

Case Report

Delayed Diagnosis of Fabry Disease Presenting as Myocardial Ischaemia

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Cardiovascular complications due to the accumulation of globotriaosylceramide in cardiac cells occur in almost all patients affected by Anderson-Fabry disease. Cardiac manifestations include left ventricular hypertrophy, mitral regurgitation, conduction disturbances and myocardial ischaemia. We report a case of Fabry's disease diagnosed several years after the onset of early cardiac symptoms.

Fabry disease (FD) is a progressive X-linked disorder of glycosphingolipid metabolism caused by a deficiency of the α -galactosidase A lysosomal enzyme. The deficiency of this enzyme leads to intracellular accumulation of neutral glycosphingolipid (chiefly globotriaosylceramide) in many tissues throughout the body, particularly the vascular endothelium, heart and kidney.¹⁻³ Clinical manifestations of this accumulation, such as angiokeratoma, gastrointestinal symptoms, corneal dystrophy and acroparesthesias, often begin in childhood and adolescence.^{1,2} Renal impairment, cerebrovascular complications and cardiac manifestations usually occur in adulthood. Cardiovascular involvement is very frequent and is associated with high morbidity and mortality.³⁻⁵ The most common cardiac lesion is left ventricular hypertrophy due to massive glycosphingolipid accumulation in cardiomyocytes.⁵⁻⁷ This abnormality mimics hypertrophic cardiomyopathy, so that the disease may be misdiagnosed and remain concealed indefinitely.^{2,8}

In addition, infiltration of the valvular leaflets and conduction system leads to mitral regurgitation and shortening of the

PR interval on the ECG, respectively. Until recently, there was no specific treatment for this progressive disease and major organ failure led to death in male patients between the fourth and the fifth decade. Nowadays, enzyme replacement therapy with α -galactosidase slows progression to the composite clinical outcome of renal, cardiac and cerebrovascular complications and death compared with placebo in patients with advanced FD. Therapeutic intervention before irreversible organ damage may provide greater clinical benefit.⁹

Case presentation

The patient was a 53-year-old male affected by cardiac failure; he was neither a smoker nor diabetic, and had no history of hypertension. His younger sister was affected by hypertrophic cardiomyopathy. Seven years earlier he had suffered from angina pectoris on effort. The ECG showed sinus rhythm and a normal PR interval. The echocardiogram evidenced slight enlargement of the left ventricle, with reduced systolic function (ejection fraction 40%), normal thickness of the ventricular wall, and mild mitral insuffi-

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ciency. Since a stress test demonstrated myocardial ischaemia he underwent coronary angiography, which ruled out significant stenosis. Accordingly, the patient was treated conservatively with an angiotensin-converting enzyme inhibitor, aspirin and a beta-blocker.

After 2 years, the patient was admitted for re-lapsing angina pectoris. Myocardial scintigraphy documented an apical perfusion defect; subsequently, a coronary arteriogram showed moderate stenosis (60%) of the mid-portion of the left anterior descending artery, which was treated with percutaneous coronary intervention and stent implantation. Two years after coronary angioplasty, the patient was again admitted to another institution complaining of chest pain, but coronary angiography ruled out other significant stenosis and demonstrated the patency of the stent lumen. Since that time, the patient has been asymptomatic for angina but he has been affected by heart failure (New York Heart Association functional class II). Serial echocardiographic studies documented diffuse hypokinesia of the left ventricle with normal wall thickness, a reduced ejection fraction (47%), and mild mitral regurgitation.

After 3 years the patient was referred to our institution for a reappraisal of cardiac failure. Physical examination revealed a grade 3/6 Levine holosystolic murmur, normal blood pressure and left leg lymphoedema. Laboratory results demonstrated a high plasma level of creatinine (1.4 mg/dL). A 12-lead electrocardiogram documented sinus rhythm, with a short PR interval and complete left bundle branch block (Figure 1). The echocardiogram showed concentric hypertrophy of the left ventricle with an average ventricular wall thickness of 13 mm and normal dimensions (Figure 2), with slightly reduced systolic function (ejection fraction was 48%). In addition, the mitral leaflets appeared to be thickened and moderate mitral insufficiency was demonstrated by colour Doppler flow mapping. A Holter electrocardiogram did not demonstrate arrhythmias.

On the basis of the medical history, ECG features and the new onset of left ventricular hypertrophy, FD was suspected, and other stigmata of the pathology, such as cornea verticillata and angiokeratoma, were discovered. Finally, the diagnosis was confirmed by demonstration of reduced plasma α -galactosidase A enzyme activity (0.4 nmol/h/mL, normal range >1 nmol/ml/h) and of mutation g.7446G>A in the α Gal gene.

