in the first year of life, but this long-held distinction is giving way to an increasing recognition that for most patients with congenital muscular dystrophy and congenital myopathy a wide spectrum of severity and progression occurs. Progression and other features are variable depending on the subtype and the severity of the specific genetic mutation.

In addition to a greater appreciation of the broad phenotypic spectrum in congenital muscular dystrophies and congenital myopathies, improvements in genetic testing have led to a rapidly growing number of new genes associated with congenital muscular dystrophy and congenital myopathy phenotypes and recognition of significant overlap in clinical and histopathologic features between patients with congenital myopathies, congenital muscular dystrophies, and congenital myasthenic syndromes.[1]

EVALUATION AND MANAGEMENT

Differential diagnosis in children with suspected congenital muscular dystrophy and congenital myopathy is shaped by clinical features, age at onset, and inheritance pattern.[2] A number of different classification and diagnostic schemes have been proposed.[3,4] Historically, these have been based on clinical features and findings on muscle biopsy. However, these algorithms are complicated by the ever increasing number of overlapping disorders and expanding number of genes identified in congenital muscular dystrophies and congenital myopathies. Newborns with congenital muscular dystrophy and congenital myopathy typically present with muscle weakness, hypotonia, and joint contractures. Etiologies for hypotonia in young children are varied and include both neuromuscular and non-neuromuscular disorders. Discrimination of neuromuscular versus non-neuromuscular causes of hypotonia in infants can be complex; however, encephalopathy, seizure, or abnormal movements are suggestive of a central rather than peripheral etiology in infants. Respiratory and feeding difficulties are common in infants with both neuromuscular and non-neuromuscular disorders. A history of polyhydramnios and decreased fetal movements is common during pregnancy in the mothers of patients with these disorders.[5] Normal cognitive functioning in the newborn period supports a neuromuscular diagnosis.

Clinical features can assist in narrowing a differential diagnosis but are rarely diagnostic on their own. Facial weakness, ptosis, and ophthalmoparesis in the newborn period are common features in severe congenital myopathy and suggest the possibility of centronuclear or nemaline myopathy.[3] Distal joint laxity and keloid scars suggest a collagen VI–related muscular dystrophy. Scoliosis and spinal rigidity are prominent features in myopathies related to deficiencies in *SELENON* (formerly *SEPN1*), *LAMA2*, *LMNA*, collagen VI, and *RYR1*. Cardiac involvement is common in *TTN-* and *MYH7-*related congenital myopathies and

FKRP- and *FKTN-*related congenital muscular dystrophies but is uncommon in most other congenital muscular dystrophies and congenital myopathies.[6,7]

Recognition of the relative frequency of disorders can guide the differential diagnosis by prioritizing more common diagnoses. Among congenital muscular dystrophies, collagen VI–related and merosin-deficient congenital muscular dystrophies are the most common, except in Japanese populations, where Fukuyama muscular dystrophy predominates because of a common founder mutation in the *FKTN* gene.[8,9]

One UK study found that collagen VI–related muscular dystrophy accounted for almost half of patients with genetically confirmed congenital muscular dystrophy, with merosin-deficient congenital muscular dystrophy and α-dystroglycan–related congenital muscular dystrophy also being relatively common, accounting for nearly 20% and 30% of cases, respectively.[9] In a separate study of congenital myopathies, *RYR1-*related central core myopathies were the most common congenital myopathy, accounting for more than half of genetically confirmed cases, with *SELENON* and *ACTA1*, each accounting for 16% of genetically confirmed congenital myopathies.[10]

Serum creatine kinase (CK) is often the first test performed in patients with suspected congenital muscular dystrophy or congenital myopathy. An elevation in CK suggests disruption of the permeability of the sarcoplasmic membrane, which allows CK to leak from the cytoplasm. This is more common in congenital muscular dystrophy and other muscular dystrophies that disrupt the α-dystroglycan complex than it is in congenital myopathies. Mild CK elevations can be caused by a number of different factors unrelated to muscle disease including race, sex, medications, and physical activity. CK elevations of 5 times or more should prompt testing for a dystrophic disorder.

Historically, muscle biopsy has been the mainstay of diagnostic testing for patients with suspected congenital muscular dystrophy or congenital myopathy.[11] Muscle biopsy findings from patients with congenital muscular dystrophy typically include dystrophic features such as fibrosis, fatty infiltration, and necrosis that distinguish them from myopathic features seen in congenital myopathies such as central displacement of nuclei, atrophy or hypertrophy of fibers, and degenerating/regenerating fibers. Fibrosis and fatty replacement are common features in muscle severely affected by any cause and do not readily distinguish congenital muscular dystrophy from congenital myopathy. Muscle biopsy can be diagnostic of a specific disorder, and specific staining for laminin (merosin) is available at most centers. Immunohistochemistry or immunofluorescent staining for glycosylation of α-dystroglycan and sarcoglycans points broadly to α-dystroglycan related muscular dystrophies but does not identify the specific gene involved. Congenital myopathies are defined primarily by their histologic appearance (nemaline rods, central cores, or centralized nuclei) (**FIGURE 6-1**) and were considered distinct clinical entities for many years until the identification of the genes underlying these disorders showed significant overlap. Heterogeneity in biopsy findings between congenital myopathy subtypes and between congenital muscular dystrophies and congenital myopathies has blurred the distinctions between disorders that were once thought to be distinct.

Muscle imaging by ultrasonography and MRI are important noninvasive tools to guide the differential diagnosis in patients with congenital muscular dystrophy
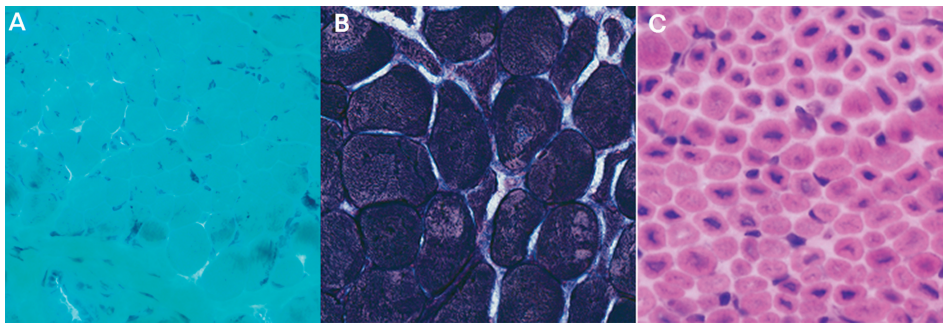
FIGURE 6-1
Muscle biopsy section from a patient with *A*, nemaline myopathy (*ACTA1*) demonstrating prominent cytoplasmic inclusions on Gomori trichrome stain; *B*, central core myopathy (*RYR1*) demonstrating multiminicores as areas of central clearing in nicotinamide adenine dinucleotide (NADH) stain; and *C*, centronuclear (myotubular) myopathy demonstrating immature fibers with predominantly centrally placed nuclei on hematoxylin and eosin (H&E) stain.
Reprinted with permission from Jahannaz Dastgir, MD. © Jahannaz Dastgir, MD.

and congenital myopathy and can guide rational selection of muscle for biopsy. Specific patterns of involvement have been identified for some phenotypes of congenital muscular dystrophy and congenital myopathy, including a "central cloud" phenomenon in the rectus femoris in patients with collagen VI–related muscular dystrophy[12,13] and marked sparing of the rectus femoris in *RYR1*-related myopathies (**FIGURE 6-2**).[14] Pattern recognition algorithms have been developed to identify muscles or muscle groups that are affected or those that are spared for congenital myopathies,[15] such as muscular dystrophies with rigidity of the spine.[16]

With rapid improvement of sequencing technology, genetic testing has become the most important part of the workup for patients with suspected congenital muscular dystrophy or congenital myopathy. Genetic testing early in the evaluation speeds diagnosis and avoids more costly and invasive tests such as nerve conduction studies and EMG, imaging, and muscle biopsy. The number of genes associated with congenital muscular dystrophy and congenital myopathy phenotypes has grown rapidly in the past few years. The useful website section of this article refers readers to a comprehensive list of neuromuscular genes and phenotypes maintained in the GeneTable of Neuromuscular Disorders.[17] The 2019 version of the GeneTable includes 34 genes associated with congenital muscular dystrophy phenotypes and 35 genes with congenital myopathy phenotypes. Targeted next-generation sequencing panels that include congenital muscular dystrophy and congenital myopathy genes are currently available from a number of commercial laboratories at relatively low cost. An accurate genetic diagnosis facilitates genetic counseling, estimation of recurrence risk, and guides appropriate surveillance.

