# Congenital Muscular Dystrophy Overview

Susan Sparks, MD, PhD
Clinical Genetics
Department of Pediatrics
Carolinas Medical Center
Charlotte, North Carolina
Susan.sparks@carolinas.org

Susana Quijano-Roy, MD, PhD
Neuromuscular Center (GNMH)
Department of Pediatrics
APHP-Raymond Poincaré University Hospital
University of Versailles Saint Quentin-en-Yvelines
Garches, France
Susana.quijano-roy@rpc.aphp.fr

Amy Harper, MD
Pediatric Neuromuscular Disorders and Neurodevelopmental Disabilities
Carolinas Pediatric Neurology Care - Charlotte
Levine Children's Hospital - Carolinas Medical Center
Charlotte, North Carolina
amy.harper@carolinasheathcare.org

Anne Rutkowski, MD
Chairman, Cure CMD
Olathe, Kansas
anne.rutkowski@curecmd.org

Erynn Gordon, MS, CGC
Coriell Institute for Medical Research
Camden, New Jersey
egordon@coriell.org

Eric P Hoffman, PhD
Research Center for Genetic Medicine
Children's National Medical Center
Washington, DC
ehoffman@childrens-research.org

Elena Pegoraro, MD, PhD
Department of Neurosciences
University of Padova
Padova, Italy
elena.pegoraro@unipd.it

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## Summary

**Clinical characteristics.** Congenital muscular dystrophy (CMD) is a clinically and genetically heterogeneous group of inherited muscle disorders. Muscle weakness typically presents from birth to early infancy. Affected infants typically appear "floppy" with low muscle tone and poor spontaneous movements. Affected children may present with delay or arrest of gross motor development together with joint and/or spinal rigidity. Muscle weakness may improve, worsen, or stabilize in the short term; however, with time progressive weakness and joint contractures, spinal deformities, and respiratory compromise may affect quality of life and life span. The main CMD subtypes, grouped by involved protein function and gene in which causative allelic variants occur, are laminin alpha-2 (merosin) deficiency (MDC1A), collagen VI-deficient CMD, the dystroglycanopathies (caused by mutation of *POMT1, POMT2, FKTN, FKRP, LARGE, POMGNT1*, and *ISPD*), *SEPN1*-related CMD (previously known as rigid spine syndrome, RSMD1) and *LMNA*-related CMD (L-CMD). Several less known CMD subtypes have been reported in a limited number of individuals. Cognitive impairment ranging from intellectual disability to mild cognitive delay, structural brain and/or eye abnormalities, and seizures are found almost exclusively in the dystroglycanopathies while white matter abnormalities without major cognitive involvement tend to be seen in the laminin alpha-2-deficient subtype.

**Diagnosis/testing.** The diagnosis of congenital muscular dystrophy relies on clinical findings, brain and muscle imaging, muscle biopsy histology (dystrophic features without the hallmarks of the structural changes seen in the congenital myopathies), muscle and/or skin immunohistochemical staining, and molecular genetic testing.

**Genetic counseling.** The congenital muscular dystrophies are inherited in an autosomal recessive manner with the following exceptions: collagen VI-deficient CMD, which may be inherited in an autosomal recessive or an autosomal dominant manner; LMNA-related CMD (L-CMD), which is inherited in an autosomal dominant manner with all cases to date caused by a *de novo* pathogenic variant.

In autosomal recessive subtypes, each sib of an affected individual 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. Carriers are asymptomatic. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in the family are known.

In autosomal dominant subtypes, the offspring of affected individuals have a 50% chance of being affected. The risk to sibs of an individual with an apparent *de novo* pathogenic variant is low, but not zero because of the possibility of germline mosaicism in one of the parents. Prenatal testing for pregnancies at increased risk is possible for families in which the pathogenic variant has been identified.

**Management.** *Treatment of manifestations:* Treatment tailored to an individual's needs is best managed by a multidisciplinary team. Speech therapy and swallowing studies are used to evaluate those with feeding difficulties and/or possible aspiration. Interventions may be needed for inadequate weight gain and poor feeding. Aspiration pneumonia and/or respiratory insufficiency may require assisted cough devices, supplemental oxygen, noninvasive ventilation, and/or mechanical ventilation via tracheostomy. Physical therapy focuses on stretching exercises of the spine and limbs and to prevent contractures, and positive pressure devices or ventilation to promote mobility of the thoracic cage. Splints, braces and surgical intervention are used to prevent and treat spinal and limb contractures and deformities; these and other assistive devices may help posture, ambulation, and mobility. Epilepsy, behavior problems, and/or intellectual disability require specific treatment and interventions. Vaccinations, early treatment of pulmonary infections, and attention to oral hygiene and care are important aspects of routine care. With support for their physical disabilities the vast majority of children with CMD who have normal cognitive development benefit socially and educationally from mainstreaming into regular educational facilities. The multidisciplinary team can provide social and emotional support for patients and caregivers.

*Surveillance:* Routine monitoring of feeding and weight gain, respiratory function, strength, and mobility; annual or biannual monitoring for orthopedic and pulmonary complications; cardiac monitoring for those with CMD subtypes involving a risk for cardiomyopathy. Those with CMD subtypes with central nervous system involvement require surveillance for possible seizures and/or behavioral problems.

## Definition of CMD

The term congenital muscular dystrophy (CMD) refers to a heterogeneous group of inherited disorders in which weakness is first apparent at birth or in infancy. With the discovery of causative pathogenic variants in multiple genes in the last two decades, the concept of CMD has evolved from a narrowly defined clinical diagnosis (onset in the first months of life) and histologic diagnosis (dystrophic muscle on biopsy) to a more inclusive group of subtypes defined by genes in which causative pathogenic variants occur [Wang et al 2010]. No complete or satisfactory classification system exists; furthermore, phenotypes overlap both within CMD subtypes and among the congenital muscular dystrophies, congenital myopathies, and limb-girdle muscular dystrophies (see Differential Diagnosis). Nonetheless, the umbrella term CMD remains useful by providing a framework for the diagnostic approach to the infant or young child with muscle weakness.

## Clinical Manifestations of CMD

Hypotonia and muscle weakness are present at birth or during infancy. Poor or decreased motor abilities, delay or arrest of motor milestones, and joint or spinal deformities are often the presenting features of CMD. The age of onset is usually

not clearly defined and often difficult to identify retrospectively. Since delay of motor skill acquisition may be a presenting symptom of CMD, onset of manifestations before age two years may be a reasonable diagnostic criterion.

Although muscle weakness of CMD may be stable in the short term, typically over time the weakness and its complications become more severe. These complications include feeding difficulties leading to poor nutrition; respiratory insufficiency; joint contractures and scoliosis; and, in some subtypes, cardiac involvement. The central nervous system, eye, and connective tissue may also be involved.

