Congenital Myopathies and Muscular Dystrophies

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KEYWORDS

- Congenital muscular dystrophy • Congenital myopathy
- Ullrich congenital muscular dystrophy • Nemaline myopathy
- Central core myopathy • Centronuclear myopathy
- Merosin deficiency congenital muscular dystrophy

KEY POINTS

- Diagnosis most often depends on muscle biopsy and mutation analysis, but the physician in charge must be aware of the expertise of both the biopsy laboratory and that of the DNA diagnostic laboratory.
- There are many pitfalls that can result in misinterpretation of both the biopsy and the DNA; these are best avoided by working with laboratories that have the highest expertise.
- It is important that patients and families receive complete information regarding the diagnostic process and the results, including hard copies for their child's own records.
- There are now published guidelines for the management of children with congenital muscular dystrophies (CMD) and congenital myopathies (CM).
- Patient groups are lobbying for support of clinical trials for patients with CMD and CM, and some studies may well be seen coming online in the next few years.

INTRODUCTION

The congenital muscular dystrophies (CMD) and myopathies (CM) are a diverse group of diseases that share features such as early onset of symptoms (in the first year of life), genetic causes, and high risks for restrictive lung disease and orthopedic deformities. The classification of these disorders is historically based and first depended on muscle biopsy findings. CMDs were identified with dystrophic biopsies and CMs with peculiar structural changes seen with histochemistry or electron microscopy. Thus,

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the CMDs were first described early in the twentieth century,[1] whereas CMs were not recognized until cryostat sections and histochemistry came into use in the late 1960s.[2] At that time, it was apparent that most patients with CMs had nonprogressive weakness, whereas the CMDs were thought to be similar to other dystrophies with progressive limb girdle weakness. As each of the entities was associated with unique gene mutations, some understanding for disease mechanism became available and a fairly well-structured genotype-phenotype correlation for all the CMDs and CMs is now available.

Diagnosis should begin with a suspicion, the consideration of whether creatine kinase (CK) is elevated, and a look at involvement outside the skeletal muscles. Abnormal brain imaging, cognitive involvement, early orthopedic deformities, epilepsy, and structural changes in the eye should suggest a CMD. Nondystrophic biopsy, facial and bulbar weakness, and no eye involvement other than gaze palsy would suggest a CM. Once brain imaging or muscle histology support a specific disease, then diagnosis should be confirmed by mutation analysis. This confirmation will allow for accurate prognostication, educated anticipatory guidance, and informed family planning.

To illustrate best the clinical spectrum and diagnostic algorithm for these diseases, this article presents 5 cases with discussion immediately following. The cases represent the most common forms of CMD and CM and provide an opportunity to review important clues to diagnosis and guidelines for management.

CASE 1

A 4-year-old boy was referred to the Neuromuscular Disease Clinic for joint laxity. Birth history was reported to be significant for hypotonia, respiratory difficulties requiring oxygen via nasal cannula, poor feeding, and congenital hip dislocation. The patient had motor delay. Specifically, he began sitting for brief periods of time at 7 months of age, and combat crawling after 1 year of age. He eventually walked without assistance but was noted to suffer from significant weakness. At presentation, he was unable to stand independently from a seated position. Social and language function was normal.

Physical examination demonstrated a well-developed child with long myopathic facies, a high palate, and mild ptosis bilaterally. Lung and heart examinations were normal. Musculoskeletal examination was significant for mild flexion contractures of both elbows and knees with hyperlaxity of both wrists. On neurologic examination, the patient was found to be hypotonic with decreased muscle bulk, proximal greater than distal muscle weakness, and decreased reflexes.

CK level was 280 iU/L. Electrodiagnostic studies were normal. Cardiac evaluation was negative. Muscle biopsy (**Fig. 1**) revealed dystrophic changes, including marked variability in fiber size with regenerating fibers and central nuclei. Immunohistochemistry demonstrated reduced reaction to 300 kDa merosin and sarcoglycan antibodies. Magnetic resonance imaging (MRI) of brain was normal. Skin fibroblast testing confirmed a splicing mutation in exon 16 of the *COL6A* gene.

The patient lost his ability to ambulate at 5 years of age. By late childhood, he had severe restrictive lung disease with a forced vital capacity of 0.4 L or 16% predicted and required noninvasive ventilation intermittently during the day and all night.

This young boy had symptoms from birth with hyptonia, weakness, and joint contractures. The differential diagnosis included CMD and CM, but the progressive nature of his contractures and restrictive lung disease are much more consistent with CMD. Furthermore, the distal laxity and normal CK level are typical of collagen mutations or