Evidence-based guideline summary: Evaluation, diagnosis, and management of congenital muscular dystrophy


ABSTRACT

Objective: To delineate optimal diagnostic and therapeutic approaches to congenital muscular dystrophy (CMD) through a systematic review and analysis of the currently available literature.

Methods: Relevant, peer-reviewed research articles were identified using a literature search of the MEDLINE, EMBASE, and Scopus databases. Diagnostic and therapeutic data from these articles were extracted and analyzed in accordance with the American Academy of Neurology classification of evidence schemes for diagnostic, prognostic, and therapeutic studies. Recommendations were linked to the strength of the evidence, other related literature, and general principles of care.

Results: The geographic and ethnic backgrounds, clinical features, brain imaging studies, muscle imaging studies, and muscle biopsies of children with suspected CMD help predict subtype-specific diagnoses. Genetic testing can confirm some subtype-specific diagnoses, but not all causative genes for CMD have been described. Seizures and respiratory complications occur in specific subtypes. There is insufficient evidence to determine the efficacy of various treatment interventions to optimize respiratory, orthopedic, and nutritional outcomes, and more data are needed regarding complications.

Recommendations: Multidisciplinary care by experienced teams is important for diagnosing and promoting the health of children with CMD. Accurate assessment of clinical presentations and genetic data will help in identifying the correct subtype-specific diagnosis in many cases. Multiorgan system complications occur frequently; surveillance and prompt interventions are likely to be beneficial for affected children. More research is needed to fill gaps in knowledge regarding this category of muscular dystrophies. Neurology® 2015;84:1369–1378

GLOSSARY

AAN = American Academy of Neurology; AANEM = American Association of Neuromuscular & Electrodiagnostic Medicine; B3GALNT2 = β-1,3-N-acetylglactosaminyltransferase 2; B3GNT1 = β-1,3-N-acetylglactosaminyltransferase 1; CK = creatine kinase; CMD = congenital muscular dystrophy; COL6A1 = collagen 6α1; COL6A2 = collagen 6α2; COL6A3 = collagen 6α3; DAG1 = α-dystroglycan; FKTN = fukutin; GMPPB = GDP-mannose pyrophosphorylase B; LAMA2 = laminin α2; LMNA = lamin A/C; MD = muscular dystrophy; MDC = merosin-deficient congenital muscular dystrophy; SEPN1 = selenoprotein 1; SGK196 = protein-0-mannose kinase; TMEM5 = TMEM5.

This document summarizes extensive information provided in the complete guideline, available as a data supplement on the Neurology® Web site at Neurology.org. Tables e-1 and e-2 and appendices e-1 through e-9, cited in the full guideline (data supplement), as well as references c1–c95, cited in this summary, are available at Neurology.org. The systematic review and practice recommendations were developed according to the processes described in the 2004 and 2011 American Academy of Neurology® Web site at Neurology.org.
Neurology guideline development process manuals. The principal audience for this guideline is clinicians caring for patients with congenital muscular dystrophies (CMDs).

The CMDs are a group of rare muscular dystrophies (MDs) that have traditionally been defined as having symptom onset at birth. CMDs are distinct from congenital myopathies, which are characterized by different pathologic features and genetic etiologies. Epidemiologic data are sparse. The prevalence has been reported to be 6.8 × 10−8 in 1993 in northeast Italy and 2.5 × 10−5 among children aged 16 years and younger in western Sweden, data which suggest that at least in European populations, the prevalence is likely to be in the range of 1 in 100,000 people.

Due in part to recent genetic advances, a broader phenotypic spectrum is now recognized for CMD, and the exact age at onset may be difficult to define in some cases, especially for the milder variants. Thus, MDs with onset in the first 2 years of life, especially during infancy (the first year of life), are now commonly considered to be CMDs. One lingering nosologic question is whether a later-onset disease that is allelic to a CMD should be classified as a CMD or a different disease.