Note: The diagnosis of a child who has delay in onset of walking during the first two years of life as having CMD versus limb-girdle muscular dystrophy (LGMD) may be considered a matter of convention especially given the overlap between the CMD and LGMD phenotypes (see Differential Diagnosis). Note that the presence or absence of intellectual impairment does not distinguish CMD from LGMD; it is strictly the age of onset of muscle weakness in late childhood or adulthood that defines LGMD.

## Subtypes of CMD

### Subtypes of CMD of Known Cause

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The classification scheme for subtypes of CMD that is used in this *GeneReview* is based on the gene in which pathogenic variants occur and organized by the cellular localization of the protein encoded by the gene: structural proteins of the extracellular matrix, defects in glycosylation, proteins of the endoplasmic reticulum, and proteins of the nuclear envelope (see Table 1). Although phenotypic classification has also been proposed, such a classification has its shortcoming because the phenotypes caused by pathogenic variants in different genes can overlap significantly and pathogenic variants in one gene can be associated with a spectrum of clinical phenotypes.

The disorders associated with mutation of the 13 genes most commonly associated with CMD are summarized in Table 1 [Muntoni & Voit 2004, Quijano-Roy et al 2008]. Description of several less known CMD subtypes, reported in a limited number of individuals, follows Table 1. To date, data for all CMD subtypes are insufficient to make any firm genotype/phenotype correlations or to provide definitive prognosis or anticipatory guidance based on CMD subtype.

Of note, in large cohorts of individuals with CMD causative pathogenic variants can be identified in 25%-50% of cases, underscoring the need for ongoing investigation into the genetic causes of CMD [Peat et al 2008] and the need to consider disorders included in the Differential Diagnosis in the evaluation of an individual with possible CMD.

### Table 1.

Congenital Muscular Dystrophies by Protein Defect and Gene

| Defect | Subtype | Gene | Protein | Other Subtype Name or Other Phenotype |
|---|---|---|---|---|
| **Defects of structural protein** [1] | Laminin alpha-2 deficiency (MDC1A) | *LAMA2* | Laminin α2 | Merosin-deficient CMD [2] |
| | Collagen VI-deficient CMD | *COL6A1* | Collagen VI | Ulrich CMD (UCMD) / Bethlem myopathy |
| | | *COL6A2* | Collagen VI | |
| | | *COL6A3* | Collagen VI | |
| | | *POMT1* | Protein-O-mannosyltransferase 1 | WWS |
| | | | | LGMD2K |
| | | *POMT2* | Protein-O-mannosyltransferase 2 | WWS, LGMD2N |

| | | | | |
|---|---|---|---|---|
| **Defects of glycosylation** | Dystroglycanopathy | *FKTN* | Fukutin | WWS, MEB-like CMD |
| | | | | FCMD |
| | | | | LGMD2M |
| | | *FKRP* | Fukutin-related protein | WWS, MEB-like CMD, MDC1C |
| | | | | LGMD2I |
| | | *LARGE* | Large | WWS, MDC1D |
| | | *POMGNT1* | O-linked mannose β1,2-N-acetylglucosaminyl-transferase | MEB, LGMD |
| | | *ISPD* | Isoprenoid synthase domain-containing protein | WWS, LGMD |
| **Defects of proteins of the endoplasmic reticulum** | *SEPN1*-related myopathy | *SEPN1* | Selenoprotein N | Rigid spine syndrome (RSMD1 [3]) |
| **Defects of nuclear envelope proteins** | *LMNA*-related CMD (L-CMD) | *LMNA* | Lamin A/C | Dropped-head syndrome, EDMD |

MDC1A = Merosin-deficient congenital muscular dystrophy type 1A

MDC1C = Merosin-deficient congenital muscular dystrophy type 1C (with muscle hypertrophy)

MDC1D = Merosin-deficient congenital muscular dystrophy type 1D (with intellectual disability and abnormal glycosylation)

WWS = Walker-Warburg syndrome

FCMD = Fukuyama CMD

MEB = Muscle-eye-brain (disease)

CMD = Congenital muscular dystrophy

LGMD2I = Limb-girdle muscular dystrophy type 2I (no intellectual disability)

LGMD2K = Limb-girdle muscular dystrophy type 2K with microcephaly, intellectual disability, normal MRI

LGMD2M = Limb-girdle muscular Dystrophy type 2M (no intellectual disability)

LGMD2N = Congenital muscular dystrophy/limb-girdle muscular dystrophy type 2N (intellectual disability)

EDMD = Emery-Dreifuss muscular dystrophy

1. Protein located in basement membrane (BM) or extracellular matrix (ECM)

2. Subtype name no longer in use; because merosin deficiency can be primary in laminin alpha-2 deficiency

or secondary in the dystroglycanopathies, the term merosin deficiency is no longer sufficiently specific.

3. Rigid spine muscular dystrophy type 1

**Clinical Findings in the Disorders Described in** Table 1

**Laminin alpha-2 deficiency** (*LAMA2*-related CMD [MDC1A]) is characterized by congenital hypotonia, delayed or arrested motor milestones, and feeding difficulties. Muscle weakness is absent or slowly progressive. Respiratory insufficiency and orthopedic complications may become severe, with diffuse joint contractures and spinal rigidity.

Progressive restrictive respiratory insufficiency occurs in all non-ambulatory persons. Nocturnal mechanical ventilation or continuous ventilation via tracheostomy may be required either early on or beyond age ten to 15 years [Bönnemann et al 2011]. Most children with laminin alpha-2 deficiency who have complete deficiency of the protein merosin do not acquire independent walking, but ambulation in those with partial merosin deficiency with later onset has been reported.

With time affected children develop typical myopathic facies and some develop external ophthalmoplegia and may appear to have an enlarged head with parents relaying difficulty in pulling T-shirts over the head. Of note, retrospective data on 15 children with laminin alpha-2 deficiency from one CMD center revealed that 53% had a head circumference above the 90th centile [Author, personal observation].

Cognitive abilities are normal in the majority of affected individuals. Seizures are observed in 20%-30% [Bönnemann 2009].

Brain MRI demonstrates diffuse white matter signal abnormalities sparing the cerebellum, corpus callosum, and internal capsule. Children may initially be misdiagnosed as having a leukodystrophy. The MRI findings can be found consistently beyond age six months. White matter changes do not regress with time. A small number of individuals have structural changes with focal cortical dysplasia that tends to involve the occipital and temporal lobes.

Nerve conduction studies show reduced velocities during disease demonstrating a peripheral neuropathy.

Inheritance is autosomal recessive.

**The collagen VI-deficient CMDs** were previously known as Ullrich congenital muscular dystrophy (UCMD) and Bethlem myopathy (see Collagen VI-Related Disorders). Although originally described as separate entities, UCMD and Bethlem myopathy represent a clinical continuum; intermediate phenotypes are common. In a recent study of 49 individuals with collagen VI myopathy, Briñas et al [2010] referred to three phenotypes:

- **Early/severe.** Ambulation never achieved

- **Moderate progressive.** Ambulation attained and lost

- **Mild.** Ambulation into adulthood

Homozygous premature termination codon-causing pathogenic variants in the triple helix domains were associated with the early/severe phenotype and dominant *de novo* in-frame exon-skipping variants; glycine missense variants were associated with the moderate progressive phenotype [Briñas et al 2010].

