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CASE REPORT

Histopathological evidence of Fabry disease in a female patient with left ventricular noncompaction

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Abstract Fabry disease is a rare X-linked lysosomal storage disorder caused by mutations in the alpha-galactosidase gene. The most frequent cardiac presentation of Fabry disease is cardiomyopathy characterized by left ventricular (LV) hypertrophy, usually concentric.

Heart disease in affected females tends to be clinically recognized later than in males and cardiac complications are the most frequently reported cause of death in females with Fabry disease. There are few data regarding the association between Fabry disease and LV noncompaction. We report a case of a 30-year-old asymptomatic woman, heterozygous for a nonsense alpha-galactosidase gene mutation (p.R220X), who presented LV noncompaction on cardiac magnetic resonance imaging, without LV wall hypertrophy. Histopathological examination of myocardial fragments showed marked deposition of glycosphingolipids in cardiomyocytes, confirming the diagnosis of Fabry cardiomyopathy. Based on this finding, the patient was proposed for enzyme replacement therapy. This case illustrates the role of endomyocardial biopsy in the clarification of doubtful or atypical findings related to cardiac Fabry disease, even in heterozygous women, and corroborates the contention that Fabry disease should be included in the differential diagnosis of LV hypertrabeculation/noncompaction.

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PALAVRAS-CHAVE
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Evidência histopatológica de doença de Fabry numa doente com não compactação do ventrículo esquerdo

Resumo A doença de Fabry é uma doença rara de armazenamento lisossómico, ligada ao cromossoma X, causada por mutações no gene da α − galactosidase. A apresentação cardíaca mais frequente é uma miocardiopatia caracterizada por hipertrofia ventricular esquerda geralmente concêntrica.

Nas mulheres afetadas a doença cardíaca tende a ser clinicamente reconhecida mais tardiamente do que em homens e as complicações cardíacas são a causa mais frequente de morte reportada em mulheres com doença de Fabry. Existem poucos dados sobre a associação entre a doença de Fabry e a não compactação do ventrículo esquerdo (VE). Reportamos o caso de uma mulher assintomática, com 30 anos de idade, heterozigota para uma mutação nonsense do gene da α−galactosidase gene (p.R220X) que apresentava critérios de VE não compactado na ressonância magnética cardíaca, sem hipertrofia das restantes paredes ventriculares. O exame histopatológico de fragmentos do miocárdio mostrou deposição acentuada de glicoesfingolípidos nos cardiomiócitos, corroborando o diagnóstico de miocardiopatia de Fabry. Com base nestes achados, foi proposto o início de terapia de substituição enzimática. Este caso ilustra o papel da biópsia endomiocárdica no esclarecimento de achados duvidosos ou atípicos relacionados com a doença de Fabry cardíaca, mesmo em mulheres heterozigotas, e corrobora a afirmação de que a doença de Fabry deve ser incluída no diagnóstico diferencial da hipertrabeculação/não compactação do VE.

Introduction

Fabry disease is a rare X-linked lysosomal storage disorder caused by mutations in the alpha-galactosidase gene (*GLA*). Partial or complete deficiency of alpha-galactosidase enzyme activity leads to progressive intracellular accumulation of neutral glycosphingolipids containing terminal alpha-D-galactosyl residues, especially of globotriaosylceramide (Gb3), in many different cell types and tissues.[1–3] The multisystemic manifestations of the classical phenotype of Fabry disease, which is typically observed in males with absent or extremely low alpha-galactosidase activity,[3] include acroparesthesias and other neuropathic symptoms, angiokeratomas, hypohidrosis, gastrointestinal problems and cornea verticillata, usually beginning in childhood or adolescence, and later-onset major kidney, cardiac and cerebrovascular complications.[2–4] Deacylated globotriaosylceramide, globotriaosylsphingosine (lysoGb3) may be an important pathogenic mediator involved in the onset and progression of some of the clinical and pathological manifestations of Fabry disease.[5]

Accumulation of Gb3 may occur in all the cellular components of the heart,[3] causing a variety of clinical manifestations, including left ventricular hypertrophy (LVH), valvular disease (especially mitral regurgitation), myocardial ischemia, and arrhythmias.[3] The most frequent cardiac presentation of Fabry disease is a cardiomyopathy characterized by progressive, usually concentric, LVH and replacement fibrosis with preferential localization in the basal posterolateral left ventricular (LV) wall segments.[6] Heart disease in affected females tends to be clinically recognized later than in males, usually after the fourth decade of life.[4,7,8] Cardiac complications are the most frequently reported cause of death in females with Fabry disease.[3]

Abnormalities of tissue Doppler mitral annulus velocities can be observed in patients with normal thickness of the cardiac wall, representing an early sign of myocardial damage.[9]

Other echocardiographic findings have been associated with Fabry disease, although none is pathognomonic. The appearance of a binary endocardial appearance,[10] prominent papillary muscles or right ventricular involvement may also be encountered in ventricular hypertrophy secondary to other etiologies.[11,12] There are fewer data regarding the association between LV noncompaction (LVNC) and Fabry disease.

We report a diagnosis of LVNC by cardiac magnetic resonance imaging (CMRI) in a young woman with histologically confirmed Fabry disease cardiomyopathy.

Case report

A 30-year-old woman, heterozygous for a nonsense *GLA* mutation (p.R220X) associated with the classical phenotype of Fabry disease, was referred to the cardiology clinic for routine screening of cardiovascular manifestations of the disease. The assay of alpha-galactosidase in leukocytes had revealed a mild deficiency of enzymatic activity (25 nmol/h/mg; normal range: 36-80), as typically observed in heterozygotes.

The patient was asymptomatic and did not manifest any other typical signs of the disease except for cornea verticillata on slit lamp ophthalmological examination, and two small angiokeratomas, on the face and in the