Genetic and Clinical Advances of Congenital Muscular Dystrophy

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Abstract

Objective: The aim was to update the genetic and clinical advances of congenital muscular dystrophy (CMD), based on a systematic review of the literature from 1991 to 2017.

Data Sources: Articles in English published in PubMed from 1991 to 2017 English were searched. The terms used in the literature searches were CMD.

Study Selection: The task force initially identified citations for 98 published articles. Of the 98 articles, 52 studies were selected after further detailed review. Three articles, which were not written in English, were excluded from the study. This study referred to all the important and English literature in full.

Results: CMD is a group of early-onset disorders encompassing great clinical and genetic heterogeneity. Patients present with muscle weakness typically from birth to early infancy, delay or arrest of gross motor development, and joint and/or spinal rigidity. The diagnosis of CMD relies on clinical findings, brain and muscle imaging, muscle biopsy histology, muscle and/or skin immunohistochemical staining, and molecular genetic testing.

Conclusions: Advances in next-generation sequencing and histopathological techniques have enabled the recognition of distinct CMD subtypes supported by specific gene identification. Genetic counseling and multidisciplinary management of CMD play an important role in helping patients and their family. Further elucidation of the significant clinical and genetic heterogeneity, therapeutic targets, and the clinical care for patients remains our challenge for the future.

Key words: Congenital Muscular Dystrophy; Diagnosis; Recent Advance

INTRODUCTION

The congenital muscular dystrophy (CMD) is defined as a heterogeneous group of early-onset muscle disorders in which the muscle biopsy is compatible with the presence of a dystrophic process (even if not fully developed) without histological evidence of another neuromuscular disease. The presenting features of CMD include hypotonia and muscle weakness typically presenting from birth to early infancy, poor or decreased motor abilities, delay or arrest of gross motor development, joint and/or spinal deformities. Although muscle weakness may improve or stabilize in the short term, typically weakness and its complications worsen with time. The complications include feeding difficulties, joint contractures, spinal deformities, respiratory compromise, and cardiac involvement. In some subtypes, eye, central nervous system, and connective tissue may also be involved.

With more causative genes and pathogenic variants were discovered, the concept of CMD has evolved to a more inclusive group of subtypes defined by pathogenic genes.[1,2] However, it has been clear that no complete or satisfactory classification system exists; furthermore, there is an overlap between the CMD, congenital myopathies, and limb-girdle muscular dystrophies. The clinical and genetic complexity of CMD has resulted in different genetic as well as clinical classification schemes.[3] Furthermore, the nomenclature of CMD subtypes is not always consistent. According to the consensus by the International Standard of Care Committee for CMD, the gene or protein name annotated by “−related dystrophy (−RD)” or “−related myopathy (−RM)” is used for several of the CMD phenotypic classes. The gene or protein name annotated by “−related CMD” is used when
referring specifically to the congenital-onset dystrophy without including late-onset presentations.\[^{[4]}\]

The prevalence and incidence of CMD in different regions of the world are poorly known. Few studies are limited to epidemiologic figures of prevalence,\[^{[5]}\] and a recent review estimated the overall prevalence of CMD to be 0.99/100,000,\[^{[6]}\] which may have been underestimated because of more limited diagnostic means available. The relative frequency of CMD subtypes also varies in different populations.

**Methods**

Data sources were articles related to CMD in the PubMed published in English from 1991 to 2017. The terms used in the literature searches were CMD. The task force initially identified citations for 121 published articles. Of the 98 articles, 52 studies were selected after further detailed review. Three articles, which were not written in English, were excluded from the study. This study referred to all the important and English literature in full. CMD-related data of clinical characteristics, diagnostics, genetic counseling, and management were extracted from the selected 49 literatures, and synthesized into the review. The research protocol was reviewed and approved by the Ethics Committee of the Peking University First Hospital (Beijing, China).

