

Clinical Approach to the Diagnosis of Congenital Myopathies

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In this issue of *Seminars in Pediatric Neurology*, each chapter will focus on the features and management of individual congenital myopathies. This introductory chapter will provide an overview of the clinical features that alert the clinician to the likely diagnosis of a congenital myopathy, and specific features on history and examination that are characteristic of a specific genetic subtype. Most congenital myopathies share a common pattern of clinical features, which makes it difficult to predict the genetic cause in a patient by clinical assessment alone. Although no single feature is specific for the congenital myopathies, the presence of this common pattern highlights patients in whom a muscle biopsy is likely to provide important diagnostic information. The diagnosis of a specific congenital myopathy should only be made when the defining morphologic feature is the predominant pathologic change, other possible causes have been excluded, and the clinical course is nonprogressive or only slowly progressive.

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The congenital myopathies are a group of genetic muscle disorders that are characterized by a range of distinctive abnormalities in the muscle biopsy. The pathologic changes originate within the myofiber, whose structural diversity allows for an enormous repertoire of pathologic changes.¹ Genes that cause congenital myopathies often encode protein components of the skeletal muscle contractile apparatus (the sarcomere) and proteins involved in Ca²⁺ signaling, resulting in inefficient muscle contraction. In contrast, all muscular dystrophies have the same “dystrophic” pathologic picture associated with degeneration of muscle fibers and replacement with connective tissue. Muscular dystrophy genes often encode components of the muscle membrane and extracellular matrix and lead to an increased susceptibility to muscle damage. In congenital myopathies, degenerating and regenerating fibers are not a prominent feature, there is usually not a marked increase in fibrous connective tissue (although there are some exceptions), and there is no storage of glycogen or lipids, allowing them to be differentiated from muscular dystrophies and metabolic myopathies.

The common forms of congenital myopathy can be subdivided based on the predominant pathologic feature observed

under light and electron microscopy into the following categories:²

Myopathies with protein accumulations: Accumulations of Z-line proteins known as nemaline bodies or rods are the defining feature of nemaline myopathy (NM).^{3,4} Cap disease, zebra body myopathy, intranuclear rod myopathy, and actin myopathy are best classified as variants of NM. Accumulations of myosin thick filaments occur in myosin storage (hyaline body) myopathy.

Myopathies with cores: Cores are regions devoid of oxidative activity and, depending on the morphology of the core, are a feature of central core and multiminicore disease (MmD). Cores and rods can occur together in core-rod myopathy.

Myopathies with central nuclei: Abnormally localized, usually centrally placed nuclei are the predominant feature in the autosomal and X-linked (myotubular) forms of centronuclear myopathy.⁵

Myopathies with fiber size variation: Congenital fiber-type disproportion (CFTD) is characterized by selective atrophy of type I (slow twitch) fibers, in the absence of other structural changes that define the other forms of congenital myopathy (eg, rods, cores, or central nuclei).⁶ Small type I fibers are a common feature in congenital myopathies, and there is overlap between the genetic basis of CFTD and the other congenital myopathies listed earlier in the text.

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Table 1 The Differential Diagnosis of the “Floppy Infant”

