Case Report

Proximal predicament: A clinical journey to limb-girdle muscular dystrophies type 2B

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ABSTRACT

Limb-girdle muscular dystrophies (LGMDs) represent a heterogeneous group of genetically inherited myopathies characterized by progressive proximal muscle weakness. LGMD Type R2 (formerly 2B), caused by mutations in the *DYSF* gene encoding dysferlin, often presents with insidious lower limb weakness and elevated creatine kinase (CK) levels. This report highlights a case with characteristic clinical features and a confirmatory genetic diagnosis. We present a 41-year-old right-handed male with progressive lower limb weakness over 8 years and upper limb involvement for the past 3 years. Clinical examination revealed proximal muscle wasting with preservation of distal strength, especially in hand and foot muscles. Notable signs included wasting of bilateral biceps and quadriceps with the presence of "lumpy-bumpy" biceps and a "diamond sign" in the thighs. Serum CK levels were elevated. Whole-exome sequencing identified a homozygous missense mutation (p.Tyr1014Cys) in exon 29 of the *DYSF* gene, consistent with a diagnosis of LGMD R2 (dysferlinopathy). Supportive management with physiotherapy and multivitamin supplementation was initiated.

Key words: Atypical myopathies, Limb-girdle muscular dystrophies type 2B, Myodegenerative disorders, Proximal myopathies

Limb-girdle muscular dystrophy (LGMD) type 2B, also known as dysferlinopathy, is an autosomal recessive muscular dystrophy predominantly affecting the proximal limb muscles more than the distal ones. This condition encompasses dysferlin-deficient LGMD type 2B, distal Miyoshi myopathy, and other less common phenotypes within the dysferlinopathy group [1]. The *DYSF* gene variant responsible for this disorder is the second most common form of LGMD [2]. Patients with LGMD type 2B typically present with elevated creatine kinase (CK) levels during the initial stages [3]. Despite significant advancements in understanding the pathomechanisms of LGMD, there are currently no definitive treatments available. Existing therapeutic approaches are focused on symptom management and improving the quality of life rather than addressing the underlying cause [4].

This case underscores the importance of clinical vigilance in diagnosing late-onset dysferlinopathies, particularly in resource-limited settings where muscle biopsy and protein assays may not be readily available. The confirmation through whole-exome sequencing (WES) highlights the growing role of genomics in clarifying neuromuscular diagnoses.

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CASE REPORT

A 41-year-old right-handed male patient presented to us with complaints of 8-year progressive lower limb weakness and 3-year progressive upper limb weakness, which was insidious in onset and gradually progressive. Initially, the patient noticed that he had difficulty standing up from a squatting position during work. Notably, he did not report slippage of footwear, which is often seen in distal myopathies. Following this, the patient developed a complaint of ipsilateral upper limb weakness in the form of lifting heavy objects over the past 3 years. However, he had no complaints of difficulty lifting his hands above his head, buttoning and unbuttoning his shirt, or difficulty in gripping objects, suggesting proximal muscle weakness. At no point did the patient report remission in symptoms. There was no history suggestive of cranial nerve involvement, respiratory distress, cardiac symptoms, muscle fasciculation, and sensory or autonomic dysfunction. Past and family histories were unremarkable. No similar illness was reported among relatives.

General examination was unremarkable. The patient had a pulse of 88 beats/min, a blood pressure of 144/72 mm of Hg, and a respiratory rate of 22 breaths/min. Higher mental functions and cranial nerves were normal. Motor examination revealed

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mild bilateral proximal, biceps, and lower quadriceps wasting. A classical lumpy bumpy sign of biceps and a diamond sign of quadriceps were noted. Tone and coordination were normal. The patient was able to perform the finger-nose test but was unable to complete the knee-heel-shin test due to hip flexor weakness. The bulk of muscles were diminished in the proximal group of muscles, but bilaterally comparable. Muscle power (graded by Medical Research Council scale) was preserved in the neck, shoulder girdle, and distal limbs, but proximal muscle weakness was noted prominently: Elbow flexors: 4/5 bilaterally, Hip flexors and extensors: 4/5 bilaterally, Hip adductors: 3/5 bilaterally, Quadriceps: 3/5 bilaterally and there was no distal weakness of foot drop.

The patient's electrocardiogram and 2D echo were normal. His creatinine kinase was elevated to 1046 U/L. A diagnosis of possible LGMD was made, and WES was sent, which showed a homozygous variant in exon 29 of the *DYSF* gene, with a missense mutation p.Tyr1014Cys, confirming a diagnosis of muscular dystrophy, limb-girdle, autosomal recessive type 2 (LGMD R2).

