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Pediatric Neuromuscular Diseases

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ABSTRACT

The diagnostic and referral workflow for children with neuromuscular disorders is evolving, particularly as newborn screening programs are expanding in tandem with novel therapeutic developments. However, for the children who present with symptoms and signs of potential neuromuscular disorders, anatomic localization, guided initially by careful history and physical examination, continues to be the cardinal initial step in the diagnostic evaluation. It is important to consider whether the localization is more likely to be in the lower motor neuron, peripheral nerve, neuromuscular junction, or muscle. After that, disease etiologies can be divided broadly into inherited versus acquired categories. Considerations of localization and etiologies will help generate a differential diagnosis, which in turn will guide diagnostic testing. Once a diagnosis is made, it is important to be aware of current treatment options, as a number of new therapies for some of these disorders have been approved in recent years. Families are also increasingly interested in clinical research, which may include natural history studies and interventional clinical trials. Such research has proliferated for rare neuromuscular diseases, leading to exciting advances in diagnostic and therapeutic technologies, promising dramatic changes in the landscape of these disorders in the years to come.

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Introduction

Neuromuscular disorders affect the motor unit, which includes the lower motor neuron (anterior horn), peripheral nerve, neuromuscular junction, and muscle.[1] Pediatric neuromuscular disorders classically present with muscle weakness or other motor difficulties, but the presenting symptoms may vary according to age and neuroanatomic localization.[1,2] Whether inherited or acquired, individual pediatric neuromuscular disorders are classified as rare, also known as orphan, diseases by standard criteria, often leading to significant disease burdens for patients and families. The evaluation and management of these disorders often require a systematic and multidisciplinary approach.[3] With recent therapeutic developments for numerous inherited and autoimmune neuromuscular disorders, it has become imperative to be familiar with these conditions, diagnose them early, and start treatment as soon as possible to achieve optimal long-term neurological outcomes.

Diagnostic approach to a child with a suspected neuromuscular disorder

Motor weakness can be due to a lesion anywhere in the motor pathway from the motor cortex to skeletal muscle. Differentiation between upper and lower motor neuron weakness is a key first step in the diagnostic process.[4] In cases where the history, physical examination, and basic laboratory/radiographic studies indicate a lower motor neuron (neuromuscular) process, further evaluation is needed to localize the lesion more precisely within the motor unit. Clinical and genetic heterogeneity in association with overlapping phenotypes frequently occurs in inherited pediatric neuromuscular disorders, which makes diagnostic confirmation challenging in many cases.[3] Providing an accurate diagnosis is a key step to providing good clinical care, appropriate genetic counseling, and specific US Food and Drug Administration (FDA)-approved therapies, which are becoming available for an increasing number of rare pediatric neuromuscular disorders.

The initial diagnostic evaluation for a suspected neuromuscular condition begins with a detailed medical history and a comprehensive physical examination. Information about pregnancy and birth, including fetal movements, can give some early clues. The

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presence or absence of a family history of neuromuscular disorders should be recorded; it is important to remember that the absence of a family history does not exclude an inherited disorder. Establishing the timeline for achieving motor milestones and any evidence for motor regression are important pieces of information. Social and language development are unaffected in some classic neuromuscular disorders such as spinal muscular atrophy (SMA), but neurodevelopmental issues occur at high rates in certain other neuromuscular disorders such as Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, and myotonic dystrophy (DM).[2]

A thorough general and neurological examination should help sharpen the differential diagnosis. Helpful findings when present include facial differences, contractures, scoliosis, hypotonia, muscle atrophy or hypertrophy/pseudohypertrophy, patterns of weakness (proximal versus distal), and reflex abnormalities. Presence of ptosis, facial weakness, oculomotor weakness, and fatigability raise the possibility of neuromuscular junction disorders, although these findings may also be present in other diseases such as congenital myopathy and myotonic dystrophy. A Gowers sign, trendelenburg gait, and muscle pseudohypertrophy in a young boy raises the suspicion for a dystrophinopathy, typically DMD.[4]

Integration of information obtained from the above evaluation helps direct further studies, which may include basic laboratory tests, most commonly the serum creatine kinase (CK) level and others depending on the differential diagnosis; electrodiagnostic studies ([EDX] including nerve conduction studies and electromyography); genetic testing; muscle/nerve biopsy; and muscle/nerve imaging studies such as ultrasound and magnetic resonance imaging (MRI).[3] In some cases the information obtained from history, physical examination, and a selection of these diagnostic studies will suggest a specific genetic diagnosis, but in many cases the genetic differential diagnosis is still broad at this stage. In either case, genetic testing is warranted when an inherited disorder is suspected.[5-8]

Traditionally, the clinical evaluation would typically be followed by a serum CK level, and then EDX and/or muscle/nerve biopsy would soon follow. Genetic testing has now become widely available, including comprehensive next-generation sequencing panels for neuromuscular disorders and whole exome sequencing, and is now often sent as the next step after the serum CK level. EDX remains valuable in cases of suspected neuropathy, in the setting of a normal or mildly elevated CK level, and when a myotonic disorder is suspected. The adoption of neuromuscular ultrasound and MRI is more variable depending on the expertise and facilities available but is becoming increasingly popular given their noninvasive approaches. Muscle and nerve biopsies are still performed in cases in which the above studies are nondiagnostic but are less commonly obtained than in past decades.

Checking serum CK is often one of the first steps in the laboratory evaluation of possible neuromuscular disorders, as elevated levels typically indicate an underlying primary muscle disease. If serum CK is significantly elevated (>5 times the upper limit of normal), DMD and sometimes Becker muscular dystrophy are high on the differential diagnosis,[9] along with some subtypes of limb-girdle muscular dystrophy (LGMD), congenital muscular dystrophy (CMD), and metabolic muscle diseases such as Pompe disease. It is important to consider all relevant possible explanations for elevated CK levels. For example, CK levels as high as 2000 U/L have been reported in SMA.

EDX are valuable when trying to differentiate between neuropathy and myopathy.[10,11] Broad subtypes of Charcot-Marie-Tooth disease (CMT), myotonic disorders, and neuromuscular junction disorders may be diagnosed based on electrophysiological findings. Even though helpful, electromyography and nerve conduction studies can be challenging to obtain in neonates and young children. The performing clinician needs significant experience and expertise in performing and interpreting studies in pediatric patients.[10-12]

Muscle biopsies can provide vital information such as fiber sizes, distributions of fiber types, evidence for degeneration, fibrosis and fatty change, accumulation of abnormal substances such as nemaline rods, and other structural changes that may be characteristic of certain subgroups of disorders. Metabolic myopathies may be suspected based on enzyme deficiency or glycogen or lipid accumulation. Muscle fiber type grouping may indicate an underlying neurogenic process. Immunohistochemical staining can assess the absence, reduction, or accumulation of certain proteins that may help indicate specific genetic diagnoses.[13] Electron microscopy can detect subtle subcellular abnormalities, including vacuoles, inclusion bodies, nemaline rods, and myofibrillar disorganization. Accumulation of abnormal inclusion material can indicate specific diagnosis like nemaline myopathy, actinopathies, and hyaline body myopathy. Myofibrillar myopathies may be detected based on abnormal myofibrillar patterns and expression of proteins such as desmin and αB-crystallin.[14]

Muscle biopsies provide a wealth of information in helping formulate a diagnosis. Muscle biopsies have become less commonly performed in many countries for two major reasons. First, it is an invasive procedure often requiring anesthesia, and second, diagnostic confirmation requires genetic testing even in the setting of abnormal biopsy results.[15] As genetic testing becomes increasingly sophisticated, comprehensive, and cost-effective, this testing is typically performed before muscle biopsies are considered. The American Association of Neuromuscular and Electrodiagnostic Medicine 2016 consensus guidelines state that genetic testing plays a vital role in the diagnosis and management of neuromuscular disorders, recognizing its cost-effectiveness and benefits in disease management, quality of life, family planning, and participation in clinical trials.[16,17] More than 600 genes have been identified as underlying etiologies for pediatric neuromuscular disorders. The availability of numerous gene panels and testing modalities adds further complexity to the diagnostic approach.