Three major categories of CMDs are commonly recognized, each of which has distinct, well-described phenotypic features: (1) collagenopathies (also known as collagen VI–related myopathies), including Ullrich CMD and Bethlem myopathy; (2) merosinopathies (also known as merosin-deficient CMDs [MDCs], laminin α2 [LAMA2]–related CMDs, and MDC1A); and (3) dystroglycanopathies (also known as α-dystroglycan–related MDs), including Fukuyama CMD, muscle–eye–brain disease, and Walker–Warburg syndrome.

Other rare CMDs do not fit into any of the classic categories. Tables 1 and 2 list these CMDs with their associated genes and clinical phenotypes. More recently, several other genes have been associated with CMDs, including GTDC2, TMEM5, B3GALT2, SGLK196, B3GNT1, GMPRB, and DAG1.

Whereas the genetic, pathophysiologic, and pathologic features of the CMDs have become better understood in recent decades, optimal diagnostic and therapeutic approaches remain unclear. However, a recently published set of algorithms will help with the diagnostic process for patients with suspected CMD.

**ANALYSIS OF EVIDENCE** To inform recommendations for the diagnosis, management, and treatment of CMD, the authors performed systematic reviews to answer the questions presented below.

For children with suspected CMD, how accurately do the (a) geographic location and ethnicity, (b) clinical features, (c) brain imaging findings, (d) muscle imaging findings, and (e) muscle biopsy findings predict the subtype-specific diagnosis? 

**Geographic location and ethnicity.** One Class I study, 4 Class II studies, and 1 Class III study demonstrated that in children with suspected CMD, founder mutations lead to clusters of certain mutations in the Japanese (Fukuyama CMD), Korean (Fukuyama CMD), Ashkenazi Jewish (Walker–Warburg syndrome), and Turkish (A200P haplotype in the POMT1 gene) populations. Other founder mutations likely exist. Thus, the geographic and ethnic background of children with suspected CMD may help predict the specific subtype when information is available for the population of interest.

**Clinical features.** Progressive skeletal muscle weakness and hypotonia are the cardinal clinical manifestations of the CMDs. Serum creatine kinase (CK) levels are typically but not invariably elevated. One Class II study and 1 Class III study demonstrated that distal joint hyperlaxity, congenital hypotonia, and joint contractures are characteristic clinical features associated with collagenopathy. One Class II study showed that the classic clinical findings of congenital hypotonia, distal joint hyperlaxity, and elevated serum CK levels, and white matter signal abnormalities on brain MRI predict the merosinopathy subtype. One Class II study and 3 Class III studies provided evidence that classic patterns of muscle weakness, structural eye abnormalities, and cortical brain abnormalities (this last often associated with migrational defects) characteristic of dystroglycanopathies are often predictive of mutations in known genes for those syndromes. A Class III study found that L-CMD (LMNA–associated CMD) is strongly associated with neck extensor weakness. Thus, in children with suspected CMD, clinical features may predict subtype-specific diagnoses and may in some cases predict the causative genes.

**Brain imaging findings.** Two Class II studies and 1 Class III study demonstrated that abnormal findings on brain imaging studies can predict the subtype-specific diagnosis in some cases, especially in merosinopathy (white matter abnormalities) and some dystroglycanopathies (polymicrogyria, white matter lesions, pontine hypoplasia, and subcortical cerebellar cysts).

**Muscle imaging.** Three Class I articles and 1 Class II article provided evidence that skeletal muscle imaging in children with suspected CMD using MRI, ultrasound, and CT often demonstrates signal abnormalities that suggest subtype-specific diagnoses. This has been most extensively documented in CMD subtypes associated with rigidity of the spine, such as collagenopathies and SEPN1–related myopathy.
Muscle biopsy findings. CMDs share characteristic muscle biopsy findings with other MDs, including necrosis, regenerating fibers, fiber size variability, and increased perimysial and endomysial connective tissue. Three Class II\textsuperscript{20,21,38} and 3 Class III\textsuperscript{39,40,e1} articles demonstrated that immunohistochemistry can identify the presence of a merosinopathy (LAMA\textsubscript{2}) or dystroglycanopathy. Evidence is insufficient to determine the capability of muscle biopsies to identify collagenopathies.

