Chapter 7
Overview of Current Treatments for Muscular Dystrophy

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Introduction

As described in earlier chapters, muscular dystrophy (MD) refers to a group of hereditary diseases characterized by progressive wasting of skeletal muscles, often related to muscle membranes or supporting proteins. Current treatment is focused on symptomatic management and rehabilitation, and monitoring for disease complications. There is no cure for MD; however, better patient care especially with multidisciplinary approach has reduced mortality and morbidity significantly.

This chapter discusses general management strategies for MD and also describes treatments for the following subtypes of MDs: dystrophinopathies [Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD)], Facioscapulohumeral muscular dystrophy (FSHD), myotonic dystrophy, and limb girdle muscular dystrophy (LGMD).

Diagnosis and Initial Evaluation

Accurate diagnosis is important as a first step for managing MD. This is contingent on a targeted history and examination, biochemical, and genetic testing; sometimes with additional testing such as muscle biopsy, neurophysiological assessment, and muscle imaging. Muscle biopsy used to be the gold standard; however, it is increasingly replaced by genetic testing. The detection rate with genetic testing for DMD and BMD is ~95% using deletion/duplication study and reflex to sequencing

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analysis if deletion/duplication study is negative [1]. The genetic basis for FSHD has been elucidated in recent decades, and the genetic testing detection rate is ~95% for patients with FSHD where a contraction mutation of the D4Z4 macrosatellite array in the subtelomeric region of chromosome 4q35 can be identified [2]. Next generation sequencing technology such as whole exome sequencing (WES) has significantly improved our ability to diagnose subtypes of LGMD, as the traditional sequencing method limits testing to one gene at a time. While electromyography and nerve conduction studies have been a traditional part of the assessment of a patient with MD, these tests are not believed to be indicated or necessary for diagnosis unless other means are inconclusive. Muscle imaging is becoming more widely accepted as it is noninvasive and various forms of MD often result in unique patterns. This approach is also very sensitive, enabling inflammatory myopathies (also called myositis) and metabolic myopathies—which may mimic MD but require different management—to be ruled out. For these conditions, specific treatments exist and accurate early diagnosis improves outcomes.

It is also worth mentioning that some subtypes of MD, such as myotonic dystrophy, are often missed in the presentation. Hilbert et al. found that patients with myotonic dystrophy type 1 (DM1) experienced an average of seven years delay to diagnosis, and members with myotonic dystrophy type 2 (DM2) had an even more stunning delay of 14 years before receiving a correct diagnosis [3]. Thus, the importance of clinical suspicion from clinicians and families cannot be overestimated.

Management of MDs

Overall Strategies

A multidisciplinary team approach has changed the landscape for the treatment of MD and represents the standard of care. Despite the lack of cures, improved supportive care has improved the life span of patients with MDs. One example is that patients with Duchenne MD lived on average until their late teens in the 1950s; today, they typically live until their late twenties and thirties, which is largely attributable to better supportive care. This may include noninvasive ventilation during the day, and at night, orthopedic care and preventive measures [4, 5]. Clinicians should refer patients with MD to a clinic that has access to multiple specialties designed to care for patients with neuromuscular disorders [6].

Specific Therapy

Very few subtypes of MD have specific treatments. Examples are corticosteroids for DMD and treatment for myotonia in myotonic dystrophy type 1 (DM1).

Corticosteroids are the only medication currently available that slows the decline in muscle strength and function in DMD. These drugs are estimated to prolong ambulation by an average of approximately two years. However, corticosteroids are associated with many side effects, especially with long-term use. The optimal age for starting corticosteroids is under investigation in a randomized double-blind trial (Clinicaltrials.gov, NCT01603407, PIs Robert Griggs MD and Kate Bushby, MD). It should be noted that corticosteroids are not indicated for BMD or LGMD.

Myotonia in DM1 is typically mild to moderate and rarely requires treatment [7]. Anecdotally, some individuals have responded to mexilitene or carbamazepine. Logigian and colleagues found mexilitene 150–200 mg TID effective and safe for treating myotonia [8].

Supplements such as coenzyme Q10, carnitine, and antioxidants sometimes are used by families and clinicians. There is not enough evidence to make recommendations.