Spinal muscular atrophy

SMA is the most common autosomal recessive disorder, with an incidence of one in 10,000 and carrier frequency of one in 50 in certain populations.[18,19] SMA is characterized by progressive weakness and muscle atrophy due to degeneration of the lower motor neurons. A homozygous deletion or other biallelic pathogenic variants of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13 are the underlying causes in about 95% of cases.[20,21] Other genetic subtypes of SMA are exceedingly rare and are often referred as “non-5q SMA” (Table 1).[22]

The *SMN2* gene is very similar to *SMN1*, with only a few sequence variants distinguishing them, most notably a C > T substitution in exon 7, leading to a lower ratio of full-length versus truncated (nonfunctional) SMN protein with *SMN2*. Thus, *SMN2* can partially but not fully compensate for *SMN1* deficiency. Humans can have variable copy numbers (one to five) of the *SMN2* gene, and about 10% to 15% of *SMN2* transcripts retain exon 7 and produce functional SMN protein. Thus, SMA has a broad phenotype spectrum, with the number of *SMN2* copies affecting disease severity.[23,24]

Until recent therapeutic advances, SMA was classically categorized into types based primarily on the highest milestones achieved, with the age of onset being a secondary clue to the subtype. The infantile form, SMA type 1, is the most common type of SMA presenting in the first six months of life. The infants can be asymptomatic at birth but rapidly develop key features of the

TABLE 1.
Non-5q Subtypes of Spinal Muscular Atrophy

Type	Inheritance	Classic Features	Gene
SMARD	Autosomal recessive	Distal and respiratory weakness	*IGHMBP2*
Distal SMA	Autosomal dominant	Prominent distal weakness	*UBA1, DYNC1H1, TRPV4, PLEKHG5, GARS, FBXO38*
XL-SMA (SMAX2)	X-linked	Severe infantile onset with arthrogryposis	*UBA1*
Kennedy disease	X-linked	Adult onset	*AR*

Abbreviations:
SMA = Spinal muscular atrophy
SMARD = SMA with respiratory distress

disease, including peripheral hypotonia, muscle weakness, areflexia, and tongue fasciculations, which are classic findings on physical examination. These children are never able to sit without support, have significant feeding difficulty, and develop early respiratory weakness.[25,26] Untreated infants without respiratory or nutritional interventions die at an average age of 13.5 months.[27] SMA type 2 is less severe and presents between six and 18 months. Affected individuals are never able to walk independently and develop significant scoliosis and respiratory and bulbar weakness. In SMA type 3, independent ambulation occurs for at least part of the course, but there are delayed motor milestones and ambulation is typically lost over time. Type 4 is the least severe, typically with adult onset of leg weakness and preservation of ambulation throughout what is usually a normal life span.[26]

Over the last decade, landmark advances have been made in targeted therapies for SMA (Table 2), drastically changing the outcomes for this disorder and making it difficult in many cases to implement the traditional phenotypic classification system. Nusinersen was the first treatment for this disease approved by the FDA in 2016. Nusinersen is an antisense oligonucleotide (ASO) that hybridizes to intron 7 of *SMN2*, leading to retention of exon 7 and expression of a higher proportion of functional SMN protein from *SMN2*. Nusinersen reduces the risk of death or permanent ventilation by 50%, and 41% of treated infants with SMA1 showed improvement in motor milestones. The greatest benefit was seen in patients treated presymptomatically or before age three months.[28-30] Due to the inability of this ASO to cross the blood-brain barrier, nusinersen has to be administered intrathecally, every four months for maintenance therapy after a series of loading doses. In 2020, risdiplam, a small molecule oral therapy, was approved by the FDA for SMA. Risdiplam increases the efficiency of splicing at exon 7 in *SMN2* mRNA leading to increased production of functional SMN protein. Patients with SMA1 aged one to seven months who were treated with risdiplam showed 90% survival with no permanent ventilation at 15 months; 41% of these patients were sitting unsupported at one-year follow-up.[31,32]

Unlike gene modulation therapies, onasemnogene abeparvovecxioi is a one-time *SMN1* gene replacement therapy packaged in an adeno-associated virus (AAV9) that was approved by the FDA in 2019 for patients with SMA younger than two years. Babies with SMA1 treated before age six months showed 100% survival without assisted ventilation and improvement in motor milestones at 24 months post-treatment. Of 12 patients 11 were sitting independently and two could even walk independently.[33,34] With multiple treatment options showing dramatic improvements in outcomes, especially when treated presymptomatically, early diagnosis of SMA has become imperative.[29,35,36] SMA has been added to the Recommended Uniform Screening Panel, and most states in the United States have adopted standard newborn screening for SMA. An expert panel recommended immediate treatment of all newborns diagnosed with SMA who have up to four copies of *SMN2*.[37] Where newborn screening is not available, individuals with suspected SMA should be tested as rapidly as possible to facilitate treatment in cases when this diagnosis is confirmed.

TABLE 2.
FDA-Approved Therapies for SMA

Drug (Brand Name)	FDA Approval	Mechanism of Action	Route of Administration	Adverse Effects
Nusinersen	December 2016	Antisense oligonucleotide that modifies splicing of *SMN2* for inclusion of exon 7 resulting in increased expression of functional SMN protein	Indefinite serial intrathecal injections	Fever, upper respiratory symptoms. Hydrocephalus in rare cases.
Onasemnogene abeparvovec	May 2019	Gene replacement therapy via a viral vector (AAV9) resulting in delivery of functional copy of the *SMN1* gene	One-time intravenous administration	Elevation of liver transaminases and vomiting. Rare fatalities due to liver failure have been reported. Thrombocytopenia and thrombotic microangiopathy have been rarely reported postinfusion. There is a potential for immune suppression with concomitant use of steroids.
Risdiplam	August 2020	Increasing SMN production by modifying *SMN2* RNA splicing	Indefinite daily oral therapy	Fever, upper respiratory infections, and diarrhea are most commonly reported. There is a potential risk for male infertility and teratogenicity.

Abbreviations:
AAV = Adeno-associated virus
FDA = US Food and Drug Administration
SMA = Spinal muscular atrophy
SMN = Survival motor neuron

Charcot-Marie-Tooth disease and other hereditary neuropathies

CMT is a category of inherited neuropathies with exclusive or predominant peripheral nerve involvement. CMT is the most common inherited neuromuscular disorder globally, with a prevalence close to one in 2500.[38] More than 70 genes have been associated with CMT; however, variants in four genes, *PMP22, GJB1, MFN2,* and *MPZ*, account for over 90% of patients with a molecular diagnosis.[39] There is significant heterogeneity with the same genes causing different phenotypes, and vice versa, making the genetic diagnosis challenging in some cases.[40] CMTs were first classified into two main categories based on nerve conduction velocities, with type 1 having a demyelinating pattern and type 2 having an axonal pattern.[41] The demyelinating type is the most common type of CMT, accounting for more than 50% of cases.[39,42,43] The mode of inheritance added a new dimension to the classification system, and thus these types were further classified into autosomal dominant demyelinating (CMT1), autosomal dominant axonal (CMT2), severe early-onset forms (CMT3) also historically known as Dejerine-Sottas disease, and X-linked CMT (CMT4). These neuropathies were also termed as hereditary sensory motor neuropathies (HSMN) and further classified based on associated features, including HSMN with spastic paraplegia (CMT5), HSMN with optic atrophy (CMT6), and HSMN with retinitis pigmentosa (CMT7).[44]

