Muscular Dystrophies

John C. Carter, MD[a], Daniel W. Sheehan, PhD, MD[b], Andre Prochoroff, MD[c], David J. Birnkrant, MD[d,*]

KEYWORDS

• Muscular dystrophy • Duchenne muscular dystrophy • Limb girdle muscular dystrophy
• Facioscapulohumeral muscular dystrophy • Respiratory failure • Cardiomyopathy

KEY POINTS

- The muscular dystrophies are a heterogeneous group of disorders defined by dystrophic pathologic features on muscle biopsy.
- Clinically, muscular dystrophies are characterized by progressive muscle weakness affecting skeletal muscles, although significant variability exists in the genetic and biochemical features, the distribution of affected musculature, degree of respiratory and cardiac compromise, and the involvement of other organ systems, such as the eyes and central nervous system.
- There is variability, even among patients with the same disorder and genetic mutations, in age of onset, severity, progression, prognosis, and thus optimal management.

INTRODUCTION

The muscular dystrophies are a heterogeneous group of disorders defined by dystrophic pathologic features on muscle biopsy. Clinically, they are characterized by progressive muscle weakness affecting skeletal muscles, although significant variability exists in the genetic and biochemical features, the distribution of affected musculature, degree of respiratory and cardiac compromise, and the involvement of other organ systems such as the eyes and central nervous system. There is also variability, even among patients with the same disorder and genetic mutations, in age of onset, severity, progression, prognosis, and thus optimal management.

This article provides an introduction to the taxonomy, basic genetics, clinical profile, natural history, and fundamentals of management of the muscular dystrophies. Pulmonologists are likely to encounter patients with muscular dystrophy across a variety of settings, including in the clinic, in the intensive care unit, and as part of multidisciplinary programs specializing in the care of neuromuscular disorders.

Substantial progress in the care of patients with muscular dystrophy has been made in recent years, driven by international collaboration, a growing understanding of the underlying genetic processes, and clinical consensus guidelines. Implementation of standards of care can improve anticipatory guidance, can promote proactive management, and has been shown to improve survival. Implementation of standards of care is also needed to provide stable baselines for assessment of the clinical effects of new treatments. Prevention of respiratory complications via anticipatory therapy with lung volume recruitment, assisted coughing and noninvasive ventilation, is a critically important component of the multidisciplinary care of patients with muscular dystrophy. Duchenne muscular dystrophy (DMD),

[a] Division of Pulmonary, Critical Care and Sleep Medicine, MetroHealth Medical Center, Case Western Reserve University School of Medicine, 2500 MetroHealth Drive, Cleveland, OH 44019, USA; [b] Division of Pediatric Pulmonology, John R. Oishei Children's Hospital, University at Buffalo, 955 Main Street, Buffalo, NY 14203, USA; [c] Division of Pediatric Neurology, MetroHealth Medical Center, Case Western Reserve University School of Medicine, 2500 MetroHealth Drive, Cleveland, OH 44019, USA; [d] Division of Pediatric Pulmonology, MetroHealth Medical Center, Case Western Reserve University School of Medicine, 2500 MetroHealth Drive, Cleveland, OH 44019, USA
* Corresponding author.
E-mail address: dbirnkrant@metrohealth.org

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the most common inherited muscle disease of childhood, is used as a model because it is by far the best studied muscular dystrophy. This article includes the latest recommendations for the respiratory management of DMD, adapted from the updated Centers for Disease Control and Prevention (CDC)-sponsored care considerations, recently published in *Lancet Neurology*.[1]

EPIDEMIOLOGY

The muscular dystrophies as individual disorders are relatively rare, but as a group represent a sizable fraction of patients with neuromuscular disease encountered in both the outpatient and the inpatient setting. DMD, the most common inherited muscle disease in childhood, is found in roughly 8.3 per 100,000 boys, whereas its cousin Becker muscular dystrophy occurs in roughly 7.3 per 100,000.[2] In adults, myotonic dystrophy is the most common form, affecting roughly 10.6 per 100,000 people, followed by facioscapulohumeral dystrophy, which affects an estimated 3 per 100,000 people.[3] The prevalence of congenital muscular dystrophies varies significantly by region. Ullrich congenital muscular dystrophy is the most common form of congenital muscular dystrophy globally,[4] although Fukuyama muscular dystrophy is the most common type in Japan due to a recessive founder mutation.[5]

CLINICAL MANIFESTATIONS

Historically, muscular dystrophies have been classified based on the age of onset, principal pattern of muscle involvement, and other clinical features. Subtypes were defined based on inheritance and the underlying genetic defect, if known. It has subsequently become clear that a wide variety of genetic defects may result in similar phenotypes,[6,7] and conversely, that substantial phenotypic variability exists among patients with the same pathogenic genotype.[8,9] This discordance highlights the importance of regular screening and monitoring of patients with muscular dystrophy, particularly for progressive changes in pulmonary and/or cardiac function. Second, it highlights the need for additional definition of subphenotypes for better anticipatory guidance, prognosis, and evaluation of therapies in both clinical and research settings.

The onset of symptoms and signs in muscular dystrophies varies from birth to adulthood (**Table 1**). The congenital muscular dystrophies typically present with signs at birth or within the first few months of life. DMD and many of the limb girdle muscular dystrophies present in early childhood or adolescence, often after independent ambulation has been achieved. Other limb girdle muscular dystrophies, as well as myotonic dystrophy and facioscapulohumeral muscular dystrophy, characteristically manifest in adulthood. Skeletal muscle weakness characterizes all muscular dystrophies, although the distribution, degree, and progressive nature of weakness differ among disorders. In most of the congenital muscular dystrophies, ambulation is never achieved. In childhood-onset forms, such as DMD, ambulation is achieved but is typically lost before adolescence. In later-onset limb girdle muscular dystrophies and facioscapulohumeral dystrophy, ambulation may be preserved throughout adulthood, with the need for wheelchair assistance developing much later. In myotonic dystrophy, motor function varies significantly, ranging from severely affected infants with congenital myotonia and significant respiratory compromise to minimally affected adults with preserved ambulation and minimal respiratory impairment. Additional features in the muscular dystrophies, such as muscle atrophy or compensatory hypertrophy, joint contractures, myotonia, degree of respiratory involvement, and cardiac abnormalities, are also variable.

Respiratory impairment is common in patients with muscular dystrophy. Although the degree and onset of impairment are variable, respiratory impairment generally develops after the loss of ambulation, related to generalized inspiratory weakness or selective diaphragmatic weakness. Weakness of the expiratory muscles and of the muscles involved in coughing and swallowing results in impaired airway clearance and secretion management, necessitating lung recruitment maneuvers and assisted coughing. Respiratory impairment typically begins as nocturnal hypoventilation, which may precede daytime respiratory compromise by months or years in slowly progressive conditions.[10–12] Respiratory complications are a frequent cause of morbidity and mortality in patients with muscular dystrophy, including atelectasis, mucus plugging, pneumonia, bulbar dysfunction, dyspnea, and respiratory failure.[13] Evaluation and management of respiratory impairment are discussed later.

DUCHENNE MUSCULAR DYSTROPHY

As the most common inherited muscle disease of childhood, DMD is the most studied muscular dystrophy with regard to respiratory issues and represents an important prototype for the respiratory management of the muscular dystrophies. Boys with DMD typically present to medical attention in early childhood, due to weakness, clumsiness,