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CASE REPORT
Cardiac imaging

Cardiac magnetic resonance diagnosis of Fabry disease leads to incidental diagnosis of Klinefelter syndrome: a case report

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Background Fabry disease is an X-linked lysosomal storage disorder resulting in deficient activity of alpha-galactosidase. Males are general more severely affected however heterozygous females can variably express the disease depending on the degree of random X chromosome inactivation (Lyonization). We present a case where cardiac magnetic resonance diagnosis of late onset Fabry Disease leads to an incidental diagnosis of Klinefelter syndrome.

Case summary A 55-year-old male was referred for cardiology assessment after developing atrial fibrillation. Echocardiography demonstrated moderate, concentric LVH (left ventricular hypertrophy). Cardiac magnetic resonance imaging confirmed the presence of concentric increase in LV wall thickness and increased LV (left ventricular) mass. T_1 mapping values (Shortened Modified Look-Locker Inversion recovery sequences) were elevated in the basal-mid inferolateral segments and low in the remaining segments. Late gadolinium acquisition showed a pattern suggestive of Fabry disease. Genetic testing of the GLA gene revealed a null variant classified as pathogenic. The variant was found to be heterozygous. This raised the possibility of Klinefelter's syndrome and the diagnosis was confirmed by chromosomal microarray and karyotype. The patient was then referred to Fabry clinic for consideration of enzyme replacement therapy and to the endocrine clinic for testosterone replacement.

Discussion The atypical 'cardiac variant' Fabry disease should be included in differential diagnosis of left ventricular hypertrophy. In a 'late onset' presentation of Fabry Disease, the concomitant presence of Klinefelter syndrome cannot be excluded due to GLA variant present in the heterozygous state.

Keywords Cardiac magnetic resonance • Fabry disease • Imaging

ESC Curriculum 2.1 Imaging modalities • 2.2 Echocardiography • 2.3 Cardiac magnetic resonance • 6.5 Cardiomyopathy

Learning points

- Cardiac magnetic resonance is crucial in the differential diagnosis of different heart conditions leading to left ventricular hypertrophy.
- Abnormally low myocardial T_1 values and the location of the late gadolinium hyper-enhancement are pathognomonic features of Fabry disease in cardiac magnetic resonance.
- In 'late-onset' Fabry disease, the association with Klinefelter syndrome can be considered and genetic testing can play an important role.

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Introduction

Fabry disease is an X-linked lysosomal storage disorder resulting in deficient activity of alpha-galactosidase. The prevalence of classic Fabry disease is estimated to range from 1:8454 to 1:117 000 males[1,2]; however, mutations associated with 'later-onset' presentation occur in approximately 1:1000 to 1:3000 males and 1:6000 to 1:40 000 females.[1] Males are generally more severely affected; however, heterozygous females can variably express the disease depending on the degree of random X chromosome inactivation (lyonization). The enzyme defect results in progressive lysosomal deposition of globotriaosylceramide in cells throughout the body. Disease presentation depends on the degree of enzyme deficiency. We present a case where cardiac magnetic resonance diagnosis of late-onset Fabry disease leads to an incidental diagnosis of Klinefelter syndrome (KS).

Timeline

A 55-year-old male was referred for cardiology assessment after developing atrial fibrillation.

Echocardiography was performed demonstrating left ventricular hypertrophy (LVH).

Cardiac magnetic resonance confirmed the presence of LVH and showed features consistent with Fabry disease.

Genetic testing of the GLA gene by next generation sequencing revealed a null variant classified as pathogenic. The variant was found to be heterozygous rather than hemizygous.

Chromosomal microarray and karyotype were performed and confirmed KS.

The patient was then referred to Fabry clinic for consideration of enzyme replacement therapy and to the endocrine clinic for testosterone replacement.

Case presentation

A 55-year-old male was referred for cardiology assessment after developing atrial fibrillation. Initial symptoms were palpitations and exertional dyspnoea. He was on treatment with anticoagulation and his heart rate was well controlled. There was no significant medical history other than erectile dysfunction. The kidney function was normal but there was evidence of proteinuria (albumin/creatinine 33.4 and protein–creatine ratio of 43). No family history of cardiac disease was reported. The patient had no offspring.