Terminology:

- UCMD (first described as "scleroatonic myopathy") is characterized by congenital weakness and hypotonia along with congenital joint or spinal rigidity or deformities. The combination of proximal joint contractures and a striking hyperlaxity of the distal joints is characteristic. Some affected children have acquired the ability to walk independently; however, disease progression often results in loss of ambulation. Early and severe respiratory involvement may require ventilatory support in the first or second decade of life.

- Bethlem myopathy is characterized by the combination of proximal muscle weakness and variable contractures, affecting most frequently the long finger flexors, elbows, and ankles.

Although the first reports of UCMD showed autosomal recessive transmission, most affected individuals identified in recent years have a *de novo* autosomal dominant pathogenic variant. Bethlem myopathy is typically caused by autosomal dominant pathogenic variants, but a few instances of autosomal recessive transmission have been reported [Allamand et al 2010].

**Dystroglycanopathies** are characterized by a broad CMD phenotypic spectrum with and without intellectual disability, eye involvement, and brain findings (Table 2).

Several CMD phenotypes known to be dystroglycanopathies were initially described as syndromes (in descending order of severity):

- Walker Warburg syndrome (WWS)
- Muscle-eye-brain (MEB) disease
- Fukuyama congenital muscular dystrophy (FCMD)
- MDC1D
- MDC1C

Eye manifestations can include either unilateral or bilateral microcornea and/or microphthalmia, hypoplastic or absent optic nerves, and colobomas that may involve the retina. Anterior chamber malformations include cataracts, iris hypoplasia or malformation, and abnormal or shallow anterior chamber angle which can result in glaucoma. Retinal dysplasia or detachment may occur. In individuals with milder manifestations of a dystroglycanopathy, high myopia or optic disc pallor may be the only ocular manifestation.

Brain MRI may demonstrate structural abnormalities (e.g., hydrocephalus, brain stem hypoplasia, cerebellar cysts) or abnormalities in neuronal migration (cobblestone lissencephaly or polymicrogyria), which are common [Kirschner & Bönnemann 2004]. White matter changes may regress with time [Louhichi et al 2004].

Hindbrain malformations can include atrophy of the cerebellar vermis and hemispheres and flattening of the pons and brain stem [Muntoni & Voit 2004]. Other findings can include partial absence of the corpus callosum, hypoplasia of the pyramidal tracts, and obstructive hydrocephalus requiring a shunt.

WWS, MEB disease, and FCMD were considered separate entities long before their molecular basis was known. When clinically defined, these three disorders did not include milder phenotypes in which the brain MRI was normal or showed less severe cortical or cerebellar malformations. The spectrum of the dystroglycanopathies is now known to include the milder phenotype of limb-girdle muscle muscular dystrophy, with and without cognitive impairment.

Pathogenic variants in a number of genes (*ISPD*, *POMT1*, *POMT2*, *POMGNT1*, *FKTN*, *FKRP*, and *LARGE*) lead to alpha dystroglycan-related muscular dystrophy. The proteins encoded by these genes (which are involved in critical steps in both O-mannosylation and the elaboration of glycan chains on alpha dystroglycan) include:

- Isoprenoid synthase (encoded by *ISPD*) involved early in O-mannosylation;
- Known glycosyltransferases (encoded by *POMT1*, *POMT2*, and *POMGNT1*); and
- Proteins involved in a specific glycan epitope that confers laminin binding (encoded by *FKTN*, *FKRP*, and *LARGE*).

Although "one gene, one syndrome" was initially postulated, it is now known that pathogenic variants in any one of the seven genes results in a broad phenotypic spectrum. The most phenotypic variability is observed with pathogenic variants in *FKTN* and *FKRP,* which result in phenotypes ranging from WWS to CMD, LGMD, elevated creatine kinase (CK), and exercise intolerance without intellectual disability and normal brain MRI. Homozygous and compound heterozygous ISPD pathogenic variants are associated with a severe dystroglycanopathy subtype of CMD with brain and eye involvement (Walker-Warburg phenotype) [Willer et al 2012].

Certain clinical findings can help direct one to the specific gene involved:

- **Microcephaly.** *POMT1* and *POMT2*
- **Macrocephaly and epilepsy.** *POMGNT1*
- **Cardiac involvement.** *FKRP, FKTN, POMT1*

It is unclear at this time if certain central nervous system abnormalities are associated with mutation of specific genes.

Inheritance is autosomal recessive.

**Table 2.**

Findings in the α-Dystroglycanopathies

| Phenotype | Findings | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Motor Function | Eye | Central Nervous System | | | | | Intellectual Disability / Epilepsy |
| | | | Cortex | Cerebellum | Brain Stem | Hydro-cephalus | |
| Walker-Warburg syndrome (WWS) | Absent psychomotor acquisitions | Severe [1] | Cobblestone lissencephaly | Very hypoplastic | Severely hypoplastic | Constant | Severe |
| Muscle-eye-brain (MEB) disease | Ambulation may be acquired | Common [2] | Frontoparietal pachygyria; polymicrogyria | Vermis hypoplasia, cyst, dysplastic | Usually hypoplastic | Common | Severe intellectual disability; refractory epilepsy; behavioral problems |
| Fukuyama CMD (FCMD) | Ambulation may be acquired | Variable / mild | Variable (from normal or only simplification of gyri to severe) | Hypoplasia, cysts, polymicrogyria | Usually normal | Rare | Moderate |
| Intermediate phenotypes (MDC1D, CRB-CMD) | Ambulation may be acquired | Rare / mild | Variable | Variable | Variable | Variable | Mild to moderate |
| CMD with intellectual disability | Ambulation may be acquired | Rare / mild | None | None | None | None | Mild to moderate |
| CMD no intellectual disability (MDC1C) | Ambulation may be acquired | None / mild | None | None | None | None | None |

1. Severe congenital myopia, congenital glaucoma, pallor of the optic discs, and retinal hypoplasia

2. Microphthalmia, retinal detachment, retinal hypoplasia, anterior chamber malformation, cataracts

***SEPN1*-related CMD.** *SEPN1* pathogenic variants were initially described in CMD characterized by selective spinal rigidity and normal expression of the protein merosin (rigid spine muscular dystrophy type 1 [RSMD1]). It is now known that "rigid spine syndrome" is not specific to this subtype of CMD and that some spinal rigidity resulting from paraspinal contractures may develop in other CMD subtypes.

Clinical features tend to be homogeneous: cervicoaxial weakness early in life that may be associated with delay in motor milestones and development of spinal stiffness often associated with thoracic spinal lordosis and a characteristic "S"-shaped thoracic scoliosis. Progressive respiratory insufficiency is aggravated by diaphragmatic weakness. Early

nocturnal hypoventilation prior to adulthood in a person who is still ambulatory is the distinct feature of this CMD subtype.