The classic phenotype of CMT typically presents with normal early childhood development followed by onset of slowly progressive sensory loss and distal weakness in the first decade of life. Pes cavus and areflexia are seen on examination, followed later in the course by hammertoes. Upper extremities typically become affected later in the disease course, when fine motor impairment becomes apparent. CMT1A secondary to a monoallelic duplication of the *PMP22* gene on chromosome 17p11.2 is the most common change seen in this classic presentation.[45,46] For demyelinating cases of CMT, if there is no *PMP22* duplication found, CMT1B associated with mutation in *MPZ* gene should be considered, as it is the third most common cause of CMT1. CMT with no male to male transmission should raise the suspicion for X-linked CMT caused by a pathogenic variant in *GJ1B* (CMT1X).[40,47] A more delayed onset in the third to fifth decade, with signs of axonal loss and pupillary defects, can in some cases be associated with pathogenic variants in *MPZ* (myelin protein zero).[47] A minority of patients with demyelinating CMT present early with severe congenital or infantile onset, commonly known as Dejerine-Sottas disease; these are typically associated with pathogenic variants in *PMP22* and *MPZ* that primarily occur *de novo*.[40]

The second most common category of CMT is the dominant axonal type, CMT2. This type has typically later onset in the second or third decade. In general, individuals with CMT2 are clinically similar to those with CMT1, although in our experience individuals with CMT2A tend to have severe weakness at the ankles and preserved thigh muscles, rather than the gradient of weakness that is typical for CMT1A. There are more than 30 different causative genes, with CMT2A due to mutations in mitofusin 2 gene (*MFN2*) being the most common. CMT2A can be associated with optic atrophy, sensorineural hearing loss, vocal cord paralysis, and diaphragmatic weakness.[48,49] Autosomal recessive CMT, type 4 is rare and has an early onset in the first few years of life and rapid progression leading to loss of ambulation and bulbar and respiratory weakness.[47] Hereditary sensory and autonomic neuropathies are characterized by severe sensory loss, calluses, ulceration, acral mutilation, and gastrointestinal dysfunction. Episodic or asymmetric presentation of neuropathies can be seen in hereditary neuropathy with liability to pressure palsies characterized by transient, recurrent mononeuropathies due to minor compression, often occurring at entrapment sites including the fibular head and ulnar groove, commonly associated with a monoallelic deletion (rather than duplication) of *PMP22*. Individuals presenting with episodic attacks of brachial plexopathy or mononeuropathies of the upper extremities might have underlying monoallelic pathogenic variants in the *SEPT9* gene leading to hereditary brachial plexus neuropathy. In CMTX1, some affected individuals may present with asymmetric neuropathy, and on occasion an acute syndrome characterized by white matter lesions and a strokelike presentation may occur.[40]

The current management of CMT is symptomatic; however, there are several potential treatments in the research pipeline. The focus of most therapeutic research is on CMT1A since it is the most common type. Clinical trials have examined ascorbic acid, progesterone antagonists, and RNA interference strategies attempting to reduce expression of *PMP22* in mouse models.[50-52] PXT3003, a combination of baclofen, D-sorbitol, and naltrexone with a goal of reducing downstream cAMP due to *PMP22* overexpression, is in human phase 3 trials.[53] Viral vector gene replacement is being studied in GJB1 null mice.[54] With evolving therapeutics, a confirmed genetic diagnosis is becoming even more important for targeted therapy.

Congenital myasthenic syndromes

Congenital myasthenic syndromes (CMS) are rare genetic disorders caused by pathogenic variants in genes controlling neuromuscular junction transmission.[55] Most of the genetic subtypes are autosomal recessive in inheritance, except classic slow channel syndrome.[56] The classic tetrad to help with diagnosis includes onset at birth or early childhood, exertion-induced weakness, absence of acetylcholine receptor (AChR)/muscle-specific kinase (MuSK) antibody elevations, and decremental response on low-frequency repetitive nerve stimulation.[57] Typically only skeletal muscles are affected with fatigable weakness seen in ocular, bulbar, limb, and respiratory muscles, presenting as weak cry, poor suck, apnea, ptosis, and/or ophthalmoplegia in the newborn period. Older children typically have delayed motor milestones and fatigability. Myopathic facies with sparing of extraocular muscles may be seen when there are pathogenic variants in *DOK7*, where a limb-girdle pattern of weakness is classic. Contractures, including arthrogryposis multiplex congenita in severe cases, raise suspicion for *RAPSN* defects. Acute exacerbation with apnea episodes triggered by fever, excitement, or extreme cold is a feature of presynaptic CMS secondary to choline acetyl transferase (*CHAT*) defects.[58] Pathogenic variants in *COLQ* cause end plate acetylcholine transferase deficiency and are distinguished by slow pupillary responses to light.[59] Cardiac and smooth muscles are not involved in CMS. Cognitive function is also preserved in the majority of patients, with the exceptions of rare conditions associated with *SNAP25, SLC25A1,* and *MYO9A* mutations, which constitute less than 1% of all CMS.[60]

When CMS is suspected based on clinical features, the confirmatory diagnostic evaluation is hallmarked by the absence of autoantibodies associated with myasthenia gravis, a decrement of the CMAP amplitude on low-frequency repetitive nerve stimulation, and normal findings on muscle biopsy. Presynaptic CMS, like CHAT deficiency, may display a distinctive electrophysiological phenotype, with absence of a decremental response upon low-frequency repetitive stimulation and abnormalities emerging with $\geq$10 Hz high-frequency repetitive stimulation.[58] Rarely, dystrophic changes are found on muscle biopsy of patients with *GMPPB*-related CMS due to overlap with LGMD.[61] Genetic testing is critical as the therapeutic approach to CMS varies widely by genetic subtype. Acetylcholinesterase inhibitors are helpful in some genetic subtypes of CMS, with the exceptions of those associated with

pathogenic variants in *DOK7* and fast-channel CMS. In *COLQ*-related CMS and slow-channel CMS, acetylcholinesterase inhibitors are contraindicated as they may cause deterioration of symptoms.[62] These patients may benefit from adrenergic agonists including ephedrine and albuterol.[56] Some patients with CMS also benefit from 3,4-diaminopyrimideine as it enhances release of acetylcholine from motor nerve terminals.[63]

Juvenile myasthenia gravis

Juvenile myasthenia gravis (JMG) is an acquired autoimmune disorder that is traditionally distinguished from adult myasthenia gravis by onset before age 18 years.[64] As in the adult form of the condition, JMG is caused by autoantibodies targeting motor end plate components. This is a rare condition with an incidence of about 1.5 per million person-years.[65] Antibodies against AChR are commonly found; in contrast, antibodies against MuSK are relatively rare in JMG.[66] Up to 18% of those who lack antibodies to AChR and MuSK have been found to have antibodies against low-density lipoprotein-4.[67] An increased risk of individuals with JMG developing aquaporin-4 antibody-positive neuromyelitis optica has been reported in a cohort of adults with myasthenia gravis.[68]

As in adult myasthenia, cases of JMG may be subdivided into two major anatomic forms, ocular and generalized. The purely ocular form, estimated to be up to 25% of cases in some populations, presents with ptosis, strabismus, and/or diplopia.[69,70] Pupils are typically not involved in JMG, and intact pupillary function can distinguish JMG from other neurological diseases. Proximal muscle weakness is present in generalized JMG, manifesting with symptoms such as difficulty rising from the floor, ascending stairs, and lifting arms above the head, with fatigability. MuSK-related JMG more commonly includes bulbar symptoms at onset with dysarthria, dysphagia, and respiratory symptoms.[71]