How often does genetic testing confirm a diagnosis of CMD? CMDs are often autosomal recessive, but some cases have been found to follow autosomal dominant patterns, by direct inheritance, spontaneous mutations, or mosaicism. The genetic origins of many cases of CMD have been discovered.\textsuperscript{e2} However, many affected individuals remain without a genetic diagnosis, an indicator that novel disease genes have yet to be identified. Clinical genetic testing is available for virtually all genes known to be associated with CMD.

Table 1  The congenital muscular dystrophies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene symbol</th>
<th>Protein</th>
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</thead>
<tbody>
<tr>
<td>Collagenopathies: autosomal recessive and autosomal dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ullrich congenital MD</td>
<td>COL6A\textsubscript{1}\textsuperscript{e15,e79}</td>
<td>Collagen 6\textsubscript{a}1</td>
</tr>
<tr>
<td></td>
<td>COL6A\textsubscript{2}\textsuperscript{e12}</td>
<td>Collagen 6\textsubscript{a}2</td>
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<td></td>
<td>COL6A\textsubscript{3}\textsuperscript{e80}</td>
<td>Collagen 6\textsubscript{a}3</td>
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<td>Bethlem myopathy</td>
<td>COL6A\textsubscript{1}\textsuperscript{e81}</td>
<td>Collagen 6\textsubscript{a}1</td>
</tr>
<tr>
<td></td>
<td>COL6A\textsubscript{2}\textsuperscript{e81}</td>
<td>Collagen 6\textsubscript{a}2</td>
</tr>
<tr>
<td></td>
<td>COL6A\textsubscript{3}\textsuperscript{e82}</td>
<td>Collagen 6\textsubscript{a}3</td>
</tr>
<tr>
<td>Merosinopathy: autosomal recessive</td>
<td>LAMA\textsubscript{2}\textsuperscript{e20}</td>
<td>Merosin</td>
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<td>Merosin-deficient CMD</td>
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<td></td>
</tr>
<tr>
<td>Dystroglycanopathies: autosomal recessive</td>
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<td></td>
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<tr>
<td>Fukuyama CMD</td>
<td>FKTN\textsuperscript{e19}</td>
<td>Fukutin</td>
</tr>
<tr>
<td>Muscle-eye-brain disease</td>
<td>POMGnT1\textsuperscript{e27,e40,e63}</td>
<td>POMGnT1</td>
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<td></td>
<td>FKBP\textsuperscript{e44}</td>
<td>Fukutin-related protein</td>
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<td>POMT2\textsuperscript{e20,e85}</td>
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</tr>
<tr>
<td>Walker–Warburg syndrome</td>
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<td>α-Dystroglycan</td>
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<td>B3GALT2\textsuperscript{e12}</td>
<td>β-1,3-N-acetylgalactosaminyltransferase 2</td>
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<tr>
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<td>GMPPB\textsuperscript{e15}</td>
<td>GDP-mannose pyrophosphorylase B</td>
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<td>Unclassified CMDs</td>
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<td></td>
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<td>Rigid spine syndrome</td>
<td>SEPN1\textsuperscript{e92}</td>
<td>Selenoprotein N, 1</td>
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<tr>
<td>Multiminicore disease</td>
<td>SEPN1\textsuperscript{e94}</td>
<td>Selenoprotein N, 1</td>
</tr>
<tr>
<td>L-CMD</td>
<td>LMNA\textsuperscript{e46}</td>
<td>Lamin A/C</td>
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Abbreviations: CMD = congenital muscular dystrophy; L-CMD = LMNA-associated CMD; MD = muscular dystrophy. See www.musclegenetable.fr for current information.
Our systematic review identified 2 Class III studies\textsuperscript{3,4} that found that the mutation detection rate for CMDs in general ranges from 20% to 46%.

