Cardiac Magnetic Resonance diagnosis of Fabry disease leads to incidental diagnosis of Klinefelter syndrome: a case report

Giulia Binda MD\textsuperscript{1,2}, John Cameron Bridgman MBChB(Hons), MRCP, FRACP\textsuperscript{1}, Ian Chapman MBBS, Phd, FRACP\textsuperscript{3,4}, Joseph B. Selvanayagam MBBS(Hons), DPhil, FRACP\textsuperscript{1,2,5}.

\textsuperscript{1}Flinders Medical Centre, Adelaide, SA. \textsuperscript{2}South Australian Health Medical and Research Institute, Adelaide, SA. \textsuperscript{3}The University of Adelaide, Adelaide, SA. \textsuperscript{4}Royal Adelaide Hospital, Adelaide, SA. \textsuperscript{5}Flinders University, Adelaide, SA

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Abstract: We present the case of a middle-aged male with left ventricular hypertrophy. Cardiac Magnetic Resonance suggested Fabry disease (FD), and subsequent genetic testing confirmed FD but also Klinefelter syndrome. The late and mild presentation of FD is rare in males and was due to concomitant Klinefelter's syndrome.

Running Title: A peculiar case of Fabry disease and Klinefelter syndrome.

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

Key words: Cardiac Magnetic resonance, Fabry Disease, Imaging

Corresponding author:
Prof Joseph Selvanayagam
Flinders Medical Centre,
Bedford Park, Adelaide

Email: Joseph.Selva@sa.gov.au
Cc: giulia.binda.gb@gmail.com

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Learning points:

1) Cardiac magnetic resonance is crucial in the differential diagnosis of different heart conditions leading to left ventricular hypertrophy.

2) Abnormally low myocardial T1 values and the location of the late gadolinium hyper-enhancement are pathognomonic features of Fabry Disease in cardiac magnetic resonance.

3) 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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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 Klinefelter syndrome.

The patient was then referred to Fabry clinic for consideration of enzyme replacement therapy and to the endocrine clinic for testosterone replacement.
Statement: The patient gave written consent and the consent form is available if required at Flinders Medical Centre.

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 vary in expressing the disease depending on the degree of random X chromosome inactivation (Lyonization). The enzyme defect results in progressive lysosomal deposition of globotriaosylceramide (GL-3) 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).

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 past medical history other than erectile dysfunction. The kidney function was normal but there was evidence of proteinuria (albumin/creatinine ratio of 33.4 and protein-creatinine ratio of 43). No family history of cardiac disease was reported. The patient had no offspring.

Investigations: ECG showed rate-controlled atrial fibrillation with prominent T wave inversion in leads V3-V5 (Fig.1). Echocardiography demonstrated moderate, concentric LVH (left ventricular hypertrophy) (Fig.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 LV (left ventricular) wall thickness. Cine images confirmed the presence of concentric left ventricular hypertrophy and increased LV mass. Systolic function was preserved overall however there was obvious loss of long axis function. There were no regional wall motion abnormalities in the inferior-lateral wall, as well as, no evidence of systolic anterior motion or left ventricular outflow tract obstruction. The RV was not dilated nor hypertrophied or fibrotic. T1 mapping values (Shortened Modified Look-Locker Inversion recovery sequences) were elevated in the basal-mid inferolateral segments and low in the remaining segments (798-859ms) (Fig.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 T2 STIR 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 (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’s 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 1 sachet topically daily (borderline low testosterone values) and alpha galactosidase infusions 24.4 mg every two weeks. The patient remains currently reasonably well at follow up with NYHA class I.
Discussion:

As discussed in the introduction, patients with greater than 1% alpha-galactosidase activity may present in late middle age with a ‘cardiac variant’ phenotype of Fabry Disease which includes left ventricular hypertrophy, 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 left ventricular 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. KS results in testosterone deficiency, azoospermia and infertility. The first described case of concomitant Klinefelter syndrome and Fabry disease was described by Sadick VJ et al. (2), however this is the first reported case whereby cardiac magnetic resonance (CMR) was integral in the diagnostic pathway. CMR has the unique ability to characterise myocardial tissue and therefore differentiate between pathologies that cause true left ventricular hypertrophy (LVH) and those infiltrative diseases that increase LV wall thickness thereby mimicking LVH. The pattern of late gadolinium enhancement is often diagnostic however additional sequences such as T1 mapping can provide additional clues. T1 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 T1 relaxation times, so native myocardial T1 is substantially lower than in other causes of LVH (5). In our patient, T1 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 T1 values and the location of the late gadolinium hyper-enhancement provided enough evidence to proceed to metabolic and genetic testing for Fabry’s disease in this situation.

Because of the patient’s relatively mild presentation of Fabry’s disease in adulthood, a diagnosis of atypical Fabry’s disease due to a missense or splicing GLA variant was suspected. However, he was found to have a null variant arguing against atypical Fabry’s 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’s 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’s disease and Klinefelter’s 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’s disease (2).

European working group on Fabry’s 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 left ventricular hypertrophy may partially regress and there is some evidence that left ventricular hypertrophy 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 (Mehta et al) we would recommend that the patients also have CMR with both T1 mapping and LGE for follow up (2).

**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 Klinefelter syndrome cannot be excluded due to GLA variant present in the heterozygous state.


Figure legends:

(Fig.1) Electrocardiogram: atrial fibrillation, abnormal repolarisation pattern with T wave inversion in leads V3-V5.

(Fig.2) Echocardiogram parasternal long-axis image showing the hypertrophied interventricular septum; no clear binary appearance of the LV border.

(Fig.3) Cardiac Magnetic Resonance findings. Top right: LGE image show non-ischemic pattern of fibrosis involving the inferior and infero-lateral wall; top left: cine short axis image of the corresponding LGE slice; bottom left: T1 mapping (ShMOLLI sequences); bottom right: the bull-eye show elevated values in the basal-mid infero-lateral segments and low values in the remaining segments. ShMOLLI: Shortened Modified Look-Locker Inversion recovery. LGE: late gadolinium enhancement.
Figure 3

118x120 mm (.70 x DPI)