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Case Report **OPEN ACCESS**

Unveiling dysferlinopathy: A rare genetic cause of progressive muscle weakness in a Malay woman

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ABSTRACT

Dysferlinopathy, which is characterized by progressive muscle weakness, especially affecting the proximal muscles, is a rare autosomal recessive neuromuscular disorder. Early detection and diagnosing of this disorder is important for management, and the aim of management is to maintain a patient's quality of life. We present a case report of a 39 year old Malay woman who presented with worsening weakness of proximal muscle since puberty, and underwent extensive investigation for a definitive diagnosis, which turned out to be dysferlinopathy. This case provides an overview of the genetic disorder dysferlinopathy in order to contribute to the limited existing literature and it highlights the importance of multidisciplinary care in the management of this rare disorders.

Keywords: dysferlinopathy, limb-girdle muscular dystrophy, myopathy, genetic disorder, neuromuscular disease

INTRODUCTION

Dysferlinopathies are one of the most common adult-onset muscular dystrophies, with a prevalence estimate of 1 in 14,000 to 1 in 2 million individuals [1]. These disorders are caused by a dysferlin deficiency due to autosomal recessive mutations in the DYSF gene, and the dysferlin is a skeletal muscle protein involved in membrane repair. The condition primarily manifests as limb-girdle muscular dystrophy type 2B (LGMD2B) and Miyoshi myopathy (MM), both characterized by muscle weakness that typically begins in late adolescence or early adulthood [2]. Elevated levels of serum creatine kinase (CK) reflecting muscle damage are often seen in the clinical presentation, and in muscle biopsies there may reveal myofiber degeneration and inflammatory infiltrates [2]. Diagnosis of dysferlinopathy can be challenging because it clinically overlaps with other diseases including inflammatory myopathies, such as polymyositis. This highlights how misdiagnosis is common in cases in which patients with dysferlinopathy were initially treated for inflammatory myopathy and suffered further deteriorating muscle strength after steroid treatment [3]. Genetic testing involving analysis for mutations in the DYSF gene as well as protein assays to determine dysferlin expression level are the gold standard for accurate diagnosis [2]. Despite the significantly advanced state of the diagnosis investigation, there are still limited options for treatment of dysferlinopathy. The current treatment policies are mostly symptomatic that aim to control muscle weakness and to prevent complications. This case presents the clinical course, investigations, and multidisciplinary management of a patient with confirmed dysferlinopathy.

CASE PRESENTATION

A 39 year old Malay woman, without any previous medical history, was referred to the clinic with progressive muscular weakness. The onset of her symptoms was at the age of 14 with complaints of frequent falls and difficulty getting up, associated with feeling unsteadier than she should. Classic Gower sign in the patient who noted that she had to use her hands and arms to get up from the floor. The weakness gradually worsening for the next two decades as it spread from her lower limbs to her upper arms, with the most severe involvement in the proximal muscles of the thighs and arms. At 36 years old, even ambulating was virtually impossible without assistance, and she required support to stand. However, all these limitations were overcame by the patient who managed to retain a full-time employment as a community nurse. On physical examination, the patient had significant proximal muscle weakness of the upper limbs (4/5) and lower limbs (3/5). Besides that, she also presented with hypotonia in both upper and lower limbs, with muscle wasting particularly in the arms and thighs. The reflexes were absent (areflexia), and the gait was unstable, with mild left hip swing. Eczema was found at the right ankle during dermatological examination, though no signs of systemic involvement, such as fever, joint pain or bulbar symptoms. The patient denied other complications of muscular dystrophy such as respiratory difficulties, cardiomyopathy or swallowing problems. In view of the patient having a family history of similar symptoms in her younger sibling whose currently used a wheelchair, this suggested a hereditary neuromuscular disorder.

Several investigations were made to establish the diagnosis. One of them was muscle biopsy and its result was suggestive of neurogenic myopathy, which was the characteristic findings. The electromyography (EMG) further supported this diagnosis, indicating abnormal muscle electrical activity. A dry blood spot test confirmed the presence of abnormal levels of biomarkers associated with neurogenic muscle injury, ruling out metabolic causes such as mitochondrial disorders. To rule out other causes of muscle weakness such as polymyositis, autoimmune and metabolic myopathy tests were done but eventually results turned out to be negative. The patient's clinical presentation and investigation results raised suspicion of a genetic neuromuscular disorder. Genetic testing was subsequently performed and identified two pathogenic DYSF variants: c.5668-7G > A and c.1020C > G (p.Ser340Arg), confirming dysferlinopathy.

Initially, the patient was treated with prednisolone, azathioprine, and calcium supplementation assuming her condition was polymyositis, an autoimmune myopathy. However, these medications were discontinued after autoimmune cause was ruled out following the results of the myopathy screen. At this stage, the diagnosis of dysferlinopathy was confirmed, and the focus of management shifted toward supportive care. Given the progressive nature of dysferlinopathy and there are no effective treatments for the disease, the patient was referred to physiotherapy and rehabilitation services to maintain functional independence. These interventions aimed to maintain muscle strength, improve mobility, and prevent contractures. The patient was educated on energy conservation techniques and the importance of regular physical therapy to maintain the best possible function. Although there were no specific definitive treatments, the patient remained independent of daily activities, despite standing and walking becoming more difficult. Due to her work as a community nurse that required prolonged periods of standing and walking, and as her condition progressed, she required to have assistance with certain tasks. Furthermore, as a result of logistical difficulties and the patient's belief that the condition is incurable, she refused to consent to additional follow up with genetic specialists.