Investigations

Electrocardiogram showed rate-controlled atrial fibrillation with prominent T-wave inversion in leads V3–V5 (*Figure 1*). Echocardiography demonstrated moderate, concentric LVH (*Figure 2*). The strain analysis was not performed as the quality of the images was significantly reduced. Cardiac magnetic resonance (CMR) imaging was requested given the unexplained increase in left ventricular (LV) wall thickness. Cine images confirmed the presence of concentric LV hypertrophy and increased LV mass. Systolic function was preserved overall; however, there was obvious loss of long-axis function. There were not regional wall motion abnormalities in the inferior-lateral wall, as well as, no evidence of systolic anterior motion or LV outflow tract obstruction. The RV was not dilated nor hypertrophied or fibrotic. T_1 mapping values (shortened modified Look–Locker inversion recovery sequences) were elevated in the basal-mid inferolateral segments and low in the remaining segments (798–859 ms; *Figure 3*). Late gadolinium acquisition showed non-ischaemic pattern of fibrosis in the inferolateral wall most suggestive of Fabry disease and not consistent of hypertrophic cardiomyopathy or hypertensive heart disease. The T_2 STIR (short-tau inversion recovery) sequence did not show any oedema. Genetic testing of the *GLA* gene by next generation sequencing revealed a null variant classified as pathogenic. The variant was found to be heterozygous rather than hemizygous as expected in a male patient. This raised the possibility of KS, which was confirmed by chromosomal microarray and karyotype showing a 47, XXY result. We then performed X chromosome inactivation studies by methylation analysis showing random inactivation patterns

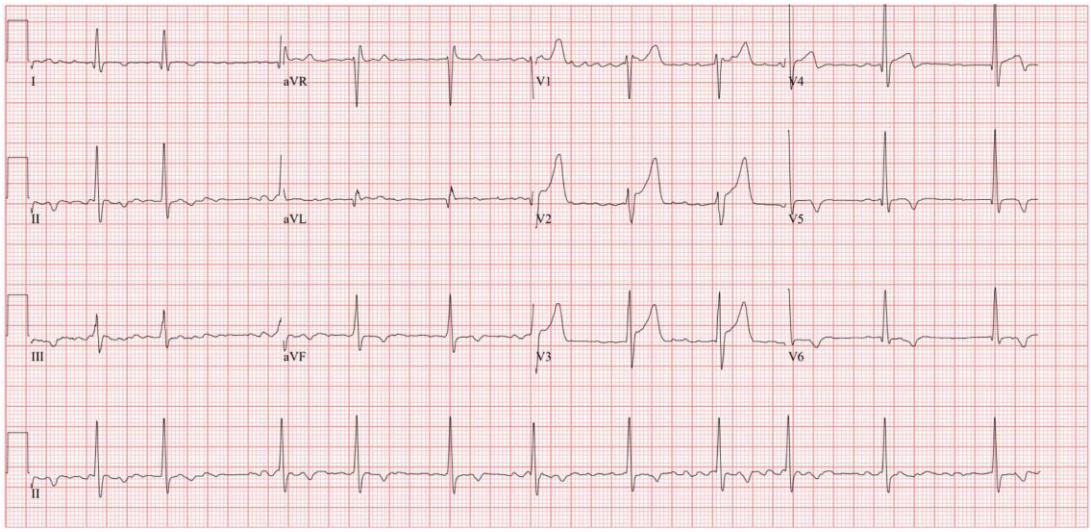

Figure 1 Electrocardiogram: atrial fibrillation, abnormal repolarisation pattern with T-wave inversion in Leads V3–V5.

