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Case Report

A case of dysferlinopathy (Miyoshi distal myopathy limb-girdle muscular dystrophy type 2b phenotype) from a tertiary care hospital

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ABSTRACT

Limb girdle muscular dystrophy type 2B (LGMD2B) and Miyoshi myopathy are caused by similar mutations in the dysferlin gene. The phenotype of these allelic disease variants can vary considerably. We report a young male with severe and rapidly progressing muscle disorder with increased creatine phosphokinase (CPK) and confirmatory muscle biopsy findings. Genetic testing was done. A homozygous nonsense variation in exon 23 of the DYSF gene, which was consistent with the patient's clinical reports of dysferlinopathy. Clinical phenomenology and preferential muscle involvement lead one to the gold standard genetic testing in heritable myopathies, which was well established in this report.

Keywords: LGMD, Muscular dystrophy, Muscle, Dysferlin

INTRODUCTION

Autosomal recessive limb girdle muscular dystrophies (LGMD type 2) is a genetically heterogeneous disorder, which includes 12 different genetic entities. It is characterized by progressive weakness and limb girdle muscle wasting. LGMD is the 4th common genetic cause of muscle weakness with a prevalence of one in 20,000.[1] LGMD type 2B, and the distal muscular dystrophy named as Miyoshi myopathy (MM), are due to the mutations in dysferlin gene. Both are linked to same locus on chromosome region 2p1311.[1] The pathogenesis in dysferlinopathies is correlated to the abnormal trafficking of vesicles, which repair muscle fiber membrane.[2] The absence of dysferlin causes a failure in muscle fiber repair. In majority of patients with LGMD2B, symptoms occur after 20 years of age. The physician should advice these patients not to perform any strenuous activities, which might exacerbate muscle breakdown. Creatinine phosphokinase (CPK) is usually elevated at the time of presentation.[3] Clinical presentation is the inability to walk on tiptoe due to the involvement of the medial gastrocnemius muscle. This clinical heterogeneity might be attributed to additional epigenetic factors resulting in variable dysferlin expression.[4] Gene expression profiling is now used to investigate modifier genes in dysferlinopathy. Clinical phenomenology is the gold standard genetic testing in heritable myopathies, which was well established in this case report.

CASE REPORT

A 27-year-old male presented to the outpatient department with insidious onset, progressive, difficulty in walking and climbing stairs from the age of 9. At present, he could walk only a few steps with support and could not get up from a sitting position. He also had difficulty in raising his hands above the shoulder and in gripping objects for the past 1 year. He had no associated sensory or cranial nerve disturbances. He was the elder of two siblings born of 2nd degree consanguineous parents. A three-generation pedigree analysis showed no similar complaints. There

was no other significant past history. General examination was unremarkable and vitals were stable. Neurological examination revealed normal higher mental functions and cranial nerves. Motor system examination showed atrophic muscle groups, hypotonia and hyporeflexia in the lower extremities (Figure 1). Gower's sign was present. Power in the proximal and mid groups of the lower limb was MRC grade 3 on both sides while it was MRC grade 2 in the distal groups in the lower limbs. His upper limb examination revealed atrophic muscle groups, hypotonia and hyporeflexia with power of MRC grade 4 in the proximal muscles and MRC grade 3 in the distal groups. The remaining neurological examination was within limits.

His baseline investigations were within normal limits. His serum CPK levels were elevated (4213 U/l, N: 22-198 U/L). Needle EMG was done in both the deltoid muscles and the left vastus lateralis. It showed complete interference, low amplitude, polyphasic motor unit action potential (MUAP) with no spontaneous activity suggestive of myopathic pattern. Muscle biopsy was done from the left vastus lateralis, which revealed the presence of lobulated fibers and incomplete fascicles with no signs of inflammation or vasculitis. Magnetic resonance imaging suggestive of inflammation (Figure 2). Whole exome sequencing test was performed, which revealed a homozygous nonsense variation in exon 23 of the DYSF gene confirmatory for dysferlinopathy (Table 1). He was advised occupational rehabilitation and physiotherapy along with other supportive aids for walking and activities of daily living.

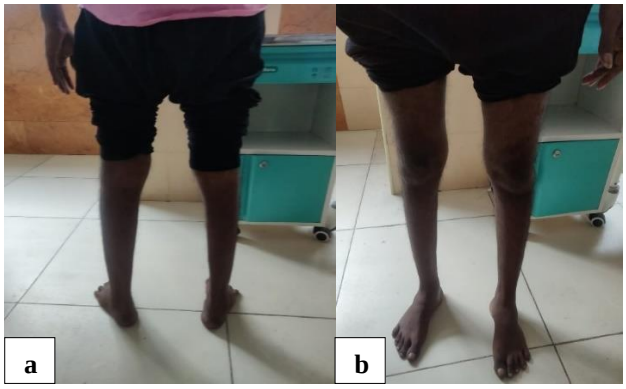

Figure 1: Calf muscle atrophy.