In children with collagenopathy (Ullrich CMD or Bethlem myopathy), 1 Class II study\textsuperscript{5,6} and 7 small Class III studies\textsuperscript{6,7,8,9,10} indicate that COL6A1, COL6A2, and COL6A3 genetic testing possibly has a high likelihood of detecting causative mutations.

Two large Class III studies\textsuperscript{11,12} provided evidence that in children with complete merosin deficiency on muscle biopsy, LAMA2 genetic testing has a high likelihood of detecting causative mutations. Two smaller Class III studies\textsuperscript{13,14} demonstrated that in children with partial merosin deficiency, LAMA2 mutation detection is less consistent. Evidence provided by 1 Class II diagnostic/Class III screening study\textsuperscript{15} and 1 Class III study\textsuperscript{16} indicates that prenatal genetic testing is highly accurate.

Seven Class III\textsuperscript{17,18,19} studies demonstrated that genetic testing can detect causative mutations in 30% to 66% of children with dystroglycanopathy. In Fukuyama CMD, FKTN mutations are detected in as many as 100% of patients (1 Class I diagnostic/Class III screening study\textsuperscript{20}) and 3 Class III screening studies\textsuperscript{21,22,23} indicate that COL6A1, COL6A4, and COL6A3 genetic testing possibly has a high likelihood of detecting causative mutations.

Two large Class III studies\textsuperscript{24,25} provided evidence that in children with complete merosin deficiency on muscle biopsy, LAMA2 genetic testing has a high likelihood of detecting causative mutations. Two smaller Class III studies\textsuperscript{26,27} demonstrated that in children with partial merosin deficiency, LAMA2 mutation detection is less consistent. Evidence provided by 1 Class II diagnostic/Class III screening study\textsuperscript{28} and 1 Class III study\textsuperscript{29} indicates that prenatal genetic testing is highly accurate.

Seven Class III\textsuperscript{30,31,32} studies demonstrated that genetic testing can detect causative mutations in 30% to 66% of children with dystroglycanopathy. In Fukuyama CMD, FKTN mutations are detected in as many as 100% of patients (1 Class I diagnostic/Class III screening study\textsuperscript{32}) and 3 Class III screening studies\textsuperscript{33,34,35} indicate that COL6A1, COL6A4, and COL6A3 genetic testing possibly has a high likelihood of detecting causative mutations.

How often do patients with CMD experience cognitive, respiratory, or cardiac complications? Numerous reports highlight a wide spectrum of complications in children and young adults with CMD.

**Functional CNS complications.** One Class II study found that 58% of patients with CMD had cognitive impairment.\textsuperscript{36} A Class III article reported a high incidence of seizures in a cohort of Japanese children with Fukuyama CMD.\textsuperscript{37} Another Class III article reported that 2 girls with dystroglycanopathy had epilepsy associated with unusual EEG findings.\textsuperscript{38}

**Respiratory complications.** A Class III study found an overall respiratory complication rate of 12% in CMD.\textsuperscript{39} Another Class III study found that forced vital capacity was 80% predicted in all patients with Ullrich CMD by age 6 years.\textsuperscript{40} One Class III study examined the use of polysomnography in 2 patients with CMD and 2 patients with rigid spine syndrome and found that all subjects experienced nocturnal hypoventilation and hypoxemia.\textsuperscript{41}

**Cardiac complications.** One Class III study noted an overall cardiac complication rate of 6% in CMD.\textsuperscript{42} Three Class III studies examining echocardiographic measurements estimated that 8% to 30% of patients with merosin-positive CMD had depressed cardiac function.\textsuperscript{43,44}

**Feeding difficulties.** In a Class III study, the families of all 14 children with merosinopathy reported that their children had feeding difficulties.\textsuperscript{45}

Are there effective treatments for complications of CMD, including scoliosis and nutritional deficiencies? Our systematic review identified 1 Class III study of spinal fusion that demonstrated correction and prevention of progression of scoliosis and pelvic obliquity over 2 years, resulting in improved or stable balance and
sitting posture. The impact on respiratory status and other complications was unclear.45

PRACTICE RECOMMENDATIONS Given the lack of literature directly relevant to CMDs for some of the clinical questions, some of the following recommendations are based in part on evidence from other neuromuscular disorders of childhood.

