ISSN: 2582-6751
Journal of Clinical Medical Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Case Report

Exertional Weakness Seen as An Important Clinical Manifestation in Female Carriers of Duchenne Muscular Dystrophy

Bryan Velasco[1], Jennifer Pagano[2], Laura Patrick[2], Nivedita U Jerath[2*]

[1]Kansas City University, College of Osteopathic Medicine, Kansas City, Missouri, USA

[2]AdventHealth Neuroscience Institute, Orlando, FL 265 E. Rollins Street, Orlando, FL 32804, USA

***Correspondence author:** Nivedita Jerath, AdventHealth Neuroscience Institute, Orlando, FL 265 E. Rollins Street, Orlando, FL 32804, USA; Email: nivedita.jerath.md@adventhealth.com

Citation: Jerath NU, et al. Exertional Weakness Seen as An Important Clinical Manifestation in Female Carriers of Duchenne Muscular Dystrophy. Jour Clin Med Res. 2023;4(2):1-5.

http://dx.doi.org/10.46889/JCMR.2023.4205

Received Date: 05-05-2023

Accepted Date: 24-05-2023

Published Date: 02-06-2023

Abstract

Introduction: Duchenne Muscular Dystrophy is an X-linked recessive condition caused by dystrophin mutations.

Case Presentation: Three unrelated women who were carrying a pathogenic dystrophin mutation were evaluated with clinical, laboratory, electrophysiological, and genetic testing.

Discussion: These cases present a common clinical trend of exertional weakness demonstrated in female carriers of dystrophic mutations.

Conclusion: Although males with dystrophin mutations get progressively weak with overt weakness, females with dystrophin mutations in our study exhibit more exertional weakness, which necessitates the need for including this mutation in the spectrum of differential for exertional weakness and fatigue.

Highlights:

- Men with Duchenne Muscular Dystrophy, an x-linked recessive disease exhibits significant progressive weakness that leads to significant disability and eventually death
- Women who are carriers for Duchenne Muscular Dystrophy exhibit more exertional weakness and fatigue

Keywords: Duchenne Muscular Dystrophy; Dystrophin; Female Carriers; Exertional Weakness

Abbreviations

DMD: Duchenne Muscular Dystrophy

Introduction

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disease caused by mutations in the dystrophin gene. This mutation will hence affect the protein "dystrophin"- which is responsible for holding muscle cells together. Consequentially, the primary symptom seen in male patients with DMD is progressive weakness due to the deterioration of muscle fibers. The proximal extremities are more likely to be affected than the distal extremities. Owing to its X-linked recessive inheritance pattern, this disease is more commonly seen in males. While females can also inherit the disease, they are less likely to exhibit symptoms. There have been variable reports as to female carriers exhibiting symptoms with some studies suggesting that almost 22% can exhibit symptoms. Though it is known that DMD causes overt weakness in males, clinical trends need to be investigated in female carriers [1,2].

At this time there is no clear phenotype to genotype association that accounts for the occurrence of symptoms in female DMD carriers. Because DMD is located on the X chromosome, the presence of a second fully functioning copy of DMD was thought to have a protective effect for women. Originally symptom onset in women was thought to be a result of skewed X-chromosome

inactivation, in which the mutant DMD allele is predominantly expressed. This has become controversial due to later studies which found a lack of relationship between skewed X-inactivation and dystrophic phenotype. In this study both symptomatic and asymptomatic carrier females were found to have equal amounts of mutated and wild-type RNAs or in some cases greater occurrence of wild-type transcripts. One study found that a higher proportion than expected of symptomatic carriers had duplication variants. The cases featured here include two deletions and 1 indel. The newest research in search of distinguishing symptomatic from a symptomatic carrier on a molecular level suggests the answer lies in microRNA(miRNA) sequencing. Mousa et al found that several miRNAs measured in leukocytes and plasma show a correlation with the severity of muscular weakness in carriers. All though genetics has not yet provided an answer as to why some female carriers develop symptoms, it is important to investigate clinical trends in this group.

Methods

Three female subjects with a known pathogenic mutation for dystrophin were retrospectively analyzed with genetic and clinical data. Genetic data included the Invitae 143 gene panel- Comprehensive Neuromuscular Disorders Panel, Comprehensive Muscular Dystrophy Panel, Limb-Girdle Muscular Dystrophy Panel, Add-on Preliminary-evidence Genes.

Results

Subject 1

Subject 1 is a 35-year-old female, originally from North Carolina, with a past medical history significant for pulmonary embolisms, cerebral vascular disease, benign hypertension, and psoriasis who presented to the clinic due to numbness and exertional weakness for several years. Family history of neuromuscular disease is unknown. Her symptoms began at the age of 33, when she developed gradual onset of numbness beginning in the left hallux, spreading up to her knees. At age 35, she began feeling numbness in her face, abdomen, tip of her tongue, and fingertips bilaterally.