No treatments specific to congenital muscular dystrophies or congenital myopathies exist, so care is focused on appropriate anticipatory guidance and addressing symptomatic issues. While genetic and phenotypic heterogeneity is the rule for diagnosis, treatment is similar for most disorders with appropriate recognition of specific features of some disorders such as early respiratory compromise in collagen VI–, LAMA2-, and SELENON-related muscular dystrophies and cardiac findings in *TTN*- and *MYH7*-related congenital
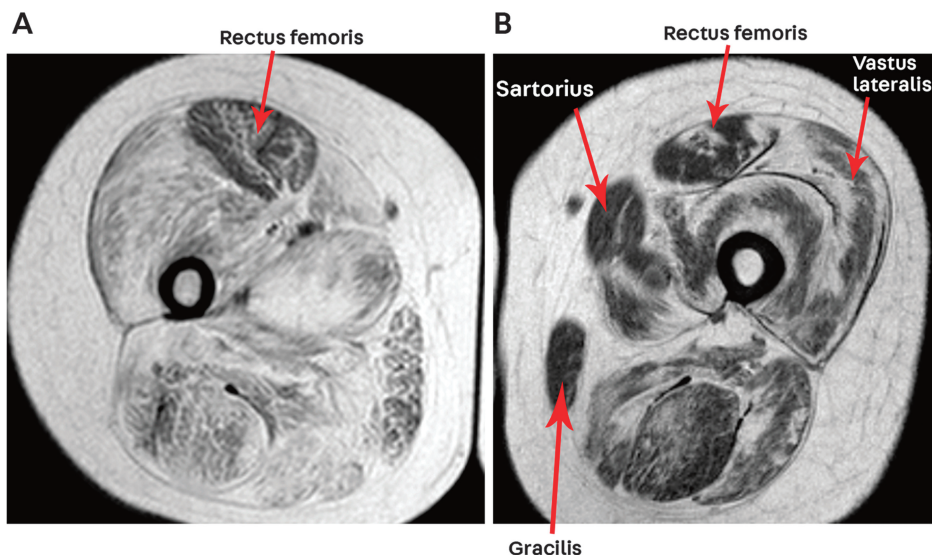
FIGURE 6-2
MRI findings in some disorders can be specific. *A*, Axial T1-weighted image of the thigh of a patient with *RYR1*-associated myopathy demonstrating sparing of the rectus femoris. *B*, Axial T1-weighted image of the thigh of a patient with Ullrich congenital muscular dystrophy demonstrating characteristic "central cloud" in the rectus femoris and rimming of vastus lateralis. Note also relative sparing of the sartorius and gracilis.
Reprinted with permission from Jahannaz Dastgir, MD. © Jahannaz Dastgir, MD.

myopathies. Care guidelines have been published for both congenital muscular dystrophies and congenital myopathies and focus broadly on orthopedic, respiratory, cardiac, nutritional, and social issues.[18,19]

CONGENITAL MUSCULAR DYSTROPHY

Congenital muscular dystrophies are disorders that vary widely in clinical features but share dystrophic features on muscle biopsy (TABLE 6-1).[20] A combination of clinical features and ancillary testing such as muscle imaging and biopsy can direct specific genetic testing. LAMA2-related (merosin-deficient) muscular dystrophy is the most common form of congenital muscular dystrophy, accounting for as much as one-third of cases, with collagen VI–related and α-dystroglycan–related congenital muscular dystrophy accounting for about 25% each.[21] Other congenital muscular dystrophy phenotypes are significantly more rare. Congenital muscular dystrophy phenotypes include a wide spectrum of clinical features from severe weakness and central nervous system (CNS) malformations in disorders such as Walker-Warburg syndrome and muscle-eye-brain disease to milder limb-girdle weakness.

Collagen VI–related muscular dystrophy is the most distinctive congenital muscular dystrophy and presents with distal joint hyperlaxity and proximal joint contractures. The presence of skin changes such as keloid scars and hyperkeratosis pilaris with distal laxity should prompt consideration of a collagen VI–related muscular dystrophy even without biopsy or imaging tests. LAMA2-related muscular dystrophy is not easily distinguished from other congenital muscular dystrophies clinically, but is readily identified by the

Overview of Genes Associated With Congenital Muscular Dystrophies[a]   TABLE 6-1

Subtype	Gene(s)	Inheritance	Clinical Features
LAMA2-related (merosin deficient) congenital muscular dystrophy	*LAMA2*	Autosomal recessive	Most patients never achieve independent ambulation; peripheral neuropathy occurs in later childhood; normal intelligence despite abnormality in white matter on brain MRI; 30% experience seizures; milder phenotypes possible with partial deficiency
Collagen VI–related muscular dystrophy	*COL6A1, COL6A2, COL6A3*	Autosomal dominant, autosomal recessive	Milder Bethlem myopathy and severe Ullrich congenital muscular dystrophy phenotypes, but most patients intermediate; distinguishing features are marked distal hyperlaxity with proximal contractures; skin changes including keloid formation, hyperkeratosis pilaris, and soft palms and soles; creatine kinase level may be normal to mildly elevated
α-Dystroglycanopathies	*FKTN, POMT1, POMT2, FKRP, POMGNT1, ISPD, POMGNT2, B3GNT1, GMPPB, LARGE, DPM1, DPM2, ALG13, B3GALNT2, RXYLT1*	Autosomal recessive	Defect in glycosylation of α-dystroglycan; broad spectrum of clinical phenotypes from very severe Walker-Warburg syndrome and muscle-eye-brain disease to milder limb-girdle muscular dystrophy phenotypes; central nervous system involvement can be profound in severe cases and includes cobblestone lissencephaly, severe mental retardation, and seizures; Fukuyama subtype due to *FKTN* mutation is common in Japan due to ancestral mutation; *FKRP* most common in other populations
Laminopathy	*LMNA*	Autosomal recessive	Neonatal onset of severe weakness for neck/postural muscles (dropped head syndrome) with early loss of ambulation; other phenotypes include Emery-Dreifuss muscular dystrophy, familial partial lipodystrophy, limb-girdle muscular dystrophy, dilated cardiomyopathy, Charcot-Marie-Tooth disease, and Hutchinson-Gilford progeria syndrome

[a] Modified with permission from Butterfield RJ, Bromberg MB.[20] © 2015 Springer Publishing Company.

absence of merosin on muscle immunohistochemistry. In these cases, genetic testing targeted to the *LAMA2* gene is readily available and confirms the diagnosis at a molecular level.

The largest group within the congenital muscular dystrophy category are disorders of glycosylation of α-dystroglycan. These disorders are diverse and include a spectrum from very severe in the Walker-Warburg syndrome and muscle-eye-brain disease phenotypes to the relatively mild limb-girdle muscular dystrophy (LGMD) phenotypes. While a disruption of α-dystroglycan glycosylation can be readily identified on muscle biopsy samples, distinction between the 15 or more genes identified to date (TABLE 6-1) is only accomplished by sequencing each of the genes.

Collagen VI–Related Muscular Dystrophy

Collagen VI–related muscular dystrophy includes a spectrum of severe, intermediate, and milder phenotypes, including Ullrich congenital muscular dystrophy and Bethlem myopathy. Collagen VI–related muscular dystrophies are among the most common congenital muscular dystrophies and account for up to 30% of patients with congenital muscular dystrophy.[8,22] The collagen VI–related muscular dystrophies are characterized by progressive muscle weakness and a combination of distal joint laxity and proximal joint contractures.[8,9] Phenotypic heterogeneity is a hallmark of collagen VI–related muscular dystrophy, with a spectrum of severity in patients from the very severe Ullrich congenital muscular dystrophy to the milder Bethlem myopathy (CASE 6-1).

Symptoms of Ullrich congenital muscular dystrophy manifest as progressive weakness in the neonatal period or early childhood, frequently resulting in loss of ambulation before age 10 and respiratory compromise even earlier.[23–25] In Bethlem myopathy, weakness and joint contractures begin in mid-childhood or early adolescence, but progression is slow and ambulation is retained into adulthood.[26,27] Ullrich congenital muscular dystrophy and Bethlem myopathy represent the ends of a clinical spectrum, with most patients having intermediate phenotypes.[28] A myosclerosis myopathy phenotype[29] and a limb-girdle muscular dystrophy phenotype have also been described.[30] Joint contractures are common and may progress rapidly with significant functional impact, even in patients with preserved muscle strength. Cardiac complications have not been reported in patients with collagen VI–related muscular dystrophy. Spontaneous pneumothoraces have been recently reported in some patients and may be a source of significant morbidity.[31]

Collagen VI is a ubiquitous extracellular protein composed of three chains, α1 (VI), α2 (VI), and α3 (VI), and is encoded by the *COL6A1*, *COL6A2*, and *COL6A3* genes. Collagen VI is an important component of the extracellular matrix of many tissues including muscle, skin, tendon, cartilage, and adipose tissues and has an important role in maintaining structural stability by anchoring the basement membrane to the extracellular matrix.[32–34] Mutations in any of the three genes encoding collagen VI can result in collagen VI–related muscular dystrophy phenotypes. The triple helical region contains a repeated Gly-X-Y motif common to all collagens that allows tight coiling of the three chains and is particularly sensitive to mutation.