**Subtypes of Congenital Muscular Dystrophy**

The main CMD subtypes, classified by pathogenic gene in which causative allelic variants occur, are laminin alpha-2 (merosin) deficiency (synonymous with MDC1A, muscular dystrophy, congenital, type 1A), collagen VI-related CMD, the dystroglycanopathies, SELENON (SEPN1)-related CMD, and LMNA-related CMD (L-CMD). Taking into account the location of the protein encoded by causative genes, CMD categories can be recognized the following:

**Basal membrane or extracellular congenital muscular dystrophy forms**

LAMA2-congenital muscular dystrophy-related dystrophy (also known as congenital muscular dystrophy with laminin α2 deficiency, merosin-deficient congenital muscular dystrophy, MDC1A)

LAMA2-CMD-related dystrophy (LAMA2-CMD-RD) is caused by mutations in the LAMA2 gene, locating on the long arm of chromosome 21q22.3 and encoding the α2 heavy chain of the laminin 211 isoform, also known as merosin.\[^{[7]}\] There are 3 subunits that comprise the merosin protein: α2, β1, and γ1. Laminin is an abundant protein in the extracellular matrix and takes the form of a cross-shaped heterotrimer through the association of an α, β, and γ chain, each of which is encoded by separate genes.\[^{[8]}\] In the genetic nomenclature, this CMD subtype is also known as MDC1A. Laminins are secreted into the extracellular matrix and bind to a number of other macromolecules such as collagen IV in the extracellular matrix, and to the two main transmembrane laminin receptors, dystroglycan (DG) and integrins. The laminins are important in extracellular matrix architecture, differentiation, cell adhesion, cell shape, movement, transmission of force, and tissue survival.\[^{[9]}\]

Clinical features of LAMA2-CMD-RD are congenital hypotonia and weakness, delayed or arrested motor milestones, feeding difficulties, and progressive restrictive respiratory insufficiency with diffuse joint contractures and spinal rigidity. Patients with complete absence of merosin are in general associated with a more severe nonambulatory phenotype, whose maximal motor ability is sitting and standing with support.\[^{[9]}\] Patients with partial merosin deficiency due to mutations in LAMA2 tend to present with milder and more variable phenotypes with later onset. Cognitive abilities are normal in the majority of affected individuals. Seizures are a frequent complication of and observed in 20–30% of patients.\[^{[10]}\] Brain magnetic resonance imaging (MRI) demonstrates high signal in the white matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, which are seen in all patients but are most obvious and consistent in patients beyond age of 6 months. The white matter signal abnormalities are diffuse. White matter abnormalities on MRI are also seen in patients with incomplete merosin deficiency, while patients with very late adulthood onset may have normal brain MRI. In addition to the white matter abnormalities, structural brain changes have been reported in a smaller percentage (about 5%) of patients with complete or partial merosin deficiency. Nerve conduction studies show reduced velocities during disease demonstrating a peripheral neuropathy.

**Collagen 6-related dystrophies**

Collagen 6 (COL6) is a ubiquitously expressed extracellular matrix protein composed of three chains (α1, α2, and α3) which are encoded by the genes COL6A1 and COL6A2 on chromosome 21q22.3 and COL6A3 on chromosome 2q37.\[^{[11]}\] The three chains form a monomer made up of two globular domains connected by a triple helical structure, which assemble in the cytoplasm into antiparallel dimers, associate laterally into tetramers, and then secrete into the extracellular space.\[^{[12]}\] COL6 is an important component of the muscle extracellular matrix where it interacts with the basement membrane of all muscle fibers. Mutations in one of the three COL6 alpha genes (COL6A1, COL6A2, and COL6A3) can lead to the COL6-RD spectrum, ranging from early onset, severe Ullrich CMD (UCMD) to an intermediate severity phenotype to milder Bethlem myopathy (BM).\[^{[13]}\]

