Chapter 5
An Overview of the Other Muscular Dystrophies: Underlying Genetic and Molecular Mechanisms

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Introduction

Muscular dystrophies (MDs) refer to a heterogeneous group of disorders associated with on going muscle degeneration and regeneration, leading to progressive weakness. They can be transmitted as autosomal dominant, autosomal recessive, or X-linked pattern of inheritance; sporadic cases may also arise as a result of de novo mutation, in the absence of any family history of affected individuals. The distribution of weakness in MDs includes a limb-girdle pattern, with shoulder and hip girdle muscle involvement; a humeroperoneal pattern, with predominantly triceps, biceps, and peroneal muscles weakness; or a distal pattern, with distal weakness in the legs and arms [1]. Examples of MDs include congenital muscular dystrophy (CMD), myotonic dystrophy (DM), limb girdle muscular dystrophy (LGMD), Emery–Dreifuss muscular dystrophy (EDMD), oculopharyngeal muscular dystrophy (OPMD), facioscapulohumeral muscular dystrophy (FSHD), Duchenne muscular dystrophy (DMD), and Becker muscular dystrophy (BMD). According to Emery, the prevalence of MDs ranged from 1.3 to 96.2 per million, with DMD being most prevalent among boys during childhood, and myotonic dystrophy as one of the most common forms of MDs worldwide [2].

Traditionally, the classification of MDs is based on a combination of clinical and pathological criteria, including the age of onset and distribution of muscle weakness, the extent of disease progression, associated symptoms, systemic features, family history, serum creatine kinase, muscle histology, as well as electromyography and nerve conduction studies (EMG/NCS). Increasingly, the diagnosis of MDs requires

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genetic confirmation, as there can be considerable variations and overlaps in the clinical phenotypes [3]. The differential diagnosis of MDs includes other inherited and acquired causes of muscle weakness such as inflammatory myopathies, congenital or metabolic myopathies, non-dystrophic myotonias, muscle channelopathies, motor neuron diseases, neuropathies, and neuromuscular junction transmission defects; a careful neurological examination plus appropriate ancillary tests should be performed to exclude these disorders [4]. This chapter aims to provide an overview of the myotonic dystrophies, LGMDs, and congenital muscular dystrophies. Duchenne and Becker muscular dystrophy as well as facioscapulohumeral dystrophy are discussed in other chapters.

Myotonic Dystrophies

Myotonic dystrophies are autosomal dominant disorders associated with myotonia, progressive muscular weakness, as well as extramuscular manifestations such as cardiac arrhythmia, cataracts, endocrine dysfunction, and variable degrees of central nervous system involvement. These diseases are classified as type 1 or type 2 myotonic dystrophy, based on clinical features as well as molecular genetic diagnosis. Type 1 myotonic dystrophy is due to an abnormal expansion of trinucleotide (CTG) repeats located in the 3′-untranslated region of the dystrophia myotonica protein kinase gene, located on chromosome 19q13.3 [5, 6]. Type 2 myotonic dystrophy is caused by an expansion of tetranucleotide (CCTG) repeats in intron 1 of the zinc finger protein 9 (ZNF9) gene, located on chromosome 3q21.3 [7, 8]; it is also known as proximal myotonic myopathy (PROMM) [9] or proximal myotonic dystrophy (PDM) [10]. The expanded repeats in both types of myotonic dystrophies are associated with intranuclear accumulations of ribonucleic acid (RNA) inclusions, resulting in abnormal interactions with RNA-binding proteins and misregulation of developmentally programmed alternative splicing [11, 12]. The altered distribution of muscleblind-like 1 and CUG-binding proteins adversely affects transcription, translation, and cell signaling functions [13, 14]. Furthermore, nuclear sequestration of muscleblind-like proteins inhibits myoblast differentiation and impairs muscle regeneration [15, 16]. Moreover, it has been shown that the highly regulated pathways of miRNA are altered in skeletal muscle and heart tissues, thus potentially contributing to disease pathogenesis [17, 18].

