A Rare Case of Dysferlinopathy in an Adolescent from a Resource-Limited Setting

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Abstract

Dysferlinopathies are rare autosomal recessive muscular disorders with varying phenotypes, including Miyoshi Myopathy (MM) and Limb-Girdle Muscular Dystrophy type 2B (LGMD2B). They result from mutations in the DYSF gene, which encodes dysferlin, a protein crucial for sarcolemmal repair. Diagnosis can be challenging due to clinical variability, necessitating genetic testing. We present the case of an 18-year-old girl with progressive lower limb weakness and elevated creatine kinase levels, who was ultimately diagnosed through genetic analysis. This case emphasizes the importance of genetic testing for accurate diagnosis, improved patient care, and appropriate genetic counseling.

Introduction

Dysferlinopathies are a group of autosomal recessive muscular dystrophies caused by mutations in the DYSF gene (chromosome 2p13.3), which encodes the dysferlin protein. The DYSF gene contains 55 exons spanning a region of 150 kb, while the dysferlin protein weighs 237 kDa and plays a key role in calcium-mediated sarcolemmal repair. Beyond its role in membrane repair, dysferlin is also involved in vesicle trafficking, muscle cell adhesion, and maintaining cellular integrity. Over 400 mutations have been identified in DYSF, leading to diverse phenotypes such as Miyoshi Myopathy (MM), Limb-Girdle Muscular Dystrophy type 2B (LGMD2B), Distal Myopathy with Anterior Tibial onset (DMAT), and an intermediate proximo-distal form.[1,2] Dysferlin is primarily located at the sarcolemma (skeletal muscle cell membrane) but is also expressed in other tissues, including the cardiac muscle cells and may be involved in cardiomyocyte membrane repair.[3] The incidence of dysferlinopathies range from 1:1300 to 1:200,000 in different populations.[4] The diagnosis may be challenging in these rare genetic myopathies, due to the high variability of phenotypes, ranging from asymptomatic high serum creatine kinase level to a severe clinical picture with loss of ambulation. Dysferlinopathies should be considered in the differential diagnosis of polymyositis to avoid unnecessary and potentially dangerous medications such as oral steroids or immunosuppressive therapies.[5,6]

Here, we report on a case of 18-year female with hypothyroidism presented with progressive muscle weakness, eventually diagnosed through genetic panel with dysferlinopathy.

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CASE PRESENTATION:

We present the case of an 18-year-old girl who presented with progressive difficulty in walking over a span of three years. Initially, she experienced difficulty climbing stairs, which gradually progressed to challenges in walking on level ground and eventually to descending stairs during the last four months. Her parents also noticed progressive wasting of her bilateral calf muscles over the same four-month period. She reported difficulty standing up after crouching but had no issues sitting down or rising from a chair. Her bowel and bladder habits were normal. She had been diagnosed with hypothyroidism two years earlier and was on thyroxine therapy.

There was no history of consanguinity, complications during pregnancy or the postnatal period, substance use, or family history of neuromuscular weakness. Her infancy and psychomotor development were unremarkable.

Three years prior, she had presented to a local hospital with a non-tender swelling in both calves, which had been present for two years and had progressively worsened, along with difficulty walking over the preceding four months. She was treated with multivitamins, steroids, and thyroxine (25 mcg) but showed no improvement while remaining on regular medication.

At the time of presentation, her vital signs were stable. Physical examination revealed high-arched feet and clubfoot deformities. There was weakness in the proximal hip extensors and flexors (4/5), as well as in the knee extensors and flexors (4/5). Bilateral calf muscles exhibited decreased bulk, and ankle reflexes were diminished bilaterally. Sensation, vibration, and tone were intact in both lower limbs, and no abnormalities were noted in the upper limbs.

Laboratory tests showed elevated transaminases with Aspartate Transaminase(AST)
at 186 U/L and Alanine Transaminase(ALT) at 197 U/L, markedly elevated lactate dehydrogenase (LDH) at 805 U/L (normal: 0–248 U/L), and serum creatine kinase (CK) at 15,478 U/L (normal: 55–170 U/L). Other parameters, including urea, creatinine, magnesium, calcium, vitamin D, and nerve conduction studies, were normal. Ultrasonography of the abdomen and pelvis was also unremarkable.

She was started on deflazacort, multivitamins, and supportive care. However, no significant improvement was observed. A myopathy gene panel was subsequently sent to higher center, although muscle biopsy and electromyography (EMG) could not be performed due to logistical constraints.
The genetic report identified a homozygous frameshift deletion mutation, c.2550_2553del (p.Thr851Serfs*3), in exon 24 of the DYSF gene (transcript NM_001130987), which is associated with dysferlinopathy. This pathogenic variant causes a premature truncation of the dysferlin protein, disrupting its normal function in muscle repair.

This finding supports the diagnosis of dysferlinopathy, likely Miyoshi muscular dystrophy or limb-girdle muscular dystrophy type 2R (LGMD2R), aligning with the patient's clinical presentation. No clinically relevant copy number variations were detected. The genetic analysis was performed at Unipath Laboratory, Ahmedabad, Gujarat.

Family genetic testing was not performed due to financial limitations. However, the possibility of heterozygosity for the mutation in the parents remains likely and was discussed with the family, highlighting the need for genetic counseling for potential carriers.