Treatment of JMG typically includes a combination of symptomatic and immunosuppressive therapies, with close ophthalmologic follow-up and, when indicated, close respiratory monitoring. Pyridostigmine, a nonselective cholinesterase inhibitor, is the first-line symptomatic treatment in most cases. Patients with MuSK-related myasthenia gravis are noted to have poorer responses to cholinesterase inhibitors.[66] Immunosuppressive therapies are more challenging in pediatrics than in adult patients. For adult patients, corticosteroids such as prednisone are often used as first-line immunosuppressant therapy. Corticosteroids are problematic in affected children due to the multiple significant side effects with chronic use. When prednisone or prednisolone is used in children with JMG, a typical starting dose is 0.5 mg/kg (capped at adult doses) and it is titrated up slowly as needed.[72]

It is important to consider steroid-sparing therapies early in the course and avoid corticosteroids whenever possible. Intravenous immunoglobulin is used in children, but the efficacy is variable; plasma exchange, when feasible, leads to a more consistent therapeutic response and can be used for both acute exacerbations and maintenance therapy.[73] The presence of a thymoma is an absolute indication for thymectomy. The role of thymectomy in the management of nonthymomatous JMG is less clear due to the lack of prospective studies on this topic. Retrospective studies suggest a beneficial effect of thymectomy in nonthymomatous JMG, particularly in AChR antibody-positive generalized cases, with anecdotal evidence suggesting potential benefit in other JMG cases. Early surgical intervention has been associated with better outcomes.[74,75]

An established immunosuppressive therapy that has been adopted more recently for JMG is rituximab, which has been used with success in a number of reported cases.[76-78] The use of other steroid-sparing therapies has been reported anecdotally, but their efficacies appear to be variable, with side effect profiles that are sometimes significant, like mycophenolate mofetil, tacrolimus, cyclosporine, and cyclophosphamide. Eculizumab, a monoclonal antibody that acts as a complement inhibitor, is approved by the FDA for the treatment of adult myasthenia gravis; its role in the therapy of JMG is unclear at this time and bears further study. Recently, efgartigimod, a monoclonal antibody that acts as an FcRn inhibitor, was approved by the FDA for the treatment of generalized myasthenia gravis in adults and is being studied for safety and efficacy in children.

Transient neonatal myasthenia

Transient neonatal myasthenia gravis is seen in about 10% to 15% of newborns born to mothers with autoimmune myasthenia gravis; some affected mothers are asymptomatic or minimally symptomatic and are only diagnosed when their infants are affected. Neonatal myasthenia gravis is caused by placental transfer of maternal AChR antibodies and typically resolves spontaneously within a few weeks. The onset of symptoms is typically in the first two days of life, with hypotonia, ophthalmoplegia, ptosis, poor suck, and in severe cases respiratory compromise. In more severe cases ventilatory support, pyridostigmine, intravenous immunoglobulin, and/or plasma exchange are needed.[79,80]

Congenital muscular dystrophies

CMD are a group of progressive disorders typically presenting with weakness at birth or early in infancy (Table 3). These disorders are rare heterogeneous disorders, which depending on the subtype can affect other organs including the eyes, brain, heart, and lungs, in addition to skeletal muscles. Serum CK is often elevated, and muscle biopsy shows dystrophic changes.[81] The overall prevalence of CMD is rare, with significant epidemiologic variability across the world due to founder effects and other genetic factors. Laminin α2-related CMD was reported to be the most common type of CMD in the United Kingdom, whereas Ullrich CMD is common in Australia and Fukuyama CMD in Japan.[82-84]

Before the availability of genetic diagnosis, CMD was classified on the basis of presence or absence of the extracellular matrix protein merosin with or without brain involvement.[85] The three major classic categories of CMD are collagenopathies (Ullrich CMD and Bethlem myopathy), merosinopathy due to laminin α2 deficiency, and dystroglycanopathy.[86,87]

Collagen VI-deficient congenital muscular dystrophy

Mutations in the *COL6* genes lead to the various types of collagen VI-deficient CMD including the more severe form, Ullrich CMD, and the milder form, Bethlem myopathy, which tend to be inherited in recessive and dominant patterns, respectively. Collagen VI is an integral protein of the extracellular matrix, helping to anchor it to the basement membranes of organs such as the skeletal muscle and skin. The underlying defect can be in any of its three α chains encoded by *COL6A1* and *COL6A2* on chromosome 21q22 or *COL6A3* on chromosome 2q37.[88] The classic Ullrich CMD presents in early life with hypotonia, progressive weakness, muscle contractures, and scoliosis. Torticollis and congenital dislocation of the hip may occur due to joint laxity. Skin findings may be present also, including hyperkeratosis and keloid formation.

Affected individuals usually have normal cognition and normal brain MRIs. Cardiac involvement is not typically seen in collagen VI-related CMD.[88-90] Serum CK levels are normal or slightly elevated. Muscle biopsy detects the deficiency or absence of collagen VI, whereas histology can show either classic dystrophic patterns or myopathic changes in some cases.[90] Genetic testing is needed to

TABLE 3.
Classification of Congenital Muscular Dystrophies

Underlying Defect/Protein Affected	Associated Gene(s)	Chromosome Location	Inheritance Pattern	Clinical Features
Collagen type VI-α 1/2/3 subunit	*COL6A1,COL6A2,COL6A3*	21q22.3, 2q37	Autosomal recessive/dominant	Ullrich CMD severe phenotype with early onset of hypotonia, progressive weakness, muscle contractures, and scoliosis. Joint laxity and skin changes including hyperkeratosis and keloid formation can be present. Milder variant is Bethlem myopathy
Laminin α2 chain (merosin)	*LAMA2*	6q22.33	Autosomal recessive	Hypotonia and weakness, most patients remaining nonambulatory. Peripheral neuropathy can be present. Cognition preserved. White matter abnormality and seizures can be seen.
Protein-O-mannosyl transferase 1, protein-O-mannosyl transferase 2, protein-O-mannose β1,2-aminyltransferase 1	*POMT1, POMT2, POMGnT1*	9q34.1, 14q24.3, 1q32-34	Autosomal recessive	Walker-Warburg syndrome typically presents at birth with severe hypotonia, weakness, and significant cognitive impairment. Brain abnormalities including lissencephaly, cobblestone cortex, hydrocephalus, pachygyria, hypo-/dysplasia of the cerebellum and brainstem, and diffuse white matter changes can be present. In addition to the above, MEB also has eye findings like microphthalmia, retinal hypoplasia, severe myopia, cataract, and anterior chamber malformations. Less severe LGMD phenotypes are also associated with several of these genes.
Protein-O-mannose kinase	*SGK196*	8p11.21		
Isoprenoid synthase domain	*ISPD*	7p21.2		
Beta-1,3-N-acetylglucosaminyltransferase 2	*B3GALNT2*	11q13.2		
Xylosyl- and glucuronyltransferase LARGE1	*LARGE1*	22q12.3-13.1		
Fukutin and Fukutin-related protein	*FKRP, FCMD*	19q.13.3, 9q31	Autosomal recessive	Presents with hypotonia, early-onset generalized weakness, seizures, and significant cognitive deficits. Brain abnormality including white matter changes, polymicrogyria, pachygyria, and fused cerebellar folia. Eye abnormalities are present in about half of the patients.
GDP-mannose pyrophosphorylase	*GMPPB*	3p21.31	Autosomal recessive	Hypotonia, weakness, significant cognitive deficits, and severe epilepsy
Dolichyl-phosphate mannosyltransferase polypeptide 2/3	*DPM2, DPM3*	1q12-q21		