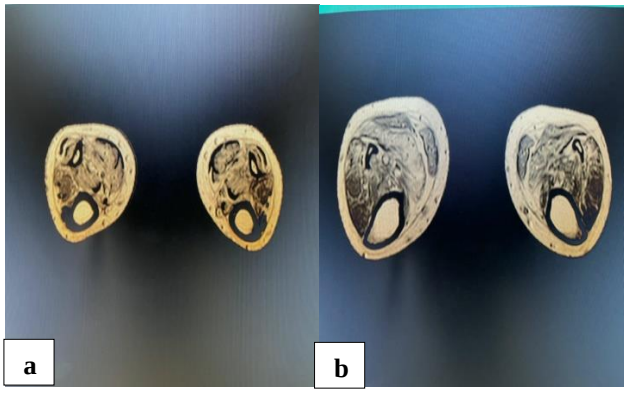

Figure 2: MRI-LEG showing STIR hyperintensity noted in all compartment of leg.

Table 1: Whole exome sequencing test.[5]

Gene# (transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
DYSF (+) (ENST00000410020.8)	Exon23	c.2266>T (p.Gln756Ter)	Homozygous	Limb-girdle muscular dystrophy 2; distal myopathy with anterior tibial onset; Miyoshi muscular dystrophy 1	Autosomal recessive	Pathogenic

*Genetic test results are reported based on the recommendations of American college of medical genetics

DISCUSSION

LGMD2B, also known as dysferlinopathy, based on its clinical manifestations and distribution of muscle weakness has two clinical phenotypes: LGMD2B (proximal onset) phenotype, and Miyoshi distal myopathy (distal onset) phenotype.[6] However, DYSF gene mutation was also the underlying pathological cause for the disease and hence included in LGMD2B. The disease initially involves the gastrocnemius muscle and hence the inability to do plantar flexion with calf muscle wasting. Due to the progressive involvement of the hamstrings and hip flexors there is difficulty in climbing the stairs and getting up from sitting posture.[7] In LGMD the upper extremities are involved at the latter stage. Muscles show selective atrophy (e.g., vastus lateralis and rectus femoris, and the biarticular muscles). Symptoms like distal myopathy with anterior tibial onset (DMAT) and intense calf muscle pain and tenderness, muscle wasting and camptocormia are some of the rare presentations in the disease. Usually, the onset of symptom is at 20-25 years of age.[7] In dysferlinopathy patients, studies have reported a prominent inflammatory response, but the origin of this feature and the background of muscle pathology are still under research. LGMD2B is a condition resulting due to the deficiency of the sarcolemmal protein dysferlin due to the mutation in DYSF (2p13.2) gene, located at the short arm of chromosome 2 at position 13.2.[8] Most mutations in this location result from nonsense mutation or abnormal truncation of dysferlin protein. This was confirmed by the genetic testing done in this case, wherein the patient had a nonsense mutation at the region of the DYSF gene, at position 1517 (NM_001130987.1(DYSF): c.4551G>A p.(Trp1517*)). This genetic description is one of three

variants, with its preferred identification as NM_003494.3(DYSF): c.4434G>A (p. Trp1478Ter). All variants have resultant truncation of dysferlin protein.[9] At present there is no definitive treatment for LGMD diseases. Management is symptomatic and monitoring the probable consequences, and improving the quality of life.[10] Treatment with steroids or immunosuppressant drugs have not shown any benefits on the long-term management. Adeno associated virus carrying DYSF cDNA (7kb) introduced in mice resulted in full length functional protein without toxicity. Advances in gene delivery and genome editing provides hope for the future.[11]

CONCLUSION

This case report manifested their own specific clinical presentation and phenomenology, with some pathognomonic signs that may point to the diagnosis. Subsequently diagnosis of LGMD is confirmed by genetic testing. This highlights the importance of genetic testing as a confirmatory diagnosis for such hereditary muscular diseases. With the preponderance of genetic development, the standard of diagnosis has shifted from biopsy and staining to genetic testing. Most importantly, routine staining of biopsied muscle yields nonspecific results. Other diagnostic modalities, such as immunostaining and immunoblotting, may be done. However, these serve as modalities that are second in line once genetic testing yields a negative result or if the latter is unavailable.

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