

Chapter 2

Clinical Manifestations and Overall Management Strategies for Duchenne Muscular Dystrophy

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Abstract

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder that causes progressive weakness and wasting of skeletal muscular and myocardium in boys due to mutation of dystrophin. The structural integrity of each individual skeletal and cardiac myocyte is significantly compromised upon physical stress due to the absence of dystrophin. The progressive destruction of systemic musculature and myocardium causes affected patients to develop multiple organ disabilities, including loss of ambulation, physical immobility, neuromuscular scoliosis, joint contracture, restrictive lung disease, obstructive sleep apnea, and cardiomyopathy. There are some central nervous system-related medical problems, as dystrophin is also expressed in the neuronal tissues. Although principal management is to mainly delay the pathological process, an enhanced understanding of underlying pathological processes has significantly improved quality of life and longevity for DMD patients. Future research in novel molecular approach is warranted to answer unanswered questions.

Key words Dystrophinopathy, Disability, Skeletal myopathy, Respiratory failure, Scoliosis, Cardiomyopathy, Transition of care to adult facility

1 Introduction

Duchenne muscular dystrophy (DMD) is a severe, progressive genetic muscular disorder affecting 1 in 3600–9300 live male births [1, 2]. Although the affected boys are generally normal at birth, they gradually present with muscle weakness and wasting, first from proximal limb muscles, then extending into more distal muscles [3]. By early adolescence, it usually becomes an intractable motor disability by their early teens with a variable degree of multiple organ system dysfunction including neuromuscular scoliosis, joint contracture, osteoporosis (orthopedic), restrictive lung disease, recurrent respiratory infection, obstructive sleep apnea (pulmonary), cardiomyopathy, heart failure (cardiac), feeding difficulty (nutritional), and psychosocial problems [4, 5]. Cognitive impairment and neuropsychological and neurobehavioral problems

are also known to occur in DMD [6, 7]. Without a cure for this disease, a supportive management of each organ dysfunction remains a mainstay of medical management, primarily for improvement of quality of life [8, 9]. It is, therefore, vital to recognize the pathophysiology of each organ dysfunction to provide optimal care for these patients.

To ensure a better understanding of its clinical picture, a typical case of DMD patient is presented. This patient has been routinely followed at our Multidisciplinary Muscular Dystrophy Clinic including Neurology (Neuromuscular), Orthopedics and Physical Therapy, Pulmonary, and Cardiology. The pathological mechanism of each involved organ system is discussed for rationale of supportive management for each affected organ system.

2 Case Presentation

Patient 1 is a 20-year-old Caucasian male who was diagnosed with DMD at 5 years of age when he was noted to have a mild delay in gross motor development, bilateral leg muscle weakness, hypertrophic calf muscles, and elevated serum creatine kinase (CK) > 10,000 IU/ml. He also developed an abnormal gait (toe walking and waddling gait). He was referred to our Neuromuscular Clinic, where the diagnosis of DMD was suspected. Genetic testing demonstrated out-of-frame deletion of exons 46–51 of the dystrophin gene, which confirmed the diagnosis. There was no family history of DMD. He was started on prednisone primarily to preserve skeletal muscle strength. Since then, he has been followed by the Multidisciplinary DMD Clinic, which includes Neurology, Orthopedics, Physical therapy, Pulmonary, and Cardiology, at Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE.

Since the diagnosis, he has shown progressive weakness and wasting of his skeletal muscles, beginning at the proximal muscles of the lower extremities and then spreading to the distal muscles. Around 9 years of age, he developed difficulty in climbing stairs and getting up from a sitting position. By age 12, he became totally wheelchair-bound. By age 14, his muscle strength of upper extremities was also lost except weak grip capacity. He has developed contractures at bilateral hamstrings and Achilles tendons. His sensory function remains intact. He requires complete assistance by his parents to change clothes, toileting, brushing his teeth, feeding, and transfer from his power chair to bed and vice versa. Although he initially had a learning problem in mathematics and language skills (reading and writing) during the elementary and middle school years, he was admitted to college for an advanced education. Currently, he uses his hand fingers to control a power-chair for transportation.