Inheritance can be dominant or recessive depending on the type of mutation. Dominant mutations allow incorporation of abnormal chains into secreted tetramers and are the most commonly identified mutations in patients with

A 4-year-old girl was referred for neuromuscular evaluation because of an abnormal gait, which was first noted by her parents at age 3. At the time of referral, she was noted to be clumsy, had a difficult time getting up from the ground, and had difficulty going up and down the stairs at home. Her parents had been increasingly concerned about the difference in her physical abilities from that of her peers. This difference had become more apparent over the past year.

She was otherwise healthy. Her mother's pregnancy and delivery had been unremarkable. Notably, the girl had torticollis that was first identified at 3 months of age and was successfully treated with physical therapy. She had congenital hip dysplasia that was treated with casting. She had normal development for language and cognitive function and was doing well in a prekindergarten classroom. No other family members were similarly affected.

Her general physical examination was notable for marked hyperlaxity in her hands, wrists, and ankles, with contracture in the shoulder and hips. She had noticeably rough skin on the upper arms and lower legs. Neurologic examination was significant for proximal muscle weakness. She arose from the floor with a Gowers maneuver and walked with a Trendelenburg gait. Her reflexes were normal.

Her creatine kinase was mildly elevated at 320 U/L. Without additional testing, a sequencing test was ordered for *COL6A1*, *COL6A2*, and *COL6A3*. A heterozygous missense mutation was identified in the triple helical region of *COL6A1* that disrupts a glycine residue in the Gly-X-Y repeat, establishing a diagnosis of Ullrich congenital muscular dystrophy. Carrier testing in the parents was normal.

COMMENT

This case demonstrates the benefit of careful examination and pattern recognition. While many congenital muscular dystrophies and congenital myopathies overlap clinically, some are distinctive and can be recognized in the clinic. Recognition of the appropriate pattern can quickly lead to a narrow differential diagnosis and appropriate diagnostic testing. In this case, the combination of distal joint hyperlaxity and proximal contracture in a child with weakness and skin changes should immediately suggest the possibility of a collagen VI-related muscular dystrophy. Other recognizable features in collagen VI-related muscular dystrophies are a normal to mildly elevated creatine kinase, soft skin on the palms and soles, a bulbous calcaneus, and keloids. Imaging studies by ultrasonography or MRI may show a central cloud in the rectus femoris, which is pathognomonic for collagen VI-related muscular dystrophies. Early diagnosis facilitates appropriate anticipatory care including early surveillance for respiratory insufficiency, which can precede loss of ambulation by several years.
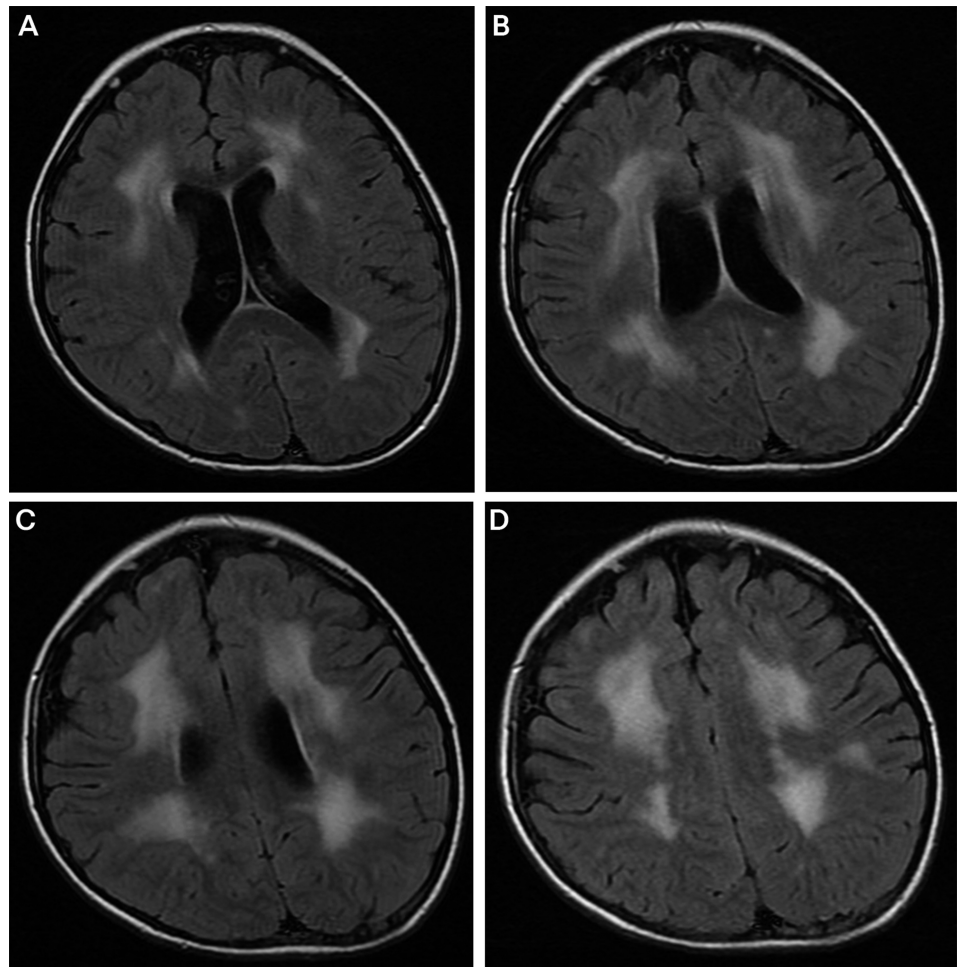
FIGURE 6-3
Serial cuts from axial fluid-attenuated inversion recovery (FLAIR) MRI of an 8-year-old girl with LAMA2-related muscular dystrophy demonstrating diffuse signal abnormality in the white matter.

collagen VI–related muscular dystrophy. Missense mutations resulting in substitution of the conserved glycine residue in the triple helical domain or splicing mutations involving exon skipping in the triple helical domain are the most common dominant mutation in patients with collagen VI–related muscular dystrophy and account for more than half of known pathogenic alleles.[35,36] Null alleles (nonsense, frameshift, and large deletions) do not allow incorporation of abnormal chains and act recessively. Pathogenicity of variants outside of the triple helical domain have been difficult to assess due to the frequency of benign variants in these domains. Disruption of collagen VI matrix in cultured fibroblasts can be performed in some research laboratories to help clarify pathogenicity of these variants. Genotype to phenotype associations in collagen VI–related muscular dystrophy have been difficult to assess because of phenotypic heterogeneity, including presentations of Ullrich congenital muscular dystrophy, Bethlem myopathy, and intermediate phenotypes in patients with similar mutations.[36–40]

LAMA2-Related Congenital Muscular Dystrophy (Merosin Deficient)

LAMA2-related congenital muscular dystrophy is caused by a deficiency of the α2 subunit of laminin due to mutation of the *LAMA2* gene. Laminin is a heterotrimeric protein composed of α, β, and γ subunits. Laminins are expressed in the basement membrane and serve to stabilize tissues by linking the cell surface to the extracellular matrix. Composition of the laminin is distinct in both different tissues and at different developmental stages. In skeletal muscle, the laminin-211 isoform, also known as merosin, predominates and mediates attachment of collagens and other muscle extracellular matrix components to the sarcolemmal membrane through interactions with α-dystroglycan.[41]

Typical LAMA2-related congenital muscular dystrophy cases present with prominent hypotonia and weakness in infancy.[4] Congenital contractures are a common finding in the hands and feet. Patients with LAMA2-related congenital muscular dystrophy typically lack merosin immunostaining on muscle biopsy, making diagnosis relatively straightforward even in patients for whom genetic testing is not available. Weakness and contractures are slowly progressive, and most patients do not achieve independent ambulation. Facial weakness and jaw contractures disrupt normal feeding, resulting in failure to thrive. Most patients require nutrition support at an early age. Cardiac involvement is rare. In addition to neuromuscular aspects of the disorder, patients with LAMA2-related congenital muscular dystrophy have CNS findings including prominent T2 and fluid-attenuated inversion recovery (FLAIR) abnormalities in the white matter on brain MRI (FIGURE 6-3). Despite the prominent changes on MRI, cognitive function is normal, although patients are at risk of seizures, which are seen in 30% of patients.