Type 1 Myotonic Dystrophy

Type 1 myotonic dystrophy (DM1) is one of the most common forms of MD in adulthood, with an estimated prevalence of 1 in 8,000 [19]. It is subdivided into several clinical phenotypes depending on the age of presentation, including the

congenital, early childhood, adult, and late onset forms. Normal alleles range from 5 to 37 CTG repeats. An abnormal increase in CTG beyond 50 repeats is unstable and may result in further expansion in the germline, leading to genetic anticipation with more severe weakness and earlier onset of disease in successive generations among affected families [20, 21]. In the severe congenital form of myotonic dystrophy type 1, 1,000 or more CTG repeats may be demonstrated, while 50–1,000 repeats are seen in the later onset form of the disease [22–25].

Congenital Myotonic Dystrophy

Infants with this severe form of type 1 myotonic dystrophy are overtly symptomatic at birth [26]. The mother is the affected parent in most cases, and polyhydramnios is commonly reported during the pregnancy because of inadequate fetal swallowing of amniotic fluid [27, 28]. Common neonatal manifestations include joint contractures, ranging from equinovarus deformities of the feet to arthrogryposis multiplex congenita, hypotonia, and generalized weakness [29]. The characteristic facies with facial diplegia, inverted V-shaped upper lip, temporalis wasting, small chin, and high-arched palate may be the first clues to the diagnosis [30]. Dysphagia is common; infants may require gavage feeding and/or subsequent gastrostomy placement due to persistence of oral motor dysfunction during childhood [31, 32]. Respiratory insufficiency also affects a significant proportion of neonates; infants with congenital myotonic dystrophy may require supplementary oxygen, positive airway pressure by nasal prongs or masks, or in some cases tracheostomy and long-term mechanical ventilation. Neonates requiring ventilatory support for more than 30 days, in particular, had increased mortality during the first year, according to a retrospective review [33]. Survivors may have chronic complications related to poor GI motility, myotonia, cardiac arrhythmias, impaired visual function, and cataracts [34]. Learning disabilities and mental retardation are also common complications in congenital DM1 [35, 36]; neuroimaging studies may show ventriculomegaly and abnormal cerebral white matter changes [37, 38]. Furthermore, affected children and adolescents are at increased risk for neuropsychiatric co-morbidities such as autistic spectrum conditions or attention deficit disorder [39, 40]. Even though their muscle tone and strength may improve beyond the neonatal period, children with congenital myotonic dystrophy generally remain developmentally delayed. On going issues including cognitive impairment, behavioral challenges, and learning disability will require multidisciplinary support.

Childhood Onset Myotonic Dystrophy

Childhood onset type 1 myotonic dystrophy can be transmitted from either parent. These children have similar symptoms to those with the congenital form of the disease, but these are generally less severe and present at a later age. Cognitive deficits and learning abnormalities may occasionally be the presenting complaints [41].

Adult Onset Myotonic Dystrophy

Patients with adult onset type 1 myotonic dystrophy are generally recognized by their clinical appearance with ptosis, facial weakness, temporalis muscle wasting, myotonia, as well as a combination of proximal and distal muscle weakness. Difficulty with muscle relaxation can result in problems with chewing, swallowing, and talking due to involvement of the bulbar, tongue, or facial muscles, in addition to the positive grip and percussion myotonia. Posterior subcapsular cataracts, obstructive sleep apnea, irritable bowel syndrome, and cardiac conduction defects are common; the latter is a significant contributor to morbidity and mortality in myotonic dystrophy [42, 43]. Endocrine dysfunction may develop, leading to testicular atrophy, type 2 diabetes mellitus, and hypothyroidism. Intellectual impairment, if present, is generally milder than with the childhood onset subtypes. Personality profiles including obsessive-compulsive, avoidant, and passive-aggressive traits have also been described [44, 45].

Late-Onset Myotonic Dystrophy Type 1

Individuals with mild expansion of CTG repeats may remain largely asymptomatic, apart from early onset cataracts. Myotonia may also be detected on clinical assessment [19].