Her symptoms are present at rest but worsened with physical activity. She noticed a significant worsening in her symptoms about 2 years prior, when she developed difficulty with balance and coordination, as well as an increased level of pain. She now has numbness and excruciating cramping pain in both legs, to the point of tears. Patient stated, "I can't go grocery shopping without having to lean on the cart the entire time because of the weakness in my legs, it's even too hard to climb stairs". Patient was unable to get up after sitting on a floor. She was diagnosed with psoriasis in 2013 after the first plaque developed on her head. The psoriasis spread throughout scalp, arms, and legs in which she was placed on biologics for treatment in 2014. Shortly after, she began experiencing fatigue, body aches, and brain fog. Prior to her symptoms developing at age 26, she led an active lifestyle and taught acrobatic classes for 30 hours a week. Unfortunately, the body aches/pain became too severe and unbearable for the patient to continue with her active lifestyle/ acrobatic career. In 2014 she was diagnosed with fibromyalgia by a rheumatologist and got a second opinion in 2020 with a different rheumatologist in which he denied the previous diagnosis of fibromyalgia [3-6].

On physical exam, her sensation was abnormal- with decreased pinprick and vibratory sensation on her shins and calves, bilaterally. Her neurological gait and coordination were intact. EMG/NCS showed sensory neuropathy and possible myopathy of upper and lower extremities. Her vitamin D level was initially low but retested within normal limits. Patient was tested with SPEP, Hba1c, CK, IFE, voltage gated calcium channel, paraneoplastic panel, striated muscle antibody, voltage gated potassium/calcium channel, acetylcholine receptor ab, anti-jo, myositis panel, hepatitis, ANA, Sjogren's were negative. Genetics: She carried a heterozygous pathogenic DMD Deletion (Exons 49-51). She underwent testing with a 143 gene Invitae sequencing panel including the comprehensive muscular dystrophy panel and comprehensive neuromuscular disorders panel. She was found to carry a heterozygous pathogenic DMD Deletion (Exons 49-51). This deletion is expected to be associated with BMD and X-linked Dilated Cardiomyopathy (DCM), as the three-exon deletion maintains the integrity of the reading frame. There has been at least one patient reported to have a DMD phenotype conjectured to be caused by genetic modifiers or spontaneous exon skipping events. Deletions of exons 45-55 is a hotspot location, associated with mild or late onset skeletal muscle involvement [6]. In-frame deletions within that hot spot have also reportedly correlated with later onset of DCM [7]. There have been no reported symptomatic female carriers to our knowledge with the same variant.

Rehab Presentation

She was referred for physical therapy, occupational therapy and speech therapy services starting in February of 2022. Upon evaluation on 2/11/22, she had frequented near falls and neuropathy was both causing excessive pain and decreased balance. She demonstrated decreased ankle strategies due to weakness with increased use of hip strategies during balance reactions. Interventions focused on core strengthening, static balance with integrating vestibular involvement with use of reducing visual dependence and increasing ankle strategy responses during loss of balance. By 3/29/22: Recommended custom AFOs based upon ankle dorsiflexion weakness and progression of extensor thrust bilaterally during midstance and terminal stance during gait. At this time added a seating and mobility evaluation based upon decreased gait speed, decreased strength, and decreased walking endurance. Patient was unable to safely perform community mobility to care for her children. Deemed a scooter to be the best option for this patient as this would give her power mobility without the current need for custom seating or power seating features.

Patient was evaluated for speech therapy due to complaints of dysphagia and evaluation demonstrated the patient presenting with overt signs and symptoms of oral decompensation noted by decreased lingual strength and coordination and decreased mastication resulting in decreased bolus control. She has no overt signs or symptoms of pharyngeal decompensation. Pt independently utilized small sip and small bites. She required regular solids and thin liquids with use of small bites/sips. Speech therapy was indicated to ensure safety of swallow function with more complex dietary items and decrease risk of aspiration.

Subject 2

46-year-old women presented to the clinic with a 5-year history of hip flexion weakness, bilateral foot drop and hand proximal and distal weakness. Family history consisted of her maternal grandfather who was diagnosed with an unspecified neuromuscular disease. She was diagnosed with scoliosis as a child. She describes having a shortened Achilles tendon on her right foot and stated she was a slow runner. Patient denied having cramps or numbness. According to the patient her symptoms included hip flexion weakness, bilateral foot drop, and hand proximal and distal weakness. Review of systems indicated right sided weakness, muscle weakness, muscle aches, arm muscle wasting, and neck pain. These have made it difficult to walk unassisted, going up stairs, carrying groceries, and getting up from a seated position.