Inheritance of LAMA2-related congenital muscular dystrophy is autosomal recessive. In typical LAMA2-related congenital muscular dystrophy cases, the mutations in *LAMA2* are nonsense mutations resulting in complete loss of the *LAMA2* transcript and can occur anywhere throughout the gene.[41] Milder cases are increasingly recognized and are usually the result of a milder missense mutation in combination with a second, more severe mutation. While nonsense mutations are spread throughout the entire length of the gene, missense mutations are clustered in the 5′ end of the gene. Milder forms of LAMA2-related congenital muscular dystrophy leave some intact expression of *LAMA2* on immunohistochemistry. Symptoms of the milder form are variable and are typical of many limb-girdle muscular dystrophy phenotypes.

α-Dystroglycan–Related Muscular Dystrophies

The largest group of the congenital muscular dystrophies are disorders of glycosylation of α-dystroglycan. α-Dystroglycan is a sarcolemmal membrane protein that mediates interactions of the cytoskeletal matrix and muscle extracellular matrix. Interactions with the muscle extracellular matrix are regulated through an extensive network of O-mannosyl-dependent glycosylations of α-dystroglycan. Fifteen or more genes with a role in the glycosylation of α-dystroglycan have been identified with congenital muscular dystrophy phenotypes including *FKTN, POMT1, POMT2, FKRP, POMGNT1, ISPD, POMGNT2, B3GNT1, GMPPB, LARGE, DPM1, DPM2, ALG13, B3GALNT2,* and *RXYLT1*.[4]

α-Dystroglycan–related congenital muscular dystrophies are diverse and include a spectrum of severity from very severe in Walker-Warburg syndrome and muscle-eye-brain disease phenotypes to the relatively mild LGMD phenotypes. The most severe phenotypes include severe weakness and malformations of the eye and brain. Brain malformations can be severe and may include a cobblestone lissencephaly pattern or a more focal pachygyria/polymicrogyria pattern. Abnormalities of the brainstem and cerebellum are also common. Seizures and cognitive delays can be severe and usually mirror the degree of CNS malformation. Milder LGMD phenotypes, even from genes where severe phenotypes have been previously reported, are increasingly recognized. The spectrum of muscle involvement and cognitive impairment is broad regardless of subtype. Weakness is progressive at a variable rate and is usually worse in a proximal than in a distal distribution. Cardiac involvement has been reported in some patients with dystroglycanopathy with *FKRP*, *POMT1,* and *POMT2* mutations, but this is not a common finding.[42]

Disruption of glycosylation of α-dystroglycan can be readily identified on muscle biopsy and has been the gold standard for diagnosis for many years; however, defects in specific genes important in the glycosylation pathway cannot be differentiated in this way. With the emergence of low-cost panel-based genetic testing, a specific genetic diagnosis is now readily accessible in most cases. Mutations in *FKRP*, *POMT1*, *POMT2,* and *POMGNT1* are the most commonly identified causes for α-dystroglycan–related muscular dystrophy, with all others being quite rare.[21,43] Inheritance is autosomal recessive in most cases. Fukuyama congenital muscular dystrophy is a severe subtype that is common in Japan because of an ancestral mutation in the *FKTN* gene. Incidence in Japan is as high as all other congenital muscular dystrophies combined at 1.9 to 3.7 per 100,000 births.[44] A milder phenotype due to mutations in the *FKRP* gene is relatively common and is increasingly recognized as the etiology for a LGMD phenotype.

Lamin A/C

Lamin A/C is a nuclear envelope protein associated with multiple phenotypes including Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy, partial lipodystrophy, peripheral neuropathy, and premature aging.[45] Skeletal myopathy phenotypes are the most commonly observed phenotypes in patients with mutations in *LMNA*, with Emery-Dreifuss muscular dystrophy phenotypes most typical. Congenital muscular dystrophy phenotypes have been described with onset of severe weakness in the first year, with marked weakness in the neck extensors, leading to the so-called dropped head syndrome.[46,47] In milder cases, affected individuals achieve independent ambulation despite significant neck and postural weakness. Generally, ambulation is lost within a few years. As with other *LMNA*-related disorders, cardiac arrhythmias are common, and frequent cardiac surveillance is essential. As with rigid spine muscular dystrophy, respiratory insufficiency is common in early childhood and may precede loss of ambulation.

CONGENITAL MYOPATHY

Congenital myopathies are a broad range of disorders that result in hypotonia and weakness in the newborn period and early childhood. In contrast to congenital muscular dystrophy, weakness in patients with congenital myopathies

is less progressive, the CK is usually normal, and no CNS involvement occurs. Weakness can be profound in the newborn period but is usually stable over time and can even show improvement. Clinical phenotypes are largely overlapping across the different disorders, making clinical diagnosis virtually impossible. Weakness is typically generalized with a proximal predominance. Involvement of the face muscles, external ophthalmoparesis, and ptosis are common features.

Patients with congenital myopathies generally have onset in the first year, but a wide spectrum of severity is seen, including later-onset phenotypes, which complicates existing classification schemes.[3] Prenatal onset is common and results in decreased fetal movements and polyhydramnios.[5] As a result, affected infants can be born with arthrogryposis and facial dysmorphisms such as ptosis, micrognathia, high arched palate, and dolichocephaly.

Classification of the congenital myopathies has traditionally centered on muscle biopsy findings. Histopathologic classes include nemaline rod myopathies, core myopathies, centronuclear myopathies, and myopathies with congenital fiber-type disproportion.[3] However, multiple genes have been identified in patients with congenital myopathy with each of the histopathologic subtypes (TABLE 6-2). Since congenital myopathies can lack clinical or histopathological features that differentiate them, genetic sequencing is necessary to make a specific diagnosis. Prior to the emergence of next-generation sequencing technologies, genetic testing was difficult because of the large size of many of these genes, including nebulin (*NEB*) (183 exons) and *TTN* (365 exons), which are among the largest in the human genome. Advances in genetic diagnosis have led to a better appreciation of the marked genetic and phenotypic heterogeneity in congenital myopathies, and classification schemes are moving toward a more genetic basis.

Nemaline Myopathy

Nemaline rods are small inclusions clustered peripherally in the cytoplasm of the myofiber. These are usually best seen on Gomori trichrome staining but may be seen with other stains as well. Nemaline rods may be absent on light microscopy in very young patients with nemaline myopathy but are usually seen on electron microscopy in these cases. Other nonspecific myopathic features are usually present as well. The most common genetic causes for nemaline myopathy are mutations in *NEB*, which can cause up to half of cases, and actin α1, skeletal muscle (*ACTA1*), which occurs in 20% to 25% of cases. As many as nine other genes can cause a myopathy with nemaline rods.[3,17] *NEB* is one of the largest genes in the human genome. Inheritance of *NEB*-associated congenital myopathy is recessive, with most patients having compound heterozygous mutations. The clinical manifestations include the full spectrum of severity from very severe neonatal onset and milder adult-onset phenotypes. Distal myopathy and core-rod myopathy phenotypes have also been described.[48,49] Severe neonatal onset accounts for about one-fourth of cases and more typical neonatal onset for about one-third of cases.[50] Symptoms in typical cases are similar to congenital myopathies from other causes and include generalized weakness with onset in early infancy and pronounced facial, bulbar, and respiratory involvement. Motor milestones are delayed but can be attained in some patients. Identification of variants of unknown significance on next-generation sequencing panels is common in *NEB* because of the large size of the gene. In most cases, pathogenic mutations disrupt splicing (34%), shift the reading frame

(32%), or result in premature termination (23%).[50] Missense mutations are rarely pathogenic.