Type 2 Myotonic Dystrophy (DM2)

In myotonic dystrophy type 2, two clinical phenotypes have been described: PROMM and PDM [9, 10, 46]. Both conditions typically affect adults and are linked to myotonia, early-onset cataracts, and proximal muscle weakness. In addition to the aforementioned genetic differences, there are a number of unique features in myotonic dystrophy type 2. In contrast to myotonic dystrophy type 1, type 2 myotonic dystrophy has not been associated with a congenital form of disease, and cognitive or behavioral problems are rare [47, 48]. If present, cognitive impairment in type 2 myotonic dystrophy is generally mild [47, 49]. Furthermore, muscle pain can be a severe and disabling problem for individuals with type 2 myotonic dystrophy, but not usually for those with type 1 disease [19]. In particular, muscle stiffness and pain are more common in PROMM [10, 50, 51]. Both PROMM and PDM can be associated with cardiac conduction defects; sudden death and severe cardiac arrhythmias have been described in small numbers of patients [51, 52]. Endocrine dysfunction may also occur and can worsen over time [53, 54].

Diagnostic Workup

The history and neurology examination is an important first step in the diagnostic approach. A detailed family history including examination of the parents (particularly of the mother in infants with congenital myotonic dystrophy) is essential. The serum creatine kinase is usually mildly elevated. Electromyography studies may reveal electrical myotonia and a myopathic pattern, but such findings may be absent or non-specific in early childhood. The single most important confirmatory diagnostic test is the molecular genetic marker for myotonic dystrophy. Muscle biopsy is now rarely indicated unless genetic testing is equivocal or not available. Roentgenograms of the chest and abdomen can help determine the status of diaphragmatic and gastrointestinal functions. A swallow study may also be indicated for infants with feeding difficulties; similarly, close respiratory monitoring including pulmonary function test, overnight pulse oximetry, and formal sleep studies are required to detect early respiratory insufficiency [55]. An echocardiography should also be performed periodically for all individuals with myotonic dystrophy, even if clinically asymptomatic [56]. Serial electrocardiograms (ECG) are also required on a regular basis to monitor for cardiac arrhythmia. The eyes should be examined with a slit-lamp for early onset cataracts; standard direct ophthalmoscopy may not be adequate. Endocrine monitoring including serum cortisol, thyroid function, insulin, and blood glucose should be performed periodically. Prenatal diagnosis is available from chorionic villus samples and cultured amniocytes, from which DNA analysis can be performed during the first half of gestation at 8–20 weeks. Fetal cord blood may be obtained in older fetuses and genetic studies performed on leukocytes. Additional guidelines for molecular approaches to the myotonic dystrophies are available [57–59].

Management

In general, the management of the myotonic dystrophies remains largely supportive. Bracing may help with distal muscle weakness such as foot drop, and devices such as scooters or wheelchairs can help conserve energy and/or improve mobility. In specific circumstances, anti-myotonic agents may be helpful, especially if muscle stiffness is frequent and persistent or if pain is prominent [60].

Congenital Muscular Dystrophy

CMD refers a heterogeneous group of early onset MDs, with an estimated prevalence ranging from 0.68 to 2.5 per 100,000 [61–64]. Affected children are usually symptomatic at birth or before their first six months of life. The salient features

include hypotonia, muscle weakness, reduced deep tendon reflexes, with or without joint contractures. Feeding and respiratory insufficiency are common due to associated bulbar and respiratory muscle involvement. Additional features may include microcephaly, eye anomalies, cerebral malformation, joint laxity, muscle atrophy or hypertrophy, adducted thumbs, and skin changes. Based on the underlying pathophysiology, the congenital muscular dystrophies can be further subdivided into disorders involving (a) the basal lamina or extracellular matrix proteins; (b) α dystroglycanopathy; (c) sarcoplasmic reticulum calcium release channel; (d) endoplasmic reticulum proteins; (e) nuclear envelope proteins, (f) mitochondrial membrane proteins; and (g) other unspecified dystrophies [65].

The differential diagnosis of CMD includes congenital myopathies, congenital myasthenic syndromes, early onset spinal muscular atrophy, congenital neuropathies, as well as other metabolic and genetic conditions. The approaches to the differential diagnosis include electromyography and nerve conduction studies to exclude neurogenic involvement or neuromuscular junction transmission disorders, selective biochemical or genetic testing, as well neuroimaging studies and muscle biopsy. As seen with other dystrophies, the muscle biopsy in CMD usually demonstrates dystrophic changes with degeneration, necrosis, and regeneration, plus variable degrees of fibrosis and fatty replacement. Serum creatine kinase can range from normal to significantly elevated. Electromyography may reveal an associated peripheral neuropathy, in addition to myopathic changes in certain subtypes of CMD. Furthermore, brain MRI may reveal central nervous system malformations as well as white matter changes.