General recommendations. Patients with CMD may develop various combinations of cardiovascular, gastrointestinal/nutritional, neurologic, ophthalmologic, orthopedic, and pulmonary manifestations. Multidisciplinary teams are recommended in the care of patients with complex neuromuscular conditions such as amyotrophic lateral sclerosis.46 Neuro muscular specialists, particularly child neurologists and physiatrists with subspecialty training, are key members of such teams, as are physicians from other specialties (e.g., cardiology, gastroenterology, neurology, ophthalmology, orthopedic surgery, pulmonology) and allied health professionals with relevant expertise (e.g., dieticians, genetic counselors, nurses, nurse practitioners, occupational therapists, physical therapists, and speech–language pathologists).

Recommendations.

1. Physicians caring for children with CMD should consult a pediatric neuromuscular specialist for diagnosis and management (Level B).

2. Pediatric neuromuscular specialists should coordinate the multidisciplinary care of patients with CMD when such resources are accessible to interested families (Level B).

3. When genetic counselors are available to help families understand genetic test results and make family-planning decisions, physicians caring for patients with CMD might help families access such resources (Level B).

Use of clinical features, MRI, and muscle biopsy in diagnosis. Patients with some of the classic CMD subtypes, including collagenopathies and dystroglycanopathies, have distinct phenotypic features that may help focus the diagnostic process.

Recommendation.

1. Physicians should use relevant clinical features such as ethnicity and geographic location, patterns of weakness and contractures, the presence or absence of CNS involvement, the timing and severity of other organ involvement, and serum CK levels to guide diagnosis in collagenopathies and in dystroglycanopathies (Level B).

Interpretation of these studies requires knowledge of the clinical context as well as availability of advanced testing capabilities. The knowledge obtained from a muscle biopsy may help families and providers better understand the disease process affecting specific patients.

Recommendations.

1. Physicians might order muscle biopsies that include immunohistochemical staining for relevant proteins in CMD cases for which the subtype-specific diagnosis is not apparent after initial diagnostic studies, if the risk associated with general anesthesia is determined to be acceptable (Level C).

2. When muscle biopsies are indicated in cases of suspected CMD, they should be performed and interpreted at centers experienced in this test modality. In some cases, optimal diagnostic information may be derived when the biopsy is performed at one center and interpreted at another (Level B).

Typical brain MRI findings of white matter abnormalities in merosinopathies can be found consistently above the age of 6 months, and the structural brain abnormalities that often accompany the dystroglycanopathies are well documented.

Muscle ultrasound and MRI studies can help distinguish neurogenic from myopathic disorders and show pathognomonic patterns for specific CMD subtypes. Muscle MRI studies likewise can help identify CMD subtypes, including collagenopathies and SEPN1-related myopathies.36

Recommendations.

1. Physicians should order brain MRI scans to assist with the diagnosis of patients with clinically suspected CMD subtypes such as merosinopathies and dystroglycanopathies, if the potential risk associated with any sedation is determined to be acceptable and if a radiologist or other physician with the appropriate expertise is available to interpret the findings (Level B).

2. Physicians might order muscle imaging studies of the lower extremities for individuals with suspected CMD subtypes such as collagenopathies (ultrasound or MRI) and SEPN1-related myopathy (MRI), if the risk associated with any sedation needed is determined to be acceptable and if a radiologist or other physician with the appropriate expertise is available to interpret the findings (Level C).

