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Diagnostic approach to the congenital muscular dystrophies ☆

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Abstract

Congenital muscular dystrophies (CMDs) are early onset disorders of muscle with histological features suggesting a dystrophic process. The congenital muscular dystrophies as a group encompass great clinical and genetic heterogeneity so that achieving an accurate genetic diagnosis has become increasingly challenging, even in the age of next generation sequencing. In this document we review the diagnostic features, differential diagnostic considerations and available diagnostic tools for the various CMD subtypes and provide a systematic guide to the use of these resources for achieving an accurate molecular diagnosis. An International Committee on the Standard of Care for Congenital Muscular Dystrophies composed of experts on various aspects relevant to the CMDs performed a review of the available literature as well as of the unpublished expertise represented by the members of the committee and their contacts. This process was refined by two rounds of online surveys and followed by a three-day meeting at which the conclusions were presented and further refined. The combined consensus summarized in this document allows the physician to recognize the presence of a CMD in a child with weakness based on history, clinical examination, muscle biopsy results, and imaging. It will be helpful in suspecting a specific CMD subtype in order to prioritize testing to arrive at a final genetic diagnosis.
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Keywords: Congenital muscular dystrophy; Collagen VI; Laminin alpha2; Alpha-dystroglycan; SEPN1; Lamin A/C; RYR1; Diagnostic guideline

☆ See table of abbreviations at end of paper.

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1. Introduction

The congenital muscular dystrophies (CMDs) and the congenital myopathies (non-dystrophic myopathies with characteristic histological and histochemical findings) constitute the two most important groups of congenital onset muscle disease. The CMDs are defined as early onset muscle disorders in which the muscle biopsy is compatible with the presence of a dystrophic process (even if not fully developed) without histological evidence of another neuromuscular disease [1,2]. However, it has become clear that there is overlap between the CMDs and and the congenital myopathies on the clinical, morphological and genetic level. For example, mutations in RYR1 and SEPN1 can cause both core disorders (belonging to the congenital myopathies) as well as CMD-like presentations. The clinical as well as genetic complexity of the disorders subsumed under the CMDs has resulted in different genetic as well as clinical classification schemes [3–5]. Also, the genetic nomenclature used is not always consistent. For instance MDC1A (muscular dystrophy, congenital, type 1A) refers to disease caused by mutations in LAMA2, but this nomenclature system has not been systematically carried forward for all CMDs. Table 1 lists most currently used names and symbols for reference. Gene symbols in this review are not italicized. We have used the gene or protein name annotated by "–related dystrophy (–RD)"

Table 1
Brief CMD classification overview (underlined: abbreviated nomenclature used in this paper).

Subtype and alternate nomenclatures Associated Genes	Associated phenotypic spectrum
Collagen VI related dystrophies (COL6-RD) COL6A1, COL6A2, COL6A3	■ Ullrich congenital muscular dystrophy (UCMD) – severe nonambulant and transient ambulant ■ Intermediate phenotype ■ Bethlem myopathy (BM, milder disease course)
Lamininα2 related dystrophy (LAMA2-RD, includes MDC1A, Merosin deficient CMD, LAMA2-CMD) LAMA2	■ Non-ambulant LAMA2-RD ■ Ambulant LAMA2-RD ■ Non-ambulant typically correlates with absent laminin α2 staining on muscle biopsy and ambulant with partial deficiency (with exeptions)
αDystroglycan related dystrophy (αDG-RD, also alpha dystroglycanopathy, αDGpathy) FKRP, FKTN, POMT1, POMT2, POMGnT1, LARGE, ISPD, GTDC2, DAG1,TMEM5, B3GALNT2, B3GNT1, GMPPB, SGK196 (DPM1, DPM2, DPM3, DOLK)	■ Walker–Warburg syndrome ■ Muscle–eye–brain disease; Fukuyama CMD; Fukuyama-like CMD ■ CMD with cerebellar involvement; cerebellar abnormalities may include cysts, hypoplasia, and dysplasia ■ CMD with mental retardation and a structurally normal brain on imaging; this category includes patients with isolated microcephaly or minor white matter changes evident on MRI ■ CMD with no mental retardation; no evidence of abnormal cognitive development ■ Limb-girdle muscular dystrophy (LGMD) with mental retardation (milder weakness, maybe later onset) and a structurally normal brain on imaging ■ LGMD without mental retardation (milder weakness, maybe later onset)
SEPN1 related myopathy (SEPN1-RM, also rigid spine CMD, RSMD1) SEPN1	■ Consistent rigid spine early respiratory failure phenotype ■ despite variable histological presentations as multiminicore disease, desmin positive Mallory body inclusions, congenital fiber-type disproportion, mild CMD, or nonspecific myopathy
RYR1 related myopathy (RYR1-RM, includes RYR1-CMD) RYR1	■ RYR1 related myopathies (RYR1-RM) include central core, multi-mini-core, centronuclear and nonspecific pathologies. which can assume CMD like characteristics ■ Clinically significant for early scoliosis and absent or limited ambulation
LMNA related dystrophy (LMNA-RD, includes LMNA-CMD, L-CMD, and Emery Dreifuss) LMNA	■ CMD presentation: Dropped head syndrome, axial and scapuloperoneal involvement, absent or early loss of ambulation ■ Milder presentations fuse with early-onset Emery–Dreifuss muscular dystrophy
CMD without genetic diagnosis	■ Congenital onset weakness with CMD compatible histology and variable clinical features, without confirmed genetic diagnosis, despite testing for currently known genes

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