CASE REPORT

Atypical patterns of cardiac involvement in Fabry disease

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SUMMARY

A 58-year-old woman was referred to our cardiology service with chest pain, exertional dyspnoea and palpitations on a background of known Fabry disease diagnosed with genetic testing in 1994. ECG showed sinus rhythm, shortened PR interval, widespread t wave inversion, q waves in the lateral leads and left ventricular hypertrophy (LVH). Coronary angiogram showed only mild atheroma. Transthoracic echocardiogram showed anterolateral LVH and reduced left ventricular cavity size in keeping with Fabry cardiomyopathy. Cardiac MRI demonstrated asymmetric hypertrophy with evidence of diffuse myocardial fibrosis in the maximally hypertrophied segments from base to apex with late gadolinium enhancement in the anterior and anteroseptal walls. This was quite an atypical appearance for Fabry cardiomyopathy. This case highlights the heterogeneity of patterns of cardiac involvement that may be associated with this rare X-linked lysosomal disorder.

BACKGROUND

Fabry disease, a rare X-linked disorder, results from deficiency of the lysosomal enzyme, α galactosidase A.

Fabry disease can cause left ventricular hypertrophy (LVH), which may be difficult to differentiate from hypertrophic cardiomyopathy.

It is an important differential to consider as there have been advances in the treatment of Fabry disease in recent years. A replacement version of the deficient enzyme has been manufactured and commercialised. This offers stabilisation and, in some cases, reversal of the cardiovascular abnormalities.

Our case also highlights that, while Fabry is most often associated with a symmetrical, concentric pattern of left ventricular hypertrophy, it can also present with asymmetrical or apical hypertrophy.

Therefore, asymmetrical or apical patterns of hypertrophy should not be used as an exclusion criteria when deciding which patients to put forward for Fabry screening.

CASE PRESENTATION

A 58-year-old woman was referred to our cardiology clinic with increasing chest pain, dyspnoea and palpitations on a background of known Fabry disease. Manifestations of her Fabry disease included acroparaesthesia, proteinuria and cardiomyopathy. She also had a background history of psoriasis and psoriatic arthropathy. She had been

identified as a mutation carrier shortly after her son was diagnosed in 1994.

A skin biopsy had been performed in 1994 with DNA analysis of α galactosidase gene in fibroblasts. Single-strand conformation polymorphism analysis showed a mutated sequence in exon 2 of the gene, showing point mutation-causing glycine substitution for aspartate (D93G).

Neither of her parents showed the same mutation and so it was presumed to be de novo. She had had proteinuria since 2004 with mildly elevated plasma and urinary globotriaosylceramide (Gb3) levels at this time.

Renal biopsy in 2005 had shown accumulation of sphingolipid and she was, at the time, initiated on Fabrazyme treatment. She was switched to Replagal in 2006 due to issues with procurement of Fabrazyme, which she currently takes fortnightly as an intravenous infusion at a dose of 0.2 mg/kg.

Her medications at the time consisted of: methotrexate 15 mg weekly, folic acid 5 mg once daily, atorvastatin 10 mg once daily, Replagal infusion 0.2 mg/kg intravenous fortnightly.

She was referred to our cardiology service from the National Centre for Inherited Metabolic Disorders for an opinion on her overall cardiac status, in December 2014.

Her main symptom at that time was chronic exertional central chest pain. She described a central, stabbing 'knife' sensation associated with shortness of breath. These episodes lasted approximately 1 min and often radiated to her jaw or left arm.

She also described palpitations, occurring mainly at night and, on very rare occasions, dizzy episodes. She did not describe any orthopnoea or paroxysmal nocturnal dyspnoea.

Cardiovascular examination was unremarkable.

On auscultation of the precordium, heart sounds 1 and 2 were present, there were no added sounds or murmurs and the apex beat was not displaced. The jugular venous pulse was not elevated and there were no signs of pedal oedema. Respiratory examination was also normal with no bibasal crepitations and normal vesicular breath sounds.

In 2005, she had had a presumptive diagnosis of Fabry cardiomyopathy based on the echocardiographic appearances of anterolateral LVH with reduced left ventricle cavity size without evidence of obstruction.

She underwent a full cardiology work-up under our service, as described below.

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INVESTIGATIONS

ECG

Normal sinus rhythm, shortened PR interval, t wave inversion in leads I, II, aVL, aVF, V2–6, q waves in the lateral leads and LVH by Sokolov-Lyon criteria.