Abbreviations:
CMD = Congenital muscular dystrophy
LGMD = Limb-girdle muscular dystrophy
MEB = Muscle-eye-brain disease

confirm the diagnosis and is recommended due to some phenotypic overlap with other muscle dystrophies like Emery-Dreifuss muscular dystrophy (EDMD), which is characterized by cardiac involvement.[91]

Merosin-deficient congenital muscular dystrophy

Congenital muscle dystrophy associated with merosin deficiency is caused by autosomal recessive pathogenic variants in the *LAMA2* gene on chromosome 6q22.33[92]; this leads to deficiency of the α2 subunit of the extracellular glycoproteins known as lamininis. The major subtype in the skeletal muscles, laminin-2, is also known as merosin, and it helps bind the cell surface to the extracellular matrix. Complete absence of merosin is symptomatic within the first few weeks of life with hypotonia, muscle weakness, need for assisted ventilation, and inability to feed due to facial muscle weakness. Those with complete absence of merosin generally never attain ambulation and have early development of muscle contractures, which are progressive.

Serum CK levels are elevated (up to five times the upper limit of normal), and the muscle biopsy often shows classic dystrophic changes. Immunofluorescence shows reduction or absence of the laminin α2 chain, which can be genetically confirmed. Brain MRI in affected individuals typically shows T2 hyperintensities and fluid-attenuated inversion recovery changes in the periventricular and frontal white matter with sparing of the internal capsule, corpus callosum, and cerebellum. These changes are due to increased water content and are not associated with demyelination or significant cognitive changes. Seizures have been reported in up to 30% of affected individuals.[93] Cortical brain malformations are not typical; cortical dysplasia or cerebellar hypoplasia may be seen in 5% of affected individuals.[94] Cardiomyopathy is rare in LAMA2-related CMD, but mitral regurgitation, pulmonary hypertension, and ventricular dysfunction can be seen in up to 35% of patients.[91]

CMD due to defects in glycosylation

Abnormal glycosylation of α-dystroglycan leads to a category of muscular dystrophies known as α-dystroglycanopathies, which include subtypes of both CMD and LGMD. Several genes have been reported to cause defects in glycosylation, including *POMT1, POMT2, POMGnT1, FCMD, FKTN,* and *LARGE*. α-Dystroglycanopathy CMDs are

TABLE 4.
FDA-Approved Exon Skipping Therapies for DMD

Name of Drug	Mechanism	FDA Approval	Side Effects
Eteplirsen	Skipping of exon 51	September 2016	Vomiting, imbalance, skin reaction
Golodirsen	Skipping of exon 53	December 2019	Headache, fever, fall, abdominal pain, cough, vomiting
Viltolarsen	Skipping of exon 53	August 2020	Fever, cough, infection, vomiting, abdominal pain
Casimersen	Skipping of exon 45	February 2021	Cough, fever, headache, joint pain

Abbreviations:
DMD = Duchenne muscular dystrophy
FDA = US Food and Drug Administration

commonly associated with brain malformations, intellectual disability, and structural eye problems. There is a wide range of severity with Walker-Warburg syndrome (WWS) having the most severe phenotype.[89]

WWS presents at birth with severe hypotonia, weakness, and significant cognitive impairment. These infants typically do not survive beyond the first year of life. Structural brain lesions that may be seen on MRI include lissencephaly, cobblestone cortex, hydrocephalus, hypo/dysplasia of the cerebellum and brainstem, and diffuse white matter changes. Occipital encephalocele and cleft lip may also be present.[91,95,96] Severe ocular findings may include myopia, cataracts, microphthalmia, retinal dysplasia, and optic nerve hypoplasia.[95] WWS is genetically heterogeneous with pathogenic variants most commonly reported in *POMT1* on chromosome 9q and *POMT2* on chromosome 14q. Pathogenic variants in *POMGnT1, FKRP, FKTN,* and *LARGE* have been reported less frequently in this setting.[97]

Muscle-eye-brain disease also presents in the neonatal period with hypotonia and weakness. Significant neurodevelopmental delay and refractory epilepsy are common. Brain MRI shows polymicrogyria, pachygyria, lissencephaly, hydrocephalus, and hypoplasia of posterior fossa.[98] Ocular abnormalities can include microphthalmia, retinal dysplasia, severe myopia, cataract, and anterior chamber malformations. The eye findings may not be apparent at birth.[99] Muscle-eye-brain disease is most commonly associated with pathogenic variants in *POMGnT1* on chromosome 1p34-p32.

Fukuyama congenital muscle dystrophy (FCMD) was originally described in Japan in 1998.[100,101] FCMD presents with hypotonia, early-onset generalized weakness, seizures, and significant cognitive deficits. Pseudohypertrophy of the calves and mild cardiac involvement may occur in this condition. Brain MRI shows white matter abnormalities, polymicrogyria, pachygyria, and fused cerebellar folia. Eye abnormalities are seen in about half of the patients.[102] FCMD is primarily caused by biallelic pathogenic variants in the fukutin (*FKTN*) gene on chromosome 9q31.

Dystrophinopathies

Dystrophinopathies are a set of muscular dystrophies associated with pathogenic variants in the *DMD* gene,[103] which causes a deficiency of the dystrophin protein.[104] Dystrophin is an integral anchor protein that connects intracellular actin to the extracellular matrix. The protein is expressed not only in skeletal muscles but also in cardiac muscles, cortical neurons, and Purkinje cells. As the *DMD* gene is on the X chromosome, almost all affected individuals are males with hemizygous pathogenic variants. Females with heterozygous pathogenic variants in DMD are carriers, some with skeletal muscle and/or cardiac manifestations; in rare cases, females may meet criteria for DMD when there are chromosomal abnormalities that lead to a hemizygous pathogenic *DMD* gene or when there are biallelic pathogenic variants in *DMD*. Dramatic elevations in the serum CK level are characteristic for but not unique to dystrophinopathies. In the past, a muscle biopsy with dystrophic changes and absent dystrophin was the gold standard for diagnosis, but today most cases are diagnosed via genetic testing without muscle biopsy. Mutation analysis for deletions, duplications, and point mutations in the DMD gene is now the primary diagnostic modality.

DMD is one of the most common neuromuscular conditions seen in children. The classic epidemiologic figure cited has been one per 3500 male births.[105] However, more recent studies indicate slightly lower numbers. For example, in certain regions of the United States for 2006 to 2010, the prevalence of DMD has been found to be 1.18 per 10,000 boys aged five to nine years.[106] Affected boys have subtle motor issues in early childhood that often go unnoticed and then develop more prominent symptoms such as toe-walking, frequent falls, difficulty getting up from floor, and difficulty climbing stairs. Pseudohypertrophy of the calves appears early. Classically, the average age of loss of ambulation has been estimated to be about 12 years[107]; however, with more consistent multidisciplinary care and thoughtful use of corticosteroids, the longevity of ambulation has increased for many affected individuals. Factors such as age at onset[108] and peak functional ability[109] are increasingly recognized as predictors for age at loss of ambulation. The risks of several major complications increase after loss of ambulation, including scoliosis, pulmonary insufficiency, contractures, and escalation of upper extremity weakness. Hypoventilation and need for assisted ventilation secondary to restrictive lung disease is common as the disease progresses. Noninvasive ventilatory options have dramatically improved the acceptance and comfort of respiratory support. Cardiac complications develop in all boys with DMD, typically presenting with sinus tachycardia and progressive dilated cardiomyopathy.[110] Intellectual disability is seen in 30% of patients with DMD. Autism, obsessive-compulsive disorders, and epilepsy also emerge in some affected individuals.[111,112]

