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Case report
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Late-Onset Cardiac Variant of Fabry Disease Responsive to Short-Term Treatment with Agalsidase Alpha

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Abstract

Cardiac involvement is very frequent with Fabry disease, an X-linked lysosomal storage disorder caused by deficiency of α-galactosidase A. Enzyme replacement therapy has been proven effective in reducing gycosphingolipid accumulation in endothelial cells of the kidney, heart and skin, as well as improving cardiac morphology and function. However, Fabry disease cardiomyopathy (FC) is often indistinguishable from hypertrophic cardiomyopathy (HCM) or other causes of left ventricular hypertrophy (LVH), based on clinical and instrumental findings. We describe a 60-year-old patient with unexplained HCM and progressive renal disease who was admitted to our centre for echocardiography evaluation. He had a history of dysrhythmias (for which he had undergone implantation of an ICD device) and presented with ECG abnormalities, echocardiographic evidence of LVH and reduced tissue Doppler imaging velocities and late-enhancement areas at gadolinium enhanced cardiac magnetic resonance evaluation. Demonstration of a total deficiency of α- galactosidase A in the leukocytes confirmed the diagnosis of Fabry disease. The patient experienced improvement of pain, oedema, exercise capacity and cardiac and renal haematological parameters after 6 weeks' treatment with agalsidase α. Fabry disease should always be considered in the differential diagnosis of unexplained LVH.

Introduction

Fabry disease is an X-linked lysosomal storage disorder caused by a genetic deficiency of the enzyme α-galactosidase A (α-Gal A), which results in progressive accumulation of glycosphingolipids (mainly globotriaosylceramide) in various cell types and organs throughout the body, including skin, kidney, heart, vascular endothelium and peripheral nervous system. Mutations in the α-Gal A gene, located on the X chromosome (locus Xq22) are responsible for the classical manifestations of Fabry disease, and over 300 mutations (mostly family specific) have been identified, including missense and nonsense mutations, gene rearrangement and splicing defects [1]. In its multisystemic classic form, occurring in males with <1% α-Gal A activity, Fabry disease becomes clinically evident in childhood or adolescence and is characterized by acroparesthesia, angiokeratomas, hypohidrosis, typical corneal and lenticular opacities and progressive deterioration of renal function. Later in life these patients usually start showing signs of cardiovascular and/or cerebrovascular disease, a major cause of mortality and morbidity. In heterozygous females, the symptoms are typically milder, sometimes silent, and develop at a later age [1].The diagnosis of Fabry disease requires demonstration of deficient α-Gal A enzyme activity in plasma or leuckocytes, while molecular genetic testing is necessary for identification of the carrier status in women. Antenatal testing is possible by analysing fetal cells obtained by amniocentesis of chorionic villus sampling. Not all Fabry disease patients present with the classical multisystemic disease, as some mutations result in residual activity of α-Gal A. Two variant phenotypes, cardiac and renal, have been identified in males with >1% enzyme activity [1].These atypical variants of Fabry disease may be difficult to diagnose. The cardiac variant, which usually presents in subjects >40 years of age, is characterized by a number of cardiac abnormalities, including left ventricular hypertrophy (LVH) mimicking the clinical features of hypertrophic cardiomyopathy (HCM), valvular insufficiency and conduction abnormalities [1-4]. Fabry disease has been reported in 3% of men with LVH, and 6% of men and 12% of women with late-onset HCM [3-5] Early diagnosis of Fabry disease is important, as enzyme replacement therapy with recombinant or gene-activated human α-Gal A has recently become available that has been proven effective in reducing and/or clearing deposits of globotriaosylceramide in endothelial cells of the kidney, heart and skin, with reported improvement in symptoms and in a number of cardiac parameters [6-9].

We report our experience with a patient affected by late-onset Fabry disease cardiomiopathy (FC) and renal failure.

A 60-year-old male with severe, unexplained HCM, was referred to our centre for echocardiographic examination. The patient had a history of hypertension since age 40 years. In 2001 (at age 52), he experienced the first episode of atrial fibrillation and HCM was diagnosed. Two years later, the patient had manifested other episodes of atrial fibrillation, with ecocardiographic examination showing reduced LV function (LVEF 45%), severe LVH (interventricular septum [IVS] thickness 26 mm) and left atrial enlargement (LA area 39 cm^2). Treatment with warfarin, then amiodarone and metoprolol, was instituted. β-blocker treatment worsened asthenia and fatigue. In 2006, the patient was in New York Heart Association (NYHA) functional class II and presented signs of reduced renal function (serum creatinine concentration 3 mg/dL, clearance 36 mL/min). Possible causes of infiltrative HCM were investigated by immunoassays, but serum and urine immunofixation failed to detect monoclonal antibodies. Immunoglobuline levels were normal, and tests were negative for antinuclear antibodies and Waaler-Rose assay. In 2007 the patient necessitated placement of an automatic implantable cardioverter-defibrillator (ICD) device following an episode of non-sustained ventricular tachycardia. Coronary angiography showed normal coronary arteries. Renal function parameters had

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deteriorated (creatinine concentration 3.6 mg/dL, proteinuria 9 g/24h) and ultrasonography revealed an enlarged left kidney (bipolar diameter 10.2 cm) with a hyperechogenic cortex. However, no renal biopsy was performed. Corticosteroid therapy was instituted, with a stabilization of renal function (proteinuria 1.2 g/24h).