Holter monitor

Normal sinus rhythm throughout. No evidence of atrial fibrillation. No evidence of supraventricular or ventricular arrhythmias. No episodes of bradycardia. No pauses.

Coronary angiogram

Summary: non-obstructive atheroma.

Left main stem—no abnormalities detected.

Left anterior descending—large vessel to apex with mild atheroma.

Diagonal system—moderate sized diagonal 1 with mild atheroma.

Left circumflex—ostial 20% atheroma.

Right coronary artery—dominant vessel with mild atheroma.

Transthoracic echocardiogram

Summary: anterolateral LVH with reduced left ventricular cavity size in keeping with Fabry cardiomyopathy. No evidence of any obstruction.

- ▶ Mitral valve: opens well with no evidence of mitral stenosis. Trace mitral regurgitation.
- ▶ Aortic valve: normal valve structure and function.
- ▶ Tricuspid valve: normal valve structure and function.
- ▶ Pulmonic valve: normal valve structure and function.
- ▶ Left atrium: normal.
- ▶ Left ventricle: reduced LV cavity of 4.5 cm. Marked anterolateral LVH as per previous study. Stage 1 LV diastolic dysfunction. Good LV function (left ventricular ejection fraction $\geq 55\%$).
- ▶ Right atrium: normal
- ▶ Right ventricle: normal structure and function.

Cardiac MRI

The patient had normal indexed LV volumes with hyperdynamic LV systolic function at rest. Despite the known diagnosis of Fabry disease, the findings on the left ventricular analysis were strongly suggestive of hypertrophic cardiomyopathy. There was asymmetrical hypertrophy particularly affecting the anterior, anteroseptal and septal walls from base to mid-ventricular level with a peak wall thickness of 16.4 mm. The reference lateral wall thickness at mid-ventricular level was 7.9 mm. There was also apical hypertrophy particularly affecting the distal and apical anterior wall, measuring 15.6 mm. This was confirmed on sequential thin slice long axis and short axis lines. No regional wall thinning was noted, and there was a normal trabecular pattern throughout. No papillary muscle hypertrophy was identified. There was markedly increased overall mass index—overall mass was 228 g. The calculated LV volumes were also validated using the area biplane method (end diastolic volume 129 mL, end systolic volume 23 mL, stroke volume 106 mL and ejection fraction 82%).

Normal right ventricle volumes and function, and no right ventricular hypertrophy were seen. Right ventricular outflow tract appeared satisfactory.

There was no valvular abnormality and no systolic anterior motion or left ventricular outflow tract obstruction at rest. The aorta was normal and there was no coarctation.

Pulmonary artery and branch pulmonary arteries were undilated, the pericardium was normal, there was no pericardial effusion and the atria were dilated.

Early images following intravenous gadolinium showed no thrombus. Late images demonstrated diffuse patchy mid-wall fibrosis in the maximally hypertrophied anterior and anteroseptal wall at basal level extending to involve the anterior and septal walls at ventricular level. From distal LV to apex, the hypertrophied anterior wall was diffusely replaced with fibrosis. (figure 1A, B, 2A, B, 3A, B).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of unexplained LVH includes:

- ▶ Hypertension
- ▶ Fabry disease
- ▶ Hypertrophic cardiomyopathy (HCM)
- ▶ Athletic training
- ▶ Cardiac amyloidosis
- ▶ Mitochondrial cytopathies
- ▶ Friedreich's ataxia

TREATMENT

The patient was started on low dose aspirin 75 mg and nebivolol 1.25 mg daily and her symptoms resolved.

Figure 1 (A) Four-chamber horizontal long axis SSFP image demonstrates apical myocardial hypertrophy, (B) postcontrast late gadolinium enhancement (LGE) images demonstrate patchy subendocardial and mid-myocardial hyperenhancement. SSFP, steady-state free precession image.

Figure 2 (A) SSFP end diastolic images in cardiac short axis at the level of the apex, demonstrate myocardial hypertrophy of the anterior and lateral segments. (B) Postcontrast LGE images demonstrate nodular subendocardial and mid-myocardial hyperenhancement in these segments. LGE, late gadolinium enhancement; SSFP, steady-state free precession image.

OUTCOME AND FOLLOW-UP

The patient continues to receive the Replagal infusion fortnightly and will be followed up to assess if her cardiomyopathy shows any response to treatment.

