pISSN 1975-4612/ eISSN 2005-9655

www.kse-jcu.org
http://dx.doi.org/10.4250/jcu.2013.21.1.26
CASE REPORT J Cardiovasc Ultrasound 2013;21(1):26-29

Fabry Cardiomyopathy

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Fabry disease is a progressive X-linked disorder of glycosphingolipid metabolism caused by a deficiency of the α-galactosidase lysosomal enzyme. The partial or complete deficiency of the lysosomal enzyme leads to an accumulation of neutral glycosphingolipids in the vascular endothelium and visceral tissues throughout the body. In the heart, glycosphingolipids deposition causes progressive left ventricular hypertrophy (LVH). We report a case of Fabry disease which was suspected based upon two-dimensional echocardiographic finding of LVH. A 44-year-old man was admitted to evaluation of aggravated exertional dyspnea of two weeks duration. He had been diagnosed with end-stage renal disease of unknown etiology at age 41 followed by renal transplantation that year. He had been treated with oral immunosuppressive agents. On hospital day two, transthoracic echocardiography revealed concentric LVH. Left ventricular systolic function was preserved but diastolic dysfunction was present. Fabry disease was confirmed by demonstration of a low plasma α-galactosidase A (α-Gal A) activity. Analysis of genomic DNA showed α-Gal A gene mutation. The patient was diagnosed with Fabry disease.

KEY WORDS: Fabry disease · Alpha-galactosidase A · Cardiomyopathies.

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by α-galactosidase A (α-Gal A) deficiency. Because the disease is X-linked, males are predominantly affected. This enzyme deficiency leads to widespread deposition of neutral glycosphingolipids (mainly globotriaosylceramide and, to a lesser extent, galabiosylceramide) on blood vessel walls throughout the body, resulting in a multiple-system disorder with a wide spectrum of physical signs and symptoms that predominantly affect the central and peripheral nervous systems, skin, heart, kidneys, and eyes.[1] In the heart, glycosphingolipids deposition causes progressive left ventricular hypertrophy (LVH) that mimics the morphological and clinical characteristics of hypertrophic cardiomyopathy (HCM).[2][3]

Enzyme replacement therapy is effective in reversing the microvascular changes in FD by catabolizing the lipid deposits and improving cardiac function in patients with cardiac involvement.[4][5] We report a case of FD with end-stage renal disease (ESRD) which was suspected based upon two-dimensional transthoracic echocardiographic finding.

Case

A 44-year-old man was admitted to evaluation of aggravated exertional dyspnea with orthopnea for two weeks in 2010. He had been diagnosed with ESRD of unknown etiology at age 41 followed by renal transplantation in 2007. He had been admitted for azotemia three times after renal transplantation. Percutaneous biopsy of the transplanted kidney was performed three times in 2008, 2009, 2010. The findings on renal biopsy were acute rejection, chronic renal calcineurin inhibitor toxicity, antibody mediated rejection and no evidence of FD in the graft kidney. He had been treated with oral immunosuppressive agents, including prednisolone (10 mg daily), tacrolimus (4 mg, bid) and mizoribine (50 mg, qd). Vital signs on arrival included a blood pressure of 162/98 mmHg and a regular pulse rate of 73 bpm, and body temperature of 36.5°C. The initial electrocardiogram showed LVH with a strain pattern, ST-T changes in leads II, III, aVF, V3-V6 and short PR interval (Fig. 1). Chest radiography demonstrated cardiomegaly (cardiothoracic ratio = 70%) and blunting of both costophrenic angle (Fig. 2). Laboratory studies revealed that hemoglobin

• Received: September 21, 2012 • Revised: November 19, 2012 • Accepted: February 13, 2013
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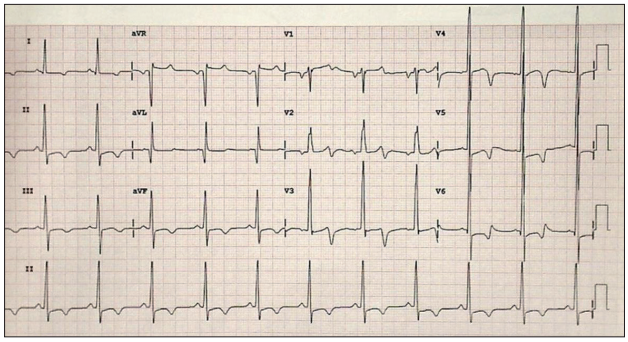

Fig. 1. The initial electrocardiogram showed left ventricular hypertrophy with a strain pattern, ST-T changes in leads II, III, aVF, V3-V6.