He has had a history of chronic respiratory symptoms and recurrent respiratory illness since his early childhood for which he uses a bronchodilator. After he became wheelchair-bound, pulmonary function test revealed moderate restrictive lung disease with respiratory muscle weakness and progressive neuromuscular scoliosis. At age 13, polysomnogram demonstrated moderate obstructive sleep apnea with significant sleep fragmentation. He was started on bi-level positive airway pressure (BiPAP) via nasal mask during sleep, which significantly improved his daytime alertness and reduced feelings of tiredness. He was also instructed to use the Acapella[®] device (positive expiratory pressure therapy) to prevent respiratory illness.

At age 13, he fell from a wheelchair and suffered from fractures of the left tibia and fibula, for which he was treated supportively. His neuromuscular scoliosis became more prominent during his growth spurt, which worsened respiratory status and made his sitting position unstable, with a concern of developing a pressure sore. At age 14, he underwent posterior spinal fusion for progressive neuromuscular scoliosis, resulting in improved respiratory function and stability on the wheelchair. However, he continues to have bilateral hip abduction contractures and bilateral knee flexion contractures; the contractures of the shoulders and arms are less significant.

He has been regularly followed by Cardiology with ECG and echocardiogram since 9 years of age. At age 13, echocardiogram showed mildly diminished left ventricular (LV) function (% fractional shortening 26%), for which he was started on angiotensin-converting enzyme inhibitor (ACEI), enalapril, for a cardioprotective purpose. At age 15, β -blocker, carvedilol, was added for persistent mild LV dysfunction with increment of dosage as tolerated. At age 19, LV systolic function was moderately diminished (% fractional shortening <20%), but LV chamber size remained within normal limits. Currently, he is taking enalapril, carvedilol, and aldactone to prevent further worsening of myocardial remodeling in addition to corticosteroid. Nevertheless, he continues to be asymptomatic from a cardiac standpoint. Recent Holter ECG showed rare isolated premature ventricular complexes (PVCs) with no evidence of pathological tachyarrhythmia.

Due to an age limitation at our pediatric institution, a transition to an adult care facility has been discussed with the patient and his family. Possible candidacy of advanced heart failure treatment (left ventricular assist device or LVAD, etc) was discussed with the patient and his family.

3 Molecular Genetics and Pathology of Dystrophinopathies

Becker muscular dystrophy (BMD), DMD, and X-linked dilated cardiomyopathy (XLDCM) comprise a clinical spectrum of dystrophinopathies [10, 11]. Dystrophin is the second largest protein in an entire human body (the largest protein, titin) that serves as a part of cytoskeleton connecting between contractile apparatus and extracellular matrix. Total or partial deficiency of dystrophin results in a loss of physical integrity of muscle cells, causing contraction-induced muscle degeneration. Muscle repair and muscle regeneration mechanisms are also compromised in dystrophinopathies [12]. Muscle wasting occurs when the speed of degeneration exceeds that of repair and regeneration of skeletal muscle cells; after this fatty tissue and fibrosis replace the loss of muscle cells [12, 13]. Although mutation is located within the same dystrophin gene, clinical phenotype is variable depending upon the degree of involvement in skeletal muscles, myocardium, and CNS [10, 14]. Duchenne muscular dystrophy is a clinical entity with complete absence of dystrophin protein in both skeletal muscle and myocardium due to frameshift mutation and has the severest clinical phenotype of all. Duchenne muscular dystrophy frequently occurs de novo without X-linked inheritance. There seems to be no significant correlation between the size or specific sites of deletion of the genotype and clinical phenotype or severity of skeletal muscle involvement [11, 15, 16].