UCMD typically presents in the newborn period with muscle weakness and hypotonia, proximal elbow and knee contractures, kyphoscoliosis, torticollis, and hip dislocation. The combination of proximal joint contractures and a striking hyperlaxity of the distal joints is characteristic. The distal joints show striking hyperlaxity with extended talipes and prominent calcaneus. The proximal contractures, kyphoscoliosis, and torticollis can be transient or at least improve with physical therapy and
orthopedic treatment. However, joint contractures tend to recur and progress, particularly in the long finger flexors, shoulders, elbows, knees, and hips. Maximum motor function is very variable. Some affected children have acquired the ability to walk independently, while some patients never walk. However, more commonly, walking is achieved for some years, and then is lost again in the late first or early second decade of life due to increased weakness and contractures. Ventilatory insufficiency almost invariably develops in the first or second decade, leading to predominantly night-time respiratory insufficiency in which the diaphragm is disproportionately affected,[14] and may require ventilatory support.[15]

BM is characterized by the combination of proximal muscle weakness and variable contractures. Compared to UCMD, clinical recognition may be later, or onset may be as early as the congenital period but with few conspicuous findings in early childhood such as mild weakness and some degree of joint hypermobility. Contractures of the long finger flexors, pectoralis muscle, elbows, and ankles develop progressively. Respiratory involvement is also less conspicuous in the BM, although weakness may progress in adulthood.[14]

UCMD and BM represent a clinical continuum, while intermediate phenotypes between these two classic presentations are common. The skin typically shows follicular hyperkeratosis, keloid formation, striae, and a softer consistency of the skin in the palms and soles.[16] Cognition is normal and often advanced for age. Thigh muscles’ MRI is useful for the diagnosis of COL6-RD.[17]

Integrin α7 deficient congenital muscular dystrophy
Integrins are heterodimeric transmembrane glycoproteins consisting of an α and β chain and play a role in mediating cell-cell and cell-matrix adhesion.[18] Integrin α7β1 is a major laminin α2 receptor in skeletal myotubes and mature myofibers.[19] The α7 subunit is encoded by ITGA7 gene, expressed mainly in skeletal and cardiac muscle.[20]

Integrin α7 deficient CMD is a rare CMD subtype. So far, this subtype has only described in three patients with normal laminin α2 but absent integrin α7 caused by mutations in ITGA7 gene.[21] Phenotype of the subtype is variable. These patients rather suffered from a mild congenital myopathy combined with delayed motor milestones and walking with 2–3 years.

Congenital muscular dystrophy with hyperlaxity
A study described and mapped the new form of CMD with joint hyperlaxity distinct from COL6-related dystrophies. Fourteen French-Canadian patients belonging to 11 families come from the southwestern part of Quebec, suggesting a new French-Canadian founder effect. CMDH candidate region was confirmed on chromosome 3p23-21, and three genes were considered as excellent candidates: ITGA9, LAMR1, and ACVR2B.[22] Patients present muscle weakness, proximal contractures coexisting with distal joint hyperlaxity,[23] milder compared to UCMD with amputation preserved into adulthood.

Alpha-dystroglycan-related dystrophies
Alpha-DG is an extracellular peripheral membrane glycoprotein anchored to the cell membrane by binding to a transmembrane glycoprotein, β-DG. The two proteins, α-DG and β-DG, are cleaved from DG, which are identified as a component of the sarcolemmal dystrophin-glycoprotein complex. Alpha-DG acts as an extracellular matrix receptor and a linker between the extracellular matrix and the intracellular cytoskeleton. The α-DG binds with high affinity to the extracellular matrix component laminin and binds to the cytoskeletal protein dystrophin through β-DG.[21] Alpha-DG is heavily glycosylated with tissue-specific differential glycosylation. It has been demonstrated that α-DG O-mannosylation plays an important role in muscle and brain development. Proper glycosylation of α-DG is also essential for its function as a receptor for lymphocytic choriomeningitis virus, Lassa fever virus, and clade C New World arenaviruses.[24]