MRI shows selective involvement of the sartorius and major adductor muscles in the thigh giving a characteristic medial thigh wasting, notable on physical examination.

*SEPN1* pathogenic variants are also reported in the classic form of multiminicore myopathy, in congenital fiber-type disproportion myopathy, and in a desminopathy with Mallory body-like inclusions.

***LMNA*-related CMD (L-CMD)** is part of the spectrum of laminopathies (also known as nuclear envelopathies). L-CMD may present with a severe picture in the first six months of life (absence of head or trunk support) or with progressive loss of head support after acquisition of sitting or walking ability (dropped head syndrome). Often hypotonia and weakness of the axial-cervical muscles is rapidly progressive, followed by more slowly progressive weakness the proximal upper limbs and distal lower limbs. Facial muscles are spared. With time, the characteristic findings are head lag, thoracic and lumbar spinal hyperextension (rigidity), lower limb contractures, and talipes equinovarus but no significant upper limb contractures. Restrictive lung disease resulting in respiratory insufficiency occurs as muscle weakness progresses. Mechanical ventilation may be required before age two years in those more severely affected.

L-CMD can be considered as an early-onset variant of Emery Dreifuss muscular dystrophy (EDMD), without some of the typical early findings of EDMD (elbow contractures and major cardiac complications). Nonetheless, these findings may develop in time.

Genetic testing has identified a number of *de novo* dominant pathogenic variants which have not been found in persons with milder phenotypes of EDMD. Moreover, among the small number of affected individuals identified to date, several share the same pathogenic variant suggesting a possible phenotype-genotype correlation.

### Less Common CMD Subtypes

**Integrin α7 deficient CMD.** This subtype has only been described in three individuals worldwide. Phenotype is variable.

**Integrin alpha 9 deficient CMD.** Recently, a phenotype caused by deficiency in integrin alpha 9 that overlaps with collagen VI-deficient CMD was described in the French-Canadian population in Quebec [Tétreault et al 2006]. Distal hyperlaxity is localized to metacarpal phalanges rather than fingers. Scoliosis of severity may be observed during disease course.

***SYNE1*-related CMD**. CMD with adducted thumbs, intellectual disability, cerebellar hypoplasia, and cataracts caused by a pathogenic variant in *SYNE1*, encoding enaptin (nesprin-1), a nuclear envelope protein [Voit et al 2007]. See *SYNE1*-Related Autosomal Recessive Cerebellar Ataxia.

***CHKB*-related muscle disease (megaconial type CMD).** Homozygous and compound heterozygous *CHKB* pathogenic variants were recently identified in individuals with early-onset muscle wasting, severe intellectual disability, and mitochondrial structural abnormalities in muscle (enlargement of mitochondrial at fiber periphery, depletion of mitochondria at fiber center). Dilated cardiomyopathy and other cardiac anomalies were identified in some affected individuals [Mitsuhashi et al 2011].

### CMD of Unknown Cause

A number of reports describe individuals with a subtype of CMD which does not resemble the known subtypes and/or is not caused by mutation of the genes currently known to be associated with CMD subtypes.

- CMD with cerebellar involvement. Cerebellar abnormalities may include cysts or other signs of cerebellar dysplasia or hypoplasia [Mercuri et al 2006].

- CMD with intellectual disability and normal MRI. Minimal ventricular dilation or minor white matter changes on MRI are observed [Mercuri et al 2009].

- CMD with no intellectual disability and normal MRI [Mercuri et al 2009]
- CMD with intellectual disability, microcephaly, cerebellar hypoplasia, feeding difficulties, and severe myoclonic epilepsy [Messina et al 2009]

## Establishing the Diagnosis of a CMD Subtype

Establishing the specific CMD subtype can help clarify prognosis and inheritance pattern. Establishing the subtype usually involves medical history, family history, physical examination, neurologic examination, eye examination by a pediatric ophthalmologist, measurement of serum CK concentration, neuroimaging, muscle imaging, muscle and/or skin biopsy for histologic examination and immunohistochemistry, and molecular genetic testing.

**Medical history.** In infants medical history focuses on fetal movement, perinatal history and birth size, acquisition of motor milestones, ability to feed, and respiratory complications, such as aspiration because of poor cry and poor cough.

In older children, medical history focuses on cognitive abilities, motor abilities, muscle weakness, disease progression, joint contractures, scoliosis and spinal deformities, nutritional status, signs of respiratory compromise, hospitalizations, and infections.

Information in the medical history that may help identify the specific CMD subtype:

- Central nervous system involvement, psychomotor delay or intellectual disability: dystroglycanopathies; occasionally, laminin alpha-2 deficiency
- Early signs of respiratory insufficiency:
  - Very severe or progressive in the first two years of life: L-CMD; some very hypotonic infants with laminin alpha-2 deficiency
  - Slowly progressive resulting in severe respiratory insufficiency in the first decade:
    - Nonambulatory: laminin alpha-2 deficiency; collagen VI-deficient CMD; L-CMD; dystroglycanopathy
    - Ambulatory: *SEPN1*-related CMD
- Development of orthopedic complications:
  - Diffuse proximal and distal joint contractures and spinal stiffness and/or scoliosis: collagen VI-deficient CMD and laminin alpha-2 deficiency; late-stage L-CMD and dystroglycanopathies
  - Selective involvement of the spine: *SEPN1*-related CMD; early in the course of laminin alpha-2 deficiency in children who are ambulatory; collagen VI-deficient CMD; L-CMD
- The presence of joint deformities, torticollis or hip dislocation at birth: collagen VI-deficient CMD
- Rapidly progressive course with loss of head control: L-CMD (dropped head syndrome)
- Congenital head lag as a result of marked cervicoaxial hypotonia associated with progressive cervical stiffness: *SEPN1*-related CMD

**Family history.** Most of the congenital muscular dystrophies described to date are inherited in an autosomal recessive manner. In the non-consanguineous, small nuclear families typical of the US and Europe, often only one individual in a family with an autosomal recessive disorder is affected. In contrast, most individuals with collagen VI-deficient CMD and all reported individuals with L-CMD have a *de novo* autosomal dominant pathogenic variant and therefore represent simplex cases (i.e., a single occurrence in a family).

Documentation of relevant findings in family members with congenital weakness can be accomplished through review of medical records. It is appropriate to review the medical records and any available tissue samples of sibs of the

proband who have died in the newborn period.

**Physical examination.** Findings that may help with identification of the specific CMD subtype:

- Muscle pseudohypertrophy: dystroglycanopathies

- Diffuse joint contractures: laminin alpha-2 deficiency, collagen VI-deficient CMD

- Distal hyperlaxity: collagen VI-deficient CMD

- Hypertrophic scars or keloid formation: collagen VI-deficient CMD

- Spinal stiffness without limb joint contractures: *SEPN1*-related CMD

- Axial hypotonia and weakness (poor trunk control) preceding spinal stiffness: in early laminin alpha-2 deficiency, L-CMD, and collagen VI-deficient CMD .