Multidisciplinary care and disease-modifying therapies have improved outcomes and prolonged survival in patients with DMD, so that now the estimated median life expectancy from birth is 23.7 years, with many individuals surviving past 30 years and some past 40 years.[113] Until recently, corticosteroids (prednisone and deflazacort) were the only medications available to prolong the duration of ambulation. More recently, several therapies that can induce expression of truncated, partially functional forms of dystrophin through ASO-mediated exon skipping have been approved by the FDA: eteplirsen (designed to skip exon 51), golodirsen and viltolarsen (both designed to skip exon 53), and casimersen (designed to skip exon 45) (Table 4). These ASOs target specific mutation types, and thus each one is applicable to a subset of the DMD population. Another therapy in development is ataluren, an oral small molecule drug that induces read-through of nonsense mutations by inhibiting the recognition of premature stop codons, thus partially restoring dystrophin expression. Ataluren is approved in the United Kingdom and the European Union for use in patients with DMD who are ambulatory aged two years and

older.[114] Other therapies are in development as well, including several adeno-associated virus-mediated gene therapies that deliver truncated versions of *DMD* (mini- and microdystrophins). One of these gene therapies, delandistrogene moxeparvovec-rokl, received conditional approval from the FDA for patients with DMD aged four and five years in 2023.[115]

Facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant condition linked to several loci to date. Most cases are classified as FSHD1 and are associated with a monoallelic contraction of the D4Z4 macrosatellite repeat region on chromosome 4q35 in the setting of a permissive allele and hypomethylation, leading to derepression of *DUX4*.[116] FSHD2 is less common, and many of those cases are associated with digenic inheritance of monoallelic pathogenic variants in *SMCHD1* in tandem with a permissive D4Z4 allele.[117,118] A very rare form of FSHD2 has been associated with a homozygous nonsense variant in *LRIF1*.[119] Regardless of the genetic subtype, FSHD presents with classic facial, periscapular, and biceps weakness. Weakness is slowly progressive in a descending pattern, with ankle dorsiflexors being affected later in disease. A distinct clinical feature of FSHD is that the weakness may be markedly asymmetric. Onset often occurs in the second decade of life with facial weakness causing inability to purse lips or squeeze eyelids. Scapular winging is prominent, and atrophy of the pectoral muscles is also noted. Hearing loss can be seen in 75% of patients and retinal changes in about 60% of patients. Retinal abnormalities leading to vision loss in FSHD is known as Coats syndrome. Cardiac arrhythmias can also be present, but overall respiratory and bulbar involvement is not seen.[120]

Myotonic dystrophy

Myotonic dystrophy type 1 (DM1) is caused by a monoallelic CTG repeat expansion in the *DMPK1* (DM1 protein kinase) gene on chromosome 19q13.3.[121-124] Myotonic dystrophy type 2 (DM2) is caused by a monoallelic tetranucleotide CCTG repeat expansion in the *CNBP* (previously known as *ZNF9*) gene on chromosome 3q21.1[125,126] These repeats lead to the sequestration of RNA-binding proteins causing dysregulation in RNA splicing. There is a direct correlation between the number of repeats in DM1 and the disease severity. This correlation, however, is not seen in DM2.

Classic DM1 presents with childhood, adolescent, or early adult onset of myotonia (delayed muscle relaxation); muscle weakness; and early onset of cataracts. Muscle weakness and atrophy is noted in the facial muscles (ptosis and temporalis wasting), distal finger flexors, and ankle dorsiflexors. Over time, other muscles, including those of respiration, can be affected.[127] Cardiac conduction defects, especially heart blocks, are the leading cause of mortality.[128] Cataracts characteristically occur before age 50 years. Central nervous system involvement can vary and when present, may manifest with intellectual disability, autism, or behavioral disorders. Brain MRI may show white matter changes and atrophy in the frontoparietal regions. DM1 is a complex multisystem disease with other features including male pattern baldness, insulin resistance, hypogonadism, gastric dysmotility, and increased risk for cancers.[129] DM2 has some features similar to DM1, but with onset almost exclusively in adulthood and proximal rather than distal weakness. Familial anticipation and correlation between disease severity and number of repeats is seen in DM1 but not DM2.[130]

About 15% of individuals with DM1 present at birth with a pattern of features that may include various combinations of hypotonia, talipes equinovarus, respiratory distress, feeding difficulties, and ventriculomegaly, often with a history of reduced fetal movements and maternal DM1, as anticipation occurs primarily with maternal inheritance. This congenital form of DM1 is usually but not exclusively seen in infants with >1000 CTG repeats in *DMPK*. Some of the neonatal symptoms, particularly the respiratory and feeding difficulties, improve during infancy, and thus decisions regarding invasive long-term interventions such as tracheostomy and gastrostomy should be considered in the context of the underlying diagnosis. However, affected children do have persistent multi-organ system complications that are as severe as, and sometimes more severe than, what occurs in classic DM1.[129]

Limb-girdle muscular dystrophy

LGMD is the most genetically heterogeneous category of muscular dystrophy (Table 5). LGMD is characterized by progressive, predominantly proximal muscle weakness and atrophy in the upper and lower extremities.[131] LGMD has traditionally been distinguished from CMD by the age of onset being after two years in the former and earlier than two years in the latter; however, more recently it has been proposed that they can be distinguished by whether affected individuals are ever able to walk independently (LGMD) or not (CMD). In 1995, the European Neuromuscular Center developed a nomenclature based on mode of inheritance (LGMD1 for autosomal dominant and LGMD2 for recessive) followed by a letter, organized alphabetically by order of discovery.[132] However, as LGMD2s proliferated and LGMD2Z came on the horizon, it became apparent that a newer nomenclature would be needed. The European Neuromuscular Center proposed a revised nomenclature in 2018, delineating the mode of inheritance as LGMDR for recessive and LGMDD for dominant, followed by a number in order of discovery.[133]

LGMDs are quite rare, with a combined prevalence estimated to be 2.27 per 100,000 in Northern England.[134] LGMD presents with weakness in the shoulder and hip girdle muscles, with distal weakness being somewhat prominent in some subtypes such as LGMDR2 dysferlin-related, which often includes calf weakness and is allelic with Miyoshi myopathy.[135] Joint contractures frequently occur at the ankles, knees, and elbows. Some features appear with variable frequency, including calf atrophy versus pseudohypertrophy, scapular winging, and macroglossia. Cardiac and respiratory muscle involvement is more variable in LGMD than in the dystrophinopathies, with specific genetic subtypes including those related to *FKTN*, *FKRP*, *ANO5*, and *LMNA* being particularly notable for cardiac complications including arrhythmias, ventricular dysfunction, and dilated cardiomyopathy.[136,137] However, as these complications are becoming increasingly recognized due to more consistent monitoring, individuals with LGMD should in general be screened periodically for cardiac and pulmonary complications.