A supportive treatment with the primary aim of preserving muscle strength, function, and quality of life, including physiotherapy and rehabilitation medicine, was adopted. Multivitamins, along with calcium and Vitamin D3, were initiated. Baseline pulmonary function tests (PFT) were carried out, and annual PFT was advised. The patient was counseled for family screening, and genetic counseling was done. Low-impact resistance training and range of motion exercises were incorporated into the exercise program. The patient, in follow-up, remained ambulatory with stable proximal muscle strength and preserved respiratory function.

DISCUSSION

LGMD is the fourth most common muscular dystrophy [5]. As per the new nomenclature developed in 2018, LGMD is followed by the suffix D (Dominant) or R (Recessive) as per the mode of inheritance, followed by further classification [6]. Thus, as per this, our patient had LDMD R2 dysferlin-related myopathy. The combined prevalence of all the disorders under LDMD is estimated to be 0.8 and 6.9/100,000 [7]. LGMD R2 dysferlin-related is the most common subtype of LGMD in Asia, but there is no specific data for the Indian sub-continent [8].

Case reports have been published, but no large sample study is available on the Indian population. A review article by Khadilkar *et al*. presented that dysferlinopathy, GNE myopathy, calpainopathy, and sarcoglycanopathies are common in India. Sarcoglycanopathies are the first one that was studied in India, followed by dysferlinopathy. It also suggests that consanguineous marriages are the main cause of the increased prevalence of the autosomal recessive type of LGMD [9]. We believe that even with such technological advances, the disease is highly underreported due to economic and resource constraints in major parts of the country.

Dysferlinopathies can present as distal weakness (Miyoshi myopathy), proximal weakness (LGMD R2), or mixed type. Some rarer phenotypes present as distal anterior tibial myopathy or asymptomatic hyperCKemia. The disorder usually has an early adult (12–25) onset, but some cases of early or late presentations have also been found, as is our case, where the presentation is late and was misattributed as fibromyalgia and mechanical strain for 8 years [10]. Elevated muscle CK is one of the first clues found during the initial evaluation. Dysferlinopathy usually presents with severely elevated CK, but our patient had moderate elevation, which was atypical [5].

We ordered a thyroid panel, lipid profile, inflammatory markers – erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and conducted a detailed physical examination to rule out other causes. The laboratory reports came back normal, and the physical examination pointed toward muscular dystrophy. The presence of family history or consanguinity helps in narrowing the diagnosis; however, our patient lacked both. We ordered a whole genome sequence, which came back positive for LGMD R2 dysferlin-related myopathy. Genetic analysis is preferred over muscle biopsy because of its non-invasive nature and precise diagnosis [7]. The Jain Foundation has developed an online tool, Automated LGMD diagnostic assistant, that helps in the diagnosis [11].

This case underscores the importance of detailed history, taking, and neurological examination with appropriate diagnostic tests to confirm such a myodegenerative. Dysferlinopathies do not have a high mortality risk due to uncommon pulmonary or cardiac involvement, but the patient is bound to a wheelchair in 10–20 years of the disease [7]. Although the mortality is not high, the disease affects the quality of life of patients severely, and hence the importance of early diagnosis. There have been advances in diagnosing the disease, and the management part involves regular follow-up and symptomatic treatment to improve the patient's quality of life. The guidelines recommend against any disease-modifying gene therapy, myoblast transplantation, antibodies to myostatin, or growth hormone treatment due to a lack of data on their effectiveness [12]. A multi-disciplinary approach should be taken to manage these cases. We referred our patient to physical therapy and a regular exercise program and we are regularly following up to monitor the involvement of new muscle groups. The exercise and therapy should be designed considering the patient's present health. Such care might be possible in tertiary centers with multiple departments, but for rural centers with Primary Health Centres, it would pose a challenge.

Ongoing research is focusing on stem-cell transplantation, exon skipping, gene delivery, RNAi, and gene editing for treating the disorder at the root [13]. In the context of India, better availability of testing will help diagnose the disease, and the accumulation of data will give better epidemiological insights. Our case report holds importance as a small contribution to the epidemiology of LGMD.

CONCLUSION

LGMD2B can present subtly with proximal limb weakness and preserved distal function, often delaying diagnosis. In patients

with unexplained hyperCKemia and progressive proximal muscle weakness, dysferlinopathy should be considered, especially in the absence of a family history. Early use of genetic testing can obviate the need for invasive diagnostics and guide appropriate counseling and supportive care.

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AUTHOR'S CONTRIBUTORS

All authors have contributed equally.

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