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CASE REPORT

New Fabry disease mutation confirms cardiomyopathy aetiology: a case report

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Background Aetiologic diagnosis should be a priority in cardiomyopathy patients, as some of them may benefit from efficient specific treatment. To achieve this, the best approach is to look for clinical and paraclinical 'red flags'.

Case summary A 55-year-old woman was referred to our centre with the diagnoses of hypertrophic cardiomyopathy (HCM), high blood pressure and dyslipidaemia. The only symptom she declared was long-term acroparesthaesia with an otherwise normal clinical exam. Lab work-up showed slightly above normal values of troponin and brain natriuretic peptide (BNP), and chronic kidney disease Stage IIIA. Both the electrocardiogram (ECG) and the echocardiography showed signs of biventricular HCM, with short PR interval on the ECG and longitudinal systolic dysfunction on the echo. Family history revealed that her son and brother had been diagnosed with Fabry disease (FD). She was then tested for FD and the results confirmed the diagnosis. Alpha-galactosidase (AGAL) levels were low and she had a severe mutation on the GLA gene (gross deletion of 3' region of the GLA gene including coding parts of exon 7), not described before. The patient was started on specific enzyme therapy.

Discussion Fabry disease is a rare X-linked disease caused by mutations on the GLA gene, which leads to low levels of AGAL and accumulation of globotriaosylceramide in the lysosomes of most tissues. Even though FD is X-linked, current medical knowledge states that most females are not mere carriers, but often present with a milder or later-onset phenotype.

Keywords Fabry disease • Hypertrophic cardiomyopathy • Mutation • Deletion • Genetic • Female • Case report

Learning points

- A red flag approach is essential in correctly diagnosing cardiomyopathies. The same red flags should be inquired about while drawing a complete family history.
- Even though Fabry disease (FD) is has an X-linked transmission, overwhelming data proves that females are usually affected.
- Sometimes an initial negative genetic test does not exclude the FD diagnosis and advanced genetic testing techniques might be required to detect rare types of mutations.

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Introduction

One of the most challenging problems in diagnosing cardiomyopathies is the aetiological workup. The best way to do this is to follow a systematic, 'red flag'-based approach, with an emphasis on taking time to construct a pedigree.[1] Moreover, hypertrophic cardiomyopathy (HCM) is now recognized as an 'umbrella' diagnosis, behind which you can find different phenocopies: from the most frequent—sarcomeric HCM to intra- or extracellular deposit disorders like amyloidosis, Fabry disease (FD), or Pompe disease. Furthermore, the importance of finding these aetiologies is derived from the fact that some of them benefit from efficient specific treatment that may stop disease progression if started in time.[2] However, even when the correct aetiological diagnosis is found, patients can present with characteristics that make them unique, as is the case of patient described in the present report.

Timeline

2010	Diagnosed with left ventricular hypertrophy
March 2016	First evaluation in our centre
	Fabry diagnosis certain based on family history
	Biology, ECG, and echocardiography suggest Fabry disease (FD)
May 2016	Negative PCR genetic test for FD
June 2016	Sanger sequencing finds a rare type of mutation (wide deletion) in the GLA gene, confirming FD

Case presentation

This is the case of a 55-year-old woman who was referred to our centre for evaluation of left ventricular hypertrophy (LVH) diagnosed a few years before, but of uncertain significance in the context of a history of hypertension.

At the current admission, the patient had no cardiovascular symptoms, but recalled rare episodes of painful acroparesthaesia. Her clinical exam showed no pathological signs. In the laboratory work-up, she had slightly elevated levels of creatinine (1.05 mg/dL, eGFR chronic kidney disease (CKD)-EPI 57.8 mL/min/1.73 m^2) and slightly elevated high sensitivity troponin I (0.03 ng/mL; $N < 0.02$). The electrocardiogram showed sinus rhythm, LVH criteria with secondary inverted T waves in lateral leads and a short PR interval (~100 ms) without a delta wave (*Figure 1*).

Transthoracic echocardiography revealed concentric LVH (maximum wall thickness of 16 mm), normal left ventricular (LV) ejection fraction, but moderately altered systolic longitudinal function using both myocardial velocities (septal S' = 6 cm/s) and speckle tracking (LV global longitudinal strain, GLS = -14.3%), with lowest deformation in the basal inferior wall. The right ventricle had normal systolic function but free wall hypertrophy (8 mm) (*Figure 2*).

As is the case for many cardiomyopathy patients, the key for the aetiologic diagnosis was the family history. We drew a complete pedigree (*Figure 3*) and found out that the patient's mother was diagnosed with HCM in her seventies and her brother was diagnosed with FD and died shortly after at age 42 years while suffering from chronic renal disease in dialysis stage. As part of family screening her son had been diagnosed with FD 6 years prior, undergoing enzyme replacement therapy (ERT) with agalsidase beta ever since. However, our patient was never considered for diagnosis, as she was thought to be just a female carrier and was lost from follow-up in that medical centre.

