A 53-year-old asymptomatic man with no family history of Fabry disease or hypertrophic cardiomyopathy (HCM) exhibited increased ECG voltages (Figure [A]) and primary cardiac hypertrophy (left ventricular maximal wall thickness 16 mm and myocardial mass 163.2 g) with preserved contractility at cardiac magnetic resonance (Figure [D]). He was diagnosed in 2006 to be affected by Fabry disease cardiomyopathy because of reduced (to 3%) leukocyte α-galactosidase A activity, N215S mutation of α-Gal gene, and extensive glycolipid deposits in the cardiomyocytes at left ventricular endomyocardial biopsy (Figure [G] and [J]). Average cardiac cell diameter was 22 μm, and the vacuoles with storage material occupied 54% of cell surface. No cardiac valve, coronary, or systemic involvement by Fabry disease was clinically evident. No mutation of the most common HCM genes was relieved. The patient was treated with agalsidase alfa (0.2 mg every other week) and followed up with ECG, Holter monitoring, and echocardiogram every 6 months and cardiac magnetic resonance every 1 to 2 years. In 2011, ECG voltages (Figure [B]), maximal wall thickness (21 mm, Figure [E]), and myocardial mass at cardiac magnetic resonance (190 g/m²) were remarkably increased compared with pretreatment values with still-normal ejection fraction. After patient consent, a control left ventricular biopsy was undertaken. At histology, cardiomyocytes seemed regularly arranged but increased in size (diameter from 22 to 46 μm), whereas cell vacuoles reduced to 26% of cell area (Figure [H]). The patient became symptomatic for dyspnea (New York Heart Association class II) and palpitation on effort so that enzyme replacement therapy (ERT) was implemented with atenolol 100 mg daily. At the end of 2015, the patient was re-evaluated because the cardiac symptoms worsened (New York Heart Association class III) and palpitation on effort so that ERT administration in patients with Fabry disease cardiomyopathy (FDCM) resistance to ERT, represented by the combined mutation of GLA, causing glycolipid accumulation into myocardiocytes, and of NEXN gene, determining an abnormal synthesis of nexilin, protein of Z-disc of sarcomere associated with familial HCM.1 Interestingly, agalsidase alfa was able to remove glycosphingolipids from cardiac cells, reducing storage vacuoles from 54% to 13% of cell surface. At the same time, cardiomyocytes increased remarkably their size and realized a pattern of cell and myofibril disarray as observed in a sarcomeric HCM. This evolution is not in line with the effects of ERT on FDCM, which is usually followed by reduction of cell size and myocardial mass along with mobilization of glycolipids and suggests the speculation that shrinkage of glycolipids by ERT may have induced an activation of mutated sarcomeric gene causing an abnormal synthesis of myofilbrilar material and then a severe hypertrophy of myocardiocytes. Combined mutation of GLA with a sarcomeric gene seems to be less rare than believed accounting for up to 0.40% of large series of HCM subjects. Clinical implications are that patients with idiopathic cardiac hypertrophy should be investigated with an extensive next generation sequencing-hypertrophic cardiomyopathy gene panel and that resistance to ERT of FDCM should be clarified in the single subject even through endomyocardial biopsy. ERT administration in patients with combined GLA and sarcomeric gene mutation may be followed by the activation of a paradox hypertrophic pathway.

Disclosures

None.

References


Key Words: atenolol ■ biopsy ■ cell size ■ dyspnea ■ Fabry disease
Figure. ECG (A–C), cardiac magnetic resonance (D–F), histological (G–I, hematoxylin and eosin magnification ×200), and ultrastructural (J–L) sequences in a 53-year-old man with FDCM and combined GLA and NEXN gene mutation before (A, D, G, and J), after 5 years (B, E, H, and K), and after 9 years (C, F, I, and L) agalsidase-alfa administration. Shrinkage of glycolipid vacuoles (from 54% to 13% cell surface) is associated with a progressive hypertrophy with disarray of myocardiocytes (hypertrophic paradox) resulting in increased ECG voltages with deeper negative T wave and myocardial mass.
Paradoxical Response to Enzyme Replacement Therapy of Fabry Disease Cardiomyopathy
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