

Case report

Duchenne Muscular Dystrophy Presenting with Cardiomyopathy and Neurological Decline: A Case Report

ABSTRACT:

Duchenne muscular dystrophy (DMD) is a lethal, X-linked neuromuscular disorder caused by the absence of dystrophin protein, which is essential for muscle fiber integrity. It is one of the most severe types of inherited muscular dystrophies affecting approximately 1 in every 3,500 male births worldwide. The estimated prevalence rates of the most common forms of muscular dystrophy are 1 in 5,000 live male births for Duchenne muscular dystrophy (DMD). Being the most common and most severe type of muscular dystrophy, Duchenne muscular dystrophy (DMD) is caused by mutations in the X-linked dystrophin gene. Loss of dystrophin protein leads to recurrent myofiber damage, chronic inflammation, progressive fibrosis, and dysfunction of muscle stem cells. The risk factors associated with DMD include family history, gender, muscle weakness, low BMI, poor lung function and genetic variation. Based on ambulation, the DMD Care Consideration working Group created a classification system for DMD patients. In most cases, there is a delay in motor development, resulting in wheelchair confinement after 3 years of disease and ultimately an early death from respiratory or cardiac issues. It is quite complicated to diagnose DMD due to the limited facilities of genetic testing and its high-cost. The accurate and early diagnosis of DMD plays an important role in effective patient management. In areas with limited facilities, the clinician should confirm the DMD not only by anamnesis and clinical features, but also by taking a patient's history, testing for genes, and detecting elevated creatine kinase and other transaminases in the lab, progressive motor weakness, myopathies on EMG is still the most significant finding of the illness. Although new treatments continue to strive for a cure for this life-threatening condition, treatment approaches include corticosteroid therapy, intermittent positive pressure breathing have improved function, ambulation, quality of life, and life expectancy. Here, we report a case of a 27 years male patient, who has DMD and exhibits notable cardiac, neurological and clinical symptoms.

KEY WORDS: Duchenne Muscular Dystrophy, Dystrophin, Ambulation, Motor Development, Transaminases.

INTRODUCTION

“Duchenne muscular dystrophy (DMD) is an early-onset, severe, rapidly progressive neuromuscular disease belonging to a pathological group of diseases known as dystrophinopathies with muscle weakness as the primary clinical manifestation” [1]. “It is a lethal progressive genetic disorder characterized by muscle deterioration and muscle wasting” [2]. “Muscular dystrophies are a heterogeneous group of inherited myopathies that share similar clinical features and dystrophic changes on muscle biopsies which was first described by French neurologist Guillaume Benjamin Amand Duchenne in 1860’s” [3].

“It is a single-gene disorder that is genetically inherited, DMD is brought on by mutations in the DMD gene. Dystrophin is a 3685 amino acid protein that is encoded by the DMD gene, the biggest known human gene, which is found on the X chromosome and has 79 exons” [4]. “The dystrophin gene is located on the short arm of chromosome X near the p21 locus and codes for the large protein Dp427. Despite the low percentage of dystrophin protein expression (about 0.002%) of the proteins in striated muscle, its importance in maintaining the membrane integrity of muscle remains high. The dystrophin gene, the largest gene yet identified in humans, spans approximately 2.3 megabases at chromosome Xp21.2, and the protein product has a large size (427 kDa). In about 60% of patients with DMD, dystrophin mutations are associated with deletions of one or more exons” [5]. “The severity of DMD depends on the mutation type. ‘Out- of frame’ mutations disrupt the reading frame and further produce the dysfunctional dystrophin, which results in the severe DMD phenotype. On the other hand, ‘In-frame’ mutations perverse the frame of DMD gene and generate partial functional dystrophin protein, which lead to less severe Becker muscular dystrophy (BMD) phenotype” [6]. It manifests as difficulty in climbing stairs, frequently falling, waddling gait, pseudo hypertrophy of the calves, lumbar lordosis, and positive Gower’s sign. Weakness is more pronounced in proximal than distal muscles [7][8]. Higher levels of cardiac damage biomarkers, a lower body mass index (BMI), and worse lung function were all linked to an increased risk of mortality. Furthermore, the onset and natural evolution of muscular dystrophies may be influenced by biological, socioeconomic, environmental, psychological, and concomitant genetic variables. Muscle contraction initiates and advances the pathophysiology of DMD. In the early stages of DMD, the amount of creatine kinase (CK) leakage into the extracellular space can be used to gauge the extent of muscle cell destruction. Numerous mechanisms have been identified as cell-damaging in DMD, including calpain activity, activation of nuclear factor kappa beta (NFκB), and buildup of reactive oxygen species. On the other hand, excessive calcium ion (Ca²⁺) inflow into skeletal muscle cells, coupled with heightened vulnerability to plasma membrane disruption, is thought to be the primary cause of muscle damage in DMD [9]. DMD eventually can also lead to cardiovascular, pulmonary and orthopaedic complications [7]. Here is a case report of DMD.