Contrast enhanced cardiac magnetic resonance (cMR) confirmed the concentric HCM, and also showed late gadolinium enhancement (LGE) in the infero-lateral wall of the LV (*Figure 4*).

The patient was tested for FD. Her enzymatic test showed low levels of alpha-galactosidase (AGAL = 1.0 µmol/L/h; $N > 1.2$), high levels of Lyso globotriaosylceramide (Gb3 7.6 ng/mL; $N < 3.5$), but the first genetic test result came negative. This unexpected finding turned our attention to the patient's son. He had been diagnosed with FD based on dermatologic signs (angiokeratoma), neurologic symptoms (acroparesthaesia, anhidrosis) and a positive enzymatic test (very low levels AGAL), which is enough for a positive diagnosis in men. At the time of diagnosis no genetic test had been performed. We undertook genetic testing, the result of which first came also negative. However, in the presence of clinical features, family history, and enzymatic tests clearly indicating FD in both mother and son, the genetic test was repeated using exon amplification techniques. This technique helped finding a pathogenic mutation in the GLA gene, c.[1224del66] (a gross deletion of 3' region of the GLA gene including coding parts of exon 7). The breakpoint was sequenced by Sanger sequencing after long distance polymerase chain reaction (PCR), to provide the exact extent of the deletion.

The patient was started on ERT (agalsidase beta) and evidence-based cardiologic treatment for heart failure with preserved left ventricular ejection fraction (LVEF), high blood pressure, and dyslipidaemia. After a 1.5 year follow-up, FD organ involvement parameters were unchanged for our patient, while her son did not develop new clinical signs or organ changes of FD.

Discussion

The present case report highlights the importance of 'red flags' which lead to the suspicion of FD (in conjunction with a thorough pedigree). This concept was very well described by the expert position statement written by Rapezzi *et al.*,[3] and goes through the different clinical and paraclinical parameters that can differentiate phenocopies in patients with the same general form of cardiomyopathy.[3]

Fabry disease is a rare X-linked disease that is caused by mutations in the GLA gene. These pathogenic mutations in the GLA gene eventually lead to the lysosomal accumulation of Gb3 in most organs and tissues. Women with FD mutations tend to be neglected for many years, resulting in a later start to specific treatment, when organ involvement might not be reversible anymore. It is now known that even in the setting of an X-linked disease, 'carrier' women often present with the phenotype (this can be explained by the process of lyonization[4]).

In the case of our patient, the most interesting feature is the finding of a severe mutation, a gross deletion of a big portion of the GLA gene that, to our knowledge, has not been reported before.

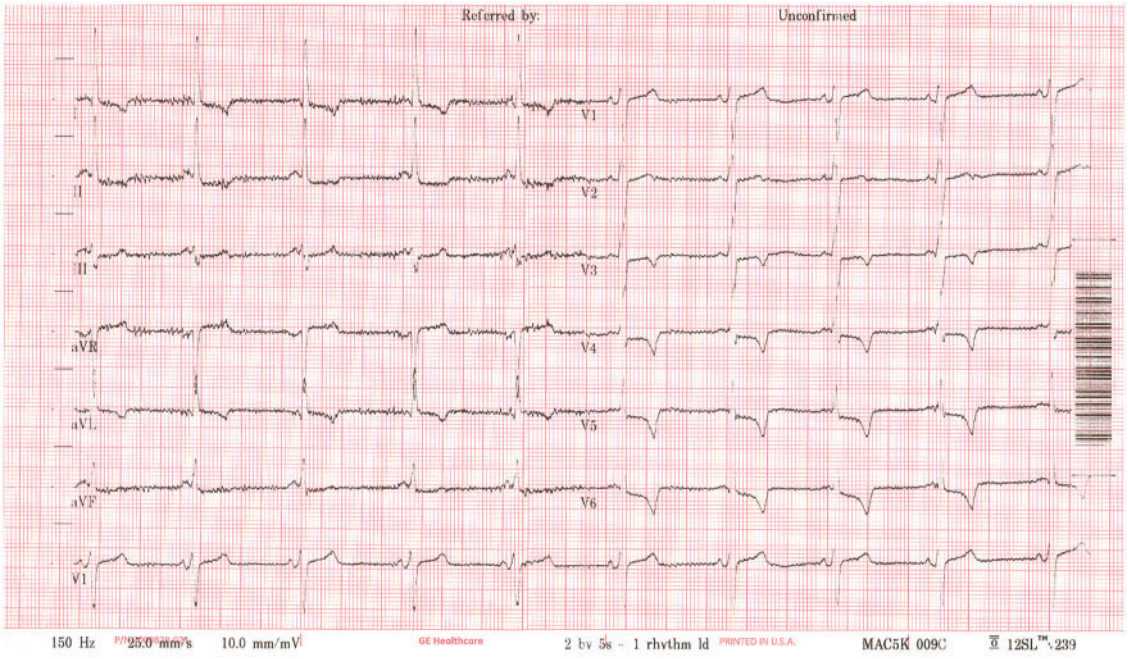

Figure 1 ECG showing left ventricular hypertrophy with inverted T waves in the lateral leads and short PR interval.