To date, 19 α-DG-RD causative genes have been discovered, including POMT1 (OMIM 607423), POMT2 (OMIM 607439), POMGNT1 (OMIM 606822), FKTN (OMIM 607440), FKRP (OMIM 606596), LARGE (OMIM 603590), POMGNT2/GTDC2 (OMIM 614828), B3GALNT2 (OMIM 610194), B3GNT1 (OMIM 605517), SGK196/POMK (OMIM 615247), TMEM5 (OMIM 605862), GMPPB (OMIM 615320), DPM1 (OMIM 603503), DPM2 (OMIM 603564), DPM3 (OMIM 605951), DOLK (OMIM 607446), ISPD (OMIM 614631), DAG1 (OMIM 128239), and INPP5K (OMIM 607875).[25–27] α-DGP causative gene products participate in the O-mannosylation pathway. The mutations of causative genes result in hypoglycosylation of α-DG, which gives rise to the malfunction of α-DG as an extracellular matrix receptor, disrupts the DG-extracellular matrix linkage, and leads to membrane fragility. Although the structures and biosynthetic pathways of O-mannosyl glycans and the relationship between muscular dystrophy and α-DG glycosylation are not fully understood, O-mannosyl glycan glyobiology has greatly progressed because of the combined effects of improvements in glycomic analysis technology and gene sequencing technology. Glycomic analysis has revealed various new O-mannosyl glycan structures, while gene sequencing has identified many new causative genes for uncharacterized α-DG-RD.

Alpha-DG-RD is a growing group of muscular dystrophies with a reduction in α-DG’s ligand-binding capacity resulting from its aberrant O-glycosylation. It has clinical and genetic heterogeneity. The conditions such as Walker-Warburg syndrome (WWWS), Fukuyama CMD (FCMD), and muscle-eye-brain disease (MEB) represent the most severe end of the clinical spectrum of alpha-DG-RD. These conditions are multi-system disorders with severe structural brain and eye abnormalities, which are often associated with
cognitive impairment and may result in premature death. At the mildest end of the clinical spectrum, limb-girdle muscular dystrophy (LGMD) patients may present in adult life without associated brain or eye involvement.\(^{[26]}\)

**Fukuyama congenital muscular dystrophy**

FCMD was first described by Yukio Fukuyama et al.\(^{[27]}\) from Japan in 1960, caused by mutations of the FKTN gene on chromosome 9q31. The disorder is the second most common form of muscular dystrophy after Duchenne muscular dystrophy in Japan. The molecular basis of a founder mutation, a 3-kb retrotransposal insertion into the 3’ untranslated region of FKTN mRNA, explains the high frequency of FCMD in Japan. Our research team reported the first FCMD case in the Chinese population and the first case in which the 3-kb insertion has been found outside of the Japanese population.\(^{[28]}\) So far, three Chinese FCMD patients have been genetically diagnosed with a heterozygous 3-kb insertion in the FKTN 3’ untranslated region, and haplotype analyses suggested that these patients had the same haplotype as Japanese patients.\(^{[29]}\)

The typical features of FCMD patients are generalized muscle weakness, severe brain involvement with mental retardation, frequent occurrence of seizures, and abnormal eye function. Most patients do not achieve walking and occasionally are able to take a few steps with support. Cardiac involvement in FCMD occurs in the second decade of life in those who survive. The clinical manifestations overlap with MEB disease.

**Muscle-eye-brain disease**

MEB was first described as a new syndrome by Pirkko Santavuori et al. in Finland in 1977. More MEB cases outside Finland have been reported, and our research team have reported three unrelated MEB disease patients in China with novel POMGNT1 mutations. So far, four more causative genes of MEB have been identified, including FKRP, FKTN, ISPD, and TMEM5.\(^{[30]}\)

MEB has similar severity to FCMD and presents with significant eye involvement (such as severe myopia and retinal hypoplasia), mental retardation, and structural brain involvement.