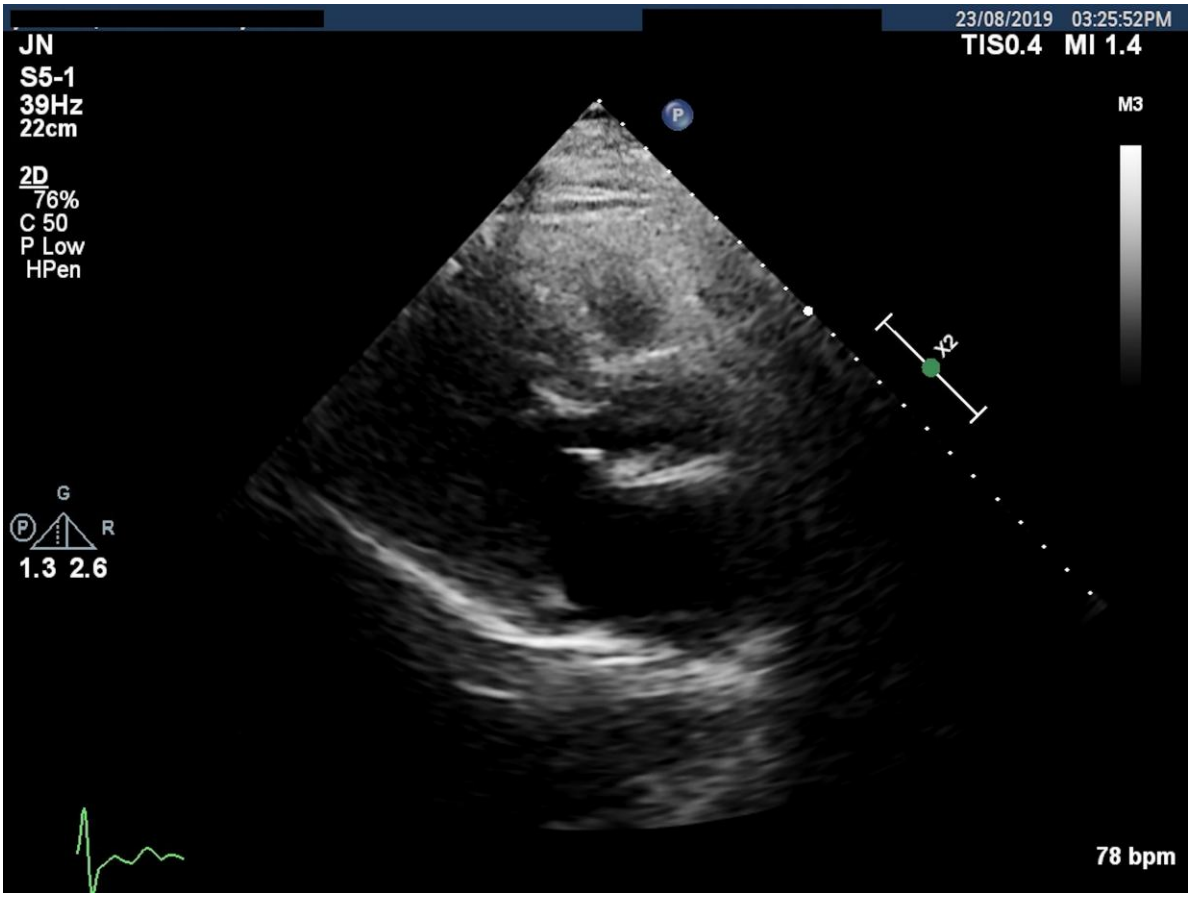

Figure 2 Echocardiogram parasternal long-axis image showing the hypertrophied interventricular septum; no clear binary appearance of the left ventricular border.

(77:23 at the *AR* locus, 70:30 at the *FRAXA* locus) and thus excluding skewed X chromosome inactivation (defined as ratios >80:20). The diagnosis of Fabry disease was supported by biochemical testing showing increased lyso-GB3 and decreased alpha-galactosidase activity (5.5 μmol/L/h; normal value ≥15.3 μmol/L/h).

Management

The patient was then referred to Fabry clinic for consideration of enzyme replacement therapy and to the endocrine clinic for testosterone replacement. He was started on testosterone as transdermal gel with dose of one sachet topically daily (borderline low testosterone values) and alpha-galactosidase infusions 24.4 mg every 2 weeks. The patient remains currently reasonably well at follow up with NYHA Class I.

Discussion

As discussed in the introduction, patients with >1% alpha-galactosidase activity may present in late middle age with a 'cardiac variant' phenotype of Fabry disease which includes LVH, arrhythmia, and proteinuria without renal impairment, whereas those with more severe enzyme deficiency present in childhood with acroparesthesia, angiokeratomas, and ocular abnormalities before developing renal failure and then cardiac involvement in the third to fifth decades.[3] Therefore, the atypical 'cardiac variant' Fabry disease should be included in differential diagnosis of conditions resulting in increased LV wall thickness such as hypertension, hypertrophic cardiomyopathy, and cardiac amyloid.