DISCUSSION

As a result of dysferlinopathy present with considerable clinical variability, and are currently without specific biomarkers, diagnosis and management of these myopathies are difficult. These conditions are primarily characterized by progressive muscle weakness and atrophy, which manifests in several phenotypes, including MM and LGMD2B. MM is a distal myopathy that initially affects the posterior calf muscles, while LGMD2B involves the scapular and pelvic girdle musculature, though it can evolve into a distal myopathy with anterior tibial onset or a proximo-distal phenotype [4]. In this case, the pattern of the patient's disease progression is similar to those described in existing literature, from muscle weakness in the distal lower limbs with progression into the proximal lower limbs and later the upper limbs. This progression aligns with the existing journal, which reported that the average age of onset for MM and LGMD2B is between 20 and 25 years, with calf or thigh weakness and atrophy presenting initially [5]. All these symptoms tend to extend to the upper limbs over time. The gradual progression in this patient further supports this clinical pattern. It is necessary to examine patients with dysferlinopathy thoroughly for better understanding of the clinical spectrum and the underlying mechanisms of the disease.

This is a situation where primary care providers commonly delay in diagnosis or misdiagnosed due to the symptoms started mildly. The diagnosis of this patient was made initially as inflammatory myopathy because serum CK was raised. However, most muscular disorders including polymyositis have elevated serum CK. But after corticosteroids and azathioprine treatment for her symptoms failed to improve and her muscle weakness worsened, this stresses the need for differential diagnosis. Furthermore, the diagnosis is often made at a late stage, as is observed in this patient, who only seek medical treatment once symptoms are more pronounced, such as exercise intolerance or muscle weakness [5].

In order to obtain an accurate diagnosis, it requires thorough clinical neuromuscular workup, including electrophysiological study, muscle imaging and genetic testing [6] to support subsequent laboratory testing. For this case, the patient underwent multiple diagnostic tests including EMG and nerve conduction studies, which turned out to be myopathic changes in the proximal muscles. Furthermore, muscle biopsies can provide histological evidence of muscle degeneration and inflammation, which are the characteristics of dysferlinopathy. Even though muscle biopsies are one of the invasive and valuable diagnostic tools for dysferlinopathy, they can sometimes lead to a misdiagnosis of inflammatory myopathy [7]. Fortunately, this patient's receptive muscle biopsy of her left thigh quadriceps muscle showed neurogenic changes. Eventually, this patient did genetic testing and the result showed two pathogenic mutations in the DYSF gene, and this confirmed her diagnosis of dysferlinopathy. Beyond everything, it was a challenge to come to the diagnosis due to the costly genetic test and its limited availability. This patient had to travel to a state hospital for the genetic test, and thus the diagnosis was delayed.

Unfortunately, there is no definitive cure for dysferlinopathy, the management calls for a multidisciplinary approach involving symptomatic treatment, physical therapy, and exploring emerging therapeutic options such as gene therapy and exon skipping [5]. Corticosteroids such as deflazacort have demonstrated a limited efficacy on increasing muscle strength as they reduce the levels of CK [8]. In this case, treatment with prednisolone and azathioprine was offered to this patient, but here it had not helped much, and the complications that came with it were thrombocytopenia. In addition, exon skipping therapy, which could potentially address the underlying genetic defect, is still experimental and unavailable at local centers, further limiting treatment options [9].

Another important management for dysferlinopathy is physical therapy, in order to maintain mobility, prevent contractures, and enhance quality of life. Yet, while the disease progresses, patients must not overexert themselves to avoid further muscle damage. This patient has been referred to as a physiotherapist with a personalized exercise plan but finding it difficult to join the low impact activities such as swimming and cycling, complicates her ability to maintain muscle strength without risking injury. Also, a referral to an occupational therapist for assistive devices such as walkers and wheelchairs are anticipated in the future as her condition advances.

Cardiac involvement is another significant complication of dysferlinopathy, and as such, regular monitoring of cardiac function is essential [5]. This patient underwent an echocardiogram that showed no abnormalities of left ventricular ejection fraction or systolic function. Furthermore, the patient was evaluated for potential development of respiratory problems, among which was lungs fibrosis, with no evidence of this from her high resolution computed tomography scan of thorax. The need for ongoing evaluation of respiratory function will be necessary as respiratory muscle weakness may develop in later stages. Another topic covered with this patient was contraception. As she already has three children, and, besides, doesn't wish to become pregnant again, she was prescribed intra-muscular depo-provera. This was the decision considering her reproductive age and the autosomal recessive nature of her condition. The psychological impact of dysferlinopathy is another important consideration. This disease can then progress and lead to depression or anxiety in the patient, but in this case, patient's depression screening was normal and the patient is still receiving strong familial support. The patient can work, which helps maintain her overall quality of life even though she has a dysferlinopathy.

The important role of family physicians in this complex genetic muscle disorder is screening, to achieve early diagnosis, offer continuing care and referral to appropriate specialists. They need to monitor the disease's complications that are associated with muscle atrophy and cardiac involvement regularly, by performing muscle strength assessments, functional mobility tests and echocardiogram. As the disease progresses, managements and care plans need to be adjusted as well to ensure them with a better quality of life. In this case, the patient decided to follow up with her family physician due to convenience and logistic issues. This underscores the importance of accessible healthcare options for managing chronic disease.

CONCLUSION

This case report emphasizes the importance of appropriately recognizing and managing dysferlinopathy from a primary care perspective. Primary care providers must maintain a high index of suspicion, particularly in early referral to correct department. Accurate diagnosis through genetic testing and muscle biopsy is crucial, follow with optimal management of this rare genetic disorder such as genetic counselling and physiotherapy. It encourages further studies to be done, aiming to improve the outcome and explore more therapeutic interventions.

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Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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