Becker muscular dystrophy is a partial deficiency of dystrophin with partially functional dystrophin protein and thus has milder clinical phenotype than DMD. Cardiac involvement occurs late in BMD, but functional deterioration may be more rapid and progressive than DMD once it starts to show myopathic changes in the myocardium [17–20]. Familial X-linked dilated cardiomyopathy (DCM) presents with progressive ventricular dysfunction and chamber dilatation without skeletal muscle abnormality or CNS involvement; however, cardiac phenotype is extremely variable in terms of severity and onset [21–23]. The correlation between genotype and clinical phenotype in the dystrophinopathies, DMD, BMD, and XLDCM remains largely unpredictable [10, 11].

4 Multiple Organ Involvement in DMD and Management Strategies

4.1 Neuromuscular

A principal clinical feature of DMD is characterized by progressive muscle weakness and wasting beginning in the proximal limb muscles, and then to the distal limb muscles [3, 4]. Affected children initially present with delayed gross motor development, gait abnormality, and difficulty climbing stairs or rising from the floor. They then inevitably become wheelchair-bound, usually by age 13.

Physical immobility accelerates the decrease in bone density and the risk of fracture. Neuromuscular scoliosis and joint contractures develop as muscle weakness worsens. Thus, attenuation of muscle wasting and prevention of secondary skeletal deformation are primary DMD management goals.

Corticosteroids are known to preserve the strength of skeletal muscles as shown by multiple studies [5, 24–27], but the underlying mechanism is not well understood. Current recommendations suggest the initiation of steroid treatment as early as time of diagnosis, usually around 4–8 years of age. However, the long-term steroid complications need to be monitored closely, including short stature, delayed puberty, obesity, osteoporosis, cataracts, and depression or psychological alteration [4]. The timing of steroid discontinuation after the patient becomes wheelchair-bound is not clearly understood. Steroid treatment is also known to attenuate progression of cardiomyopathy [24, 26].

4.2 Orthopedic (Musculoskeletal)

Neuromuscular scoliosis is a frequent complication in DMD because truncal muscles weaken, usually after ambulation is lost. Scoliosis can be delayed by proper wheelchair fitting or steroid treatment. Surgical correction of scoliosis (posterior fusion) can improve respiratory function, stability of sitting in the wheelchair, prevention of pressure sore, and quality of life [28]. However, the validity of published data on clinical benefits of spinal surgery for DMD patients is somewhat limited because it is largely retrospective and anecdotal. Based on our experience, the surgical correction of scoliosis in DMD patients significantly improves functional stability in the wheelchair and quality of life, without notable complications. Earlier intervention is recommended while the lumbar spine is still stable and straight to prevent the fusion of the iliac crest [28]. Annual orthopedic consultation is warranted if the spinal curve exceeds 20 degrees. Other noninvasive supportive devices may be offered in milder cases.

Decreased bone density, significant muscle weakness, and diminished power and motor agility make bone fractures more common in patients with DMD [29]. Steroid use has not been shown to increase the risk of fracture [29]. Internal fixation is warranted for severe lower limb fractures in ambulatory patients, whereas splinting and casting is usually sufficient for nonambulatory patients [8].

4.3 Pulmonary

Respiratory status in DMD is characterized by ventilatory insufficiency, diminished cough capacity, increased incidence of respiratory tract infection, and sleep-disorder breathing [30]. Ventilatory insufficiency due to weakness of respiratory muscles has been responsible for major morbidity and mortality in DMD patients [30, 31]. In particular, weakness of the diaphragm advances after the loss of ambulation. Progression of neuromuscular scoliosis may

result in a loss of lung volume, which contributes to restrictive lung disease [32]. Serious acute respiratory failure may be induced by pneumonia or even a benign upper respiratory infection in DMD as a result of retained secretion due to inability to cough effectively. Routine cough training is essential in improving airway clearance and reducing atelectasis, as expiratory muscles may be more affected than inspiratory muscles in DMD [33, 34].

Other critical issues include the recognition and treatment of obstructive sleep apnea ([OSA] or nocturnal ventilator insufficiency), primarily due to a decrease in strength of respiratory muscles [35, 36]. The OSA is not only responsible for snoring, increased daytime tiredness and drowsiness, and headache. It is also known to increase cardiovascular morbidity by inducing hypertension, stroke, and heart failure even in a normal population [37, 38]. Those who complain of these symptoms should have a sleep study (polysomnogram) and are indicated for bilevel continuous pressure ventilation (BiPAP) upon positive sleep apnea, hypoxia, and/or hypercapnia.