Klinefelter syndrome results from non-disjunction of the X chromosome resulting in a 47, XXY karyotype. Klinefelter syndrome results in testosterone deficiency, azoospermia, and infertility. Sadick *et al.*[2] first described the case of concomitant KS and Fabry disease; however, this is the first reported case, whereby CMR was integral in the diagnostic pathway. Cardiac magnetic resonance has the unique ability to characterize myocardial tissue and therefore differentiate between pathologies that cause true LVH and those infiltrative diseases that increase LV wall thickness thereby mimicking LVH. The pattern of late gadolinium enhancement (LGE) is often diagnostic; however, additional sequences such as T_1 mapping can provide additional clues. T_1 values can be normal or elevated in hypertrophic cardiomyopathy due to fibrosis and are often more significantly elevated in cardiac amyloidosis related to amyloid deposition.[4] However, in Fabry disease the intracellular accumulation of sphingolipids shortens myocardial T_1 relaxation times, so native myocardial T_1 is substantially lower than in other causes of LVH.[5] In our patient, T_1 mapping values were elevated in the areas of prominent replacement fibrosis induced by the underlying pathology but reduced in the other segments. The combination of abnormally low myocardial T_1 values and the location of the late gadolinium hyperenhancement provided enough evidence to proceed to metabolic and genetic testing for Fabry disease in this situation.