DISCUSSION

Dysferlinopathies are rare autosomal recessive muscular dystrophies caused by mutation in the dysferlin (DYSF) gene, resulting in varied phenotype.7 The phenotypic spectrum includes Miyoshi muscular dystrophy (MMD), limb-girdle muscular dystrophy type R2.8 Dysferlinopathy is a challenging diagnosis due to a varied clinical picture and low incidence. The patients with dysferlinopathies usually have first symptoms before the age of 13 years. Independent of the initial mode of presentation, the gastrocnemius muscle was the most severely affected muscle leading to an inability to stand on tiptoes, and lower limbs were affected more severely than upper limbs.[9]

To diagnose dysferlinopathy, a clinical neuromuscular workup, including electrophysiological and muscle imaging investigations, is essential to support subsequent laboratory testing. Increased serum creatine kinase levels, distal or proximal muscle weakness, and myalgia with onset in the second or third decades leads towards the suspicion of this disease. Molecular techniques for gene mutation detection, such as next generation sequencing, have improved the genetic diagnosis, which is crucial for confirmatory diagnosis, treatment and genetic counselling.10Although there is no curative treatment for this disease, an accurate diagnosis is important to avoid using steroids as steroid treatment is not an effective therapy for dysferlinopathy patients and it did not prevent disease progression.[11,12]

Although the DYSF gene contains 55 exons, our report focuses on the clinical manifestation and genetic diagnosis of a patient with a homozygous mutation in DYSF, which supports the diagnosis of dysferlinopathy, likely Miyoshi Muscular Dystrophy (MMD) or Limb-Girdle Muscular Dystrophy type 2R (LGMD2R).

This case highlights the challenges in diagnosing dysferlinopathy, especially considering the broad spectrum of symptoms. The patient visited multiple health centers without receiving a definitive diagnosis, leading to frustration and inadequate treatment. Although calf muscle atrophy and progressive muscle weakness were present, these are symptoms common across various forms of muscular dystrophies, making misdiagnosis frequent. This patient's initial diagnosis of hypothyroid myopathy is an example of how symptoms can overlap with other neuromuscular diseases, such as polymyositis, often leading to inappropriate treatments, including steroids or immunosuppressive agents.[13] However, the absence of significant inflammation and the lack of systemic inflammatory signs, coupled with the non-resolution of muscle pain with thyroxine treatment, ruled out polymyositis. This case highlights the importance of thorough and comprehensive evaluations, including genetic testing, to avoid misdiagnosis and ensure proper treatment.

In our case, a genetic panel revealed a homozygous frameshift mutation (c.2550_2553del, p.Thr851Serfs*3) in exon 24 of the DYSF gene, confirming the diagnosis of dysferlinopathy. The mutation is inherited in an autosomal recessive manner. It is important to note that this mutation has not been previously reported in population frequency databases such as GenomAD, and was also reported in ExAC with a minor allele frequency (MAF) of 0.008%, signifying its rarity in the general population. Additionally, the absence of copy number variations in the DYSF gene further supports the diagnosis. While genetic mutations in dysferlin have been well-documented, the rarity of this particular mutation adds valuable insight to the literature.

Regarding family genetic testing, we were unable to conduct testing on the patient's parents due to financial limitations. Genetic counseling would be beneficial for the family, as the parents may be carriers of the DYSF mutation, with potential implications for future children. Testing the parents could also provide insights into the inheritance pattern of the disorder, helping confirm whether the mutation is de novo or inherited from both parents.

The absence of electromyography (EMG) and muscle biopsy in this case was a limitation. Ideally, a muscle

biopsy would have provided histopathological findings, such as the absence of dysferlin staining in muscle tissue, which is characteristic of dysferlinopathies. Similarly, EMG studies would have been useful in assessing the electrophysiological properties of the muscles, which can aid in differentiating muscular dystrophies from inflammatory myopathies.[14]

This case highlights the critical role of genetic testing in diagnosing dysferlinopathy, particularly when clinical signs are subtle or overlap with other conditions. Genetic counseling is essential for the patient and family, given the autosomal recessive inheritance pattern. Future studies should aim to better characterize rare mutations like the one identified in this case and explore potential therapeutic strategies, such as gene therapy, which could offer new hope for patients with dysferlinopathy. In addition, ensuring the affordability of genetic testing and therapy for families is crucial in increasing access to care for underserved population.

CONCLUSIONS

The diagnosis of dysferlinopathy is challenging due to high variability of phenotype ranging from asymptomatic picture to severe disability. In our case, corroboration of clinical picture with lab parameters, along with genetic diagnostics, contributed to final diagnosis. The identification of a rare homozygous mutation in the DYSF gene (c.2550_2553del, p.Thr851Serfs*3) emphasized the importance of access to genetic studies for the accurate diagnosis and adds to rare literature of dysferlinopathy. Early diagnosis can aid in providing appropriate counseling, supportive care, and monitoring for complications. Further studies and resources are necessary to enhance our understanding of dysferlinopathy and improve diagnostic and management strategies, especially in underserved populations.

DATA AVALAIBILITY

The data used to support the findings of this study are included within the article.

CONFLICTS OF INTEREST

The authors declared that they have no conflict of interest.

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CONSENT

Informed written consent was obtained from the patient.

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