Diagnostic Aspects of Specific Subtypes

Laminin Alpha 2-Related or Merosin-Deficient CMD

Mutations in the LAMA2 gene located on Ch 6q22-23 result in merosin-deficient CMD. The gene encodes the alpha 2 heavy chain of the laminin 211 isoform, which is also known as merosin [66, 67]. Patients with complete merosin deficiency present at birth with severe hypotonia, proximal more than distal muscle weakness, and multiple joint contractures. Respiratory insufficiency and feeding difficulties are common. Affected children with complete deficiency seldom achieve independent ambulation. Brain MRI may show hyperintense T2-weighted and fluid attenuated inversion recovery (FLAIR) changes affecting the subcortical white matter; similarly, nerve conduction study may reveal a demyelinating polyneuropathy as merosin is also expressed in central and peripheral myelin. Cognition is generally normal. A small minority of children may have additional brain anomalies including occipital cortical dysplasia, subcortical band heterotopia, and cerebellar hypoplasia [68]; approximately 30% of children with merosin-deficient CMD may have associated seizure disorders.

Alpha-Dystroglycan-Related Dystrophies

Alpha-dystroglycan is an integral sarcolemmal membrane protein. Defects in glycosylation of alpha-dystroglycan result in a number of disorders including CMD. The spectrum of involvement may include prenatal onset weakness precluding ambulation to a variable degree of LGMDs. There are currently 13 genes directly or putatively involved in the glycosylation pathway, including POMT1, POMT2, POMGnT1, FKRP, Fukutin, LARGE, ISPD, GTDC2, B3GALNT2, B3GNT1, TMEM5, GMPPB, SGK196 [69, 70]. Mutation in dystroglycan (DAG1) that specifically interferes with its glycosylation can also lead to alpha-dystroglycan-related dystrophies [71]. Additional mutations in the dolichyl-phosphate mannosyltransferase subunit genes of DPM1, DPM2, and DPM3 can cause an overlapping of syndromes of MD with under-glycosylated alpha-dystroglycan [72–74]. A range of central nervous system involvement including type II lissencephaly, polymicrogyria, pachygyria, brainstem, or cerebellar dysplasia may be present on brain MRI studies. Variable degrees of cognitive impairment including severe mental retardation and learning disability have also been observed. In addition, mutations involving the FKRP and FKTN genes are more likely to be associated with dilated cardiomyopathy.

Collagen VI-Related Dystrophies

Collagen VI deficiency results in a spectrum of disorders ranging from severe CMD to a milder form of Bethlem myopathy [75, 76]. It is related to mutation of one of three collagen VI alpha genes, located on Ch 2q (A3) or 21q22 (A1 & A2). The disease can be inherited in an autosomal recessive or dominant fashion. Clinical features of collagen VI-related dystrophies or Ullrich CMD include hypotonia, proximal more than distal weakness, marked distal joint hyperlaxity, skin changes, and progressive contractures from birth. Respiratory and feeding problems are common, leading to failure to thrive and nocturnal hypoventilation [77, 78]. Cognition is normal and may be advanced for age. CK can be normal or minimally elevated. Affected individuals may lose independent ambulation during childhood [79]. Characteristic skin findings are diagnostically helpful and include a tendency for keloid or atrophic scar formation, striae, and hyperkeratosis pilaris [80]. Serum creatine kinase is normal or mildly elevated.

SEPN1-Related Myopathy

SEPN1-related myopathies are autosomal recessive disorders caused by mutations of the SEPN1 gene on 1p3. This encodes selenoprotein N (SelN), an endoplasmic reticulum protein that plays an essential role in protecting human cells against

oxidative stress [81, 82]. Mutations of SEPN1 can result in either a congenital myopathy or a more severe CMD phenotype. The key features include early onset weakness, particular involving the axial muscle groups, including neck flexor and sometimes extensor weakness, leading to a "dropped head" phenotype [83, 84]. In contrast, strength in the extremities is generally preserved until later in life. Other clinical features include distal hyperlaxity, facial weakness, and relative atrophy of the inner thigh muscles; nocturnal hypoventilation may be evident after the first decade of life due to restrictive pulmonary function [85]. Progression is slow, with reduced independent mobility after the fourth decade of life. Serum creatine kinase is normal or mildly elevated.