Disorder	Differentiating Features and Investigations
Congenital muscular dystrophy	Facial sparing, distal laxity (collagen VI), calf hypertrophy (α -dystroglycanopathies), raised CK, abnormalities on cranial MRI: T2-hyperintensity (laminin- α 2), neuronal migration defects (α -dystroglycanopathies), dystrophic muscle biopsy
Congenital myotonic dystrophy	Affected mothers can be clinically asymptomatic. If family history is not documented, examine mother clinically and by EMG for myotonia. Genetic testing for <i>DM1</i> . Note that facial weakness is common, and muscle biopsy can show central nuclei reminiscent of X-linked centronuclear (myotubular) myopathy.
Metabolic myopathies	Organomegaly (liver and heart) in Pompe disease. Raised serum or CSF lactate. Metabolic acidosis, elevated ammonia, abnormal urinary amino and organic acid screen. Glycogen or lipid accumulation, ragged red fibers on muscle biopsy. CNS involvement clinically or on cranial MRI.
Congenital myasthenic syndromes*	Can present with facial weakness, ptosis, ophthalmoplegia, and bulbar weakness. Single-fiber EMG and repetitive nerve stimulation. Maternal AChR antibodies.
Spinal muscular atrophy	Tongue fasciculations, facial sparing. Denervation on EMG. <i>SMN1</i> gene testing.
Congenital hypomyelination neuropathy	Abnormal sensory findings. Denervation on EMG, slowing on nerve conduction studies. Nerve biopsy.
Prader-Willi syndrome	Marked hypotonia associated with bulbar weakness and failure to thrive. Gene testing—chromosome 15q methylation studies.

CK, creatine kinase; MRI, magnetic resonance imaging; EMG, electromyography; CSF, cerebrospinal fluid; CNS, central nervous system; AChR, acetylcholine receptor.

*Disorders most closely mimicking congenital myopathies because of presence of facial and bulbar weakness.

The relationship between each congenital myopathy, defined on histologic grounds, and the genetic cause is complex. Most congenital myopathies can be caused by mutations in more than one gene, and many of the causative genes are associated with more than one histologic diagnosis ((Goebel, see pages 213-215 in this issue;) Table 1). In addition, the histologic abnormalities on biopsy can evolve, and a patient's diagnosis may therefore change over time as additional biopsies are performed. Thus, detailed clinical evaluation, identification of specific diagnostic clinical clues, and ancillary investigations such as muscle imaging, in addition to muscle biopsy findings, play an increasingly important role in prioritizing gene testing and in reaching a final genetic diagnosis.

Clinical Features of Congenital Myopathies

Clinically, the congenital myopathies have the following common features: generalized weakness, hypotonia, hyporeflexia, poor muscle bulk, and dysmorphic features secondary to the myopathy (eg, pectus carinatum, scoliosis, foot deformities, a high-arched palate, and elongated facies). Most congenital myopathies present at birth or in early infancy; however, it is now recognized that there can be a wide variation in clinical severity within each subtype, ranging from neonates with profound generalized weakness to patients with subtle weakness that first manifests during childhood with delayed motor milestones or even adult onset.

The most severe forms of congenital myopathy present in infancy—the “floppy infant”—with hypotonia and generalized muscle weakness, and a “frog leg” posture, often

in association with respiratory and bulbar weakness. Other common clinical signs in infancy are prominent facial weakness (including ptosis) and associated dysmorphic facial features such as dolichocephaly, long face, and high-arched palate. Ophthalmoparesis (ie, involvement of the extraocular muscles) is a feature of several congenital myopathies, and may be present at presentation or develop during childhood. Most infants have depressed deep tendon reflexes and normal intelligence, and many have difficulty swallowing and sucking. Weakness is most often generalized or more prominent in limb-girdle and proximal limb muscles, although some congenital myopathies have prominent axial and/or respiratory muscle weakness or weakness of ankle dorsiflexion.⁶ In patients with severe weakness, respiratory insufficiency is common, and the most severely affected infants require continuous ventilation for survival.

Investigations

Creatine kinase levels are within normal limits or only mildly elevated (although it must be noted that creatine kinase levels can be nonspecifically elevated in the first week of life). Electromyography results are either normal or myopathic (although neuropathic changes can be observed with severe neonatal weakness or in distal muscles later in the disease course). Nerve conduction study results are normal.