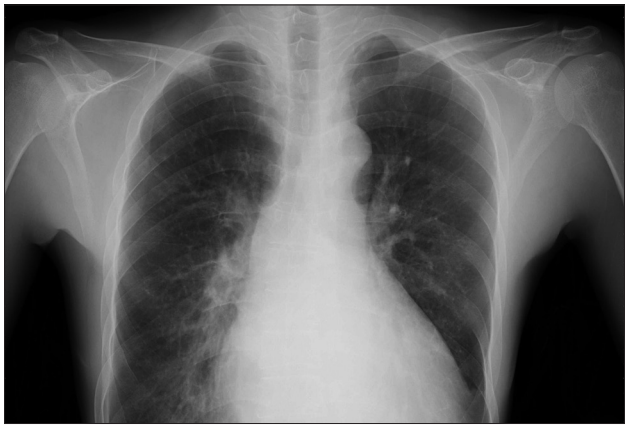

Fig. 2. Chest radiography. Chest radiography demonstrated cardiomegaly (cardiothoracic ratio = 70%) and blunting of both costophrenic angle.

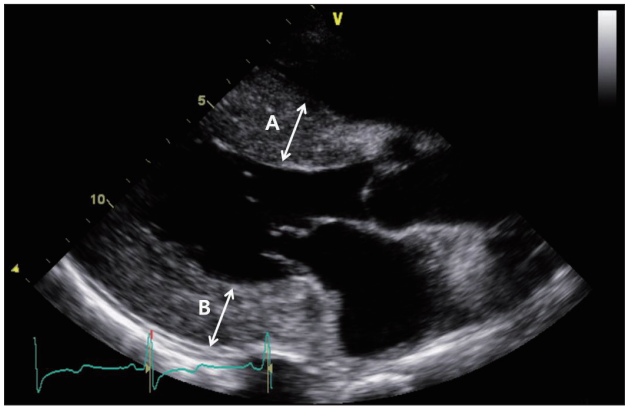

Fig. 3. Two dimensional echocardiography. Severe concentric left ventricular hypertrophy is shown in a parasternal long-axis view. The interventricular septal dimension (A) was 23 mm and the left ventricular posterior wall dimension (B) was 22.8 mm in thickness.

was 6.2 g/dL, BUN 64.2 mg/dL, creatinine 6 mg/dL, sodium 134 mEq/L, potassium 6.1 mEq/L, and serum N-terminal pro-B type natriuretic peptide level 126043 pg/mL. On hospital day two, two-dimensional transthoracic echocardiography revealed concentric LVH (interventricular septal dimension 23 mm, LV posterior wall dimension 22.8 mm), mimicking non-obstructive HCM (Fig. 3). The interventricular septal dimension and posterior wall dimension was thicker than 3 years ago (interventricular septal dimension 17 mm, LV posterior wall dimension 17 mm). And left atrial enlargement was seen (4.5 cm). Left ventricular systolic function was preserved (ejection fraction = 59%), but diastolic dysfunction was present. Pulsed-wave Doppler recording of mitral inflow revealed a phase resembling an abnormal relaxation diastolic filling pattern, with an ratio between early (E) and late (A) mitral inflow velocity (E/A) of 0.82 (Fig. 4A). The mitral annulus early diastolic tissue Doppler velocity (E') and the E/E' index were 2.64 cm/s and 26.4, respectively, indicating increased LV filling pressure and a pseudonormal pattern (Fig. 4B). The patient was prescribed diuretics for dyspnea and epokine for anemia. And the patient's condition improved. The patient's history of early onset ESRD and echocardiographic findings were suggestive of Fabry cardiomyopathy as well as idiopathic HCM. Alpha-galactosidase activity assay was performed. The assay was performed by fluorescence assay with 4-methylumbelliferyl and sequencing. The patient was confirmed FD by demonstration of a low plasma α-Gal A activity of 3.8 nmoles/hr/mg (normal mean, 7.5-12.5 nmol/hr/mg). Sequent analysis of genomic DNA showed c.639 + 5G > A [IVS4 (+5)G > A] mutation