RYR1-Related Myopathy

Autosomal recessive mutations in the RYR1 gene can result in a distinct CMD-like presentation (RYR1-CMD), in addition to the congenital myopathy phenotype. The gene encodes for the sarcoplasmic reticulum calcium release channel. It is allelic to other recessive RYR1-related myopathies that include centronuclear, central core, multi-minicore, congenital fiber type disproportion, as well as other non-specific histological presentations [86, 87]. Affected children with RYR1-CMD may present with a histological and clinical picture suggestive of CMD. Unlike RYR1-related congenital myopathy, RYR1-CMD may lack the features of core formation on muscle biopsy [65].

Lamin A/C-Related CMD

Mutations in the lamin A/C (LMNA) gene result in a spectrum of genetic disorders in humans, including CMD and LGMDs [88, 89]. Lamin A/C is part of the nuclear membrane proteins. In LMNA-CMD, weakness becomes evident in infancy; severe axial and neck muscle involvement may result in a dropped head syndrome [90, 91] due to prominent neck extensor weakness. In addition, there is often pronounced lumbar hyperlordosis at a very early age, with arm and hand weakness as well as peroneal predominant weakness, as seen with an early axial–scapulo–peroneal pattern of involvement. Progressive weakness may lead to motor developmental regression early in life, with loss of independent ambulation as well as other gross motor milestones before age 3. Feeding, cardiac, and respiratory complications are common, leading to nocturnal hypoventilation before the end of the first decade of life [92]. Cognition is normal. Serum creatine kinase levels can be mildly to moderately elevated. The cardiac manifestation in lamin A/C-related CMD may take the form of an initially atrial arrhythmogenic cardiomyopathy with conduction block; subsequent development of ventricular tachyarrhythmias requires the use of an automatic implantable cardioverter defibrillator (AICD).

Mutations in Metabolic (Mitochondrial Membrane Protein) Pathway Genes

Several genetic causes for CMD like presentations have been described recently and involve mutations in genes involved in the metabolic pathways, including choline kinase B in 22q13. The gene is involved in phosphatidylcholine biosynthesis; mutations result in a congenital onset MD. Muscle biopsy reveals abnormally large mitochondria on oxidative stains and ultrastructure, in addition to dystrophic changes [93]. The constellation of clinical signs together with the biopsy findings of mitochondria depleted in center of muscle fibers, accumulated and enlarged at the periphery, is diagnostic of CHKB-related CMD. Dilated cardiomyopathy may develop over time. Affected patients in addition show cognitive impairment but normal brain MRI findings. Skin changes may include acanthosis nigricans and ichthyosis [65].

Other Congenital Muscular Dystrophies

Integrin α7 (*ITGA7*) is a transmembrane laminin receptor, located on chromosome 12q13. Deficiency of integrin α7 is a rare cause of CMD. Similarly, integrin α9 deficiency (*ITGA9*) related to mutations on 3p23-21 has also been described from French Canadian families. The clinical feature is similar to Ullrich CMD but is generally less severe [65].

Management of congenital muscular dystrophies includes genetic counseling for family and relatives, physical therapy, range of motion stretching exercises, and supportive strategies for mobility, respiratory, and feeding issues. Use of mechanical assistive devices as well as surgery for scoliosis and gastrostomy tube placement may be required. Regular cardiac respiratory monitoring is essential. The overall life expectancy in CMD is presently unknown. Premature death may result from respiratory and cardiac complications. In one series of merosin-deficient CMD, the mortality rate was approximately 20% (4 out of 22 patients) during childhood, with death occurring between five and ten years of age [94].

Limb-Girdle Muscular Dystrophy

LGMD refers to a heterogeneous group of autosomal muscular dystrophies with progressive weakness affecting predominantly the hip and shoulder girdles. The facial and distal muscles are generally spared early on in the disease. Historically, the MDs are classified as either type 1 (dominant) or type 2 (recessive) depending on the mode of inheritance. As well, the disorders are labeled consecutively by the

alphabet according to when the individual genes were identified. The main classes of proteins involved in these conditions are extracellular matrix and external membrane proteins, enzymes or proteins with putative enzymatic function, sarcolemma-associated proteins, nuclear membrane proteins, sarcomeric proteins, and others [1]. The diagnostic approach for LGMD is often challenging because of significant disease heterogeneity.