- Cardiac involvement: rhythm disturbances in L-CMD; cardiomyopathy in dystroglycanopathies; right heart failure in any CMD subtype if chronic severe respiratory failure is untreated

- Nocturnal hypoventilation or respiratory failure in a person who is ambulatory:*SEPN1*-related CMD; occasionally collagen VI-deficient CMD.

- The type and location of spinal deformity:

  - Thoracic kyphosis: collagen VI-deficient CMD

  - Thoracic lordosis: laminin alpha-2 deficiency, *SEPN1*-related CMD, and L-CMD; late stage of dystroglycanopathies. Lumbar hyperlordosis is frequently seen in all subtypes.

**Neurologic examination.** Findings that may help with identification of the specific CMD subtype:

- Occipital-frontal circumference (OFC): may be abnormal in laminin alpha 2 deficiency (macrocephaly) or in dystroglycanopathies (microcephaly or macrocephaly).

- Muscle pseudohypertrophy (calves and tongue): dystroglycanopathies. Calf pseudohypertrophy may resemble that seen in Duchenne muscular dystrophy

- CNS malformation and abnormal white matter: may be evident as:

  - Pyramidal signs (hyperreflexia, clonus) and cognitive involvement: dystroglycanopathies

  - Seizures easy to control with routine antiepileptic drugs: typical for laminin alpha-2 deficiency

  - Seizures refractory to polytherapy: often in MEB disease, especially those with *POMGNT1* pathogenic variants

  - Intellectual disability associated with marked behavioral disturbances: suggestive of MEB disease, especially those with *POMGNT1* pathogenic variants

**Eye examination by a pediatric ophthalmologist.** Eye examinations are recommended in the presence of signs or symptoms of ocular involvement or if dystroglycanopathy is suspected.

**Serum CK concentration.** In general CMD subtypes with no abnormality in merosin expression (collagen VI-deficient CMD, *SEPN1*-related CMD, L-CMD) show normal or mildly increased serum concentration of CK, while those with primary merosin deficiency (laminin alpha-2 deficiency) or secondary merosin deficiency (dystroglycanopathies) have high serum concentration of CK (>4x normal values). (See Table 3.)

**Neuroimaging.** MRI can be used to guide diagnosis. The two CMD subtypes with brain abnormalities visualized on MRI are laminin alpha-2 deficiency and the dystroglycanopathies.

- In laminin alpha-2 deficiency abnormal white matter signal after age six months helps establish the diagnosis. White matter changes do not regress with time.

- In the dystroglycanopathies, structural changes (including hydrocephalus, brain stem hypoplasia, cerebellar cysts) or abnormalities in neuronal migration (lissencephaly or polymicrogyria) are common [Kirschner & Bönnemann 2004]. White matter changes may regress with time [Louhichi et al 2004].

**Muscle imaging.** Distinct recognizable patterns on muscle MRI in persons with spinal rigidity, normal merosin staining of skin or muscle biopsy, and normal serum CK concentrations can help distinguish between collagen VI-deficient CMD, *SEPN1*-related CMD, and L-CMD and between the CMDs and the overlapping phenotypes considered in the differential diagnosis that are caused by pathogenic variants in *RYR1*, *GAA* (encoding acid maltase) or *DNM2* (see Differential Diagnosis).

**Molecular genetic testing.** With the expanding role of molecular genetic testing in confirming the diagnosis of a CMD subtype, the trend recently has been to perform molecular genetic testing without muscle biopsy when the medical history, physical examination, and neurologic examination support the diagnosis of a CMD. For example, in the past the evaluation of an infant with head lag, hypotonia, and brain white matter abnormalities on MRI who is suspected of having laminin alpha-2 deficiency may have been to perform a skin biopsy first to demonstrate merosin deficiency followed by *LAMA2* molecular genetic testing. However, currently the evaluation may proceed directly to molecular genetic testing (without skin biopsy) depending on the level of suspicion, the exclusion of other more common diagnoses, and the confidence of the neurologist in the diagnosis.

In contrast, when multiple genes may need to be tested, as in the confirmation of the diagnosis of a dystroglycanopathy, performing immunohistochemical analysis of a muscle biopsy may identify the subtype prior to proceeding with molecular genetic testing.

**To establish/confirm the diagnosis of a CMD subtype in a proband using molecular genetic testing**

- **Alternative 1.** Sequential molecular genetic testing. In some, but not all, instances the clinical examination may assist in prioritizing the order in which genes are tested.

- **Alternative 2.** Multi-gene testing. Consider using a multi-gene congenital muscular dystrophy panel that includes a number of genes associated with CMD.
  Note: The panels vary by methods used and genes included; thus, the ability of a panel to detect a causative pathogenic variant(s) in any given individual with CMD also varies.

Once the pathogenic variants in an autosomal recessive disorder or the pathogenic variant in an autosomal dominant disorder is identified, molecular genetic testing of the parents is needed to clarify mode of inheritance and to provide accurate recurrence risk information to family members [Allamand et al 2010]. It is always necessary to determine if the proband has two autosomal recessive variants (one inherited from each parent) or if the proband has a *de novo* autosomal dominant variant that is not present in either parent (if they are not affected).

**Muscle histology** typically shows a dystrophic or myopathic nonspecific pattern that does not suggest a congenital myopathy, mitochondrial disorder, or denervating disorder (Table 3). The most significant dystrophic features are fiber size variability, presence of increased endomysial fibrosis, and variably necrotic and/or regenerative fibers. In some individuals with CMD, muscle biopsy may only show fiber size variation with absence of or only mild manifestations of fibrosis, necrosis, or regeneration [Wang et al 2010].

A muscle biopsy may be indicated if the diagnosis based on clinical examination remains unclear or molecular genetic testing does not confirm a diagnosis.

**Immunohistochemical staining** of muscle and/or skin can in some instances confirm protein deficiencies that can establish or exclude the diagnosis of a CMD subtype or help guide confirmatory molecular genetic testing. Immunostaining of muscle can detect deficiencies of the proteins laminin alpha-2 (merosin), collagen VI, and alpha

dystroglycan (Table 3); immunostaining of skin can detect deficiencies of laminin alpha-2 and collagen VI. Immunostaining is not diagnostic or specific in *SEPN1*-related CMD or L-CMD.

When testing for presence of large proteins in muscle (e.g., laminin alpha-2) it may be necessary to use more than one antibody in order to detect partial deficiencies. Partial merosin deficiency may be primary (i.e., caused by mutation of *LAMA2*, encoding laminin alpha-2) or secondary (i.e., caused by mutation of one of the genes associated with the dystroglycanopathies).