4.4 Cardiac

Myocardial involvement is inevitable for DMD patients because dystrophin serves the same biological role in cardiomyocytes as in skeletal muscle cells [39–41]. Pathological alteration of ventricular myocardium in DMD is heterogeneous [42] and probably a result of a combined consequence of myocardial wasting (atrophy) [43, 44] and secondary geometric changes (remodeling) due to decreased systolic function secondary to progressive cardiomyocytes destruction [45]. The latter process occurs in combination with secondary fatty infiltration and fibrosis upon myocyte death. Although we routinely address DMD cardiomyopathy as DCM, the affected heart does not always show ventricular dilatation. The majority show normal ventricular dimension with decreased systolic or diastolic function but always with a thin ventricular wall. Thus, it is not appropriate to stereotypically describe DMD cardiomyopathy as DCM. The earliest visible clinical signs of cardiomyopathy in DMD are either decreased systolic function [13, 45] or resting sinus tachycardia [46]. The mechanism of resting tachycardia is not well understood, but it may be, in part, induced by dysautonomia [47]. Myocardial damage and fibrosis may precede visible ventricular dysfunction, which can be detected by MRI with late gadolinium (Gd) enhancement [48]. Currently, early initiation of ACE inhibitor before age 10 is recommended, as earlier treatment is shown to be effective in attenuating cardiomyopathy in DMD [49–51]. Several studies have indicated that corticosteroid is beneficial in preserving myocardial function, just as in skeletal muscle [24, 26, 52, 53].

4.5 Cognitive, Neuropsychological, and Neurobehavioral

In addition to muscular tissues, dystrophin is also expressed in retina, kidney, and central nervous system (CNS) [54]. Consequently, there is an increased incidence of cognitive impairment, neuropsychological problems, and neurobehavioral abnormalities among patients with DMD [7, 55]. Susceptibility to seizure is also reported to be higher in DMD patients when compared with the normal population [56]. Early and thorough recognition of cognitive impairment and neuropsychological and neurobehavioral problems in DMD is necessary because they have a major impact on quality of life, self-esteem, and self-confidence and because they may affect understanding of and adherence to medical treatments [7]. The essential goals of management of DMD are to preserve the skeletal muscle function, to optimize the support of related organ failures, and to improve the quality of life. Further research is warranted for a better understanding of neuropsychological and neurobehavioral aspects of DMD.

5 Transition of Care to Adult Facility

Due to improved supportive management of patients with DMD, a longevity has improved significantly over the last few decades. The average lifespan of these patients is now reported up to early 30s [8]. Young men with DMD need specialized adult care. However, the transition of young adults with DMD from pediatric to adult health service is a complex, time-consuming, and ongoing process and frequently results in poor health outcomes [57]. Common challenges include limited knowledge of child-onset conditions among adult care providers, fragmented information and limited specialty services, and the fact that transition takes place when the progression of the disease is worsening [57]. There is also increased stress on the aging parents, as they are the principal caregivers of the patients with DMD [58]. The concept of a “Lifespan Care” approach has been proposed to introduce gradual transitions from a pediatric care team to a young adult care team and eventually to an adult care team, not by the patient age but by classic markers of emerging adulthood including consolidation of an adult male identity, greater level of independence, access to work, education, and training, and adult friendships and intimate relationships [59].

6 Conclusions

Duchenne muscular dystrophy causes multiple organ system failure caused by progressive muscle weakness and wasting including neuromuscular, skeletal (orthopedic), respiratory, and cardiac problems. Separately, certain CNS related problems are reported independent of muscle degeneration. Recent advancement of

medical care has significantly improved life expectancy and quality of care of patients with DMD. Although multiple novel therapeutic modalities are under clinical trial, there is still work to be done. Thus, it is crucial to recognize and understand the underlying mechanisms of the disease for better patient management.

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