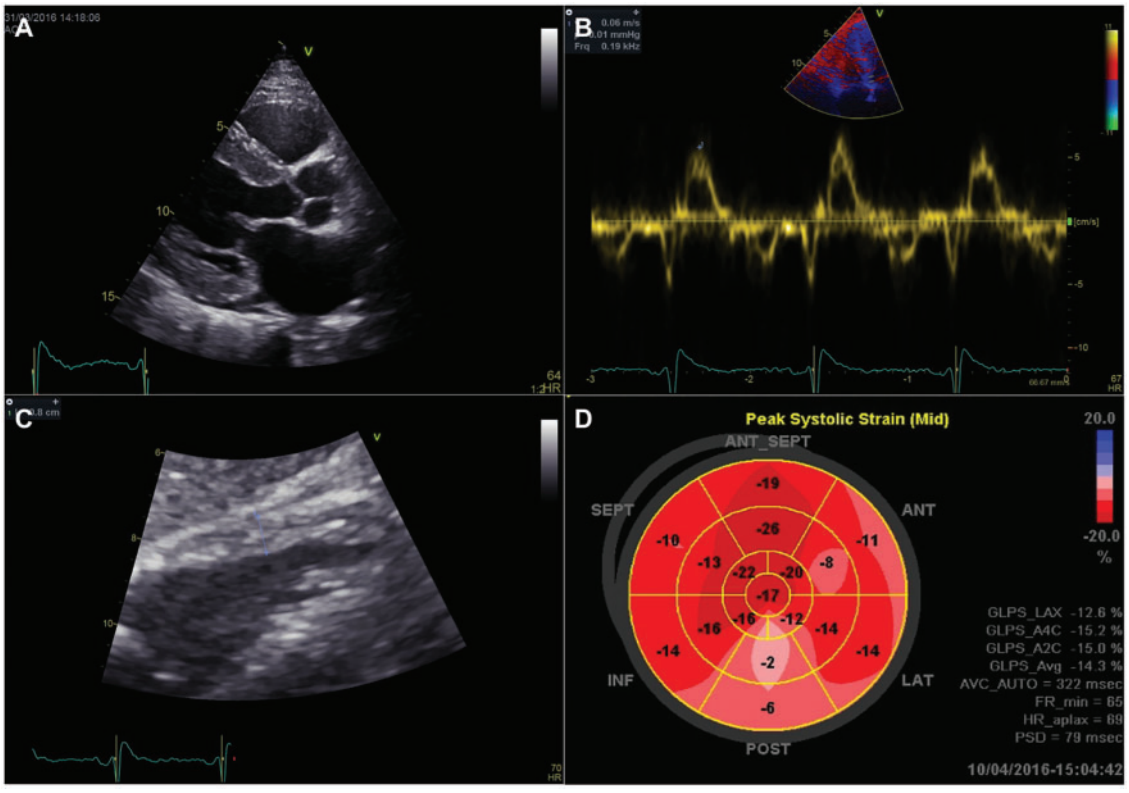

Figure 2 Echocardiography. (*A*) Concentric left ventricular hypertrophy in parasternal long axis view. (*B*) Low septal tissue velocities. (*C*) Right ventricular hypertrophy. (*D*) Low longitudinal strain with inferior wall of the left ventricle.