**Walker-Warburg syndrome**

WWS was first described as lissencephaly by Walker in 1942, and the full delineation of the syndrome was completed by Warburg later on. POMT1 gene was the first causative gene of WWS reported by Beltrán-Valero de Bernabé et al. in 2002.\(^{[31]}\) So far, 11 more genes have been implicated in WWS, including POMT2, FKRP, FKTN, ISPD, CTDC2, TMEM5, POMGNT1, B3GALNT2, GMPPB, B3GNT1, and SGK196. Our research team have reported one case with a typical clinical manifestation of WWS who died at the age of 10 months.\(^{[32]}\)

WWS is the most severe phenotype of αDG-RD and associated with a life expectancy of <1 year. Characteristic features are CMD in combination with cobblestone (Type II) lissencephaly, cerebellar malformations, and retinal malformation. The variable features include macrocephaly or microcephaly, hypoplasia of midline brain structures, ventricular dilatation, microphthalmia, cleft lip/palate, and congenital contractures.

**Congenital muscular dystrophy/limb-girdle muscular dystrophy without magnetic resonance (including MDC1C)**

MDC1C was first reported by Brockington et al.\(^{[33]}\) in 2001 reported in seven families with a unique form of CMD and was described in detail by Mercuri et al.\(^{[34]}\) in 2003. The clinical features of MDC1C include onset in the 1st week of life, inability to walk, and muscle hypertrophy. The mildest end of the spectrum is limb-girdle muscular dystrophy type 2I (LGMD2I) characterized by wide clinical variability, childhood to adult onset, and a relatively benign course.

Besides MDC1C and LGMD2I caused by pathogenic mutations in FKRP gene, CMD/LGMD without MR was also reported in patients with mutations of other three genes, including FKTN, ISPD, and GMPPB.

**Large-related congenital muscular dystrophy (MDC1D)**

MDC1D was first described in a 17-year-old girl presented with CMD, profound mental retardation, and white matter changes and subtle structural abnormalities on brain MRI by Longman et al.\(^{[35]}\) in 2003. At the same study, two compound heterozygous mutations in the LARGE gene were identified in the patients.\(^{[36]}\) Later on, more MDC1D patients with LARGE mutations were reported. The clinical presentations are variable and may blend with the MEB/WWS spectrum.

**Congenital muscular dystrophy with partial merosin deficiency (MDC1B)**

MDC1B was first described by Muntoni et al. in 1998, which was characterized by proximal muscle weakness, muscle hypertrophy, and early respiratory failure. Brockington et al.\(^{[37]}\) performed genomewide linkage analysis and found that all four affected children in the family reported by Brockington et al. showed an identical homozygous region on 1q42. However, the pathogenic gene is still not known.

**Congenital muscular dystrophy/limb-girdle muscular dystrophy with magnetic resonance**

CMD/LGMD with MR is a subtype in the intermediate of the clinical spectrum of αDG-RD, characterized by early onset of muscle weakness, usually before ambulation is achieved; mental retardation and mild brain anomalies are variable.\(^{[38]}\) The causative genes of the subtype include FKRP, POMT1, POMT2, ISPD, and GMPPB.

**Intracellular and nuclear congenital muscular dystrophy forms**

**SEPN1-related myopathy**

SEPN1-related myopathy (SEPN1-RM) was first recognized as the rigid spine syndrome by Victor Dubowitz et al. in 1973. Further study assigned the locus for rigid spine muscular dystrophy 1 (RSMD1) to chromosome 1p35–36 and found evidence of linkage disequilibrium associated with the SEPN1 gene.\(^{[39]}\) SEPN1 gene encodes a selenoprotein N
which is a glycoprotein localized within the endoplasmic reticulum.\textsuperscript{[40]} Selenoprotein N may play a key role in the physiology of skeletal muscles such as the diaphragm by maintaining the redox homeostasis and protection against oxidative stress.\textsuperscript{[41]}