Cardiac Management

Cardiac muscles resemble skeletal muscles in some ways, and many, though not all, forms of MD have associated cardiac involvement, which is a major cause for mortality and morbidity. The main cardiac involvements are progressive cardiomyopathy and/or cardiac arrhythmia. Patients with MD with cardiac involvements often do not have symptoms such as chest pain or pedal edema, but are often identified only by cardiac testing. Angiotensin-converting enzyme (ACE) inhibitors are the first line for managing cardiomyopathy. Pacemakers can be life-saving in MD with cardiac arrhythmia, especially in Emery–Dreifuss muscular dystrophy (EDMD) and myotonic dystrophy type I. Regular monitoring of cardiac function using echocardiogram, EKG, and cardiac Holter monitoring are indicated and early referral to cardiologist is highly recommended.

Respiratory Management

The majority of forms of MD are associated with oropharyngeal and/or ventilator muscle weakness, which predispose patients to respiratory failure, which is a major cause of mortality and morbidity in MD. The diaphragm is a skeletal muscle, and weakness plays a significant role in respiratory failure in MD patients. Patients with respiratory failure often do not have symptoms such as dyspnea, which typically precede the onset of respiratory failure. Patients with respiratory failure secondary to muscle weakness in MD often have improved quality of life and outcomes with noninvasive pulmonary ventilation [9, 10]. Early monitoring using a lung function test and referral to pulmonologist is important.

Sleep Disorder Management

Sleep disorders in MD patients are under-recognized, as these patients often do not present with excessive daytime sleepiness, and fatigue is often attributed to the MD itself. Diaphragm weakness makes patients with MD at greater risk during certain sleep stages such as rapid eye movement (REM) sleep, which relies on the diaphragm for ventilation. Sleep-related hypoventilation often precedes daytime hypoventilation.

Our preliminary data show that patients with DMD have sleep-related hypoventilation without clinical symptoms. Patients with MD are also at risk of obstructive sleep apnea (OSA) due to upper airway muscle weakness and obesity that is more prevalent in MD due to reduced activity level and corticosteroid usage. Both sleep-related hypoventilation and OSA can be effectively treated with PAP therapy and treatment improves outcome and quality of life. High clinical suspicion and overnight sleep study (polysomnography) should be considered in MD patients with considerable weakness, especially in those who are non-ambulatory.

Rehabilitative Management

The goal for rehabilitative management is to maintain mobility and functional independence for as long as possible, with a focus on maximizing quality of life. Patients should have periodic assessments by physical and occupational therapists who are familiar with MD, including symptomatic and preventive screenings. Bracing and assistive devices are adapted to the patient's deficiencies and contracture, in order to preserve mobility and function and prevent contractures. With the advancement of electric wheelchairs and assistive devices, non-ambulatory patients with MD are often able to preserve a certain degree of independence and quality of life [11, 12].

In general, low-intensity aerobic exercise and strength training are recommended. Swimming is often recommended and especially enjoyed by non-ambulatory patients with MD. Swimming uses upper extremity muscles and truncal muscles that are not used much by routine aerobic exercise. There are concerns about exercise-induced muscle damage and myoglobinuria following supramaximal high-intensity exercise [13].

Orthopedic Management

Spinal deformities, such as scoliosis, kyphosis, and rigid spine, can occur in subtypes of MD. These deformities can result in pain and functional impairment, such as interfering with pulmonary function. Patients with spinal deformity and foot contractures should be referred to orthopedic surgeons for monitoring and surgical interventions if deemed necessary [4].

Winging of the scapula can be common in subtypes of MD such as FSHD and EDMD. The benefit of scapular fixation surgery is debatable. There is no evidence from randomized trials to support the suggestion from observational studies that operative interventions produce significant benefits. However, this has to be balanced against postoperative immobilization, the need for physiotherapy, and potential complications [14].

Nutrition

Patients with MD may have difficulty receiving adequate oral food intake due to dysphagia or inability to feed themselves linked to arm weakness. Maintaining adequate nutrition and body weight is important for optimizing strength, function, and quality of life. When oral food intake is inadequate, other means of maintaining intake (e.g., gastrostomy or jejunostomy feeding tubes) may be needed to maintain optimal nutrition [4, 6].

Psychosocial Management

In addition to its medical burden, MD may be associated with marked psychosocial stress for patients and their families. Assessments are targeted at the areas of emotional adjustment and coping, neurocognitive functioning, possible autism spectrum disorder, depression, and social support [4]. Referral to a psychologist and psychiatrist should be made if concerns are identified. Children with DMD often highly appreciate activities such as "Make a Wish" trips. Families with MD also benefit from useful resources provided by foundations such as the Muscular Dystrophy Association (MDA), Parent Project Muscular Dystrophy (PPMD), TREAT NMD, and the FSH society.