Genetic diagnosis. Targeted genetic testing often identifies causative mutations in the classic CMD subtypes. However, the cost of traditional Sanger sequencing for some of the larger causative genes presents an obstacle to universal application of such
sequencing, even though the testing is readily available. Genetic diagnoses are beneficial to the patient, as they often enable physicians to provide more accurate prognoses and facilitate genetic counseling and family-planning discussions, and may enable patients to become more aware of future clinical trials for which they may be eligible.

Recommendation.

1. When available and feasible, physicians might order targeted genetic testing for specific CMD subtypes that have well-characterized molecular causes (Level C).

Our systematic review indicates that many patients with CMD do not have mutations in one of the currently known genes. The cost of next-generation sequencing (whole-exome and whole-genome sequencing) is dropping rapidly, to the point where these technologies are now readily available to many researchers who seek novel causative disease genes.

Recommendation.

1. In individuals with CMD who either do not have a mutation identified in one of the commonly associated genes or have a phenotype whose genetic origins have not been well characterized, physicians might order whole-exome or whole-genome sequencing when those technologies become more accessible and affordable for routine clinical use (Level C).

Complications and treatment. Patients with CMD experience a broad spectrum of respiratory, musculoskeletal, cognitive, and cardiac complications with variable tempo between individuals. Providers may, in appropriate circumstances, extrapolate from early-onset neuromuscular and neuromotor diseases for which consensus guidelines have been developed on the basis of both established principles of care and limited outcomes and intervention trials. There are currently no curative CMD subtype-specific interventions. Thus, all complication screening and interventions are intended to promote growth and potential development, mitigate cumulative morbidities, optimize function, and limit mortality while maximizing quality of life.

Recommendation.

1. At the time of diagnosis, the physician should advise families regarding areas of uncertainty such as clinical outcomes and the value of interventions as they pertain to both longevity and quality of life. Physicians should explain the multisystem implications of neuromuscular insufficiency and guide families as they make decisions regarding the monitoring for and treatment of CMD complications (Level B).

Respiratory complications. Patients with respiratory failure from neuromuscular-related weakness may experience conspicuous respiratory symptoms but often do not have symptoms such as dyspnea that precede the onset of respiratory failure. Noninvasive and invasive interventions are routinely utilized for children with CMD. Pulmonologists, critical care specialists, and respiratory therapists with pediatric training and experience with neuromuscular disorders are most likely to offer treatment options that optimize respiratory outcomes and minimize infection risks and complications.

Recommendation.

1. Physicians should counsel families of patients with CMD that respiratory insufficiency and associated problems may be inconspicuous at the outset (Level B).

2. Physicians should monitor pulmonary function tests such as spirometry and oxygen saturation in the awake and sleep states of patients with CMD, with monitoring levels individualized on the basis of the child’s clinical status (Level B).

3. Physicians should refer children with CMD to pulmonary or aerodigestive care teams, when available, that are experienced in managing the interface between oropharyngeal function, gastric reflux and dysmotility, and nutrition and respiratory systems, and can provide anticipatory guidance concerning trajectory, assessment modalities, complications, and potential interventions (Level B).

Complications from dysphagia. Patients with neuromuscular disorders often experience dysphagia (impaired swallowing), with implications for growth and nutrition. Swallowing dysfunction may manifest as failure to thrive and may also increase the risk of admission to critical care units and mortality. Dysphagia may be diagnosed through standard multidisciplinary evaluations and radiologic studies. Safe and adequate nutrition is necessary for optimal health, and thus the potential benefits of improved nutrition with a gastrostomy must be weighed against the potential risks associated with an invasive procedure.

Recommendation.

1. Neuromuscular specialists should coordinate with primary care providers to follow nutrition and growth trajectories in patients with CMD (Level B).

2. For patients with CMD, physicians should order multidisciplinary evaluations with swallow therapists, gastroenterologists, and radiologists if there is evidence of failure to thrive or respiratory symptoms (or both) (Level B).

3. For patients with CMD, a multidisciplinary care team, taking into account medical and family
considerations, should recommend gastrostomy placement with or without fundoplication in the appropriate circumstances (Level B).