Upon neurological motor examination, exam showed right deltoid 4/5, right triceps/biceps 4/5, left triceps 4/5, first dorsal interosseous muscles/abductor pollicus brevis/accessory abductor digiti minimi bilaterally 4/5, and finger extensors on right 4/5. Bilateral foot drop was observed along with hip flexion weakness and knee extension weakness 4/5. Coordination/gait was unable to be assessed due to use of a wheelchair. Sensation was intact for upper and lower extremity bilaterally. Bicep reflexes were abnormal at 0/4 bilaterally. Patients muscle biopsy revealed marked variation in myofiber diameter with frequent small rounded myofibers, rare large rounded myofibers, increased internal nuclei and evidence of myofibrillar architecture changes. The findings of moderately to markedly increased endomysial connective tissue with early fatty replacement indicate a chronic process. No inflammation was seen to suggest a histopathologic diagnosis of inflammatory myopathy.

Genetics testing revealed a heterozygous pathogenic deletion of the DMD gene c.988_997delinsCACTC (p.Phe330Hisfs*7). Patient underwent testing with a 143 gene Invitae sequencing panel including the comprehensive muscular dystrophy panel and comprehensive neuromuscular disorders panel. She was found to carry a heterozygous pathogenic deletion insertion, c.988_997delinsCACTC (p.Phe330Hisfs*7) in exon 10. This variant is classified as pathogenic as it is expected to cause truncated or absent protein product due to the creation of a premature stop codon. Loss of function mutations leading to complete or partial loss of dystrophin expression are known to be pathogenic. This variant to our knowledge has not been reported in the medical literature in association with either male or female dystropinopathy patients. Patient's test report also returned four variants of uncertain significance. These results were all heterozygous variants in genes associated with recessive disease and are unlikely to contribute to patient's phenotype.

Subject 3

44-year-old woman presents to the clinic with complaints of weakness in her arms and legs with significant difficulty when walking, shortness of breath, and difficulty with her day-to-day activities. Patient has a past medical history of dysautonomia, diabetes insipidus and a family history consisting of a brother with DMD. Patient stated that around age 8 she began having knee and body pain which after she developed fatigue and weakness. During childhood she could never push herself out of the

pool and could never run correctly. Patient explained she would have periods of fatigue. She described herself as clumsy during that time. Around age 15, she had pain in her knee, back, and leg as well as hip aches. In her 20's she hurt her back and had to have her first back surgery at age 23 as well as two knee surgeries. She was later found to have degenerative disc disease which had needed fusion surgery to correct at age 27.

She started to have a drastic shift in fatigue after a major gallbladder infection in which the fatigue never went away. Currently she is unable to walk or take showers. Patient has weakness in her legs and generalized cramps and states the larger the muscles are, the more they are affected. Currently she is unable to walk and has weakness in her legs. She is unable to reach over her head as her arms will fatigue. Moving up and down stairs is hard for the patient and states she has "pain in her muscles, joints, tendons, and ligaments." She also has a hard time taking a shower due to not being able to get in and out of the shower. A recent motor vehicle accident made her symptoms worse and she's currently in an electric wheelchair.

Review of symptoms were positive for difficulty initiating and maintaining sleep, blurred vision, jaw fatigue, raspy voice, shortness of breath when walking, palpitations and fatigue. On physical examination, cranial nerve examination was intact. Motor exam showed bilateral hip flexion weakness and during assessment of gait, she had a wide based gait with upper body swaying, difficulty walking, and feeling winded.

Genetics

Genetic Testing

DMD Deletion (Exons 8-9) heterozygous PATHOGENIC
SYNE2 c.2270T>C (p.Leu757Ser) heterozygous Uncertain Significance
SYNE2 c.6511C>G (p.Leu2171Val) heterozygous Uncertain Significance

Subject 3 underwent genetic testing using a commercial Invitae genetic testing panel. She carries one pathogenic deletion of exons 8-9 of the DMD gene. This out of frame deletion results in a premature termination codon causing disrupted or absent deficient protein product. Loss of function is a known method of pathogenicity in the DMD gene. Additionally, patient's brother had a diagnosis of DMD and died at age 21. Patient's mother is an obligate carrier of the pathogenic variant, although it is unclear whether she is symptomatic. This variant has been previously reported in association with an affected female carrier. Previously reported subject had age of onset at 23 years old and progressive, asymmetric weakness primarily in the limb and girdle regions. The SYNE2 gene currently does not have a well-established disease association, and genetic testing that the patient underwent cannot determine if the two variants are in cis or trans. There is preliminary evidence for an association between SYNE2 and autosomal dominant Emery-Dreifuss Muscular Dystrophy.

