Muscular Dystrophies and Other Genetic Myopathies

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KEYWORDS

• Muscular dystrophy • Myopathy • Limb-Girdle • FSHD • Myotonic dystrophy • Congenital • Metabolic

KEY POINTS

- Muscular dystrophy refers to a collection of genetic progressive muscle diseases.
- If relevant, preventive screening for cardiac manifestations and ventilatory insufficiency is an important management consideration.
- Novel therapies tailored to the genetics of the disease are entering clinical trials for some of these diseases.
- Definitive genetic diagnosis is important to optimally manage patients with muscle disease.

INTRODUCTION

Historically, the term, *muscular dystrophy*, was used to describe a progressive genetic myopathy with muscle histologic changes, including fibrosis, muscle fiber size variation, and abnormal internalization of muscle nuclei (**Fig. 1**). Fibrofatty replacement, inflammation, and degenerative fibers are also commonly described histologic features. Hence, the diagnostic evaluation often included a muscle biopsy to demonstrate these histologic features. The most common muscular dystrophies include Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), facioscapulohumeral muscular dystrophy (FSHD), and myotonic dystrophy. Other conditions were also recognized, but these syndromes were defined clinically.

The classification of many muscular dystrophies has been based on clinical presentation. Specifically, the pattern of weakness has been the means of identifying clinical syndrome. For example, limb-girdle muscular dystrophy (LGMD), distal myopathies, and FSHD are muscular dystrophy syndromes named based on the pattern of weakness.

With improved understanding of the underlying genetics of muscle disease, the list of genetic syndromes associated with muscle disease has expanded dramatically and

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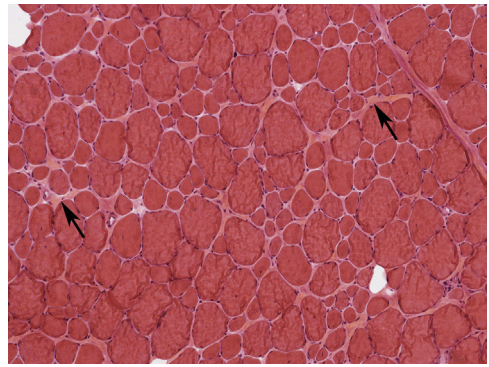

Fig. 1. Cryostat sections of a muscle biopsy from a boy with BMD (original magnification x100). Hematoxylin-eosin preparation shows muscle fibers in cross-section that have significant variability of fiber diameter. Mildly increased fibrosis is also seen in the space between the muscle fibers (endomysial space, examples indicated by *arrows*). Increased internalization of muscle fiber nuclei, however, is not a significant feature of this particular biopsy.

the classification of muscular dystrophy has been revised to incorporate genetic testing. Thus, previously recognized clinical syndromes (eg, DMD) may also be referred to by their genetic locus (eg, dystrophinopathy). Furthermore, conditions that were thought to be different genetic syndromes, such as DMD and BMD, are now recognized as allelic variants of the same genetic locus. Additionally, conditions previously classified as nonprogressive, such as the congenital myopathies, are now loosely categorized as muscular dystrophies based on slow clinical progression and recognition of allelic variability.

The diagnostic criteria for nearly all muscular dystrophies now incorporate genetic testing. Patients with characteristic clinical features and a documented causative mutation may be diagnosed without extensive and invasive diagnostic testing, such as electromyography (EMG) and muscle biopsy, among other tests. In many cases, however, the clinical presentation is not specific and DNA testing may yield sequence variants of unclear clinical significance. Thus, the role of muscle biopsy and other traditional diagnostic tests continues to be helpful although not always essential in the diagnostic evaluation of these patients. With next-generation sequencing and continued improvement in the documentation of causative mutations, it is anticipated that the diagnostic yield of genetic testing will continue to improve in the years to come.

An aggressive effort to identify a definitive diagnosis is recommended because a specific diagnosis affects the management of these patients. For example, many of these conditions are associated with cardiac and pulmonary complications that may require early intervention. Furthermore, potential medical treatments of several of these conditions are available or in the pipeline. An obvious prerequisite for these treatments is for patients to have an accurate genetic diagnosis. This review discusses the clinical and diagnostic features of DMD/BMD, FSHD, and myotonic dystrophy before briefly describing the complex diagnostic landscape of the other muscular dystrophies.

DUCHENNE MUSCULAR DYSTROPHY AND BECKER MUSCULAR DYSTROPHY

DMD affects up to 1 in 3600 boys,[1] making this muscular dystrophy the most common by incidence. Because of the shorter life expectancy, however, DMD ranks second in