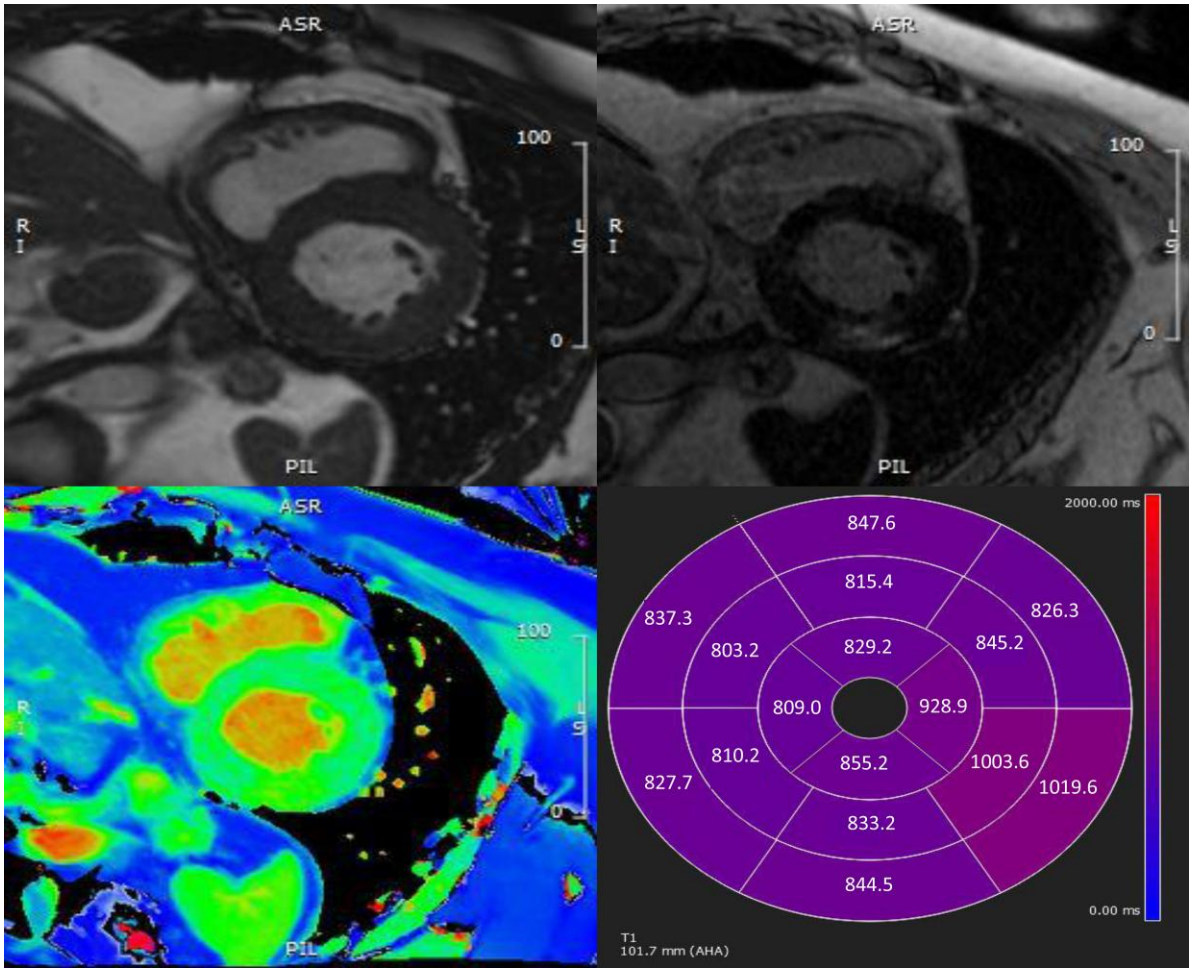

Figure 3 Cardiac magnetic resonance findings. Top right: late gadolinium enhancement image shows non-ischaemic pattern of fibrosis involving the inferior and inferolateral wall; top left: cine short-axis image of the corresponding late gadolinium enhancement slice; bottom left: T_1 mapping (shortened modified Look–Locker inversion recovery sequences); bottom right: the bull-eye shows elevated values in the basal-mid inferolateral segments and low values in the remaining segments.

Because of the patient's relatively mild presentation of Fabry disease in adulthood, a diagnosis of atypical Fabry disease due to a missense or splicing *GLA* variant was suspected. However, he was found to have a null variant arguing against atypical Fabry disease. His milder presentation was instead explained by his concomitant KS with the *GLA* variant present in the heterozygous state and the normal *GLA* allele allowing for some alpha-galactosidase activity. X chromosome inactivation studies showed random inactivation, as expected in the milder female phenotype of Fabry disease. Interestingly, the X chromosome inactivation ratio was approximately 70:30 and we found alpha-galactosidase activity to be approximately 30% of the lower limit of normal, suggesting that it is the X chromosome with the normal *GLA* allele that is expressed in 30% of cells. The combination of Fabry disease and Klinefelter disease has been reported previously, but the patient was homozygous for the *GLA* variant and his presentation in adulthood might be better explained by his splicing variant which may have produced atypical Fabry disease.[2]

European working group on Fabry disease achieved the general consensus that for males with classical Fabry disease, the treatment with enzyme replacement therapy may be considered in patients from 16 years of age even if there are asymptomatic and even if they have no clinical signs of organ involvement (Class IIB recommendation). In this set of patients, the diagnosis of classical FD is based on the presence of a GLA mutation, absence or really low residual enzyme activity and the presence of at least one of the following: angiokeratoma, cornea verticillate, or a very high (lyso) Gb3 level. On the other hand, males with non-classical Fabry disease should be treated as soon as there are early signs of organ involvement (kidney, heart, and/or central nervous system) consistent with Fabry disease and not fully explained by other pathology (Class I recommendation).[6]

Regarding the enzyme replacement therapy, there is currently evidence from previous long-term follow-up studies and registries that enzyme replacement therapy when started early may slow the disease progression and reduce the burden of clinical events. Mild LVH may partially regress and there is some evidence that LVH may be prevented by early therapy. However, no data are available regarding the prevention of myocardial fibrosis.[6] Although the longitudinal follow-up data at present mainly centres around echocardiography, we would recommend that the patients also have CMR with both T_1 mapping and LGE for follow up.

Conclusion

Left ventricular hypertrophy can be related to several different aetiologies. Cardiac magnetic resonance is crucial for the definitive diagnosis of Fabry disease. In a 'late-onset' presentation of Fabry disease, the concomitant presence of KS cannot be excluded due to *GLA* variant present in the heterozygous state.

Lead author biography

I got my degree in Medicine and Surgery in 2012. I specialized in cardiology in 2018. I worked as fellow in echocardiography at San Raffaele Hospital in Milan and as cardiac magnetic fellow at Flinders Medical Centre in Adelaide. I am currently working as consultant cardiologist at York Teaching Hospital in UK.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The patient gave written consent and the consent form is available if required at Flinders Medical Centre.

Conflict of interest: None declared.

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