After being diagnosed with FD, the patient was administered intravenous agalsidase- α 0.2 mg/kg ev-

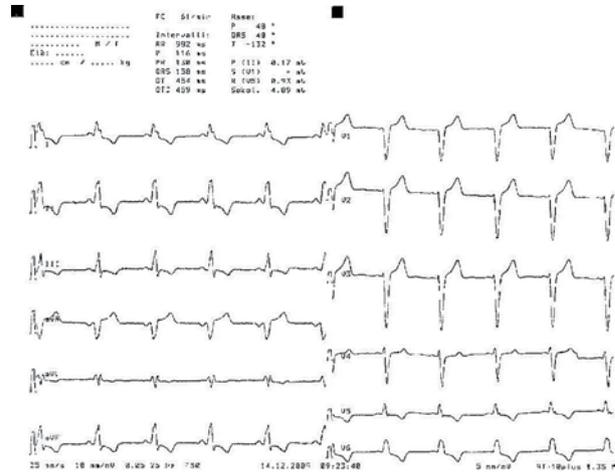


Figure 1. The patient's electrocardiogram.

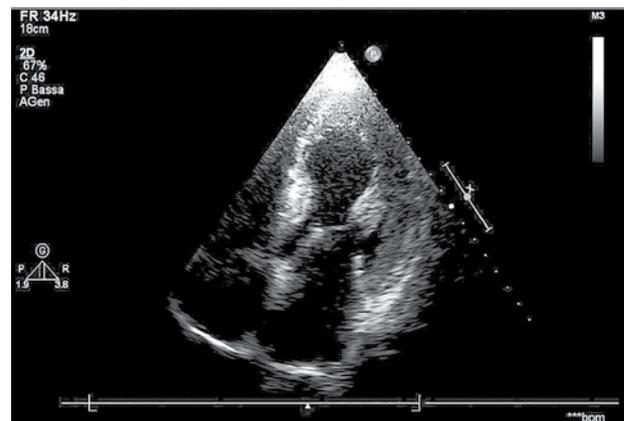


Figure 2. Echocardiographic apical four-chamber view.

ery two weeks. He was also advised to inform his relatives of the opportunity to undergo diagnostic testing and to participate in the clinical survey.

Discussion

Since enzyme replacement therapy may attenuate or reverse hypertrophy and improve myocardial function,⁹ early diagnosis of FD is crucial for prognosis and survival. Unfortunately, diagnosis of FD is often missed or delayed.²⁻⁸ It should be noted that the case reported here is quite uncommon, because the disease became manifest only in adulthood with angina pectoris, which is not one of the most common symptoms of FD. Myocardial ischaemia is caused mainly by the progressive deposition of glycosphingolipid in cardiac capillary endothelium and vascular smooth muscle.¹⁰⁻¹² In

addition, a minority of patients develop premature atherosclerosis of the epicardial coronary arteries. In all likelihood, both pathogenetic mechanisms coexisted in our patient, since he initially complained of angina and cardiac insufficiency without angiographically detectable lesions, which became manifest only after 2 years. The diagnosis of FD was suspected after 7 years, with the onset of unexplained concentric left ventricular hypertrophy, associated with thickening of the mitral leaflets and a shortened PR interval. In addition, a clinical history of mild renal impairment and the existence of a sister affected by hypertrophic cardiomyopathy, together with the demonstration of corneal and dermatological abnormalities supported the diagnostic hypothesis.

As this report demonstrates, some clinical, ECG and echocardiographic characteristics could help to differentiate hypertrophic cardiomyopathy from FD; however, a careful medical history has a pivotal role in raising suspicion of the existence of the disease. Specifically, normal blood pressure, renal dysfunction and a familial history of hypertrophic cardiomyopathy, consistent with X-linked inheritance, associated with a shortened PR interval and thickening of the mitral leaflets, should alert the clinician to the possible diagnosis of FD.^{2,3,8,13}

On the basis of this consideration, any patient with unexplained left ventricular hypertrophy, or relatively early onset of ischaemic heart disease without coronary stenosis, should be carefully examined in order to evidence extracardiac hallmarks of FD, such as angiokeratoma, acroparesthesias, proteinuria and corneal opacity. FD, however, can be readily confirmed in patients at high risk for this disease by simple enzymatic assay, and the diagnosis must be confirmed by molecular genetic analyses, especially

in heterozygous females, who could have normal or slightly reduced enzymatic activity.

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