Muscle imaging, particularly muscle magnetic resonance imaging (MRI), can be particularly helpful to differentiate between different forms of congenital myopathy by identifying patterns of selective muscle involvement associated with specific genetic abnormalities. Muscle ultrasonography is a

practical way to image muscle at the bedside; however, it is reliant on the expertise and experience of the ultrasonographer. Muscle imaging is usually used in conjunction with results from a muscle biopsy to prioritize gene testing.⁷ Specific MRI patterns of muscle involvement will be reviewed under specific disorders and in the chapter by Quijano-Roy et al (See pages 221-229 in this issue) on muscle imaging.

Muscle biopsy is usually performed when the clinical assessment is highly suggestive of a primary myopathic process and once other appropriate investigations have been performed to exclude the more common differential diagnoses (mentioned later in the text).

Clinical examination and muscle imaging (MRI or ultrasonography) can be used to select the most appropriate muscle for biopsy if muscle involvement is patchy. Muscles that are weak, but are not at the end stage of the degenerative process, are the best for biopsy. Muscle biopsy can be performed as an open procedure or as a needle biopsy (if the practitioner is experienced), and, if possible, the biopsy should be processed in a specialized center by personnel experienced in handling muscle tissue and interpreting muscle pathology and performing specialized staining.⁸ A single biopsy site is usually sufficient; the most commonly biopsied muscles are vastus lateralis, deltoid, and biceps.

Most congenital myopathies can be diagnosed using light microscopy. Immunohistochemical studies are rarely needed, unlike in cases of muscular dystrophies, for which immunohistochemistry and Western blotting are often essential to characterize which muscle proteins are absent or reduced (eg, absence of laminin- α 2 [merosin] in congenital muscular dystrophy type 1A). Electron microscopy is indicated to clarify or confirm equivocal abnormalities observed under light microscopy or to exclude subtle morphologic changes (such as small rods or cores) in patients with CFTD.

Genetic testing for different congenital myopathies is usually prioritized based on a combination of information gained from clinical presentation and examination, family history, and muscle biopsy, with or without muscle MRI. Genetic testing before muscle biopsy is usually only considered to exclude an alternative diagnosis (mentioned later in the text), or when there is a severely ill infant or child in whom muscle biopsy is considered to be a risky procedure, and the decision to withdraw care is being considered. Genetic testing for myotubularin (*MTM1*), congenital myotonic dystrophy (*DM1*), and α -skeletal actin (*ACTA1*)^{9,10} responsible for 50% of severe congenital lethal cases of NM) may be appropriate if a biopsy cannot be obtained antemortem. All of these disorders are recognized to be associated with severe congenital-onset muscle weakness, with a relatively poor prognosis. In these circumstances, it is advisable to collect muscle and blood for biopsy and DNA testing, respectively, and to establish a fibroblast cell line immediately after death so that additional diagnostic testing can be performed to guide genetic counseling.

Common Differential Diagnoses

There is marked clinical overlap between congenital myopathies and other neuromuscular disorders, including the muscular dystrophies, congenital myotonic dystrophy, metabolic myopathies such as Pompe disease, congenital myasthenic syndromes, spinal muscular atrophy, congenital hypomyelination neuropathy, and Prader-Willi syndrome, all of which can present in the newborn period with marked hypotonia. As noted earlier in the text, congenital myopathies are often a diagnosis of exclusion, and sometimes other investigations are warranted before confirming the diagnosis by muscle biopsy. Investigations to exclude the common differential diagnoses are summarized in Table 1.

The differential diagnosis is similar in patients presenting in childhood or later with delayed motor milestones or more subtle weakness, with the addition of the limb-girdle muscular dystrophies, myotonic dystrophy, other forms of hereditary motor and sensory neuropathy, less severe forms of spinal muscular atrophy (eg, spinal muscular atrophy type 3), and acquired inflammatory and autoimmune disorders (eg, viral myositis, autoimmune myasthenia gravis, Guillain-Barre syndrome).

Increased reflexes or central nervous system dysfunction makes the diagnosis of a congenital myopathy unlikely, although weak infants have an increased risk of perinatal asphyxia and may have coexisting hypoxic encephalopathy. The presence of dysmorphic features, other than those due to myopathic facies, should prompt the clinician to consider other diagnoses and perform chromosomal analysis including comparative genomic hybridization array.

