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Case Report

Limited effects of long-term enzyme replacement therapy on the cardiac conduction system in Fabry disease

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ABSTRACT

The long-term effects of enzyme replacement therapy (ERT) on cardiac function and the conduction system in Fabry disease are not clearly understood. We report a case of a 48-year-old man with non-classical Fabry disease treated with ERT for 11 years. He was diagnosed with Fabry disease at age 27 years based on the presence of decreased alpha-galactosidase A activity in the peripheral leukocytes and of the causal alpha-galactosidase A mutation (Val339Gln). Subsequently, peritoneal dialysis was initiated for renal failure at age 35 years. ERT was initiated at age 39 years to halt the progression of cardiac dysfunction. Electrical conduction disturbances progressed gradually to complete atrioventricular block with atrial standstill during 9 years of ERT despite the lack of progression of ventricular hypertrophy. Although he underwent permanent pacemaker implantation to prevent sudden cardiac death, the atrioventricular junctional rhythm remained, thereby lowering the ventricular pacing rate. Based on this case, we recognize that the effects of ERT are limited for inhibiting the progression of Fabry disease and especially for inhibiting arrhythmia and conduction disturbances. Early diagnosis of Fabry disease and early initiation of ERT might be the key to further improvements in this disease and its associated conditions.

<**Learning objective:** We encountered a patient with Fabry disease treated with long-term enzyme replacement therapy (ERT) in whom conduction disturbances progressed without progression of left ventricular hypertrophy. This case suggests that ERT is limited for inhibiting the progression of Fabry disease and especially of arrhythmia and conduction disturbances. Early diagnosis of Fabry disease and initiation of ERT may be important for providing further improvements of this condition.>

Introduction

Anderson-Fabry disease is an X-linked lysosomal storage disorder caused by deficient activity of the lysosomal hydrolase, α-galactosidase A, resulting in accumulation of glycosphingolipids within the lysosomes [1]. It may result in progressive multiple organ dysfunction, and the development of renal, cardiac, and cerebral complications is associated with a risk of premature death. Cardiac manifestations frequently include left ventricular (LV) hypertrophy (LVH), conduction abnormalities, arrhythmia, and valvular dysfunction [2]. The efficacy and safety of enzyme replacement therapy (ERT) with agalsidase alfa or agalsidase beta have been confirmed. Five years of treatment with ERT resulted in regression of LVH and an improvement in myocardial function in subgroups of patients [3], thus preventing these patients from experiencing cardiac function decline [4] in two previous studies. However, the long-term effects of ERT on cardiac dysfunction in Fabry disease are not clearly understood. We report a case of a man with non-classical Fabry disease treated with ERT for 11 years.

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Case report

A 48-year-old man was evaluated for bradycardia in 2014. At age 18 years, he tested positive for proteinuria. Subsequently, renal failure developed, and medication for hypertension and peritoneal dialysis was initiated at age 35 years. He was diagnosed with Fabry disease at age 27 years in 1991 due to the presence of decreased alpha-galactosidase A activity in the peripheral leukocytes and the causal alpha-galactosidase A mutation (Val339Gln). No acroparesthesias, skin lesions, or cerebrovascular manifestations were found. He had a twin brother who had also been diagnosed with the same disease. ERT with agalsidase beta (1 mg/kg body weight) intravenously every 2 weeks was initiated at age 39 years; 5 years later, the treatment was switched to agalsidase-α (0.2 mg/kg) every 2 weeks. At initiation of ERT, an electrocardiogram (ECG) showed sinus rhythm and LVH with ST-wave and T-wave strain abnormalities (Fig. 1A). Ultrasound cardiography (UCG) revealed regional LVH measuring 15 mm and 11 mm in the inferolateral wall and the septal wall at end diastole, respectively. Mild left atrial enlargement and normal LV dimension measuring 41 mm and 46 mm, respectively, were observed (Fig. 2A). The LV wall motion was hyperdynamic, with an ejection fraction of 80%. No valvular disease was observed. His blood pressure remained within normal range with the use of medication. Subsequently, conduction disturbances gradually progressed and showed atrial standstill at age 41 years and bradycardia at age 44 years on ECG. After 9 years of ERT, ECG showed complete atrioventricular block with atrial standstill at a rate of 49 bpm. The QRS complexes showed an intraventricular conduction disturbance, with a QRS duration of 106 ms. LVH was augmented and showed increased ST-wave and T-wave strain abnormalities (Fig. 1B). UCG showed LV wall thickness and contractility similar to that at the initiation of ERT (Fig. 2B). The thickness in the LV inferolateral wall was 15 mm at end diastole and remained within the normal range in other regions; the thickness was 11 mm in the septal wall. However, the left atrium and ventricle progressively enlarged and measured 51 mm and 57 mm, respectively, at LV end diastole, resulting in increased LV mass. Mitral regurgitation was mild. After 9 years of ERT, the coronary angiogram showed normal coronary arteries. Right ventricular biopsy specimens revealed diffuse vacuolated myocytes (Fig. 3A) along with electron-dense concentric lamellar bodies on electron microscopy (Fig. 3B), consistent with Fabry disease. Consequently, the patient underwent implantation of a permanent pacemaker to prevent sudden cardiac death. At the present time, after 11 years of ERT, the atrioventricular junctional rhythm remains, thus lowering the ventricular pacing rate. No ventricular tachycardia has been observed. In addition, the LV wall thickness and contractility on UCG remain unchanged compared with those after 9 years of ERT.