Mutations in *ACTA1* are the second most common cause of nemaline myopathy. Skeletal muscle actin is the principal component of the thin filament of the sarcomere where its binding to the myosin thick filament is the primary driver of muscle contraction. In contrast to *NEB*-associated congenital myopathy, *ACTA1*-associated congenital myopathy is usually dominant and sporadic, with no family history.[51] Mutations in *ACTA1* are usually associated

TABLE 6-2		Overview of Genes Associated With Congenital Myopathies[a]		
Myopathies and Genes	**Proteins**	**Inheritance**	**Muscle Biopsy**	**Unique Features**
Nemaline myopathies[b]				
NEB	Nebulin	Autosomal recessive	Nemaline rods	Most common nemaline myopathy; 50% of cases
ACTA1	Actin α1 skeletal muscle	Autosomal dominant, autosomal recessive	Nemaline rods, cores or multiminicores, congenital fiber-type disproportion	20% to 25% of nemaline myopathy; 50% of severe neonatal cases
KBTBD13	Kelch repeat and BTB (POZ) domain containing 13	Autosomal dominant	Nemaline rods, cores or multiminicores	Rare; slow voluntary movements; spares face
CFL2	Cofilin 2 (muscle)	Autosomal recessive	Nemaline rods	Rare; only three families reported
KLHL40	Kelch-like family member 40	Autosomal recessive	Nemaline rods	Severe neonatal, often lethal
TNNT1	Slow troponin T1	Autosomal recessive	Nemaline rods	Only reported in Amish families
TPM2	Tropomyosin 2 (beta)	Autosomal dominant	Nemaline rods, congenital fiber-type disproportion	Also seen in congenital arthrogryposis, pterygia
TPM3	Tropomyosin 3	Autosomal dominant, autosomal recessive	Nemaline rods, congenital fiber-type disproportion	Common cause of congenital fiber-type disproportion without nemaline rods
Core myopathies				
RYR1	Ryanodine receptor 1 (skeletal)	Autosomal dominant, autosomal recessive	Cores or multiminicores, congenital fiber-type disproportion, central nuclei	Most common core myopathy; usually autosomal dominant; associated with susceptibility to malignant hyperthermia; overlap with severe congenital muscular dystrophy phenotype with early scoliosis and loss of ambulation

with nemaline rods on muscle biopsy, but these can be absent in young children (younger than 1 year of age). Cases with congenital fiber-type disproportion, cores, and other mixed pathologic features have been described as well.[51] Clinical phenotypes are variable, from very severe neonatal and even prenatal involvement to milder adult-onset cases.[52,53] Most cases are undistinguishable from *NEB*-associated congenital myopathy and include weakness in infancy with prominent face, bulbar, and respiratory muscle involvement and limited progression over time.

Myopathies and Genes	Proteins	Inheritance	Muscle Biopsy	Unique Features
SELENON	Selenoprotein N	Autosomal recessive	Cores or multiminicores, congenital fiber-type disproportion	Multiminicore; axial weakness and respiratory involvement out of proportion to weakness; congenital muscular dystrophy phenotype with early spinal rigidity and weakness in neck, postural muscles (rigid spine muscular dystrophy)
MYH7	Myosin, heavy polypeptide 7, cardiac muscle, beta	Autosomal dominant	Cores or multiminicores, central nuclei	May have cardiac involvement
TTN	Titin	Autosomal dominant, autosomal recessive	Cores or multiminicores, central nuclei	Rare severe myopathy phenotype with early respiratory failure; may have cardiac involvement; significant overlap with several muscular dystrophy phenotypes including limb-girdle muscular dystrophy type 2J, tibial muscular dystrophy, distal myopathy
Centronuclear myopathies				
MTM1	Myotubularin	X-linked	Central nuclei	Myotubular myopathy; congenital myotonic dystrophy is phenocopy histologically
BIN1	Bridging integrator 1	Autosomal dominant, autosomal recessive	Central nuclei	
DNM2	Dynamin 2	Autosomal dominant, autosomal recessive	Cores or multiminicores, central nuclei, congenital fiber-type disproportion	
SPEG	Striated muscle enriched protein kinase	Autosomal recessive	Central nuclei	Overlapping but milder than myotubular myopathy; may have early cardiomyopathy

[a] Modified with permission from Butterfield RJ, Bromberg MB.[20] © 2015 Springer Publishing Company.
[b] Novel genetic associations in nemaline myopathies (all are rare, autosomal recessive): *KHL41, LMOD3, MYPN, MYO18B,* and *RYR3.*

Core Myopathies

Cores are areas of clearing seen on muscle biopsy due to absent mitochondria and subsequent absent oxidative enzyme activity on stains such as nicotinamide adenine dinucleotide (NADH) and succinate dehydrogenase. Core morphology can be a single central core or multiple smaller cores (multiminicores). Central core myopathies are the most common congenital myopathies and are associated in most cases with mutations in the ryanodine receptor 1 gene (*RYR1*).[5,54] The ryanodine receptor encoded by *RYR1* is a calcium channel in the sarcoplasmic reticulum that is important in excitation-contraction coupling. Like *NEB*, *RYR1* is a very large gene, composed of 106 exons. Until the advent of next-generation sequencing techniques, genetic testing focuses on a handful of mutational hot spots. With the newer sequencing technology, full coverage of the *RYR1* gene is possible, and mutations have been identified throughout the gene. Mutations in *RYR1*-related congenital myopathies can be either dominant or recessive, and variants of unknown significance are common, making interpretation of genetic testing difficult. Dominant mutations in *RYR1* are associated with susceptibility to malignant hyperthermia and can have overlap with myopathy phenotypes.

Clinical features in *RYR1*-mediated myopathies span the full spectrum of severity but are usually relatively mild and include low tone and weakness in dominant cases. Weakness can be exacerbated by physical activity, and facial and extraocular weakness is less common than in nemaline myopathies. Recessive cases are more severe, and symptoms can mirror those of severe nemaline myopathies, including severe weakness from the newborn period. The most severe cases include fetal akinesia, congenital arthrogryposis, and respiratory failure.[55] Central cores on muscle biopsy are a common histologic finding in *RYR1*-related myopathies, but this finding is not always seen in early-onset cases, where type 1 fiber predominance is a common feature. A dystrophic pattern on muscle biopsy has also been reported and is more consistent with a severe congenital muscular dystrophy phenotype.[56] Multiminicores on muscle biopsy are patchier and less prominent that those in central core myopathies. They can be seen in *RYR1*-mediated myopathies but are most prominently associated with selenoprotein N–associated myopathies. Selenoprotein N, encoded by the *SELENON* gene, is involved with redox-regulated calcium homeostasis. Mutations in *SELENON* were first identified in patients with congenital myopathy with multiminicores. Later, a rigid spine muscular dystrophy phenotype was described.[57] These phenotypes are largely overlapping, and both include early spinal rigidity and marked weakness in neck and postural muscles. Inheritance is autosomal recessive. Most patients achieve independent ambulation despite motor delays. Early respiratory compromise is severe and out of proportion to the muscle weakness. The need for respiratory support invariably precedes loss of ambulation. Cardiac involvement is not reported in multiminicore disease, and heart involvement in combination with multiminicore pathology suggests the possibility of a mutation in *TTN* or *MYH7*.[58] Mutations in titin, encoded by the *TTN* gene, are an increasingly recognized cause for myopathy phenotypes. *TTN* is the largest protein coding sequence in the human genome, including 364 exons. Its large size severely limited diagnostic testing by Sanger sequencing. With the emergence of next-generation sequencing technologies, sequencing of the entire coding region of *TTN* is now possible, and an increasingly large number of pathogenic variants

are being reported. However, variants are also found in most control populations, and because of its large size and many isoforms, variants identified in patients with myopathy are difficult to interpret.[59] Early reports focused on core myopathies, but a wide phenotypic spectrum is now recognized, including a limb-girdle muscular dystrophy, tibial muscular dystrophy, distal myopathy, and centronuclear myopathy. Congenital phenotypes include early-onset hypotonia, contracture, and respiratory compromise, with rapid progression and frequent cardiac involvement.[60]

Centronuclear Myopathies

Centronuclear myopathies are characterized by predominance of centralized nuclei on muscle biopsy. Genetically, centronuclear myopathies are caused by mutations in genes associated with formation of the complex membrane systems including T tubules and the triad that allow efficient excitation-contraction coupling.[61] X-linked myotubular myopathy caused by mutations in the *MTM1* gene is the most distinctive form.[62] Mutations in dynamin 2 (*DNM2*) and bridging integrator 1 (amphiphysin 2) (*BIN1*) are also common causes of centronuclear myopathies.[63,64] Consistent with the growing appreciation of the breadth of phenotypic and genetic heterogeneity in congenital myopathies and congenital muscular dystrophies, mutations in *RYR1* (which commonly causes central core myopathy) and *TTN* have been described in individuals with centronuclear myopathies.[65,66] X-linked myotubular myopathy is one of the most severe congenital myopathies, with severe generalized weakness at birth including marked ophthalmoparesis and facial, bulbar, and respiratory weakness. Most patients do not survive the first year of life without significant respiratory and nutritional support.[67] Patients with milder disease can survive into adulthood. Symptomatic female patients are also increasingly recognized and reflect findings seen in adult male patients with mild disease.[68] Asymmetric weakness in manifesting female carriers is a common feature and may reflect asymmetric X inactivation.