Clinical Clues to the Diagnosis of Specific Subtypes of Congenital Myopathy

As outlined previously (Goebel, Introduction: Table 1), the congenital myopathies are genetically heterogeneous. For example, there are currently 7 known genetic loci for NM. In addition, mutations in the same gene can cause different muscle pathologies. Mutations in the ryanodine receptor 1 gene (*RYR1*) are classically associated with dominant central core disease, relatively mild late-onset weakness, and increased risk of malignant hyperthermia; however, recent studies have shown that recessive (and some dominant) *RYR1* mutations can result in a much more severe clinical phenotype associated with MmD, centronuclear myopathy, CFTD, and even congenital muscular dystrophy.^{11,12} Thus, clinical clues that suggest a specific genetic cause are invaluable in guiding and prioritizing additional investigations including genetic testing.

Facial weakness has already been mentioned as an important clinical sign for differentiating congenital myopathies from congenital muscular dystrophies and spinal muscle atrophy. Pronounced facial weakness, predominantly affecting the lower face and mouth (resulting in an open mouth, drool-

ing, articulation difficulties, tented upper lip, and high-arched palate) is particularly associated with severe congenital onset forms of NM (caused by mutations in *ACTA1* and *NEB*) and severe forms of centronuclear (myotubular) myopathy (*MTM1*, *DNM2*¹³, and *RYR1*¹¹). Facial weakness is often accompanied by bulbar and respiratory muscle weakness, and the same disorders tend to have significant respiratory muscle involvement in the newborn period. The most important differential diagnoses are congenital myotonic dystrophy (*DM1*) and congenital myasthenic syndromes.

Ophthalmoparesis (involvement of the extraocular muscles) is a feature of centronuclear myopathies (*MTM1*, *DNM2*¹⁴, *RYR1*), and the main differential diagnosis is congenital myasthenic syndrome.

Mutations in the gene encoding selenoprotein N (*SEPN1*) are associated with a range of muscle pathologies (eg, MmD, congenital muscular dystrophy) but present with a distinctive clinical phenotype with predominantly axial weakness (pronounced head lag and early-onset scoliosis) and respiratory muscle involvement out of proportion to skeletal muscle weakness. Typically, patients are still ambulant when they require nocturnal ventilation. The main differential diagnosis of pronounced axial weakness is muscular dystrophy associated with mutation in the gene encoding lamin A/C (*LMNA*). Patients with NM caused by mutations in *NEB*, *TPM3*, or *ACTA1* can also develop respiratory muscle weakness out of proportion to their skeletal muscle weakness, and they are at risk of insidious nocturnal hypoxia if regular sleep studies are not included as part of their disease surveillance.

Orthopedic complications such as kyphoscoliosis and contractures can occur in all forms of NM,³ but are particularly common in NM and *RYR1*-related myopathies. Hip dislocation at birth is suggestive of *RYR1* mutations, with collagen VI-related/-associated muscle dystrophy (Ullrich) as the main differential diagnosis. Fetal akinesia associated with arthrogyrosis can be caused by reduced fetal movement at any level of the neuraxis; however, among the congenital myopathies, mutations in skeletal muscle α -actin (*ACTA1*), nebulin (*NEB*), ryanodine receptor (*RYR1*)¹¹, and fast β -tropomyosin (*TPM2*) can present in this way.

Distal muscle involvement is observed in a subset of congenital myopathies, particularly those associated with mutations in *NEB*, *TPM3*, *MHY7*, and *DNM2*, and can result in foot drop and pes cavus. The main differential diagnosis is a peripheral neuropathy.

Cardiac involvement is unusual in congenital myopathies. Cardiomyopathies have rarely been reported in patients with mutations in *ACTA1*-related NM, but may be a predominant feature of patients with mutations in the genes encoding titin (*TTN*) and myosin heavy chain 7 (*MYH7*).