CASE REPORT

A 20 years old male patient was referred to hospital already diagnosed with dilated cardiomyopathy presented with mild grade fever, loss of appetite and nausea, shortness of breath grade 1 to 3 with orthopnoea in the last one week. Upon detailed investigation the patient had complaints of low-grade intermittent fever not associated with arthralgia, myalgia and rash in the past 6 months and high-grade intermittent fever in the last 10 days which was relieved with medication (acetaminophen 650mg). Loss of weight, Loss of appetite for 1 year. Dysphagia (solids >> liquids) in the past 3 months which increased in the last 10 days, Dysphagia to solids followed by vomiting in the last 1 month.

The past medical and medication history revealed that the patient had psychiatric symptoms for 5 years (not on medications), hearing loss 7 years ago (cause not identified) and multiple episodes of vomiting (4-5 hospital admissions). No significant family history was presented. The provisional diagnosis of dilated cardiomyopathy with cardiogenic shock, post infectious

metabolic encephalopathy was made and further laboratory investigations revealed. Upon further referral to neurologist and ENT specialist the parent reports a history of delayed milestones, aggressive behaviour, talking to self, weakness of lower limb for 3 years, weakness of UL in the last one year, weakness of LL Proximal > Distal increased since last 6 months. Inability to lift heavy objects, hoarseness of voice from 3 years, difficulty in getting up from sitting position and climbing stairs for 2 years, difficulty in wearing slippers for 6 months and dysarthria since 1yr. The patient was subjected to radiological and laboratory investigations. Serological analysis showed elevated levels of Creatine kinase (7342 U/L), lactate dehydrogenase (565 µg/dl) and aspartate aminotransferase (543U/L). The echocardiography revealed all 4 chambers dilated, severe LV systolic dysfunction, no DDF, severe MR, TR, PAH, no veg/clot/PE. An electromyography examination revealed motor sensory axonal neuropathy B/L LL>UL. MRI Brain revealed no abnormality and urine culture sensitivity revealed presence of candida species.

Based on history and laboratory investigations, the diagnosis was established as Duchenne Muscular Dystrophy which was confirmed by high serum marker levels of CK, lactate dehydrogenase, and aspartate aminotransferase levels were markedly increased. The patient was treated with aldosterone receptor antagonists (Spironolactone- 50 mg/day/BD), ACE inhibitors (Lisinopril 40 mg/ day), beta blockers (Metoprolol 50 mg/ OD) and counselled to undergo regular physiotherapy and regular assessment for further complications.



Figure 1: Muscle wasting; patient with DMD showing muscle wasting of the upper limb.

DISCUSSION

“Duchenne muscular dystrophy (DMD) is a lethal, X-linked neuromuscular disorder caused by the absence of dystrophin protein, which is essential for muscle fiber integrity”^[6]. It is the most prevalent form of muscle dystrophy in both India and the rest of the globe”^[8]. DMD is caused by mutations in DMD (encoding dystrophin) that prevent the production of the muscle isoform of dystrophin (Dp427m). Mutations in DMD can also cause Becker muscular dystrophy (BMD). According to the sarcolemma hypothesis, DMD is caused by structural and functional defects of a sarcolemma protein owing to mutations in the encoding gene^[10]. It is characterized by progressive muscle weakness that affects limb, axial, and facial muscles to a variable degree. In specific forms, other muscles including respiratory muscles, cardiac smooth muscles and swallowing muscles, can also be affected. In rare variants, the disorder is associated with involvement of other organs or tissues, such as the brain, inner ear, eyes, or skin^[11]. Analyzing serological testing can lead to early detection, the diagnosis is rarely made before the patient is 2 to 6 years old. The appearance of the disease is insidious and usually overlooked in its early stages. The disease becomes apparent with the onset of a clumsy, waddling gait, frequent falling, and delayed motor milestones (sitting, walking, running)^[12]. Here the patient is presented with delayed milestones like muscle weakness, dysphagia, dysarthria, and cardiomyopathy is