Surviving patients can have systemic features including risk for vascular abnormalities of the liver. *MTM1* encodes myotubularin, a phosphoinositide phosphatase important in promotion of membrane trafficking and endocytosis. Muscle biopsy findings in myotubular myopathy include prominent central nuclei in immature-appearing fibers resembling myotubes. In addition to central nuclei, myofibers also have a characteristic rim of decreased enzyme activity on the periphery. On longitudinal section, nuclei are prominent centrally in chains. Recently, mutations in the striated muscle enriched protein kinase (*SPEG*) gene have been associated with a centronuclear myopathy, with features that overlap clinically but are probably milder than X-linked myotubular myopathy. *SPEG* was first identified as a cause for myopathy after it was found to be a binding partner with *MTM1* in the laboratory, and patients with genetically undiagnosed myopathy were found to have mutations in *SPEG*.[69] Clinical features include onset in the neonatal period with weakness, ophthalmoplegia, and face muscle weakness (CASE 6-2).[70] Some patients have early severe cardiomyopathy, which can be more severe than the muscle weakness.

Dynamin 2, encoded by the *DNM2* gene, is a ubiquitously expressed large guanosine triphosphatase (GTPase) important in membrane trafficking. *DNM2*-related myopathies are usually dominantly inherited and are generally

milder than *MTM1*-related myopathies, with typical onset in childhood or early adolescence. Muscle involvement is typical of other congenital myopathies and includes diffuse weakness with involvement of the face muscles, eye movements, and ptosis.[71] More severe recessive forms, including a very severe early neonatal form, have also been described.[72] In addition to congenital myopathy, mutations in *DNM2* have been seen in patients with mixed axonal and demyelinating Charcot-Marie-Tooth disease.[61] *DNM2* is ubiquitously expressed, and it is unclear why disorders of *DMN2* have a tissue specificity in the peripheral nerve and skeletal muscle. Mutations in bridging integrator 1, encoded by the *BIN1* gene, are rare causes for centronuclear myopathy that were first seen in consanguineous families with children affected from birth to early childhood.[63,73] Clinically, features are similar to that of *DMN2*-related myopathy and include early childhood–onset weakness with involvement of the face and eye movements. *BIN1*-associated myopathies share a common pathologic mechanism with *MTM1* and *DNM2* in disruption of membrane trafficking and T tubule formation.[63] Inheritance is recessive in most reported cases, but milder

---

CASE 6-2

A 12-month-old boy was brought for evaluation of hypotonia and poor feeding, which he had experienced from birth. He had been born at 37 weeks gestational age by induced vaginal delivery because of preeclampsia. He was born small for his gestational age, and his Apgar scores were 2, 5, and 9. He required positive pressure ventilation for 7 minutes after birth and then briefly transitioned to continuous positive airway pressure. He was in the neonatal intensive care unit for 2 weeks with stridor due to vocal cord paresis, feeding difficulties, micrognathia, and concern for aspiration. He was discharged home on room air and nasogastric feeding. He was readmitted the following day with two bradycardic events around 40 beats/min. A gastrostomy tube was placed when he was 1 month old because of ongoing concerns for dysphagia with aspiration. He was discharged at 41 days old.

By 12 months of age, he had persistent failure to meet normal developmental milestones but had no regression. Stridor had improved after tonsillectomy and adenoidectomy. A follow-up swallow study showed continued silent aspiration on thin liquids. He was not taking any nutrition by mouth, and his growth was adequate, following the growth curve at the fifth percentile. He was making age-appropriate progress in speech and language. He had made some gains in motor skills and was able to sit and roll front to back, but he could not pull himself up to stand or bear weight on his own.

General examination also at 12 months of age was significant for a high arched palate, micrognathia, and pectus excavatum. Neurologic examination at this time was significant for low tone with decreased resistance to passive range of motion in all extremities and prominent head lag. His reflexes were normal.

dominant forms with onset in adulthood have been described, demonstrating a broad clinical spectrum.[74,75]

CONCLUSION

Congenital muscular dystrophies and congenital myopathies are common causes of weakness and hypotonia in infants and young children and result in significant morbidity and mortality in affected individuals. With rapid advances in genetic sequencing in the past few years, long-standing phenotypic and histopathologic classifications are being challenged. While histologic features on muscle biopsy have been the mainstay of existing clinical classification, genetic advances have led to an increasing recognition of the broad phenotypic spectrum, including overlap of clinical phenotypes for most congenital muscular dystrophies and congenital myopathies. Rapid advances in gene manipulation, gene replacement, and technologies, including US Food and Drug Administration (FDA)–approved treatments for Duchenne muscular dystrophy and spinal

---

Workup completed by 12 months of age included creatine kinase, which was normal at 47 U/L, and echocardiogram and brain MRI that were normal. He was referred for a genetics consultation with concern for hypotonia with motor delays, micrognathia, vocal cord palsy, and laryngomalacia. Whole-exome sequencing was obtained, and the results showed two variants of unknown significance in the *SPEG* gene, one inherited from the mother and one from the father. The initial interpretation was that these were unrelated to his syndrome based on his dysmorphic features and overall developmental progress.

Based on review of the variants in *SPEG* and clinical picture consistent with a congenital myopathy, he was referred for muscle biopsy to assess the pathogenicity of the variants in *SPEG*. Muscle biopsy showed marked variation in fiber size with frequent atrophic fibers and a moderate number of hypertrophic fibers. Nearly all fibers demonstrated internal nuclei, with atrophic fibers having large nuclei reminiscent of myotubes. His final pathologic diagnosis was focal myonecrosis, centronuclear (myotubular) myopathy.

This case demonstrates the difficulty in diagnosing rare disorders when the phenotypic spectrum is broad and falls outside the spectrum of previously reported cases. In this case, motor function and hypotonia were milder than reported in published cases, and cardiomyopathy was absent in this case but was present in published cases. Variants of unknown significance are a common finding in whole-exome and other next-generation sequencing tests. In this case, muscle biopsy served as an important confirmatory test to establish the pathogenicity of the variants identified by exome sequencing and to confirm the diagnosis of a centronuclear myopathy related to *SPEG* mutation.

COMMENT

---

muscular atrophy, have led to hope that similar treatments will soon be forthcoming for congenital muscular dystrophies and congenital myopathies. Indeed, a gene replacement therapy for myotubular myopathy is currently in a phase 1 clinical trial.[76] Success of this and other trials will depend on continued improvements in identification and genetic characterization of patients with these disorders and careful attention to the natural history and phenotypic spectrum.

USEFUL WEBSITE

GENETABLE OF NEUROMUSCULAR DISORDERS
The GeneTable of Neuromuscular Disorders is an annually updated list of all genes known to have neuromuscular phenotypes with annotations about phenotype, inheritance, and gene-specific information.
musclegenetable.fr

REFERENCES

1   Ravenscroft G, Bryson-Richardson RJ, Nowak KJ, Laing NG. Recent advances in understanding congenital myopathies. F1000Res. 2018;7. doi:10.12688/f1000research.16422.1.

2   Fardeau M, Desguerre I. Diagnostic workup for neuromuscular diseases. Handb Clin Neurol 2013;113:1291–1297. doi:10.1016/B978-0-444-59565-2.00001-0.

3   North KN, Wang CH, Clarke N, et al. Approach to the diagnosis of congenital myopathies. Neuromuscul Disord 2014;24(2):97–116. doi:10.1016/j.nmd.2013.11.003.

4   Bönnemann CG, Wang CH, Quijano-Roy S, et al. Diagnostic approach to the congenital muscular dystrophies. Neuromuscul Disord 2014;24(4):289–311. doi:10.1016/j.nmd.2013.12.011.

5   Colombo I, Scoto M, Manzur AY, et al. Congenital myopathies: natural history of a large pediatric cohort. Neurology 2015;84(1):28–35. doi:10.1212/WNL.0000000000001110.

6   Carmignac V, Salih MA, Quijano-Roy S, et al. C-terminal titin deletions cause a novel early-onset myopathy with fatal cardiomyopathy. Ann Neurol 2007;61(4):340–351. doi:10.1002/ana.21089.