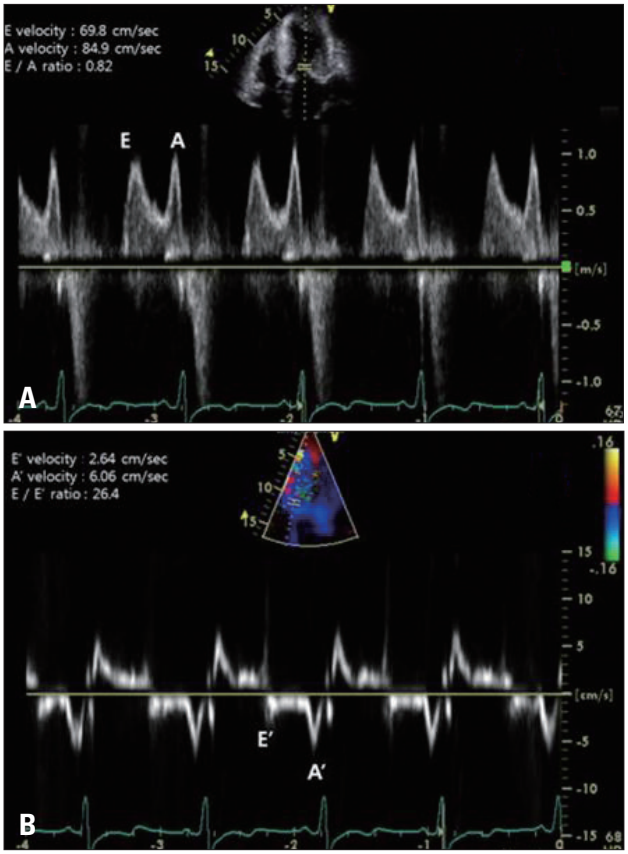

Fig. 4. Pulse-waved Doppler echocardiography (A) and tissue Doppler echocardiography (B). Decreased mitral annulus velocities (E') and increased mitral peak Doppler E-wave (E) to peak mitral annulus velocity ratio (E/E') are seen, suggesting a pseudonormal pattern.

in the α-Gal A gene leading to a low plasma α-Gal A activity. Family screening was done, and his brother was also confirmed FD by α-Gal A enzyme activity test and renal biopsy. Enzyme replacement therapy with recombinant α-Gal A was started on an out-patient basis.

DISCUSSION

FD is a progressive X-linked disorder of glycosphingolipid metabolism caused by a deficiency of the α-galactosidase lysosomal enzyme.[1)] Overall, the prevalence of FD has been estimated to be 1 in 40000 to 117000 male individuals.[6-8)] However, several recent studies suggested that the prevalence may be higher in the hemodialysis population, in which values up to 1.2% have been reported.[6)9-13)] The progressive accumulation of neutral glycosphingolipids in many tissues throughout the body, particularly the vascular endothelium, heart, and kidney.[1)] The manifestation of FD varies and may include angiokeratoma, corneal opacity, acroparesthesia, cerebrovascular disease, ischemic heart disease, and chronic kidney disease. Most men and some women with FD exhibit deterioration of renal function, and many eventually develop ESRD.[14)15)] Typically the diagnosis of FD is made in male adolescents, but it may be missed or delayed. The "variant" phenotypes usually have a low level of residual α-galactosidase activity resulting in a lack of the classic phenotype. The heart can be the only organ involved in male patients with specific gene mutations and in female carriers provided by low enzymatic activity, the so called "cardiac Fabry variant". The cardiac variant of FD has primarily cardiac manifestations, including LVH, valvular involvement, arrhythmia, and diastolic dysfunction, but no other classical symptoms of FD.[16)17)] Because effective enzyme replacement therapy is now available for FD, it is important to diagnosis the disease earlier, when it is potentially treatable.[4)5)]

We present a case of FD with cardiac involvement and early onset ESRD of unknown etiology. In our patient, transthoracic echocardiography revealed concentric LVH and grade 2 diastolic dysfunction. Recently, both enzyme activity enhancement and enzyme-replacement therapy have been revealed effective in reducing glycosphingolipid accumulation and in clearing existing deposits with improvement and even regression of the cardiomyopathy.[9)] Patients with ESRD can be protected from cardiovascular and cerebrovascular complications by treatment with enzyme replacement therapy.[16-19)]

Therefore, early diagnosis of Fabry cardiomyopathy has become important to allow prompt institution of the treatment and prevent cardiac complications as LVH with diastolic heart failure, in addition to cardiac arrhythmias, ischemic heart disease, and systemic thromboembolic events.

Because the prevalence may be higher in the hemodialysis population than other patients without ESRD in several studies, screening test for FD is needed for early diagnosis and treatment in the patient with ESRD who has LVH and/or diastolic dysfunction in transthoracic echocardiography.

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