**Table 3.**

Serum CK Concentration and Muscle Biopsy Findings in the Congenital Muscular Dystrophies Discussed in Table 1

| Disorder | Serum CK Concentration [1] | Muscle Biopsy | |
|---|---|---|---|
| | | Histology | Immunohistochemistry |
| **Defects of structural protein** | | | |
| Laminin alpha-2 deficiency (MDC1A) | Variable CK from mildly elevated to markedly elevated (before muscle wasting is severe) | Neonatal: myopathic or dystrophic with or without inflammatory changes | Merosin: partial or total deficiency [2]<br>Laminin alpha-5: overexpression |
| | | End stage: dystrophic changes | |
| Collagen VI-deficient CMD | Normal or mildly elevated (~2-3x normal) | Fiber size variation | Collagen VI:<br>• Variable reduction in muscle<br>• Abnormal secretion in fibroblast culture<br>• Deficiency difficult to detect if partial [3] |
| | | Variable necrotic or regenerative fibers | |
| | | Variable endomysial fibrosis | |
| **Defects of glycosylation** | | | |
| Dystroglycanopathies | Elevated: 2-15x normal | Myopathic or dystrophic | Merosin: normal or reduced<br>Glycosylated alpha dystroglycan: deficient<br>Beta dystroglycan: normal |
| **Defects of proteins of the endoplasmic reticulum** | | | |
| *SEPN*-related CMD | Normal | Variable fiber size | Merosin and collagen VI: normal |
| | | Occasional necrotic fibers | |
| | | Minimally increased endomysial connective tissue | |
| **Defects of nuclear envelope proteins** | | | |
| L-CMD | 2-5x normal | Dystrophic changes (deltoid> quadriceps) | Merosin: normal<br>Alpha-dystroglycan: possible secondary abnormal expression |
| | | Nonspecific myopathic changes (quadriceps) | |
| | | Markedly atrophic fibers, most often type 1, occasional positive inflammatory markers | |

1. Normal serum CK concentration = 35-160 µ/L (may vary slightly in different laboratories)

2. Ideally using antibodies recognizing different regions of the protein

3. May need co-staining with merosin, perlecan, or other proteins to demonstrate abnormal sarcolemmal staining of collagen VI

## Differential Diagnosis of CMD

Congenital muscular dystrophies are distinguished from other conditions in which muscle disease, anterior horn cell disease, and/or central nervous system involvement produce muscle weakness and low muscle tone [Klein et al 2008].

- **Congenital myopathies** (including X-linked myotubular myopathy, central core disease, centronuclear myopathy, and nemaline myopathy) typically have normal or near-normal serum CK concentration and histologic evidence on muscle biopsy of developmental/structural muscle changes rather than dystrophic changes. The prognosis depends on the severity of presentation, which can range from fetal akinesia or congenital floppy infant syndrome requiring mechanical ventilation to later-onset milder symptoms. Affected individuals do not develop significant joint contractures and the motor impairment is stable or may even slowly improve, although spinal deformities and respiratory complications may be severe or progressive. Severe facial or oculomotor weakness seen in certain congenital myopathies is not found in the early stages of CMD, but may occur in the late stages of the subtypes laminin alpha-2 deficiency and the dystroglycanopathies. Congenital myopathy caused by mutation of *RYR1* can be a phenotypic mimic of several conditions, including *SEPN1*-related CMD with a clinical picture of multiminicore myopathy or a CMD-like presentation, with early onset hypotonia, axial weakness, and respiratory insufficiency.

- **Limb-girdle muscular dystrophy (LGMD).** The disease spectrum within the dystroglycanopathies ranges from congenital onset with CNS and eye involvement, to congenital onset without eye involvement and mild development delay, to a later-onset muscle weakness or limb-girdle muscular dystrophy (LGMD) with or without intellectual disability. Pathogenic variants in any of the six dystroglycanopathy-associated genes can result in CMD or LGMD. Similarly, the collagen VI-deficient myopathies range from Ullrich CMD to Bethlem myopathy, which is considered a LGMD.

- **Myotonic dystrophy type 1 (DM1)** is a multisystem disorder that affects skeletal muscle and smooth muscle as well as the eye, heart, endocrine system, and central nervous system; it spans the continuum from mild to severe. Congenital DM1 is the severe early-onset form, characterized by hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death; intellectual disability is common. Diagnosis is based on detection of an expansion of the GTC trinucleotide repeat in *DMPK*. Inheritance is autosomal dominant.

- **Pompe disease (glycogen storage disease type II, GSD2, acid maltase deficiency)** in the infantile form presents within the first months of life with hypotonia, head lag, and marked cardiomegaly. Respiratory insufficiency in the first year can lead to frequent pulmonary infections. Additional features include moderate hepatomegaly and macroglossia. Diagnosis is confirmed through identification of pathogenic variants in *GAA*, the gene encoding alpha-glucosidase (GAA), or by measuring deficient serum GAA enzyme (also called acid maltase) activity.

  A later-onset presentation of GSD2 may include non-progressive or slowly progressive proximal muscle weakness and spinal stiffness without major limb contractures. Progressive respiratory failure results from diaphragmatic failure. This clinical picture may overlap with other congenital muscular dystrophies associated with rigid spine syndrome and particularly *SEPN1*-related CMD.

- **Congenital onset of facioscapulohumoral muscular dystrophy (FSHD)** is characterized by congenital facial diplegia, congenital deafness, intellectual disability, and seizures. Most children become wheelchair users in childhood. Facial weakness is the earliest and most prominent sign, distinguishing FSHD from CMD: the infant is unable to smile and has little or no facial expression. Infantile FSHD may be inherited as a *de novo* pathogenic variant or in autosomal dominant fashion. FSHD is diagnosed by a molecular genetic test that identifies deletion

of integral copies of a 3.3-kb DNA repeat motif, D4Z4, which is located in the subtelomeric region of chromosome 4q35.

- **Mitochondrial myopathies** may have overlapping phenotypes and are often associated with oculo-facial involvement and variability in weakness and fatigability, as in the myasthenic syndromes. Central nervous system involvement is also observed in many mitochondrial myopathies. Overall, the diagnosis is based in specific histologic, biochemical, and molecular genetic testing.

- **Spinal muscular atrophy (SMA)** is characterized by progressive degeneration and loss of the anterior horn cells in the spinal cord, and sometimes in the brain stem nuclei, resulting in muscle weakness and atrophy. The onset of weakness ranges from before birth to adolescence or young adulthood. The weakness is progressive. Onset before age six months is designated SMA1. Diagnosis is based on molecular genetic testing of *SMN1* and *SMN2*, the two genes known to be associated with SMA. Inheritance is autosomal recessive.

- **Prader-Willi syndrome (PWS)** is characterized by severe hypotonia and feeding difficulties in early infancy, followed in later infancy by excessive eating and gradual development of morbid obesity unless externally controlled. Individuals with PWS have some degree of intellectual disability and a distinctive behavioral phenotype. Hypogonadism is present in both males and females. The methylation-specific pattern of the PWS/AS region of chromosome 15q11 establishes the diagnosis in more than 99% of individuals.