7   Overeem S, Schelhaas HJ, Blijham PJ, et al. Symptomatic distal myopathy with cardiomyopathy due to a MYH7 mutation. Neuromuscul Disord 2007;17(6):490–493. doi:10.1016/j.nmd.2007.02.007.

8   Okada M, Kawahara G, Noguchi S, et al. Primary collagen VI deficiency is the second most common congenital muscular dystrophy in Japan. Neurology 2007;69(10):1035–1042. doi:10.1212/01.wnl.0000271387.10404.4e.

9   Clement EM, Feng L, Mein R, et al. Relative frequency of congenital muscular dystrophy subtypes: analysis of the UK diagnostic service 2001-2008. Neuromuscul Disord 2012;22(6):522–527. doi:10.1016/j.nmd.2012.01.010.

10 Maggi L, Scoto M, Cirak S, et al. Congenital myopathies—clinical features and frequency of individual subtypes diagnosed over a 5-year period in the United Kingdom. Neuromuscul Disord 2013;23(3):195–205. doi:10.1016/j.nmd.2013.01.004.

11 Dubowitz V, Sewry CA. Muscle biopsy: a practical approach. 3rd ed. Philadelphia: Saunders/Elsevier, 2007:xiii. 611 pp.

12 Mercuri E, Lampe A, Allsop J, et al. Muscle MRI in Ullrich congenital muscular dystrophy and Bethlem myopathy. Neuromuscul Disord 2005;15(4):303–310. doi:10.1016/j.nmd.2005.01.004.

13 Bönnemann CG, Brockmann K, Hanefeld F. Muscle ultrasound in Bethlem myopathy. Neuropediatrics 2003;34(6):335–336. doi:10.1055/s-2003-44665.

14 Jungbluth H, Davis MR, Müller C, et al. Magnetic resonance imaging of muscle in congenital myopathies associated with RYR1 mutations. Neuromuscul Disord 2004;14(12):785–790. doi:10.1016/j.nmd.2004.08.006.

15 Quijano-Roy S, Carlier RY, Fischer D. Muscle imaging in congenital myopathies. Semin Pediatr Neurol 2011;18(4):221–229. doi:10.1016/j.spen.2011.10.003.

16 Mercuri E, Clements E, Offiah A, et al. Muscle magnetic resonance imaging involvement in muscular dystrophies with rigidity of the spine. Ann Neurol 2010;67(2):201–208. doi:10.1002/ana.21846.

17 Bonne G, Rivier F, Hamroun D. The 2019 version of the gene table of neuromuscular disorders (nuclear genome). Neuromuscul Disord 2018; 28(12):1031–1063. doi:10.1016/j.nmd.2018.09.006.

18 Wang CH, Bonnemann CG, Rutkowski A, et al. Consensus statement on standard of care for congenital muscular dystrophies. J Child Neurol 2010;25(12):1559–1581. doi:10.1177/0883073810381924.

19 Wang CH, Dowling JJ, North K, et al. Consensus statement on standard of care for congenital myopathies. J Child Neurol 2012;27(3):363–382. doi:10.1177/0883073812436605.

20 Butterfield RJ, Bromberg MB. Pediatric muscular dystrophies: the role of neurophysiology, genetics, and ancillary testing. In: Galloway GM, ed. Clinical neurophysiology in pediatrics: a practical approach to diagnosis and management. New York, NY: Demos Medical Publishing, 2016: 97–126.

21 Sframeli M, Sarkozy A, Bertoli M, et al. Congenital muscular dystrophies in the UK population: clinical and molecular spectrum of a large cohort diagnosed over a 12-year period. Neuromuscul Disord 2017;27(9):793–803. doi:10.1016/j.nmd. 2017.06.008.

22 Norwood FL, Harling C, Chinnery PF, et al. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain 2009;132(pt 11):3175–3186. doi:10.1093/brain/awp236.

23 Ullrich O. Kongenitale, atonisch-sklerotische Muskeldysrophie, ein weiterer typus der heredonodegenerativen Erkankungen des neuromuskularen Systems. Z Gestamte Neurol Psychiat 1930;126:171–201. doi:10.1007/ BF02864097.

24 Nadeau A, Kinali M, Main M, et al. Natural history of Ullrich congenital muscular dystrophy. Neurology 2009;73(1):25–31. doi:10.1212/ WNL.0b013e3181aae851.

25 Foley AR, Quijano-Roy S, Collins J, et al. Natural history of pulmonary function in collagen VI-related myopathies. Brain 2013;136(pt 12): 3625–3633. doi:10.1093/brain/awt284.

26 Jöbsis GJ, Boers JM, Barth PG, de Visser M. Bethlem myopathy: a slowly progressive congenital muscular dystrophy with contractures. Brain 1999;122(pt 4):649–655. doi:10.1093/brain/122.4.649.

27 Jöbsis GJ, Keizers H, Vreijling JP, et al. Type VI collagen mutations in Bethlem myopathy, an autosomal dominant myopathy with contractures. Nat Genet 1996;14(1):113–115. doi:10.1038/ng0996-113.

28 Butterfield RJ, Foley AR, Dastgir J, et al. Position of glycine substitutions in the triple helix of COL6A1, COL6A2, and COL6A3 is correlated with severity and mode of inheritance in collagen VI myopathies. Hum Mutat 2013;34(11):1558–1567. doi:10.1002/humu.22429.

29 Merlini L, Martoni E, Grumati P, et al. Autosomal recessive myosclerosis myopathy is a collagen VI disorder. Neurology 2008;71(16):1245–1253. doi:10.1212/01.wnl.0000327611.01687.5e.

30 Scacheri PC, Gillanders EM, Subramony SH, et al. Novel mutations in collagen VI genes: expansion of the Bethlem myopathy phenotype. Neurology 2002;58(4):593–602. doi:10.1212/WNL.58.4.593.

31 Fraser KL, Wong S, Foley AR, et al. Pneumothoraces in collagen VI-related dystrophy: a case series and recommendations for management. ERJ Open Res 2017;3(2). doi:10.1183/23120541.00049-2017.

32 Keene DR, Engvall E, Glanville RW. Ultrastructure of type VI collagen in human skin and cartilage suggests an anchoring function for this filamentous network. J Cell Biol 1988;107(5): 1995–2006. doi:10.1083/jcb.107.5.1995.

33 Kuo HJ, Maslen CL, Keene DR, Glanville RW. Type VI collagen anchors endothelial basement membranes by interacting with type IV collagen. J Biol Chem 1997;272(42):26522–26529. doi:10.1074/jbc.272.42.26522.

34 Kanagawa M, Toda T. The genetic and molecular basis of muscular dystrophy: roles of cell-matrix linkage in the pathogenesis. J Hum Genet 2006; 51(11):915–926. doi:10.1007/s10038-006-0056-7.

35 Lampe AK, Bushby KM. Collagen VI related muscle disorders. J Med Genet 2005;42(9): 673–685. doi:10.1136/jmg.2002.002311.

36 Brinas L, Richard P, Quijano-Roy S, et al. Early onset collagen VI myopathies: genetic and clinical correlations. Ann Neurol 2010;68(4):511–520. doi:10.1002/ana.22087.

37 Baker NL, Mörgelin M, Pace RA, et al. Molecular consequences of dominant Bethlem myopathy collagen VI mutations. Ann Neurol 2007;62(4): 390–405. doi:10.1002/ana.21213.

38 Baker NL, Mörgelin M, Peat R, et al. Dominant collagen VI mutations are a common cause of Ullrich congenital muscular dystrophy. Hum Mol Genet 2005;14(2):279–293. doi:10.1093/hmg/ddi025.

39 Reed UC, Ferreira LG, Liu EC, et al. Ullrich congenital muscular dystrophy and Bethlem myopathy: clinical and genetic heterogeneity. Arq Neuropsiquiatr 2005;63(3B):785–790. doi:/S0004-282X2005000500013.

40 Lampe AK, Dunn DM, von Niederhausern AC, et al. Automated genomic sequence analysis of the three collagen VI genes: applications to Ullrich congenital muscular dystrophy and Bethlem myopathy. J Med Genet 2005;42(2): 108–120. doi:10.1136/jmg.2004.023754.

41 Yurchenco PD, McKee KK, Reinhard JR, Ruegg MA. Laminin-deficient muscular dystrophy: molecular pathogenesis and structural repair strategies. Matrix Biol 2018;71–72:174–187. doi:10.1016/j.matbio.2017.11.009.

42 Pane M, Messina S, Vasco G, et al. Respiratory and cardiac function in congenital muscular dystrophies with alpha dystroglycan deficiency. Neuromuscul Disord 2012;22(8):685–289. doi:10.1016/j.nmd.2012.05.006.

