CASE REPORT

Cardiac magnetic resonance imaging illustrating Anderson–Fabry disease progression

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ABSTRACT. Anderson–Fabry disease is an X-linked lysosomal storage disorder resulting from a deficiency of the enzyme α -galactosidase A (α -Gal A) and subsequent cellular storage of the enzyme’s substrate globotriaosylceramide (Gb3) and related glycosphingolipids. We report a case of Anderson–Fabry disease with cardiac involvement evaluated with cardiovascular MRI. Disease progression was observed despite enzyme replacement therapy.

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Case report

A 44-year-old man presented as an outpatient with atypical, non-exercise-induced chest pain, palpitations and increasing dyspnoea on exertion over the past 3 years. His family history was unremarkable. His past medical history, in childhood and adolescence, included acroparaesthesia, hypohidrosis, cornea verticillata, angiokeratoma, abdominal pain, non-nephrotic proteinuria and progressive renal failure requiring dialysis treatment at 36 years of age. Transthoracic echocardiography was performed, which showed left ventricular (LV) hypertrophy with septal and posterior wall thicknesses of 16 mm and 15 mm, normal ejection fraction (65%) and impaired diastolic function. Further evaluation included coronary angiography and myocardial perfusion assessment by ^{99m}Tc^m-Sestamibi single photo emission computed tomography (SPECT) imaging, both of which yielded normal results. Upon biochemical analysis, a low α -galactosidase A (α -Gal A) enzymatic activity of 0.20 nmol h⁻¹ ml⁻¹ (normal range 4.0–21.9 nmol h⁻¹ ml⁻¹) was seen in the patient’s plasma. A diagnosis of Anderson–Fabry disease [1–3] was made and the patient was immediately started on enzyme replacement therapy (ERT); therapy comprised iv administration of recombinant α -Gal A (agalsidase beta, Fabrazyme®; Genzyme Corporation, Inc., Cambridge, MA) at a dose of 1 mg kg⁻¹ body weight once every 2 weeks. In 2003, at the age of 45 years, a cardiac MRI study was performed on the patient and showed normal LV systolic function (ejection fraction 65%) with an LV myocardial mass of 267 g. Furthermore, post-contrast late enhancement MRI showed increased gadolinium uptake involving the basal segment of the posterolateral wall of the LV, typical for myocardial fibrosis in advanced

Anderson–Fabry cardiomyopathy (Figure 1a). End-diastolic thicknesses of the LV septum and posterolateral walls were 16 mm and 15 mm, respectively (Figure 2a,b). In 2005, at the age of 47 years, the patient underwent a successful renal transplantation. A second cardiac MRI study was performed when the patient was 50 years old, after 6 years of ERT. The second study showed reduced LV systolic contractility (ejection fraction 55%) with an LV myocardial mass of 233 g — a remarkable decrease compared with the previous MRI examination. In addition, the patient showed more extensive gadolinium uptake, entirely involving the posterolateral wall and extending to the apical region (Figure 1b). Furthermore, the posterolateral wall showed significant thinning compared with the previous MRI study: the end-diastolic thicknesses of the LV septum and posterolateral wall were 18 mm and 9 mm, respectively (Figure 2c,d).

Discussion

Anderson–Fabry disease is an X-linked recessive lysosomal storage disorder that is caused by a deficiency of the lysosomal enzyme α -Gal A (also termed ceramide trihexosidase). The enzyme is responsible for the hydrolysis of terminal α -galactosyl residues from glycolipids and glycoproteins [1–3]. In the classical form of males with Anderson–Fabry disease have no or very low levels of α -Gal A activity, resulting in severe renal, cerebrovascular and cardiac disease manifestations [3, 4]. Cardiac involvement is very common and represents the most important cause of death in such patients [5]. The unremitting accumulation of glycosphingolipids in cardiac structures can lead to a variety of cardiac signs and symptoms, including LV hypertrophy, arrhythmias, coronary artery disease (mainly small-vessel disease) and heart failure. In some patients, cardiac symptoms

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Figure 1. Four-chamber horizontal long-axis three-dimensional inversion recovery image showing an area of enhancement involving the basal segment of the posterolateral wall (a) in the baseline study (arrows) and (b) after 6 years of enzyme replacement therapy (arrows). The extension is significantly increased following therapy (b).

Figure 2. Four-chamber horizontal long-axis and biventricular short axis balanced fast-field echo images show progressive thinning of the posterolateral wall from (a, b) baseline (arrows) to (c, d) the follow-up study (arrows).

predominate over other typical symptoms such as skin signs, pain crisis and progressive renal impairment.

In 2001, ERT with recombinant α -Gal A became available in Europe for the treatment of patients with Anderson–Fabry disease [6]. Several studies have shown that ERT is able to reduce microvascular deposits of globotriaosylceramide in the kidneys, skin and heart. A previous paper demonstrated a significant regression in cardiac hypertrophy, associated with reduced myocardial T_2 relaxation times as assessed by MRI, in patients with Anderson–Fabry disease following sustained ERT with agalsidase beta after a mean treatment duration of 45 months. Moreover, amelioration of a variety of clinical signs and symptoms was observed in all patients [7]. Recent data suggest that, to achieve long-term improvement in myocardial morphology and function and exercise capacity, it is best to start treatment of Anderson–Fabry cardiomyopathy with recombinant α -Gal A before myocardial fibrosis has developed. Thus, it is of crucial importance to test cardiology patients with hypertrophic cardiomyopathy for Anderson–Fabry disease and make an early diagnosis; affected family members should also be tested [8].

In the case presented here, replacement of the hypertrophied myocardium by massive fibrosis significantly progressed during a long-term follow-up period. This finding suggests there is a point of no return where cardiac impairment is irreversible and progresses despite ERT. In addition, it is reasonable to emphasise that ERT might be less effective in patients of advanced age and with extensive areas of myocardial fibrosis, thereby providing an argument for the early initiation of therapy in patients with Anderson–Fabry disease before fibrosis has developed. In such patients, it is not expected that ERT will reverse structural fibrotic changes in the heart. Furthermore, other factors such as pre-treatment severity of renal disease are thought to contribute to the variable effects of ERT on LV mass in patients with this microvascular disease. The reduced LV mass observed in the second MRI study might be related to the more extensive presence of fibrosis and to the reduced thickness of the posterolateral wall compared with the

first MRI examination. Finally, in the case presented the extent of fibrosis showed a predilection for the posterolateral wall of the LV. The circumflex and/or the right coronary arteries usually supply this region of the heart, but in our patient coronary angiography showed no evidence of epicardial coronary artery disease. It is possible that other factors such as regional wall mechanics or microvascular anatomy could influence enzyme deficiency within the myocardium.

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