When the patient was brought to our attention in 2009, he was in NYHA class III and presented with lower limb edema and painful joints, with restricted walking capacity. BP was 100/80 mm Hg and oxygen saturation was 95%. ECG showed sinus bradycardia, right bundle branch block and LVH with a marked strain pattern, while echocardiography in basal conditions confirmed LV severe hypertrophy (IVS and posterior wall thickness 27 mm) without obstruction, with hyperechogenic areas in the subendocardial layer and posteromedial septum. There was no binary appearance of the LV endocardial border, as described by Pieroni et al. [10]. LV contractility was slightly impaired (LVEF 45-50%), while both atria appeared markedly enlarged and the aortic root dilated (48 mm). Pulmonary arterial pressure values appeared to be normal, as estimated by measurement of the tricuspid pressure gradient and no pericardial effusion was present (Video 1-2). Tissue Doppler imaging (TDI) systolic and diastolic velocities were reduced. Contrast-enhanced cardiac magnetic resonance (CMR) revealed severe concentric hypertrophy (LV mass 605 g), while diffuse late enhancement was apparent in the lateral wall, with areas of focal enhancement in the septum, 25 minutes after injection of Gd-DTPA (Figure 1-2). A diagnosis of cardiac amyloidosis

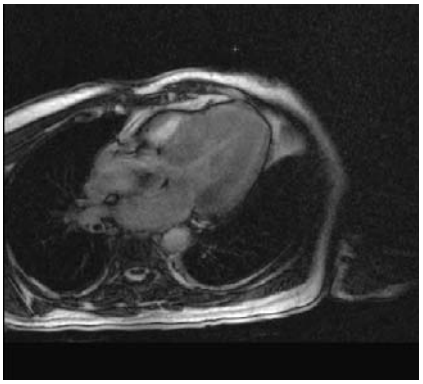


Figure 1:

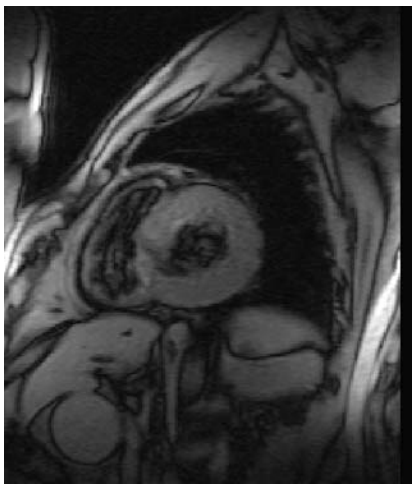
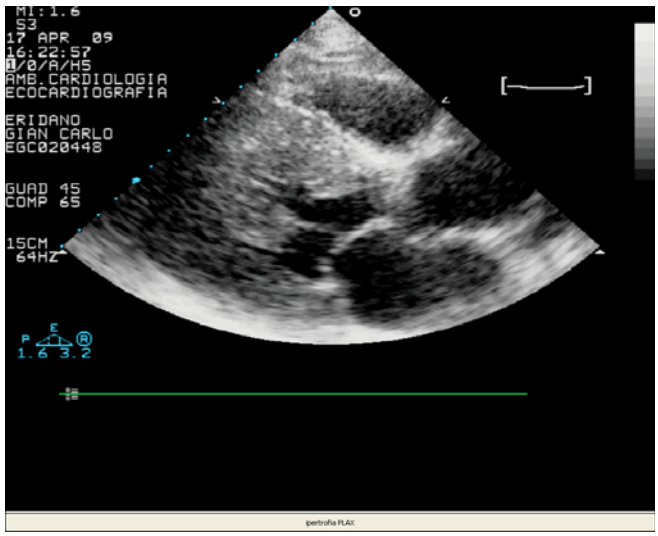
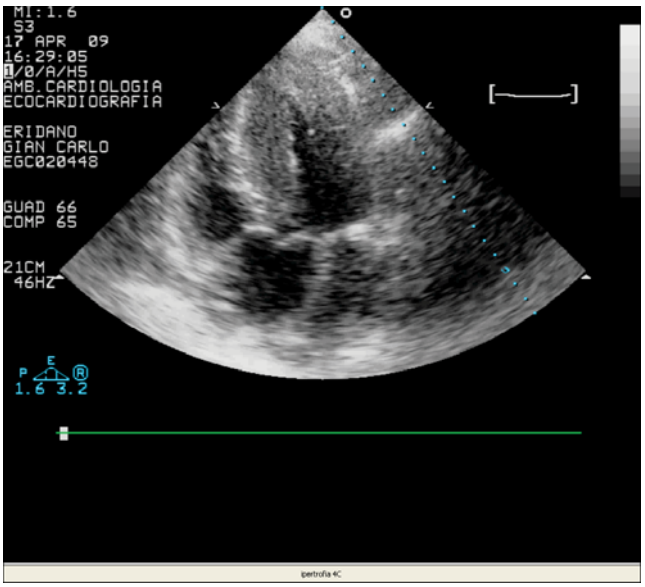