In addition to the distribution of weakness, ethnicity, and family history, clues to the diagnosis of LGMD include age of onset of symptoms, rate of disease progression, presence of associated signs such as contracture, rigidity, rippling muscle, muscle hypertrophy or atrophy, as well as systemic involvement including cardiac, pulmonary, and skin complications [1]. By definition, the term "limb-girdle muscular dystrophy" usually excludes other defined types of MDs such as Duchenne and Becker MD, myotonic dystrophies, and FSHD [4]. An understanding regarding the epidemiology of various MDs is also helpful. Among LGMD, the recessive forms are generally more prevalent than the dominant variants in certain regions, including LGMD 2A in southern Europe, and LGMD 2I, followed by LGMD 2B in northern Europe. Substantial overlaps exist, as mutations in different proteins that share similar cellular functions can result in nearly identical clinical phenotypes. Conversely, allelic disorders can give rise to divergent diseases, as may be seen in lamin A/C (LMNA) gene mutations resulting in EDMD, LGMD 1B, as well as axonal Charcot-Marie-Tooth disease and several other phenotypes with no muscle involvement [1].

Accordingly to Nigro and Savarese [95], there are currently eight subtypes of autosomal-dominant (type 1) LGMD. The genes and respective locus involved include myotilin, on 5q31.2 (1A); lamin A/C, on 1q22 (1B); caveolin 3, on 3q25.3; DNAJ/Hsp40 homolog subfamily B member 6, on 7q36 (1D); desmin, on 2q35 (1E); transportin 3, on 7q32 (1F); heterogeneous nuclear ribonucleoprotein D-like protein, on 4q21 (1G); and an un-named gene, on 3p23-p25 (1H). Similarly, there are 23 subtypes of autosomal recessive (type 2) LGMD. The genes and respective locus include calpain 3, on 15q15 (2A); dysferlin, on 2q13.2 (2B); γ-sarcoglycan, on 13q12 (2C); α-sarcoglycan, on 17q21.33 (2D); β-sarcoglycan, on 4q12 (2E); δ-sarcoglycan, on 5q33 (2F); telethonin, on 17q12 (2G); tripartite motif containing 32, on 9q33.1 (2H); fukutin-related protein, on 19q13.3 (2I); titin, on 2q24.3 (2J); protein-*O*-mannosyl transferase 1, on 9q34.1 (2K); anoctamin 5, on 11p13-p12 (2L); fukutin, on 9q31 (2M); protein-*O*-mannosyl transferase 2, on 14q24 (2N); protein-O-linked mannose beta 1,2-*N*-acetylglucosaminyl transferase, on 1p34.1 (2O); dystroglycan, on 3p21 (2P); plectin, on 8q24 (2Q); desmin, on 2q35 (2R); transport protein particle complex 11, on 4q35 (2S); GDP-mannose pyrophosphorylase B, on 3p21 (2T); isoprenoid synthase domain containing, on 7p21 (2U); alpha-1, 4-glucosidase, on 17q25.3 (2V); and lim and senescent cell antigen-like domains 2, on 2q14 (2W) [95].

The differential diagnosis of LGMD is broad; it includes other MDs such as congenital muscular dystrophies, myotonic dystrophy, FSHD, and EDMD, as well as congenital myopathies, myofibrillar myopathies, distal myopathies, metabolic myopathy (such as Pompe or lipid storage disease), channelopathies, inflammatory myopathies, neurogenic disorders, and neuromuscular junction transmission disorders.

Example 1: LGMD 2D, α-*Sarcoglycanopathy with a Duchenne-Like Phenotype*

A seven-year-old girl presented with a three-year history of progressive difficulty walking and high serum CK. Her exam was noted for proximal muscle weakness, mild calf hypertrophy, scapular winging, and Achilles tendon contractures. She had a positive Gowers sign, and she walked with a waddling gait with increased lumbar lordosis. Her muscle biopsy showed dystrophic changes with pronounced reduction of α-sarcoglycan and mildly reduced dystrophin on immunostaining. Subsequent genetic analysis confirmed that the primary abnormality is due to mutation of α-sarcoglycan.