43 Graziano A, Bianco F, D'Amico A, et al. Prevalence of congenital muscular dystrophy in Italy: a population study. Neurology 2015;84(9):904–911. doi:10.1212/WNL.0000000000001303.

44 Gilbreath HR, Castro D, Iannaccone ST. Congenital myopathies and muscular dystrophies. Neurol Clin 2014;32(3):689–703, viii. doi:10.1016/j.ncl.2014.04.006.

45 Maggi L, Carboni N, Bernasconi P. Skeletal muscle laminopathies: a review of clinical and molecular features. Cells 2016;5(3). pii: E33. doi:10.3390/cells5030033.

46 Quijano-Roy S, Mbieleu B, Bönnemann CG, et al. De novo LMNA mutations cause a new form of congenital muscular dystrophy. Ann Neurol 2008; 64(2):177–186. doi:10.1002/ana.21417.

47 Chemla JC, Kanter RJ, Carboni MP, Smith EC. Two children with "dropped head" syndrome due to lamin A/C mutations. Muscle Nerve 2010;42(5): 839–841. doi:10.1002/mus.21820.

48 Lehtokari VL, Pelin K, Herczegfalvi A, et al. Nemaline myopathy caused by mutations in the nebulin gene may present as a distal myopathy. Neuromuscul Disord 2011;21(8):556–562. doi:10.1016/j.nmd.2011.05.012.

49 Romero NB, Lehtokari VL, Quijano-Roy S, et al. Core-rod myopathy caused by mutations in the nebulin gene. Neurology 2009;73(14):1159–1161. doi:10.1212/WNL.0b013e3181bacf45.

50 Lehtokari VL, Kiiski K, Sandaradura SA, et al. Mutation update: the spectra of nebulin variants and associated myopathies. Hum Mutat 2014; 35(12):1418–1426. doi:10.1002/humu.22693.

51 Laing NG, Dye DE, Wallgren-Pettersson C, et al. Mutations and polymorphisms of the skeletal muscle alpha-actin gene (ACTA1). Hum Mutat 2009;30(9):1267–1277. doi:10.1002/humu.21059.

52 Moreno CAM, Abath Neto O, Donkervoort S, et al. Clinical and histologic findings in ACTA1-related nemaline myopathy: case series and review of the literature. Pediatr Neurol 2017; 75:11–16. doi:10.1016/j.pediatrneurol.2017.04.002.

53 Witting N, Werlauff U, Duno M, Vissing J. Prevalence and phenotypes of congenital myopathy due to α-actin 1 gene mutations. Muscle Nerve 2016;53(3): 388–393. doi:10.1002/mus.24765.

54 Wu S, Ibarra MC, Malicdan MC, et al. Central core disease is due to RYR1 mutations in more than 90% of patients. Brain 2006;129(pt 6):1470–1480. doi:10.1093/brain/awl077.

55 Alkhunaizi E, Shuster S, Shannon P, et al. Homozygous/compound heterozygote RYR1 gene variants: expanding the clinical spectrum. Am J Med Genet A 2019;179(3):386–396. doi:10.1002/ajmg.a.61025.

56 Bharucha-Goebel DX, Santi M, Medne L, et al. Severe congenital RYR1-associated myopathy: the expanding clinicopathologic and genetic spectrum. Neurology 2013;80(17):1584–1589. doi:10.1212/WNL.0b013e3182900380.

57 Flanigan KM, Kerr L, Bromberg MB, et al. Congenital muscular dystrophy with rigid spine syndrome: a clinical, pathological, radiological, and genetic study. Ann Neurol 2000;47(2):152–161. doi:10.1002/1531-8249(200002)47:2<152::AID-ANA4>3.0.CO;2-U.

58 Jungbluth H, Sewry CA, Muntoni F. Core myopathies. Semin Pediatr Neurol 2011;18(4): 239–249. doi:10.1016/j.spen.2011.10.005.

59 Chauveau C, Rowell J, Ferreiro A. A rising titan: TTN review and mutation update. Hum Mutat 2014;35(9):1046–1059. doi:10.1002/humu.22611.

60 Oates EC, Jones KJ, Donkervoort S, et al. Congenital titinopathy: comprehensive characterization and pathogenic insights. Ann Neurol 2018;83(6):1105–1124. doi:10.1002/ana.25241.

61 Zhao M, Maani N, Dowling JJ. Dynamin 2 (DNM2) as cause of, and modifier for, human neuromuscular disease. Neurotherapeutics 2018; 15(4):966–975. doi:10.1007/s13311-018-00686-0.

62 Laporte J, Hu LJ, Kretz C, et al. A gene mutated in X-linked myotubular myopathy defines a new putative tyrosine phosphatase family conserved in yeast. Nat Genet 1996;13(2):175–182. doi:10.1038/ng0696-175.

63 Nicot AS, Toussaint A, Tosch V, et al. Mutations in amphiphysin 2 (BIN1) disrupt interaction with dynamin 2 and cause autosomal recessive centronuclear myopathy. Nat Genet 2007;39(9): 1134–1139. doi:10.1038/ng2086.

64 Bitoun M, Maugenre S, Jeannet PY, et al. Mutations in dynamin 2 cause dominant centronuclear myopathy. Nat Genet 2005;37(11): 1207–1209. doi:10.1038/ng1657.

65 Jungbluth H, Zhou H, Sewry CA, et al. Centronuclear myopathy due to a de novo dominant mutation in the skeletal muscle ryanodine receptor (RYR1) gene. Neuromuscul Disord 2007;17(4):338–345. doi:10.1016/j.nmd. 2007.01.016.

66 Ceyhan-Birsoy O, Agrawal PB, Hidalgo C, et al. Recessive truncating titin gene, TTN, mutations presenting as centronuclear myopathy. Neurology 2013;81(14):1205–1214. doi:10.1212/WNL. 0b013e3182a6ca62.

67 Amburgey K, Tsuchiya E, de Chastonay S, et al. A natural history study of X-linked myotubular myopathy. Neurology 2017;89(13):1355–1364. doi:10.1212/WNL.0000000000004415.

68 Biancalana V, Scheidecker S, Miguet M, et al. Affected female carriers of MTM1 mutations display a wide spectrum of clinical and pathological involvement: delineating diagnostic clues. Acta Neuropathol 2017;134(6):889–904. doi:10.1007/s00401-017-1748-0.

69 Agrawal PB, Pierson CR, Joshi M, et al. SPEG interacts with myotubularin, and its deficiency causes centronuclear myopathy with dilated cardiomyopathy. Am J Hum Genet 2014;95(2): 218-226. doi:10.1016/j.ajhg.2014.07.004.

70 Wang H, Castiglioni C, Kaçar Bayram A, et al. Insights from genotype-phenotype correlations by novel SPEG mutations causing centronuclear myopathy. Neuromuscul Disord 2017;27(9): 836-842. doi:10.1016/j.nmd.2017.05.014.

71 Böhm J, Biancalana V, Dechene ET, et al. Mutation spectrum in the large GTPase dynamin 2, and genotype-phenotype correlation in autosomal dominant centronuclear myopathy. Hum Mutat 2012;33(6):949-959. doi:10.1002/humu.22067.

72 Bitoun M, Bevilacqua JA, Prudhon B, et al. Dynamin 2 mutations cause sporadic centronuclear myopathy with neonatal onset. Ann Neurol 2007;62(6):666-670. doi:10.1002/ana.21235.

73 Claeys KG, Maisonobe T, Böhm J, et al. Phenotype of a patient with recessive centronuclear myopathy and a novel BIN1 mutation. Neurology 2010;74(6):519-521. doi:10.1212/WNL.0b013e3181cef7f9.

74 Böhm J, Biancalana V, Malfatti E, et al. Adult-onset autosomal dominant centronuclear myopathy due to BIN1 mutations. Brain 2014; 137(pt 12):3160-3170. doi:10.1093/brain/awu272.

75 Garibaldi M, Böhm J, Fattori F, et al. Novel dominant mutation in BIN1 gene causing mild centronuclear myopathy revealed by myalgias and CK elevation. J Neuromuscul Dis 2016;3(1): 111-114. doi:10.3233/JND-150125.

76 Clinicaltrials.gov. Gene Transfer Clinical Study in X-Linked Myotubular Myopathy (ASPIRO) (NCT03199469). *https://clinicaltrials.gov/ct2/show/NCT03199469*. Updated July 15, 2019. Accessed August 21, 2019.