Cardiac complications. Patients with CMD experience both functional and structural cardiac complications, but the frequency of these for many of the subtypes is unknown.\(^6\) On the basis of more extensive experience with cardiac complications in Duchenne MD and Becker MD, cardiac involvement may be subclinical and evident only on echocardiography or ECG (or both) in the earlier stages; such involvement may be amenable to pharmacologic therapy.\(^3\)

Recommendation.
1. Physicians should refer children with CMD, regardless of subtype, for a baseline cardiac evaluation. The intervals of further evaluations should depend on the results of the baseline evaluation and the subtype-specific diagnosis (Level B).

Periprocedural complications. Patients with neuromuscular diseases are at increased risk of periprocedural complications, including airway problems, suboptimal pain control, pulmonary complications, prolonged recovery times, and complications of bed rest and deconditioning.\(^2\)

Recommendations.
1. Before any surgical interventions and general anesthesia in the setting of CMD, physicians should discuss the potential increased risk of complications with patients’ families, because these factors may affect decision-making regarding consent to certain elective procedures (Level B).
2. When children with CMD undergo procedures involving sedation or general anesthesia, physicians should monitor longer than usual in the immediate postoperative period to diagnose and treat respiratory, nutritional, mobility, and gastrointestinal mobility complications (Level B).

Musculoskeletal complications. Patients with CMD are at increased risk of musculoskeletal complications, including skeletal deformities and contractures. Range-of-motion exercises are straightforward interventions that generally do not involve significant risk, but the efficacy of such exercises has not been established. Data on the efficacy of bracing are also lacking for children with CMD. It is generally accepted that orthopedic surgical interventions such as heel cord–lengthening procedures relieve tendon contractures at least in the short term; however, the long-term efficacy is unclear. Neuromuscular blocking agents (e.g., botulinum toxin) can cause prolonged worsening of weakness in patients with neuromuscular diseases.\(^3\)

Recommendations.
1. Physicians should refer children with CMD to special education advocates, developmental specialists, and education specialists when appropriate for individual circumstances (Level B).

Educational adjustments. Before school age, children at risk of developmental delays are eligible for early intervention services as federally mandated. The Individuals with Disabilities Education Improvement Act of 2004 guarantees children with disabilities a free and appropriate public education.\(^7\)

Recommendation.
1. Physicians should refer children with CMD to special education advocates, developmental specialists, and education specialists when appropriate for individual circumstances (Level B).

RECOMMENDATIONS FOR FUTURE RESEARCH
Despite the advances in genetic knowledge of the CMDs, novel CMD genes remain to be discovered. Gaps in knowledge remain in the clinical courses of, complications associated with, and optimal treatment regimens for the various CMD subtypes. Standardized outcome measures would promote more rigorous research that would help identify complications and optimize treatment in these patients.\(^5\)

The following topics merit further research:
1. Gene discovery in CMD
2. Genotype–phenotype studies in CMDs, especially longitudinal studies
3. Frequency and risk factors for various complications in CMDs
4. The merits of various therapeutic interventions for CMDs

AUTHOR CONTRIBUTIONS
Peter Kang: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision.
of the manuscript for important intellectual content, study supervision. Leslie Morrison: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Susan Iannaccone: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Robert Graham: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Carsten Bönnersmann: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Anne Rutkowski: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Joseph Hornyak: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Maryam Osokou: analysis or interpretation of data. Thomas Getchius: study supervision. Julie Cox: drafting/revising the manuscript. Erim Hagen: study supervision. Gary Gronseth: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Joseph Hornyak: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Ching Wang: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Kathryn North: study concept and design, acquisition of data, analysis or interpretation of data, mapping. Maryam Osokou: analysis or interpretation of data. Thomas Getchius: study supervision. Leslie Morrison: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Leslie Morrison: study concept and design, critical revision of the manuscript for important intellectual content.