Example 2: LGMD 2I, *FKRP Dystroglycanopathies*

A 12-year-old boy presented with a 5-year history of difficulty with running and high serum CK. His older sister was previously diagnosed with a type of LGMD based on muscle biopsy showing dystrophic features. His exam was noted for proximal hip and shoulder girdle weakness, with calf hypertrophy, and mild bilateral heel cord contractures. Molecular genetic testing for dystrophinopathy was negative. Mutations in the fukutin-related protein gene FKRP (19q13.3) were found by molecular genetic testing, thus confirming the diagnosis of limb-girdle muscular dystrophy type 2I (LGMD2I).

Example 3: LGMD 2A, *Calpainopathy*

A 24-year-old woman presented with insidious onset of muscle weakness and difficulty climbing stairs. Her serum CK was moderately elevated. Her exam revealed proximal more than distal muscle weakness; the weakest muscles involved the hip adductors and extensors, with mild contractures in her heel cords and hamstring. Molecular genetic testing confirmed a mutation of calpain 3, which belongs to a family of calcium-activated neutral proteases. Calpain 3 interacts with several proteins including dysferlin and titin that are crucial for muscle function. It is one of the most common forms of autosomal recessive LGMD, with a reported frequency ranging from 9 to 40% in published series [1].

Example 4: LGMD 1B, *Laminopathy*

An 18-year-old man presented with a long-standing history of gross motor developmental delay and elevated CK. His father had similar history of muscle weakness and died prematurely due to cardiac arrest. His exam limb girdle distribution of

muscle weakness, with mild contractures and reduced subcutaneous fat in his extremities. Cardiac work revealed prolonged QTc interval with atrial tachyarrhythmia. He was subsequently confirmed to have LGMD 1B due to a mutation in the LMNA gene.

Example 5: LGMD 2B, *Dysferlinopathy*

A 16-year-old athletic teenager presented with a 2-year history of exercise-induced myalgia. He was found to have moderately elevated serum CK. His examination was normal apart from mild proximal muscle weakness. Muscle biopsy revealed a mildly dystrophic pattern with reduced immunostaining for dysferlin. Subsequent genetic testing confirmed a diagnosis of LGMD2B. LGMD2B is a relatively mild disease with a predominantly proximal slowly progressive involvement of the pelvic and shoulder girdles presenting in the late second or third decade of life. It is linked to Ch2p12-14 [96]. Individuals are often normal or even athletic in their early years. Mutation in the dysferin gene is associated with several phenotypes, including LGMD 2B, Miyoshi myopathy, and distal anterior compartment myopathy. Miyoshi myopathy presents with early involvement of the posterior compartment of the lower extremities, with inability to stand on the toes [97]. Another allelic disorder results in a distal anterior compartment myopathy, with inability to stand on heels due to rapidly progressive weakness of the anterior tibial muscles [98].

Diagnosis and Management of LGMD

Similar to other MDs, the approach to LGMD requires a detailed history, a thorough physical examination, and serum creatine kinase level. Other genetic and acquired causes of proximal muscular weakness should be excluded. The diagnosis may be confirmed by molecular genetic testing, muscle biopsy, or a combination of both. Muscle biopsy will typically reveal the characteristic dystrophic features; further immunostaining may demonstrate the presence or absence of specific muscle proteins such as dystrophin, dysferlin, sarcoglycans, emerin, collagen VI, merosin, and glycosylated alpha-dystroglycan. Women should also be offered appropriate testing to exclude manifesting carrier of dystrophinopathy as a potential cause for their MD. The future of molecular testing may shift away from targeted genetic analysis toward whole genome or exome sequencing that will allow rapid and cost-efficient means of confirming the diagnosis. General treatment principles include offering genetic counseling for affected individuals and families, connecting them with patient organization and disease registries, providing rehabilitation through multidisciplinary clinics to maximize function, supporting education, career, social, and financial needs, screening and treating the associated complications, and evaluating new treatment options for specific diseases when available.

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