- **Marinesco-Sjögren syndrome (MSS)** presents with cerebellar ataxia with cerebellar atrophy, early-onset cataracts, mild to severe intellectual disability, hypotonia, and muscle weakness. Initial hypotonia is followed by evidence of cerebellar involvement with truncal ataxia, dysdiadochokinesia, and dysarthria. Serum CK is two to four times normal. Diagnosis is confirmed by clinical picture, brain MRI cerebellar findings, electron microscopic changes (autophagic vacuoles, membranous whorls, and electron-dense double membrane structures associated with nuclei) on muscle biopsy, and molecular genetic testing of *SIL1*, the only gene known to be associated with MSS. Inheritance is autosomal recessive.

- **Congenital myasthenic syndromes (CMS)** are a group of diseases with pathogenic variants in genes that are implicated in the neuromuscular junction leading to weakness and fatigability and often respiratory and feeding complications. Arthrogryposis; club feet resulting from fetal immobility; bulbar, oculomotor, or facial involvement; diurnal variability of performance; and unexpected rapid failure in motor, respiratory, and/or feeding functions are typical clinical findings but are not always present. Electrophysiologic studies specific for the neuromuscular junction (EMG with repetitive stimulation, stimulated single fiber) may identify abnormal neuromuscular transmission but are often difficult and require expertise.

**Rigid spine.** Included in the differential diagnosis of early-onset muscle disease associated with rigid spine are the following disorders:

- **Central core disease** and **multiminicore disease,** caused by pathogenic variants in *RYR1*, the gene encoding skeletal muscle ryanodine receptor

- Centronuclear myopathy (*DNM2*-related CNM) caused by pathogenic variants in *DNM2*, the gene encoding dynamin 2

- **Pompe disease (glycogen storage disease type II) (GSD2)** also known as acid maltase deficiency

## Prevalence of CMD

The incidence and prevalence of CMD in populations are not well documented because of limited molecular genetic confirmation of the diagnosis and use of different diagnostic classification systems in the past.

The incidence of all forms of congenital muscular dystrophies has been estimated at 1:21,500 with a prevalence of 1:125,000 in northeastern Italy [Mostacciuolo et al 1996] and an incidence of 1:16,000 in western Sweden [Darin et al 2002].

The point prevalence (i.e., the total number of cases of a specific disease in existence in a given population at a specific point in time) ranges from 0.68 to 2.5 per 100,000. The failure to diagnosis primary muscle disease in individuals with mild muscle weakness with and without intellectual disability may continue to result in underestimation of the prevalence of CMD [Peat et al 2008, Mercuri et al 2009, Norwood et al 2009].

In addition, the relative frequency of CMD subtypes varies in different populations. For example, in Japan the most commonly diagnosed CMD subtype is Fukuyama CMD caused by a founder variant in *FKTN* (the gene encoding fukutin), followed by collagen VI-deficient CMD [Okada et al 2007]. In contrast, *FKTN* pathogenic variants are rare in other populations.

Laminin alpha-2 deficiency and collagen VI-deficient CMDs are the most common subtypes in many countries with populations of European origin.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.*

### Mode of Inheritance

The congenital muscular dystrophies are inherited in an autosomal recessive manner with the exception of collagen VI-deficient CMD, which can be inherited in an autosomal dominant or autosomal recessive manner [Pan et al 2003], and *LNMA*-related CMD (L-CMD), which has only been reported in persons with a *de novo* dominant pathogenic variant [Quijano-Roy et al 2008].

### Risk to Family Members — Autosomal Recessive CMD

**Parents of a proband**

- The parents of an affected child are obligate heterozygotes and therefore carry a single copy of a pathogenic variant.

- Heterozygotes (carriers) are asymptomatic.

**Sibs of a proband**

- 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.

- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.

- Heterozygotes (carriers) are asymptomatic.

**Offspring of a proband**

- If individuals with autosomal recessive congenital muscular dystrophy reproduce, all of the offspring are obligate carriers.

- Because the general population carrier frequency is low, the risk to offspring of an individual with autosomal recessive CMD of being affected is greater than the risk to the general population but less than 1%.

**Other family members of a proband.** Each sib of an obligate carrier for autosomal recessive CMD is at a 50% risk of being a carrier.

### Carrier Detection

Carrier detection using molecular genetic techniques is possible if the pathogenic variants in the family are known.

### Risk to Family Members —Autosomal Dominant CMD

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents: if the pathogenic variant found in the proband cannot be 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.

**Offspring of a proband.** Each child of an individual with a dominantly inherited CMD has a 50% chance of inheriting the pathogenic variant.

### Related Genetic Counseling Issues

**Family planning.** The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

**Muscle biopsy banking.** Future research and diagnostic studies may be performed on muscle tissue that has been flash frozen. Banking tissue or storing leftover samples from a diagnostic biopsy may be worthwhile for future studies.

**DNA banking** is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

A CMD BioBank, part of the NIGMS repository at Coriell Medical Institute, offers DNA banking as well as banking or cell lines.

### Prenatal Testing and Preimplantation Genetic Diagnosis

**Molecular genetic testing.** Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing and preimplantation genetic diagnosis for a pregnancy at increased risk for CMD are possible options.

**Biochemical testing.** Prenatal testing for pregnancies at 25% risk for laminin alpha-2 deficiency is possible provided that immunostaining has documented complete merosin deficiency in the muscle of an affected sib who has typical clinical findings. This method may be most useful when only one *LAMA2* pathogenic variant has been identified on molecular genetic testing. Immunostaining must be done on flash-frozen chorionic villi (obtained at 10-12 weeks' gestation). In 70 prenatal cases, concordance between immunostaining of chorionic villi and linkage analysis for the *LAMA2* locus was 100%, suggesting that immunostaining on CVS is both accurate and sensitive [Vainzof et al 2005].

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **Cure CMD**
  PO Box 701
  Olathe KS 66051
  **Phone:** 866-400-3626
  **Email:** info@curecmd.com
  www.curecmd.org

- **European Neuromuscular Centre (ENMC)**
  Lt Gen van Heutszlaan 6
  3743 JN Baarn
  Netherlands
  **Phone:** 31 35 5480481
  **Fax:** 31 35 5480499
  **Email:** enmc@enmc.org
  www.enmc.org

- **Muscular Dystrophy Association - USA (MDA)**
  222 South Riverside Plaza
  Suite 1500
  Chicago IL 60606
  **Phone:** 800-572-1717
  **Email:** mda@mdausa.org
  www.mda.org

- **Muscular Dystrophy Campaign**
  61A Great Suffolk Street
  London SE1 0BU
  United Kingdom
  **Phone:** 0800 652 6352 (toll-free); 020 7803 4800
  **Email:** info@muscular-dystrophy.org
  www.muscular-dystrophy.org

- **Congenital Muscle Disease International Registry (CMDIR)**
  *The CMD International Registry is a patient self-report registry with the goal to register the global congenital muscle disease population which includes congenital myopathy and congenital muscular dystrophy.*
  1712 Pelican Avenue
  San Pedro CA 90732
  **Phone:** 800-363-2630
  **Fax:** 310-872-5374
  **Email:** counselor@cmdir.org
  www.cmdir.org

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with congenital muscular dystrophy, the following evaluations are recommended:

- Neurologic examination

- Assessment of respiratory function with baseline pulmonary function tests, including forced vital capacity (FVC) in sitting and supine positions and blood gas exchange

- Polysomnography to identify individuals with nocturnal hypoventilation, to evaluate individuals with symptoms of hypercapnea (daytime headache, restless sleep, loss of concentration), and to evaluate individuals with reduced forced vital capacity, particularly those with CMD subtypes associated with a rigid spine, axial weakness, and/or signs of diaphragmatic weakness (detected by a drop in FVC from sitting to supine). Additional indications for polysomnography include testing in the very young or those with developmental delay in whom reliable, consistent pulmonary function testing can be difficult to obtain.