Discussion

The present case addressed the important clinical issue of the long-term effects of ERT on Fabry disease. In this case, at the initiation of ERT, the patient's renal failure advanced to the terminal stage and the LV wall was already locally hypertrophic. Although the cardiac conduction remained normal at the time of ERT initiation, and although the LV wall thickness was not progressive during the course of ERT, the conduction disturbances gradually progressed, resulting in the need for cardiac pacemaker implantation. This finding indicates that ERT cannot halt the progression of Fabry disease. At present, ERT is recommended as soon as early clinical signs of kidney, heart, or brain involvement are seen in males with non-classical Fabry disease [5]. With Fabry disease, accumulation of globotriaosylceramide (Gb3) in endothelial cells and vascular smooth cells impairs the microcirculation, leading to fibrosis in organs such as the kidney and heart [6,7]. Previous reports have shown that ERT cannot halt or reverse

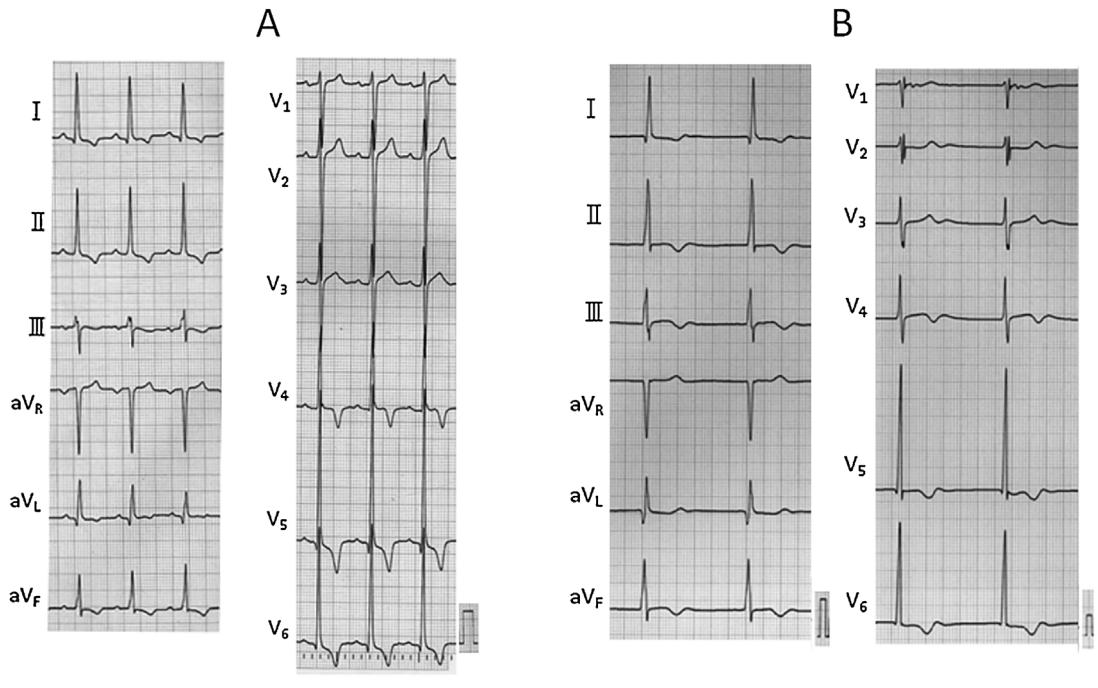

Fig. 1. Electrocardiogram findings. (A) At the initiation of enzyme replacement therapy (ERT), sinus rhythm and left ventricular hypertrophy (LVH) with ST-wave and T-wave strain abnormalities were observed. (B) After 9 years of ERT, complete atrioventricular block with atrial standstill was found. LVH was augmented, with increased ST-wave and T-wave strain abnormalities.