The most common presentation of SEPN1-RM is axial hypotonia and weakness often noticed in the 1st month of life, but usually in a child with otherwise normal motor milestones and no significant contractures. Muscle weakness and slenderness remain more marked in axial groups during later infancy and childhood, especially in neck flexors and sometimes extensors. The overall muscle bulk is reduced, particularly the inner thigh. Joint contractures usually are absent or mild in the ankles, but they are severe in the spine leading to spinal rigidity and scoliosis which may appear around 5–6 years of life or even earlier. In typical cases, thoracic lordoscoliosis with lateral translation is a frequent complication later on.\textsuperscript{[4,10]} Progressive respiratory insufficiency is aggravated by stiffness of the rib cage and diaphragmatic weakness. Early nocturnal hypoventilation prior to adulthood in a person who is still ambulatory is the distinct feature of this CMD subtype.

**LMNA-related congenital muscular dystrophy**

The *LMNA* gene encodes lamin A and lamin C. Lamins are structural protein components of the nuclear lamina, a protein network underlying the inner nuclear membrane that determines nuclear shape and size. Mutations in the *LMNA* gene cause a wide range of genetic disorders in humans, including LMNA-related CMDs (LMNA-CMDs), Emery-Dreifuss muscular dystrophy, LGMD1B, and other phenotypes.\textsuperscript{[42]} The first LMNA-CMD patient was reported by Mercuri et al.\textsuperscript{[43]} in 2004.

In LMNA-CMD, weakness becomes evident in the first 6 months of life, sometimes including a brief phase of more rapid progression during the first 24 months of age with loss of early motor milestones. The clinical phenomenon of head-drop is caused by characteristic weakness of axial and neck muscles (flexors and extensors), especially due to very weak extensors. Progressive weakness of the proximal upper limbs and distal lower limbs is more slow, and facial muscles are spared. Contractures manifest in the lower limb and spine with considerable spinal rigidity, with less contractures in upper limb flexors or extensors when compared to classic Emery-Dreifuss phenotype and COL6-RD. Night-time respiratory insufficiency with hypoventilation and hypercapnia may occur early as muscle weakness progresses. Similar to Emery-Dreifuss phenotype, cardiac involvement in LMNA-CMD may take the form of an initially atrial arrhythmogenic cardiomyopathy with conduction block, and also ventricular tachyarrhythmias.

**Recessive RYR1-related myopathy presenting as RYR1 congenital muscular dystrophy**

The *RYR1* gene encodes the skeletal muscle ryanodine receptor, which serves as a calcium release channel of the sarcoplasmic reticulum as well as a bridging structure connecting the sarcoplasmic reticulum and transverse tubule. Mutations in the *RYR1* gene cause a wide range of genetic disorders in humans, including central core disease, minicore myopathy with external ophthalmoplegia, and other phenotypes.\textsuperscript{[46]} RYR1-CMD present with a distinct CMD subtype which falls into the larger context of recessive RYR1-RM.

Disorders caused by *RYR1* mutations can share clinical features of both congenital myopathy and CMD. RYR1-CMD lacks evidence for typical core formation on muscle biopsy staining with NADH and other oxidative stains, which is a characteristic feature in central core disease. Meanwhile, the histological picture shows fibrosis, small fibers, nonspecific myopathic changes, and a predominance of type 1 fibers, which is most suggestive of CMD. The clinical features of patients with RYR1-CMD include significant congenital onset hypotonia, proximal weakness, axial and facial weakness, arthrogryposis, hip dislocation, early-onset severely progressive scoliosis, ophthalmomeresis, feeding difficulties, and respiratory insufficiency.

**Choline kinases β-related congenital muscular dystrophy**

Choline kinases β encoded by *CHKB* catalyze phosphorylation of choline by ATP in the presence of Mg (2+), yielding phosphocholine and ADP. This step commits choline to the enzymatic pathway for biosynthesis of phosphatidylcholine.\textsuperscript{[45]} CHKB-related CMD was first described by Nishino et al. in 1998, while the causative *CHKB* gene of this CMD subtype was later identified in individuals by Mitsuhashi et al.\textsuperscript{[46]} in 2011.