Conclusion

Accurate genetic diagnosis is essential in guiding management, for prediction of prognosis and recurrence risk, for prevention through prenatal and preimplantation diagnosis, for presymptomatic diagnosis, and, increasingly, for eligibil-

ity to participate in clinical trials of new therapeutic agents. Historically, the congenital myopathies have been categorized based on muscle biopsy findings, but the exponential growth in our understanding of the genetic basis for these disorders has revealed marked genetic heterogeneity and overlap in the genes that can result in a specific ultrastructural findings on muscle biopsy. In fact, it is increasingly evident that diverse pathologies, such as rods, cores, central nuclei, and type 1 fiber hypotrophy, can be caused by a variety of disease mechanisms and represent a limited response of the muscle fiber to a range of pathologic processes. Although muscle biopsy findings are an important factor in reaching a diagnosis, specific clinical and muscle imaging clues to the underlying genetic cause are of increasing importance. It is likely that the classification of congenital myopathies will become “gene-based” rather than “muscle pathology-based” in the future. This will become increasingly the case as new methods of genetic analysis such as next-generation sequencing and muscle chip “array” technologies increase the ease of mutation detection.

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References

1. Sewry CA: Pathological defects in congenital myopathies. *J Muscle Res Cell Motil* 29:231-238, 2008
2. North KN: What's new in congenital myopathies? *Neuromuscul Disord* 18:433-442, 2008
3. Ryan MM, Schnell C, Strickland CD, et al: Nemaline myopathy: A clinical study of 143 cases. *Ann Neurol* 50:312-320, 2001
4. Ryan MM, Ilkovski B, Strickland CD, et al: Clinical course correlates poorly with muscle pathology in nemaline myopathy. *Neurology* 60:665-673, 2003
5. Romero NB: Centronuclear myopathies: A widening concept. *Neuromuscul Disord* 20:223-228, 2010
6. Clarke NF, Kolski H, Dye DE, et al: Mutations in *TPM3* are a common cause of congenital fiber type disproportion. *Ann Neurol* 63:329-327, 2008
7. Fischer D, Herasse M, Ferreira A, et al: Muscle imaging in dominant core myopathies linked or unlinked to the ryanodine receptor 1 gene. *Neurology* 67:2217-2220, 2006
8. Dubowitz V, Sewry CA: *Muscle Biopsy: A Practical Approach*, 3rd ed. Saunders Elsevier, 2007. Available at: http://www.amazon.com/Muscle-Biopsy-Practical-Approach-Consult/dp/1416025936/ref=sr_1_1?s=books&ie=UTF8&qid=1321789409&sr=1-1.

9. Nowak KJ, Wattanasirichaigoon D, Goebel HH, et al: Mutations in the skeletal muscle alpha-actin gene in patients with actin myopathy and nemaline myopathy. *Nat Genet* 23:208-212, 1999
10. North KN, Laing NG: Skeletal muscle alpha-actin disease. *Adv Exp Med Biol* 642:15-27, 2008
11. Romero NB, Monnier N, Viollet L, et al: Dominant and recessive central core disease associated with RYR1 mutations and fetal akinesia. *Brain* 126:2341-2349, 2003
12. Monnier N, Marty I, Faure J, et al: Null mutations causing depletion of the type 1 ryanodine receptor (RYR1) are commonly associated with recessive structural congenital myopathies with cores. *Hum Mutat* 29:670-678, 2008
13. Bitoun M, Bevilacqua JA, Prudhon B, et al: Dynamin 2 mutations cause sporadic centronuclear myopathy with neonatal onset. *Ann Neurol* 62:666-670, 2007
14. Bitoun M, Maugendre S, Jeannet PY, et al: Mutations in dynamin 2 cause dominant centronuclear myopathy. *Nat Genet* 37:1207-1209, 2005