consistent with DMD. The diagnosis was confirmed by elevated creatine kinase (CK) levels, electromyography (EMG) findings, and characteristic clinical features of DMD. Due to the mutations in the dystrophin gene, leading to absent or deficient dystrophin protein. This protein plays a crucial role in maintaining muscle cell membrane integrity. Without dystrophin, muscle cells undergo necrosis, leading to progressive weakness and degeneration. Patients also suffer from Cardiomyopathy which is a common complication of DMD, occurring in approximately 90% of patients, whereas echocardiography findings revealed that dilated cardiomyopathy, severe left ventricular systolic dysfunction, mitral regurgitation (MR), tricuspid regurgitation (TR), and pulmonary arterial hypertension (PAH) are consistent with DMD-related cardiomyopathy. The patient has beneficial effect in reducing the symptoms of the disease by the usage prednisolone but due to its side effects it was discontinued and administrated with Ataluren. It is a non antibiotic molecule that promote ribosomal read through of nonsense (stop) mutations to allow the pathogeneic varients, ACE inhibitors (Lisinopril 40 mg), Aldosterone antagonists (Spironolactone 50 mg), beta blockers (Carvedilol 50 mg) and regular sessions physiotherapy.

Table-1: Laboratory Findings

Lab Parameters	Results
Serum creatinine	7342 U/L
Lactate dehydrogenase	565 ug/dl
Aspartate Aminotransferase (AST)	543U/L

⚡ Elevated CK levels (7342 U/L) and abnormal EMG findings confirm muscle damage.

⚡ Serum lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) elevations indicate muscle and cardiac damage.

Treating Duchene muscular dystrophy (DMD) primarily aims to control symptoms and enhance quality of life because there is presently no cure for the condition. The patient is administered with the following supportive therapy like corticosteroids (prednisolone 40 mg), which help to improve lung function, prevent the loss of muscle strength, reduce the onset of cardiomyopathy (heart weakness), and increase survival. The lifelong usage of steroids requires an optimal follow-up is necessary for the monitoring its side effects (behavioural disturbance, weight gain, gastric irritation and adrenal suppression). Aldosterone receptor antagonists (Lisinopril), ACE inhibitors (Spironolactone)and beta blockers (carvedilol) are given to manage cardiomyopathy and regular sessions of physiotherapy helps to maintain muscle strength and mobility on another hand ensuring adequate nutrition to prevent malnutrition the patient has beneficial effect in reducing the symptoms of the disease. There are some advanced therapies for DMD that include gene therapy (AON - Mediated Exon Skipping Therapy, Vector mediated gene therapy), Eteplirsen is used for the region of exon 51 of the DMD gene Inflammatory modulators, (Pentraxin 3, polyunsaturated fatty acids, statins & purinergic receptors), calcium channel Targets, gap junction protein targets, neurohormonal modulators (BDNF / Tyrosine kinase B), antiarrhythmic agents, CRISPR therapy (gene editing therapy).

CONCLUSION

Duchenne muscular dystrophy is a progressive inherited myopathy with an early onset in childhood. It progresses to the bed-bound state in the second decade of life and patients are usually prone to respiratory or heart complications. Conservative management, active physiotherapy, genetic counselling and other supportive therapies hold the key to successful management of the case. A lack of disease awareness and subsequent failure to recognize DMD signs and symptoms, especially atypical presentations of disease, leads to delayed diagnosis of DMD worldwide. This case highlights the necessity for ongoing investigations into novel therapies, improved management strategies, and enhanced supportive care to improve the quality of life for patients with DMD. Different therapeutic strategies for DMD have been developed. Numerous researches and clinical trials have been performed as detailed above. Nevertheless, there is still no effective disease modifying therapy and many questions remain unsolved. By sharing this case, we hope to increase awareness and promote better understanding of DMD, which will ultimately lead to improved patient outcomes and advancements in the field.

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Consent

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

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