CK levels vary significantly from subtype to subtype and from individual to individual, from mild elevations to dramatic ones overlapping the levels seen in DMD. For example, dramatic elevations of CK are often seen in sarcoglycanopathies. Individuals with milder disease may present with only exercise-induced myoglobinuria or isolated hyperCKemia. Owing to this phenotypic variability, an individual with a working diagnosis of inflammatory myopathy that is unresponsive to standard immune therapy should undergo genetic testing for LGMD and potentially other muscle diseases. Lower extremity MRIs may show a proximal to distal gradient of fatty and fibrous replacement within skeletal muscles, particularly the hamstrings, gluteii, gastrocnemius, and paraspinal muscles. Muscle biopsy shows dystrophic changes; however, the findings may be variable due to subtype and sampling issues. Significant inflammatory infiltrates resembling polymyositis may be seen, particularly in dysferlinopathies. When available, absent or reduced immunostaining may point toward a specific genetic

TABLE 5.
Classification and Features of LGMD

Name (Old Nomenclature)	Gene	Chromosome	Protein	Onset	Associated Features	Cardiac Involvement
Autosomal dominant						
LGMD D1 (LGMD1D)	*DNAJB6*	6q23	DnaJ heat shock protein family member B6	Adult onset	Ventilatory function can be impaired	Cardiac conduction defects and, later, dilated cardiomyopathy may be present
LGMD D2 (LGMD1F)	*TNPO3*	7q	Transportin	Adult onset	Arachnodactyly and scapular winging	None reported
LGMD D3 (LGMD1G)	*HNRNPDL*	4q.21	Heterogeneous nuclear ribonucleoprotein D-like protein	Late onset	Early cataracts, distal contractures	Not typical
LGMD D4 (LGMD1I)	*CAPN3*	15q15	Calpain 3	Late onset, mild variant	Myalgia and elevated CK may be seen	None
LGMD D5	*COL6A1* *COL6A2* *COL6A3*	21q22 21q22 2q37	Collagen type VI alpha 1 chain	Variable onset and severity	Contractures and muscle pain	Respiratory and cardiac involvement reported
(LGMD1A)	*MYOT*	5q31.2	Myotilin	Adult onset	Distal weakness more prominent with neuropathy in half of patients (foot drop). Facial weakness also present	Cardiomyopathy seen
(LGMD1B)	*LMNA*	1q21.2	Lamin A/C	Variable	Emery-Dreifuss-like phenotype with contractures and scapular winging	Cardiomyopathy and conduction defects seen
(LGMD1C)	*CAV3*	3p25.3	Caveolin 3	First two decades of life	Rippling muscle disease	Cardiomyopathy and long QT syndrome may be seen
(LGMD1E)	*DES*	2q.35	Desmin	Adult onset	Dysphagia	Not typical but may be associated
	RYR1	19q13.2	Ryanodine receptor 1	Variable	Exercise-induced rhabdomyolysis, periodic paralysis, malignant hyperthermia, hyperlaxity of joints, extraocular muscle involvement, and camptocormia may be seen.	Not typical
Autosomal recessive						
LGMD R1 (LGMD2A)	*CAPN3*	15q15	Calpain 3	Typically adolescent onset	Most common AR LGMD. Scapular-humeral-pelvic weakness.	Not reported
LGMD R2 (LGMD2A)	*DYSF*	Chr 2	Dysferlin	Variable	Wide spectrum from mild LGMD to distal myopathy	Not reported
LGMD R3-R6 (LGMD2D-2F)	*SGCA* *SGCB* *SGCG* *SGCD*	Chr 17 Chr 4 Chr 13 Chr 5	Sarcoglycan α Sarcoglycan β Sarcoglycan ϒ Sarcoglycan Δ	Infancy to adulthood	Limb girdle pattern with scapular winging, calf hypertrophy, and ankle contractures	Dilated cardiomyopathy can be seen
LGMD R7 (LGMD2G)	*TCAP*	Chr 17	Telethonin	Variable	Spectrum of proximal and distal weakness predominantly in the lower extremities	Can be associated with hypertrophic and dilated cardiomyopathy
LGMD R8 (LGMD2H)	*TRIM32*	Chr 9	Tripartite motif-containing 32	Typically second or third decade of life.	Slowly progressive proximal muscle weakness, calf psuedohypertrophy, joint contractures, scapular winging, muscle cramping, and/or facial and respiratory muscle involvement. May be associated with Bardet-Biedl syndrome.	Not typical
LGMD R9 (LGMD2I)	*FKRP*	Chr 19	Fukutin related protein	Variable	Wide spectrum from infant onset of MEB to asymptomatic elevation of CK	Dilated cardiomyopathy
LGMD R10 (LGMD2J)	*TTN*	Chr 2	Titin	Childhood onset	Severe progressive proximal weakness	Not typical
LGMD R11 (LGMD2K)	*POMT1*	9q34	Protein O-mannosyltransferase	Infant-early childhood onset		Not typical

(*continued on next page*)

Table 5 (*continued*)

Name (Old Nomenclature)	Gene	Chromosome	Protein	Onset	Associated Features	Cardiac Involvement
					Facial dimorphism with cognitive deficits may be present. Eye and MRI examination normal	
LGMD R12 (LGMD2L)	*ANO5*	11p14	Anoctamin 5	Adult onset in second to fifth decade	Milder variant with slow progression. Males more severely affected than females.	Cardiomyopathy and conduction defects may be seen
LGMD R13 (LGMD2M)	*FCMD*	9q31	Fukutin	Infant onset	Severe weakness with contractures. Joint contractures and pseudohypertrophy of calves may be seen. Posterior fossa brain abnormalities may be present.	Not typical
LGMD R14 (LGMD2N)	*POMT2*	14q24	O-mannosyltranferase 2	Infant-childhood onset	Cognitive deficits with brain anomalies present. (Allelic with WWS)	Not typical
LGMD R15 (LGMD2O)	*POMGnT1*	1p32	Protein-O-mannose β1,2-N-aminyltransferase 1		Rare LGMD with hypertrophy of calves	Not reported
LGMD R16 (LGMD2P)	*DAG1*	3p21	Dystroglycan 1	Childhood onset	Delayed motor development with moderate to severe cognitive deficits. CK greatly elevated. MRI brain normal	Not reported
LGMD R17 (LGMD2Q)	*PLEC1*	8q24	Plectin	Early childhood onset	Familial junctional epidermolysis bullosa seen associated with weakness.	Not reported
LGMD R18 (LGMD2S)	*TRAPPC11*	4q35	Trafficking protein particle complex 11	Childhood onset	Upper extremities more affected. Muscle hypertrophy with scapular winging seen. Seizures, choreiform movements, and intellectual disability may be present.	Not reported
LGMD R19 (LGMD2T)	*GMPPB*	3p21	GDP-mannose pyrophosphorylase	Variable	Rhabdomyolysis, epilepsy, and brain and eye abnormalities maybe seen.	Conduction defects reported
LGMD R20 (LGMD2U)	*CRPPA*	7p21	CDP-L-ribitol pyrophosphorylase A	Childhood onset with loss of ambulation in adolescence	Brain and eye abnormalities in severe phenotypes	Cardiomyopathy seen
LGMD R21 (LGMD2Z)	*POGLUT1*	3q13	Protein-O-glucosyltransferase 1	Third decade	Scapular winging, respiratory weakness	Not reported
LGMD R22	*COL6A1/2/3*	21q22.3, 2q37	Collagen VI subunits A1, A2, A3	Childhood onset	Contractures	Not typical
LGMD R23	*LAMA2*	6q22	Laminin subunit alpha 2	Variable	Epilepsy, leukodystrophy, basal ganglia changes, and neuropathy maybe seen	Dilated cardiomyopathy
LGMD R24	*POMGNT2*	3p22	Protein-O-mannosyl-transferase 2	Early onset	Calf hypertrophy, intellectual impairment	Not typical
LGMDR25 (LGMD2X)	*BVES*	6q21	Blood vessel epicardial substance	Adult onset	Slow progressive	Conduction defect and AV block may be seen
LGMDR26	*POPDC3*	6q21		Adult onset	Slowly progressive	Not typical
LGMDR27	*JAG2*	1q32.33	Jagged2	Onset from infancy to adulthood	Neck weakness, scoliosis, contractures	Cardiomyopathy and arrhythmias reported
(LGMD2W)	*LIMS2*	2q14.3	LIM zinc finger domain containing 2	Childhood onset	Rare	Cardiomyopathy
(LGMD2Y)	*TOR1AIP1*	1q25.2	Torsin 1A interacting protein 1	First decade	Rigid spine and contractures may be seen	Cardiomyopathy seen