DISCUSSION

Fabry disease is an X-chromosome linked disease of lysosomal metabolism resulting in decreased or absent activity of the enzyme, α -galactosidase A. The manifestations of the disorder are due to impaired breakdown of glycosphingolipids and systemic lysosomal accumulation of Gb3.

Hundreds of different mutations have been identified, with varied patterns of enzyme activity and clinical presentation.¹

It is estimated that the prevalence in the general population is 1 in 117 000.¹

Cardiac involvement in Fabry disease is frequent, due to structural and functional changes related to Gb3 deposition in the myocardium, valves and conduction system.

Figure 3 (A) SSFP short axis image at the mid-myocardial level demonstrates asymmetric myocardial hypertrophy of anterior and anteroseptal segments. (B) LGE images demonstrate nodular myocardial hyperenhancement in these segments. LGE, late gadolinium enhancement; SSFP, steady-state free precession image.

It has been suggested that Fabry disease may account for up to 4% of patients with undifferentiated myocardial hypertrophy.^{2 3}

Effects of Fabry disease on the heart can include:

ECG changes: LVH, shortened PR interval, varying degrees of heart block, T wave inversion and ST segment changes.

Holter monitoring: Fabry disease is associated with arrhythmias, most commonly atrial fibrillation and ventricular tachycardia.

Echocardiography: Concentric LVH is most commonly encountered. Right ventricular and papillary muscle hypertrophy is also common.

Less commonly, asymmetrical hypertrophy may be present, mimicking hypertrophic cardiomyopathy.

Apical hypertrophy has also been described.

Cardiac MRI: Late gadolinium enhancement in the inferior LV wall. A recent study showed that patients with Fabry disease-related hypertrophy showed delayed enhancement with a typical and consistently found pattern characterised by the

involvement of the inferolateral basal or mid-basal segments and a mesocardial distribution sparing the subendocardium.^{3 4}

Cardiac MRI can be used to demonstrate increasing wall thickness, regional functional abnormalities and replacement fibrosis. Interestingly, women have been shown to demonstrate replacement fibrosis prior to the development of LVH. Therefore, it is essential to assess for replacement fibrosis in women with late gadolinium enhancement on MRI as this may have implications regarding initiation of treatment.⁵

It can be difficult to differentiate Fabry cardiomyopathy from symmetric hypertrophic cardiomyopathy solely on the basis of clinical characteristics, ECG or echocardiographic evaluation. There has been recent interest in the patterns of gadolinium enhancement seen on MRI in the various cardiomyopathies.

It has been noted in small studies utilising cardiac MRI that patients with Fabry cardiomyopathy show a specific pattern of delayed mesocardial enhancement in the inferolateral wall of the left ventricle, with at least a thin portion of subendocardial and subepicardial layer always spared.^{4 6}

It has been proposed that, by evaluating the myocardial location and distribution patterns of delayed enhancement, it may help differentiate between Fabry cardiomyopathy and symmetrical HCM.⁴

Similarly, infiltrative cardiomyopathies such as amyloidosis and sarcoidosis have also been shown to demonstrate specific patterns of cardiac involvement and enhancement on MRI,

reinforcing the usefulness of MRI as a clinical tool to differentiate between these conditions.^{7 8}

It has been recommended that all patients with unexplained left ventricular hypertrophy, at an onset above the age of 40 years, should be screened for α -galactosidase A deficiency.⁹ This is initially with α -galactosidase A enzyme activity analysis and subsequently with DNA mutation analysis. Early initiation of treatment prior to the onset of myocardial fibrosis has been shown to result in reduced LV mass, increased exercise tolerance and improved myocardial function. However, fibrosis secondary to Gb3 accumulation may be irreversible once it has been established.¹⁰

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Contributors JJC was primary author for the case report. KE obtained patient information and consent. JO'B was responsible for images and captions. TK provided guidance and editorial input.

Competing interests None declared.

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Learning points

- Fabry disease is a rare but important cause of cardiomyopathy to consider in patients with unexplained left ventricular hypertrophy (LVH).
- Cardiac MRI is an excellent modality to identify specific patterns of cardiomyopathy.
- Fabry disease classically presents with predominantly concentric LVH and cardiac MRI showing late gadolinium enhancement in the inferior left ventricular wall.
- However, apical and asymmetric hypertrophic variants are also well described.

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