Discussion

The clinical features of women who are carriers of DMD in this study revolved around overt and especially exertional weakness. 100% of patients in this study showed exertional weakness in the lower extremities while 66.67% showed signs of both overt upper and lower extremity weakness. These results had commonalities with the results from a case study on muscular strength in symptomatic female carriers of DMD. Their results included female carriers with muscular weakness and patients had compensatory movements and longer timed performance on functional tasks. Functional performance deterioration was seen with all three patients in our case study as exertional weakness caused the patients to not be able to complete everyday tasks. These examples include, walking upstairs (all three patients) or affecting posture with compensatory movements as one subject having to lean over the grocery cart in order to grocery shop due to exertional weakness. Using genetics, such as X linked inactivation, as a means to determine which female patients will be symptomatic is not a completely defined answer. According to Brioschi, there seems to be a lack of a relationship between a dystrophic phenotype and an X-inactivation pattern in females. In the study only a percentage of the participants showed skewed X inactivation in both the symptomatic and asymptomatic [5]. While according to Mousa, et al., Micro RNA seems to have a relationship with the severity of the subject's muscular weakness [3]. Micro RNA is subset of RNA class that regulates genetic expression in the human body. In this study MiR-494-3p was elevated in patients who were symptomatic [3]. MMiR-206 and miR-4103p were the most elevated in a subset of participants who were the most symptomatic [3]. The data suggests that these Micro RNA's can be useful to identify patients with DMD but most importantly it can applicable to identify and diagnose female patients [3]. Though the genetic reasoning why some females

present with symptoms and others do not is not concretely certain at this time, understanding the common clinical features is important in diagnosing these rare conditions in females. Through case studies, physical commonalities during clinical exams can be organized in a fashion that can help providers take care of subsets of populations such as females with DMD. Being able to diagnose through the knowledge of common clinical features especially the symptom of exertional weakness and fatigue will lead to faster diagnosis and treatment for a better quality of life in this particular population [8-10].

Perspectives and Significance

Three female carriers of DMD in this particular case study showed similar clinical features of overt and exertional weakness especially in the lower extremities. With the discovery and grouping of common clinical features in female DMD carriers, it can lead to a better/faster diagnostic approaches and impaction of their quality of life through earlier treatment.

Availability of Data and Material

Clinical database at AdventHealth.

Conflict of Interest

The authors have no conflict of interest to declare.

References

1. Hoogerwaard EM, Bakker E, Ippel PF, Oosterwijk JC, Majoor-Krakauer DF, Leschot NJ, et al. Signs and symptoms of Duchenne muscular dystrophy and Becker muscular dystrophy among carriers in the Netherlands: a cohort study. Lancet. 1999;353:2116-9.
2. Juan-Mateu J, Rodríguez MJ, Nascimento A, Jiménez-Mallebrera C, González-Quereda L, Rivas E, et al. Prognostic value of X-chromosome inactivation in symptomatic female carriers of dystrophinopathy. Orphanet J Rare Dis. 2012;7:82.
3. Brioschi S, Gualandi F, Scotton C. Genetic characterization in symptomatic female DMD carriers: lack of relationship between X-inactivation, transcriptional DMD allele balancing and phenotype. BMC Med Genet. 2012;13:73.
4. Zhong J, Xie Y, Bhandari V, Chen G, Dang Y, Liao H, et al. Clinical and genetic characteristics of female dystrophinopathy carriers. Molecular Medicine Reports. 2019;19(4):3035-44.
5. Mousa NO, Sayed AA, Fahmy N, Elzayat MG, Bakry U, Abdellatif A, et al. miRNome profiling in Duchenne muscular dystrophy; identification of asymptomatic and manifesting female carriers. Bioscience Reports. 2021;41(9).
6. Lim KRQ, Nguyen Q, Yokota T. Genotype-Phenotype correlations in duchenne and becker muscular dystrophy patients from the canadian neuromuscular disease registry. J Pers Med. 2020;10(4):241.
7. Kaspar RW, Allen HD, Ray WC, Alvarez CE, Kissel JT, Pestronk A, et al. Analysis of dystrophin deletion mutations predicts age of cardiomyopathy onset in becker muscular dystrophy. Circ Cardiovasc Genet. 2009;2(6):544-51.
8. Santos R, Gonçalves A, Oliveira J, Vieira E, Vieira JP, Evangelista T, et al. New variants, challenges and pitfalls in DMD genotyping: implications in diagnosis, prognosis and therapy. J Hum Genet. 2014;59(8):454-64.
9. Brioschi S, Gualandi F, Scotton C, Armaroli A, Bovolenta M, Falzarano MS, et al. Genetic characterization in symptomatic female DMD carriers: lack of relationship between X-inactivation, transcriptional DMD allele balancing and phenotype. BMC Med Genet. 2012;13:73.
10. Silva THD, Anequini IP, Fávero FM, Voos MC, Oliveira ASB, Telles JAR, et al. Functional performance and muscular strength in symptomatic female carriers of Duchenne muscular dystrophy. Arq Neuropsiquiatr. 2020;78(3):143-8.