Abbreviations:
AR = Autosomal recessive
AV = Atrioventricular
CK = Creatine kinase
LGMD = Limb-girdle muscle dystrophy
MEB = Muscle-eye-brain disease
MRI = Magnetic resonance imaging
WWS = Walker-Warburg syndrome

subtype, although it is important to remember that secondary deficiencies may be misleading regarding the genetic etiology, particularly in the sarcoglycanopathies.[138] At present, there are no targeted therapies available to treat LGMD and management is mostly symptomatic. However, viral vector gene replacement, gene editing, small molecules, and cell replacement therapies are in the research pipeline. Some of these drugs are already in phase 1 and 2 human trials, making targeted gene therapies a real possibility in the near future.[139]

Emery-Dreifuss muscular dystrophy

EDMD is a rare condition with prevalence of about 0.4 per 100,000.[14] EDMD has a distinctive clinical presentation described as a triad of (1) progressive weakness and atrophy; (2) early contractures, particularly at the neck, elbows, and heel cords; and (3) cardiac involvement. Several genetic subtypes have been described. The most common subtypes are EDMD1 and EDMD2, related to hemizygous variants in the X-linked gene *EMD* and monoallelic variants in the *LMNA* gene, respectively. In the classic form of EDMD contractures typically present in the first decade of life, with rare subtypes presenting with contractures in infancy. The weakness pattern is "humeroperoneal" affecting the upper arms but sparing the deltoids, and affecting the distal legs, predominantly the peroneal muscles with sparing of the intrinsic foot muscles. Neck weakness may be seen, but facial muscles are spared, distinguishing it from FSHD. In EDMD2, true hypertrophy of the quadriceps may be noted.[140] Cardiac complications including arrhythmias and cardiomyopathy develop in most patients with EDMD, often as an early manifestation. In EDMD2, cardiac symptoms may present even before onset of muscle weakness. The X-linked subtypes primarily affect males, but female carriers may have mild symptoms and are at increased risk for cardiac complications. Serum CK levels vary from normal up to 10 times the upper limit of normal. MRI of the leg muscles may show fatty infiltration of hamstrings and gastrocnemius with muscle biopsy showing classic dystrophic or myopathic changes. Immunohistochemical staining is not established as a diagnostic tool for most EDMD subtypes and is not helpful for EDMD2, which has normal staining for lamin A/C. Thus genetic testing is the gold standard for confirming the diagnosis and subtype of EDMD. Management is symptomatic and preventative with some preclinical studies mostly targeting the mitogen-activated kinase pathway focusing on the cardiac phenotype caused by pathogenic variants in *LMNA*.[141]

Congenital myopathies

Congenital myopathies are a group of rare inherited muscle disorders with a predicted prevalence of one in every 135,000[134] that are classified based on their histopathological, immunohistochemical, and electron microscopic features on muscle biopsy.[142] Congenital myopathies are distinguished from CMD due to the presence of morphologic myofiber abnormalities in the former and signs of degeneration, regeneration, inflammation, and fibrofatty replacement in the latter. The main subtypes in order of descending severity are (1) centronuclear myopathies (including myotubular myopathies), (2) nemaline rod myopathies, (3) core myopathies (including central core disease), and (4) congenital fiber-type disproportion. Congenital myopathies typically present in the neonatal period with hypotonia and weakness with normal to mildly elevated serum CK values, with life-threatening early respiratory failure occurring in some of the most severe cases. The more severely affected infants may have evidence of prenatal onset including reduced fetal motility, polyhydramnios, congenital arthrogryposis, dolichocepahly, and micrognathia. The less severely affected infants may have a nonprogressive or mildly progressive course in the early stages of the disease.

Ophthalmoparesis and facial weakness are features of centronuclear myopathies, which tend to have severe phenotypes. Centronuclear myopathy associated with pathogenic variants in *DNM2* presents from infancy to childhood with a pattern of symptoms that commonly include a combination of extremity weakness, oculomotor weakness, facial weakness, ptosis, dysphagia, and respiratory failure.[143] Nemaline myopathy classically presents with severe facial and extremity weakness in the context of preserved oculomotor movements. Core myopathy has been reported to be the most common subtype and is most often associated with monoallelic pathogenic variants in *RYR1*.[144] Individuals with core myopathy may have preserved oculomotor and facial movements. A clinical presentation with spinal muscle rigidity, neck weakness, and severe respiratory compromise out of proportion to muscle weakness are features classic for multiminicore myopathy associated with biallelic pathogenic variants in *SEPN1*. Cardiac involvement is uncommon but may occur in specific settings such as multicore myopathy associated with pathogenic variants in *TTN* or *MYH7*. As the genetic etiologies of congenital myopathies have become more fully characterized, later-onset clinical variants have become increasingly recognized. In rare cases, cognitive involvement is associated with congenital fiber-type disproportion myopathies.[81,91] Of note, individuals with pathogenic variants in *RYR1* are susceptible to malignant hyperthermia.

Traditionally, muscle biopsy was the key to diagnosis given that the distinguishing features of the major subtypes of congenital myopathy relied on distinct muscle histologic features. Genetic testing has come to the fore in the diagnostic evaluation of these diseases, but given the genotype-phenotype overlaps that have been reported, muscle biopsy may be indicated in cases of ambiguous or nondiagnostic genetic test findings, or when the prognosis is not clear based on the genetic diagnosis. Centronuclear myopathies are characterized by a high percentage of centralized nuclei, whereas the biopsies of nemaline myopathies show irregular inclusions clustered peripherally in the sarcoplasm, known as nemaline rods and best seen on Gomori trichrome staining and electron microscopy.[81] Core myopathies are characterized histologically by areas of clearing due to absent mitochondria and lack of nicotinamide adenine dinucleotide (NADH) staining due to lack of oxidative enzyme activity. The cores are most commonly seen as one single central core for each myofiber in central core myopathy or as multiple smaller cores in multiminicore myopathy.

Much excitement surrounded a gene therapy trial for X-linked myotubular myopathy, associated with hemizygous pathogenic variants in *MTM1*. Unfortunately, multiple deaths occurred during the clinical trial, which is currently on hold.[145] However, such studies show the promise of advanced molecular therapies for rare neuromuscular diseases, and as the approaches become more refined, future iterations of such therapies are expected to have good efficacy with an improved safety profile.

Conclusion

Each pediatric neuromuscular disorder is rare; however, both individually and collectively they have significant multidimensional impacts on affected individuals, their families, and the society as a whole. The diagnostic and therapeutic approaches to these conditions have been transformed in recent decades. However, early diagnosis and treatment are still not universal, and numerous disorders do not have disease-modifying therapies available. Our experiences in recent decades have also made clear the tangible benefits to life expectancy and quality of life when care

is provided in multidisciplinary clinic settings. Such complex care clinics are needed to optimize supportive care, provide access to novel sophisticated therapies, and provide access to advanced clinical trials for those families who wish to participate in research studies. The future looks brighter than ever before for children with neuromuscular disorders; however, sustained efforts to provide access to early diagnosis, multidisciplinary clinics, and early treatment are needed to continue our progress toward this future.

Declaration of competing interest

G.R. reports no competing interests. P.B.K. reports consulting or advisory relationships with Novartis, NS Pharma, Teneofour, and Sarepta Therapeutics and grant support from Sarepta Therapeutics, Edgewise Therapeutics, and ML Bio Solutions.

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