Palliative care is important part of care for subtypes of MD patients in later stages of the disease. This not only provides pain control, but also includes emotional and spiritual support, assists families in clarifying treatment goals and making difficult treatment decisions, and addresses issues related to grief and bereavement [4].

Genetic Counseling and Preventive Measures

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders, to help them make informed medical and personal decisions. All forms of MD are genetic disorders, either inherited from parents or as a de novo event. Risks to family

members should be assessed. Options such as prenatal testing should be offered to female carriers. All patients with MD should be referred for genetic counseling after diagnosis.

The risk of malignant hyperthermia in patients with MD is a concern for families. Gurnaney and colleagues did not find an increased risk of malignant hyperthermia susceptibility in patients with DMD or BMD compared with the general population. However, dystrophic patients who are exposed to inhaled anesthetics may develop disease-related cardiac complications, or rarely, a malignant hyperthermia-like syndrome characterized by rhabdomyolysis. This latter complication may also occur postoperatively. Succinylcholine administration is associated with life-threatening hyperkalemia and should be avoided in patients with DMD and BMD [13]. It is important for patients with MD to discuss malignant hyperthermia-like risk with the anesthesiologist in any pre-op assessment.

Therapies Under Investigation

MD is an area of active research, including multiple clinical trials. Updated information can be found by searching the www.clinicaltrials.gov website. Despite many trials in progress, such as exon skipping for DMD patients with certain genotypes (DMD exon 50 deletion), none has yet successfully completed registration trials. Several approaches for patients with LGMD, such as gene therapy, myoblast transplantation, neutralizing antibody to myostatin, and growth hormone, have promise, but clinical evaluation is not yet complete [6].

Summary

MD comprises a group of heterogeneous genetic conditions with progressive skeletal muscle weakness. Despite the fact that there is no cure for MD, a multidisciplinary team approach with supportive care, such as noninvasive ventilation, improves outcomes including life span and quality of life.

References

1. Darras B, Miller D, Urion D. Dystrophinopathies. In: Pagon R, Adam M, Ardinger H, editors. GeneReviews® [Internet], vol. 1993–2014. Seattle: University of Washington; 2014.
2. Lemmers R, Miller D, van der Maarel S. Facioscapulohumeral muscular dystrophy. In: Pagon R, Adam M, Ardinger H, editors. GeneReviews® [Internet]. Seattle: University of Washington; 2014.
3. Hilbert JE, Ashizawa T, Day JW, Luebbe EA, Martens WB, McDermott MP, et al. Diagnostic odyssey of patients with myotonic dystrophy. J Neurol. 2013;260:2497–504.

4. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol. 2010;9:177–89.
5. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010;9:77–93.
6. Narayanaswami P, Weiss M, Selcen D, David W, Raynor E, Carter G, et al. Evidence-based guideline summary: diagnosis and treatment of limb-girdle and distal dystrophies: report of the guideline development subcommittee of the American Academy of Neurology and the practice issues review panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology. 2014;83:1453–63.
7. Ricker K. Myotonic dystrophy and proximal myotonic myophathy. J Neurol. 1999;246:334–8.
8. Logigian EL, Martens WB, Moxley RT, McDermott MP, Dilek N, Wiegner AW, et al. Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1. Neurology. 2010;74:1441–8.
9. Benditt JO, Boitano LJ. Pulmonary issues in patients with chronic neuromuscular disease. Am J Respir Crit Care Med. 2013;187:1046–55.
10. Villanova M, Brancalion B, Mehta AD. Duchenne muscular dystrophy: life prolongation by noninvasive ventilatory support. Am J Phys Med Rehabil. 2014;93:595–9.
11. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009;73:1227–33.
12. Aitkens SG, McCrory MA, Kilmer DD, Bernauer EM. Moderate resistance exercise program: its effect in slowly progressive neuromuscular disease. Arch Phys Med Rehabil. 1993;74:711–5.
13. Gurnaney H, Brown A, Litman RS. Malignant hyperthermia and muscular dystrophies. Anesth Analg. 2009;109:1043–8.
14. Orrell, RW, Copeland, S, and Rose, MR. Scapular fixation in muscular dystrophy. Cochrane Database Syst Rev. 2010;CD003278. doi:10.1002/14651858.CD003278.pub2.