

Fabry's Disease and Dysferlinopathy: co-occurrence of two rare genetic disorders

Doença de Fabry e Disferlinopatia: coocorrência de duas doenças genéticas raras

DOI:10.34119/bjhrv6n4-093

Recebimento dos originais: 19/06/2023

Aceitação para publicação: 17/07/2023

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ABSTRACT

Fabry's Disease (FD) is a rare X-linked inherited disorder of glycosphingolipid metabolism due to absent or deficient activity of α -galactosidase A (GLA) enzyme that can present with multisystemic involvement, including painful small fiber neuropathy. Dysferlinopathy is a heterogeneous spectrum of neuromuscular disorders inherited in an autosomal recessive manner. In this report, we present a case of co-occurrence of these two rare genetic disorders

Keywords: Fabry's Disease, Dysferlinopathy, limb-girdle muscular dystrophy, case report.

RESUMO

A doença de Fabry (DF) é um distúrbio hereditário raro, ligado ao cromossomo X, do metabolismo de glicoesfingolípídeos devido à ausência ou deficiência da atividade da enzima α -galactosidase A (GLA), que pode se apresentar com envolvimento multissistêmico, incluindo neuropatia dolorosa de fibras finas. A disferlinopatia é um grupo heterogêneo de distúrbios neuromusculares herdados de forma autossômica recessiva. Neste relato, apresentamos um caso de coocorrência desses dois distúrbios genéticos raros.

Palavras-chave: Doença de Fabry, Disferlinopatia, distrofia muscular da cintura escapular, relato de caso.

1 INTRODUCTION

Fabry's Disease (FD) is an X-linked disease caused by abnormalities on the α -galactosidase A (GLA) gene, with a prevalence estimated of 1: 40.000 - 117.000 habitants¹. As a disorder of glycosphingolipid metabolism owing to absent or deficient activity of lysosomal GLA, progressive accumulation of globotriaosylceramide (Gb3) within lysosomes occurs in a variety of cell types². In the nervous system, the most common affected locale is dorsal root ganglion neuronal cells. This provokes characteristic features, such as painful small fiber neuropathy (SFN). Later in life, cerebrovascular disease can also occur¹.

Dysferlinopathy is also an inherited disorder, but recessive autosomal, and its prevalence is not known due to its rarity³. The neuromuscular features of this disease correspond to four phenotypes: Miyoshi muscular dystrophy, limb-girdle muscular dystrophy (LGMD), asymptomatic hyperCKemia and distal myopathy with anterior tibial onset³.

Although rare, clinical suspicion and correct diagnosis through genetic testing are important to guide clinical follow-up in both disorders and specific enzyme replacement therapy for FD.

With this report, we aim to shed light on a rare association between two genetic disorders presenting with neurological features.

2 CASE REPORT

A 60-year-old male presented with shoulder and pelvic girdle muscle weakness starting at age 18 associated with progressive atrophy of muscles on both thighs and arms. At the age of 30, he started using support to walk and became wheelchair-bound at age 55.

He has a previous history of renal failure caused by FD, diagnosed at age 50 through molecular testing that identified a pathogenic variant (p.R356W) on GLA gene. He has two brothers with progressive proximal weakness without etiological diagnosis. There was no history of consanguinity amongst his family members.

At neurologic examination, he presented worse proximal than distal weakness in all four limbs, diffuse areflexia and atrophy of shoulder and pelvic girdle muscles.

Laboratory tests showed elevation of serum CPK (397 U/L) and electromyography featured a myogenic pattern. Molecular testing identified two pathogenic variants in DYSF gene (p.Glu1335Lys and p.Asp1163Profs*11).

3 DISCUSSION

FD is a rare X-linked inherited disorder of glycosphingolipid metabolism due to absent or deficient activity of GLA enzyme, causing a progressive accumulation of Gb3 within lysosomes in endothelial, renal, cardiac and dorsal root ganglion neuronal cells. Clinical picture is composed of a multisystemic involvement, including progressive renal failure, hypertrophic cardiomyopathy, painful small fiber neuropathy (SFN) and cerebrovascular disease¹. Neurological involvement in FD includes the last two features.

SFN form a subgroup of painful sensory neuropathies caused by impairment of the thinly myelinated A-delta and unmyelinated C nerve fibers⁴. SFN is present in 80% of FD diagnosed patients¹. It is responsible for a length-dependent painful neuropathy that first affects both feet and hands and then progresses to other body regions. Conventional nerve conduction studies (NCS) are usually normal, since these only evaluate large fibers, and QST and skin biopsy shows evidence of SFN in FD, with cold sensation impairment¹.

Cerebrovascular complications usually starts later in life. Signs and symptoms vary and comprise headache, vertigo, transient ischemic attacks, ischemic strokes and vascular dementia¹.

Apart from managing pain and treating cerebrovascular disorders, there is specific treatment for FD. Enzyme replacement therapy (ERT) is thought to slow or prevent irreversible changes in the cardiac and renal systems if started at an earlier age, but has limited efficacy in advanced cases¹. ERT, through Agalsidase alfa or Agalsidase beta, is recommended to all symptomatic patients and for asymptomatic boys from the age of 7 or 8 years or over⁶. There is no data supporting ERT initiation in asymptomatic boys under 7 years old and for asymptomatic girls⁶.

Since proximal weakness and atrophy as experienced by our patient could not be explained by the previous diagnosis of FD⁵, we sought to pursue another etiology for his symptoms.

Dysferlinopathies includes a heterogenous spectrum of neuromuscular disorders that can be clinically apparent through four phenotypes: Miyoshi muscular dystrophy, limb-girdle muscular dystrophy type 2B (LGMD2B), asymptomatic hyperCKemia and distal myopathy with anterior tibial onset³.

Our patient presented a LGMD2B phenotype, which is characterized by weakness and atrophy of the pelvic and shoulder girdle muscles. The clinical picture starts to present in adolescence or young adulthood and it continues to progress slowly³.

Diagnosis is made in a patient with suggestive findings and biallelic pathogenic variants in DYSF identified by molecular genetic testing.

There is no approved treatment for all four phenotypes of Dysferlinopathies. Follow-up is granted with symptom management, including physical therapy, respiratory vigilance for complications such as restrictive ventilatory disorder, genetic counseling and emotional support.

4 CONCLUSION

These two independent disorders have different genetic genesis and pathological mechanisms. To our best knowledge, this is the first case report in the literature showcasing co-occurrence of FD and Dysferlinopathy, two rare genetic disorders.

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