Sleep-disordered breathing can be seen with FVC of less than 60%, while nocturnal hypoventilation correlates with FVC of less than 40% [Wallgren-Pettersson et al 2004, Shahrizaila et al 2006]. Independent of the FVC values, a very high suspicion for nocturnal hypoventilation must be maintained in those with *SEPN1*-related CMD to avoid a life-threatening respiratory failure.

- Radiologic examinations if spinal deformity is observed. Assessment of spine and joint deformities by physiatrists and orthopedists

- Feeding and nutritional assessment, weight and height measurement, serum vitamin D concentration and calculation of body mass index (BMI)

- Assessment of strength and joint contractures by an occupational therapist and physical therapist

- Assessment of cardiac function in those with a dystroglycanopathy or L-CMD, with particular awareness that cardiomyopathy and/or arrhythmia can occur in the absence of severe muscle disease

- Evaluation for pulmonary hypertension and/or secondary right heart failure in those with significant respiratory involvement (mechanical ventilation, severe respiratory failure)

- Complete eye examination in those with a dystroglycanopathy or if clinically indicated

## Treatment of Manifestations

No definitive treatments exist for the congenital muscular dystrophies; however, multidisciplinary medical care improves quality of life and longevity. Management should be tailored to each individual, their specific CMD subtype, and rate of progression.

Respiratory therapy and use of respiratory aids including assisted cough and hyperinsufflation devices, Percussionaire®, noninvasive ventilatory support, or mechanical ventilation via tracheostomy are appropriate for those with respiratory insufficiency [Wallgren-Pettersson et al 2004].

Physical therapy and stretching exercises help promote mobility and prevent contractures. Mechanical assistive devices including canes, walkers, orthotics, and wheelchairs can be used as needed to help ambulation and mobility. Posture in vertical, sitting, and supine positions has to be evaluated and assisted if necessary as improved posture may positively affect chest expansion.

Surgical intervention may be needed for orthopedic complications such as foot deformity, joint contractures, and scoliosis. Pros and cons of surgery for hip dislocation or joint contractures need to be considered given that any functional benefit may be insignificant compared to the high risk of pain and rapid relapse. Proactive trunk bracing (plexidur Garchois brace) is used in some countries to reduce the degree of deformity and to slow the progression of scoliosis in order to delay consideration of surgical intervention until puberty [Quijano-Roy et al 2010].

Speech therapy may be indicated.

Close attention to oral hygiene is indicated.

Assistance in education (school technical aide) and social and emotional support and stimulation can improve the sense of social involvement and productivity and can reduce the sense of social isolation common in those with CMD [Eggers & Zatz 1998].

Steroid treatment using dosages based upon guidelines used in the treatment of Duchenne muscular dystrophy has been reported in the dystroglycanopathies. In those who respond, the use of steroids appears to support prolonged ambulation [Godfrey et al 2006].

## Prevention of Secondary Complications

The following are appropriate:

- Stretching exercises to prevent contractures

- Positive-pressure hyperinsufflation pulmonary exercises to enhance thoracic growth and reduce thoracic cage rigidity and contractures

- Medications such as laxatives to prevent constipation, medication for gastroesophageal reflux (GER), and oral caloric supplements as required

- Trunk bracing in those with severe axial or cervical hypotonia with spinal collapse to prevent severe spinal deformities and to allow a stable and comfortable position when sitting or standing (during use of an upright stander). Of note, when such bracing is used, pulmonary assessment is needed to monitor for evidence of secondary respiratory compromise or complications.

## Surveillance

Surveillance includes the following:

- Monitoring of respiratory function using pulmonary function testing or spirometry with measurements in sitting and supine positions to detect diaphragmatic involvement that increases the risk of nocturnal hypoventilation. When the forced vital capacity in the supine position is less than 60% of normal values, respiratory function should be monitored by pulse oximetry and/or arterial blood gases and, where available, polysomnography.

- Clinical examination and x-rays as needed to monitor for orthopedic complications such as foot deformity, joint contractures, and spinal deformity (scoliosis, thoracic lordosis or kyphosis, lumbar hyperlordosis)

- Monitoring of cardiac function every six to 12 months (by echocardiography, ECG, 24-hour Holter-ECG recording) in those individuals with respiratory insufficiency with or without mechanical ventilation and/or CMD subtypes prone to cardiomyopathy (L-CMD, dystroglycanopathies) and cardiac rhythm disturbances (L-CMD)

- Monitoring of neurologic function and EEG in those with CMD subtypes associated with seizures or if clinically indicated

- Routine complete eye examinations in those with dystroglycanopathies to monitor for changes in vision and/or changes that suggest development of cataracts and/or evidence of retinal detachment

Note: In those with laminin alpha-2 deficiency the white matter changes do not require follow-up brain MRI.

## Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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## Suggested Reading

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## Chapter Notes

### Author History

Erynn Gordon, MS, CGC (2003-present)
Amy Harper, MD (2011-present)
Eric P Hoffman, PhD (2001-present)
Elena Pegoraro, MD, PhD (2001-present)
Susana Quijano-Roy, MD, PhD (2011-present)
Anne Rutkowski, MD (2011-present)
Cheryl Scacheri, MS; GeneDx, Inc (2001-2003)
Susan Sparks, MD, PhD (2011-present)

### Revision History

- 23 August 2012 (cd) Revision: sequence analysis for *ISPD* mutations available clinically

- 24 May 2012 (cd) Revision: sequence analysis for *CHKB* mutations and multi-gene CMD panels available clinically

- 4 January 2011 (me) Comprehensive update posted live

- 22 December 2006 (cd) Revision: clinical testing, carrier testing, and prenatal testing available for CMD with early spine rigidity; clinical testing and carrier testing available for CMD with merosin deficiency

- 13 January 2006 (me) Comprehensive update posted to live Web site

- 25 March 2005 (cd) Revision: Clinical testing available for MDC1D

- 26 July 2004 (eh) Revision: Bethlem and Ullrich CMD

- 2 January 2004 (cd) Revision: test availability

- 22 September 2003 (cd) Revision: test availability, prenatal testing

- 19 June 2003 (ca) Comprehensive update posted to live Web site

- 22 January 2001 (me) Overview posted to live Web site

- 20 April 2000 (eh) Original submission