Figure 2:



Video 1:



Video 2:

was considered unlikely based on ECG findings (high-voltage QRS) and absence of pericardial effusion. The global clinical picture and low tolerance of β-blocker therapy oriented us toward a diagnosis of Fabry disease, confirmed by the results of α-Gal an activity analysis in the patient's leukocytes showing a total enzyme deficiency. Enzyme replacement therapy with agalsidase α was started at a dosage of 1mg/kg of body weight intravenously every two weeks. After 6 weeks of therapy, there was marked improvement of lower limb pain and functional disability, and only on major exertion did the patient experience dyspnoea (NYHA class II). Asthenia resolved completely upon withdrawal of β-blockers and lower limb oedema was no longer present. There was also improvement in hematochemical parameters, with a reduction of creatinine concentration (from 7.8 pre-treatment to 5.4 mg/dL) and brain natriuretic peptide (BNP) levels (from 1250 to 380 pg/mL).

Cardiac involvement is frequent in Fabry disease, with LVH

being the most common finding [9]. In classically affected patients, LVH, angina, conduction abnormalities, valvular disease, aortic root dilatation and coronary artery disease, often leading to congestive heart failure and myocardial infarction are frequently reported cardiac signs and symptoms due to the accumulation of glycosphingolipids in vascular endothelial and smooth muscle cells and in cardiomyocites[1,11].The atypical, late-onset cardiac variant of Fabry disease, generally described in patients with low but detectable activity of α-Gal A, is often underdiagnosed due to the lack of multysistemic involvement. Our patient, who had undetectable levels of α-Gal A, presented with severe HCM (firstly diagnosed at 52 years of age) and progressive renal disease. In his history, dysrhythmias had been a prominent feature of cardiac pathology, resulting in treatment with amiodarone and β-blockers (which were poorly tolerated) and finally, placement of an ICD device. ECG, echocardiographic and CMR findings were consistent with previous reports of FC, showing sinus bradycardia and a marked strain pattern, severe hypertrophy of the LV with slightly impaired LV contractility, enlargement of both atria and the aortic root, reduced TDI contraction and relaxation velocities and late gadolinium enhancement suggestive of myocardial fibrosis [1-5,9,10,12,13].

Prompt diagnosis of Fabry disease is imperative, since specific enzyme replacement therapy is now available. Furthermore, it has been suggested that starting treatment early, before myocardial fibrosis has developed, results in better long-term outcomes in terms of myocardial morphology and function [9]. However, non-invasive diagnosis of FC can be challenging. FC and HCM (osbstructive, non-obstructive or apical) share several morphologic and functional characteristics, including ECG and echocardiographic features indicative of LVH, reduced TDI velocities and late enhancement areas detected by CMR. The two forms are often indistinguishable based on clinical, instrumental and imaging findings. A binary appearance of the LV endocardial border, which is not visible in patients with HCM, has been identified as an ecocardiographic diagnostic hallmark of FC [10].However, this sign is not always present in Fabry disease and like other authors, we failed to detect it in our patient [14]. Other cardiac conditions causing LVH, such as amyloidosis, hemochromatosis, sarcoidosis or lysosomal storage disorders (including glycogenoses, mucolipidoses and mucopolysaccharidoses) should also be included in the differential diagnosis. Fabry disease is readily confirmed in males by determining α-Gal A activity in plasma or peripheral leukocytes, while genetic testing is required in females [1,11,5]. It is important, therefore, that Fabry disease be always considered in patients with unexplained causes of LVH, especially if renal impairment is also present.

Enzyme replacement therapy has been proven effective in clearing glycosphingolipid accumulation in affected tissues, improving clinical and QoL parameters, reducing pain and slowing the progression of cardiac, renal and cerebrovascular complications in Fabry disease [1,6-9]. In a study based on the analysis of endomyocardial biopsies, five months of enzyme replacement therapy resulted in complete cardiac microvascular clearance of globotriaosylceramide deposits in 72% of treated patients compared with 3% of placebo recipients [8]. Studies in small cohorts have also documented reduction or stabilization of LV mass and improvement of LV function and exercise capacity [6,9,15]. However, clinical studies have evaluated the long-term effects of therapy (≥5 months). In our patient, a 60-year-old man with end-stage renal disease, clinical improvement was already evident after 6 weeks of treatment with agalsidase α, as manifested by pain reduction, resolution of oedema and improved exercise capacity, as well as decreased serum levels of creatinine (from 7.4 to 5.4 mg/dL) and BNP (from 1250 to 380 pg/mL).

Other contributing factors to explain the observed clinical improvement, maybe considered as the withdrawal of a β-blocker treatment.

In conclusion, FC should always be considered in the differential diagnosis of unexplained LVH, as improvement with enzyme replacement therapy is possible even in elderly, severely affected patients.

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