CHKB-related CMD is characterized by early-onset muscle wasting and severe intellectual disability but normal brain MRI findings. Muscle biopsy shows mitochondrial structural abnormalities on oxidative stains and ultrastructure. Peculiar enlarged mitochondria are prevalent toward the periphery of the fibers but are sparse at fiber center. Some affected individuals develop fatal cardiomyopathy and other cardiac anomalies.

**SYNE1-related congenital muscular dystrophy (congenital muscular dystrophy with adducted thumbs)**

The *SYNE1* gene encodes nesprin-1 protein, a member of the spectrin family of structural proteins that link the plasma membrane to the actin cytoskeleton.\textsuperscript{[47]} SYNE1-related CMD was first described as a new CMD subtype by Voit et al. in 2002, characterized by CMD with adducted thumbs, intellectual disability, and cerebellar hypoplasia.

**Diagnosis and Genetic Counseling**

Clinical diagnosis of specific CMD subtype is important to help clarify prognosis and inheritance pattern. Establishing the subtype usually involves family history, physical examination, neurologic examination, eye examination, serum CK concentration, neuroimaging, and muscle imaging. With the increasing availability and expanding role of molecular genetic testing in confirming the diagnosis of a CMD subtype, muscle biopsy for histologic and
immunohistochemical staining can sometimes be skipped when the medical history, physical examination, and neurologic examination support the diagnosis of a CMD. Considering the panels vary by methods used and genes included, appropriated panel should be chosen depending on the level of suspicion, the exclusion of other diagnoses, and the confidence of the neurologist in the diagnosis. As a multigene CMD panel includes a number of genes associated with CMD, the interpretation of molecular genetic results is the most important for genetic diagnosis. The interpretation includes to assess the mutations pathogenicity and to determine whether the mutations are consistent with the known pattern(s) of inheritance in a given condition.

Genetic counseling is the process by which the patients or relatives at risk of an inherited disorder are advised of the consequences and nature of the disorder, the probability of developing or transmitting it, and the options open to them in management and family planning. Almost all CMD subtypes are inherited in an autosomal recessive manner with the exception of COL6-related dystrophies, which can be inherited in an autosomal dominant or autosomal recessive manner,[48] and L-CMD, which has only been reported in persons with a de novo dominant pathogenic variant.[49]

Once the pathogenic variants in an autosomal recessive disorder or the pathogenic variant in an autosomal dominant disorder are identified, molecular genetic testing of the parents is needed to clarify mode of inheritance and to provide accurate recurrence risk information to family members. In autosomal recessive CMD subtypes, heterozygotes (carriers) are asymptomatic, and the parents of an affected child are obligate heterozygotes and therefore carry single copy of a pathogenic variant. At conception, each sib of an individual with autosomal recessive CMD has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. In autosomal dominant CMD subtypes, if the proband has a de novo autosomal dominant variant that is not detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism, and thus prenatal diagnosis in subsequent pregnancies is offered. Once the pathogenic variant(s) have been identified in an affected family member, it is possible to perform prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for CMD.

MANAGEMENT

Despite recent breakthroughs in understanding the molecular pathogenesis of CMD have enabled better diagnosis and highlight therapeutic targets, medical management for CMD patients remains extremely diverse. In addition, advances in many areas of genetic and medical technology have not been widely adopted in clinical practice. The consensus statement on standard of care for CMD was published in 2010 by the International Standard of Care Committee for CMD, including neurological care, pulmonary care, gastrointestinal/nutritional/speech/oral care, orthopedics/rehabilitation care, cardiological care, and palliative care.[31]

Management should be tailored to each individual, their specific CMD subtype, and rate of progression. Providing well-coordinated multidisciplinary care and creating strong provider–patient relationships and individualized care plans are essential throughout the changing course of the disease. Primary care providers should be included in care to ensure that children’s developmental and primary care needs are met. Multidisciplinary medical management plays an important role in improving quality of life and longevity of CMD patients.

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Conflicts of interest

There are no conflicts of interest.

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