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DISCLOSURE
P. Kang has received funding for travel from the American Academy of Neurology (AAN), the American Academy of Pediatrics (AAP), and Saropta Therapeutics; has received consulting fees from Third Rock Ventures, Saropta Therapeutics, and C1 Consulting for work unrelated to continuing medical education; has received honoraria for continuing medical education lectures from the AAN, AAP, American College of Medical Genetics, and HealthmatteCME; and has received research support from the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH and the Muscular Dystrophy Association (MDA). L. Morrison has received funding for travel from the AAN; currently receives funding from the NINDS/NIH and the University of New Mexico (UNM) Myotonic Dystrophy Foundation; has received support from the UNM La Tierra Sagrada Foundation; and serves as director for the pediatric MDA Clinic at UNM, for which she receives annual support. S. Iannaccone has received funding for travel from the AAN, Cure CMD, the GBS/CIDP Foundation, and NINDS/NIH; has received research support from the NINDS/NIH, Isis Pharmaceuticals, PTC Therapeutics Inc., Santhera Pharmaceuticals, and GlassoSmithKline; and serves as director of the MDA Clinic at Children’s Medical Center Dallas (for which she receives annual support) and as medical director for the Dallas MDA Summer Camp. R. Graham has served as a one-time, paid consultant for Hoffmann-La Roche Ltd. for a Pulmonary Advisory Panel on investigations pertaining to spinal muscular atrophy (SMA). C. Bönnersmann has served on the scientific advisory board of Cure CMD and CMD-IR, without any compensation; has received funding for travel from BioMarin (for scientific advice, no personal compensation), Novartis (no personal compensation), and the Third Rock Ventures (no personal compensation); has served as editor-in-chief of the Journal of Neuromuscular Disorders; sees patients with congenital muscular dystrophy (CMD) and performs muscle ultrasound on patients with CMD; has received intramural funds from the NINDS/NIH and National Human Genome Research Institute of the NIH; and has received a research grant from MDA. P. A. Rutkowski has received funding for clinical research from Kaiser Southern California Permanente Medical Group. T. Getchius has received funding for research from the AAN; C. Wang reports no disclosures relevant to the manuscript. K. North has received funding to attend a CMD workshop hosted by Cure CMD; has received clinical trials funding from PTC Therapeutics and GSK Procosa; and has received funding from the Australian National Health and Medical Research Council (for research into congenital myopathies, dystrophin-related muscular dystrophy, and the effect of n-actinin-3 deficiency on skeletal muscle performance); from the Australia Research Council (for research into n-actinin); and from the US Army Department of Defense (for a clinical trial on lovastatin for the treatment of cognitive deficits in neurofibromatosis type 1). M. Osokou has received funding for travel from the AAN and Isis Pharmaceuticals; has received fellowship funding from the Spinal Muscular Atrophy Foundation; has received research support from Griroils (Guillain–Barré syndrome), Isis Pharmaceuticals (SMA), and SickKids Foundation (cerebral palsy); and is a member of the Canadian Pediatric Neuromuscular Group and the Canadian Neuromuscular Disease Registry and Network. T. Getchius, J. Cox, E. Hagen, and G. Gronseth report no disclosures relevant to the manuscript. R. Griggs receives support for service on data safety monitoring boards from Novartis, PTC Therapeutics, and ViroMed; consults for Saropta Pharmaceuticals; consults and has received research support from Marathon Pharmaceuticals and Taro Pharmaceuticals; receives royalties from Elsevier for Cecil Textbook of Medicine, and Cecil Essentials of Medicine, and from Oxford University Press for Evaluation and Treatment of Myopathies, Second Edition; receives a stipend from the AAN for editorial work; has received grants from the NINDS/NIH, the MDA, and Parent Project for Muscular Dystrophy; and chairs the Executive Committee of the Muscle Study Group, which receives support from numerous pharmaceutical companies. Go to Neurology.org for full disclosures.

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by at least 3 AAN committees, at least one AANEM committee, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed

REFERENCES

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