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CASE REPORT

Fabry disease presenting as apical left ventricular hypertrophy in a patient carrying the missense mutation R118C

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Apical hypertrophic cardiomyopathy;
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Abstract Anderson-Fabry disease is an X-linked lysosomal storage disorder caused by abnormalities of the *GLA* gene, which encodes the enzyme α-galactosidase A. A deficiency of this enzyme leads to the lysosomal accumulation of glycosphingolipids, which may cause left ventricular hypertrophy that is typically concentric and symmetric.

We present the case of a 60-year-old woman with symptoms of dyspnea, atypical chest pain and palpitations, in whom a transthoracic echocardiogram revealed an apical variant of hypertrophic cardiomyopathy. Analysis of specific sarcomeric genetic mutations was negative. The patient underwent a screening protocol for Anderson-Fabry disease, using a dried blood spot test, which was standard at our institution for patients with left ventricular hypertrophy. The enzymatic activity assay revealed reduced α-galactosidase A enzymatic activity. Molecular analysis identified a missense point mutation in the *GLA* gene (p.R118C).

This case report shows that Anderson-Fabry disease may cause an apical form of left ventricular hypertrophy. The diagnosis was only achieved because of systematic screening, which highlights the importance of screening for Anderson-Fabry disease in patients with unexplained left ventricular hypertrophy, including those presenting with more unusual patterns, such as apical variants of left ventricular hypertrophy. This case also supports the idea that the missense mutation R118C is indeed a true pathogenic mutation of Anderson-Fabry disease.

PALAVRAS-CHAVE
Miocardiopatia hipertrófica apical;
Ecocardiograma;
Genética;

Doença de Fabry com padrão apical de hipertrofia ventricular esquerda numa doente portadora da mutação *missense* R118C

Resumo A doença de Anderson-Fabry é uma doença do lisossoma associada ao cromossoma X, causada por alterações no gene GLA que codifica a enzima α-galactosidase A. A deficiência

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Doença de Anderson-Fabry; Rastreio

desta enzima leva à acumulação de glicosfingolípidos, podendo causar hipertrofia ventricular esquerda, tipicamente concêntrica e simétrica.

Apresentamos o caso de uma mulher de 60 anos com queixas de dispneia, dor torácica atípica e palpitações, que realizou um ecocardiograma transtorácico que mostrou uma variante apical de miocardiopatia hipertrófica. A pesquisa de mutações nos genes das proteínas do sarcómero foi negativa. A doente foi incluída num protocolo de rastreio de doença de Anderson-Fabry, usando o teste da gota de sangue seca, para doentes com miocardiopatia hipertrófica. Foi documentada uma redução da atividade enzimática da enzima α-galactosidase A. A análise molecular identificou uma mutação *missense* do gene GLA (p.R118C).

Este caso clínico mostra que a doença de Anderson-Fabry se pode apresentar com um padrão de hipertrofia ventricular apical. Este diagnóstico apenas foi feito devido ao rastreio sistemático realizado em todos os doentes com hipertrofia ventricular esquerda de causa não esclarecida, incluindo mesmo os doentes com padrões de hipertrofia menos usuais. Este caso clínico também suporta a ideia de que a mutação *missense* R118C é de facto uma mutação patogénica de doença de Anderson-Fabry.

Introduction

Anderson-Fabry disease (AFD) is an inborn error of metabolism caused by a genetic defect in the *GLA* gene, located in the Xq22 region of the X chromosome, which encodes the lysosomal enzyme α-galactosidase A.[1] Absent or deficient activity of this enzyme leads to progressive lysosomal accumulation of neutral glycosphingolipids and α-galactosyl breakdown products in cells throughout the body.[1] This has a profound effect on cellular function and leads to a wide range of manifestations in various organs, including the heart, kidneys and brain. Symptoms typically begin in childhood, although they become more frequent and severe with age, and patients may experience heart disease, renal failure or stroke.[2] AFD is an X-linked disorder, and many years passed until it was recognized that heterozygous females were not merely carriers, but could indeed develop the full range of manifestations of the disease.[3]

Cardiac involvement is common (40–60%)[4,5] and is currently the main cause of death in patients with AFD,[6] which leads to structural and functional changes in the myocardium, conduction system and valves. The main cardiac manifestation is left ventricular (LV) hypertrophy.

It is currently recognized that the formerly reported annual incidence of AFD of 1 in 100 000 seriously underestimated the true prevalence of the disease.[7] Recent prospective screening programs have revealed a much higher prevalence, of about 1 in 3100 hemizygous male newborns, mainly due to the diagnosis of late-onset phenotypes, such as late-onset hypertrophic cardiomyopathy.[8,9] It has been estimated that AFD is responsible for at least 0.5% of cases of hypertrophic cardiomyopathy.[10] LV hypertrophy secondary to AFD is typically concentric and symmetric.

We report an unusual case of an apical variant of LV hypertrophy in a patient with AFD carrying the missense mutation R118C, who was diagnosed during systematic screening of patients with unexplained LV hypertrophy.

Case report

A 60-year-old woman with a history of hypertension, dyslipidemia and chronic obstructive pulmonary disease presented to her general practitioner with dyspnea on moderate exertion (NYHA functional class II/IV), atypical chest pain and palpitations for several years. She underwent a transthoracic echocardiogram that revealed an apical variant of hypertrophic cardiomyopathy and she was referred to a cardiologist.

On clinical assessment the patient also complained of vertigo, hearing loss and tinnitus. There was no history of syncope or relevant family history. The physical examination was unremarkable.

The electrocardiogram showed sinus rhythm (66 bpm), increased QRS voltage and diffuse, deep, symmetric T-wave inversion (Figure 1).

The transthoracic echocardiogram revealed apical LV hypertrophy with a typical spade-like geometry of the LV cavity at end-diastole (LV wall thickness 17 mm) (Figure 2) and LV diastolic dysfunction (impaired relaxation) (Figure 3) with normal ejection fraction. No structural or functional valve disease was present.

There were no complex ventricular dysrhythmias on 24-hour Holter monitoring. A treadmill test was inconclusive for myocardial ischemia due to baseline electrocardiographic abnormalities, but there was a normal blood pressure response to exercise and no arrhythmias were found. Myocardial perfusion scintigraphy was normal.

The patient suffered from claustrophobia and refused to undergo cardiac magnetic resonance imaging.

A search for specific mutations in sarcomere protein genes was negative.

The patient was included in a screening protocol for AFD, using a dried blood spot test, which was standard at our institution for patients with unexplained LV hypertrophy. The enzymatic activity assay revealed reduced α-galactosidase A enzymatic activity (14 nmol/h/mg protein; normal range