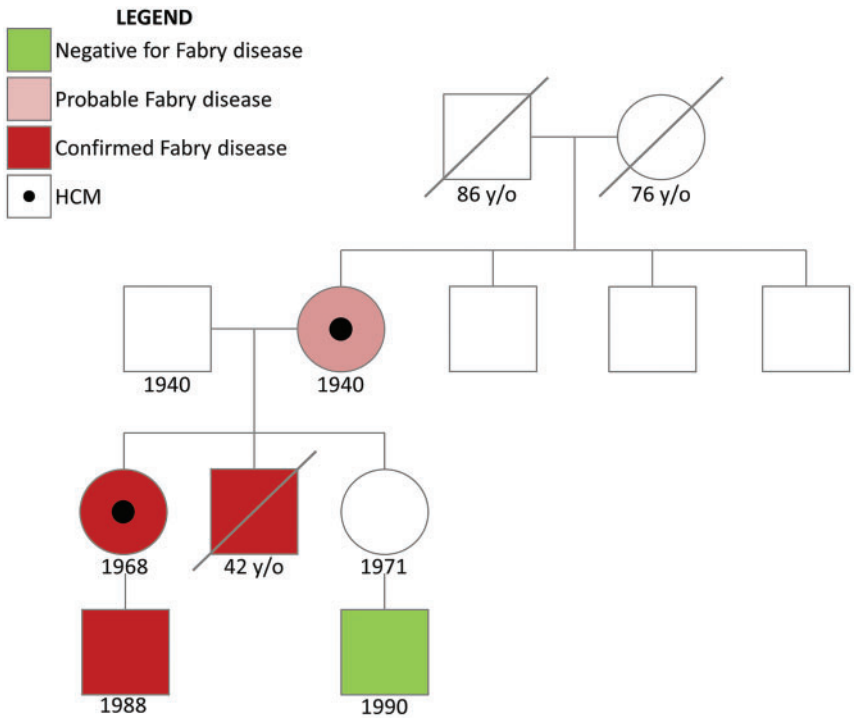

Figure 3 Family pedigree showing confirmed Fabry diagnosis in the patient's son and deceased brother.

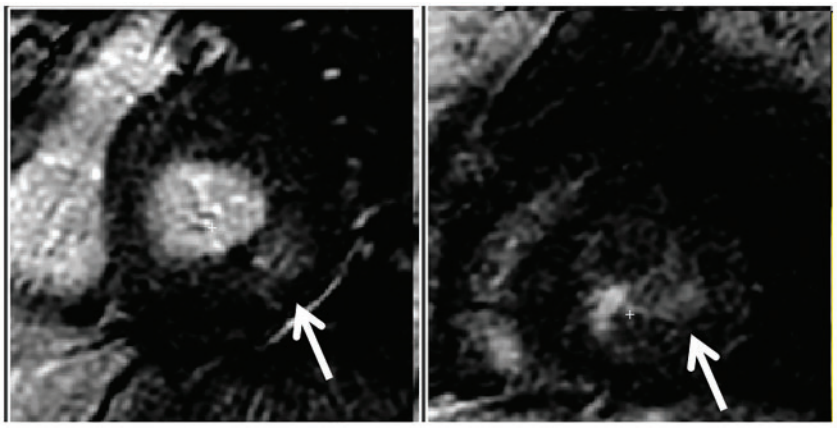

Figure 4 Late enhancement cardiac magnetic resonance images showing late gadolinium enhancement (arrows) in the infero-lateral wall of the left ventricle.

Even though FD can affect virtually every organ, the three that most influence the prognosis are: cardiac, renal (chronic kidney disease, often leading to kidney failure), and central nervous system (stroke) involvement.[5]

The classical cardiac manifestation is HCM, and there are certain features that were reported to help differentiate FD from other causes of HCM. In FD the heart presents most commonly with non-obstructive concentric LVH,[6] often associated with right ventricle hypertrophy. Subtle features include more severe involvement of the inferior wall (*Figure 2D*) on the GLS bullseye, which was reported to have a good correlation with the presence of fibrosis on cMR (as shown by LGE in the infero-lateral wall in FD), which was also the case for this patient.[7] Beyond cardiac imaging, a short PR interval on the ECG in the absence of a delta wave[8] or continuously increased

troponin level[9] in a patient with HCM can raise the suspicion of FD. Further, it has been demonstrated that the level of AGAL correlates with disease severity in women.[10]

Therefore, such 'red flags' should lead to including FD in the differential diagnosis of a patient with HCM. However, our patient had undergone several cardiologic evaluations without being properly diagnosed, and this can be explained by suboptimal awareness for this disease among cardiologists. Large registries and studies done for both available AGAL products confirm that early treatment is very important in stopping severe organ involvement.[2,11] More to this point, other studies have shown continued progression of cardiac fibrosis if the treatment was started after significant cardiac fibrosis had already set in.[12,13] However, one way of demonstrating treatment efficacy is dosing lyso-Gb3, with rapid reduction in the elevated plasma lyso-Gb3 level in the classic Fabry males, and a gradual one or stabilization in most of the later-onset Fabry males and Fabry females.[14]

Another important message is that deletions of one or more entire exons in a heterozygous setting can be missed by qualitative analysis by PCR and gene dosage (quantitative analysis) is needed in such cases.[15]

The case of this family further illustrates the importance of early enzymatic treatment, as the patient's son, who was started on ERT in his early 20's, does not have any significant organ involvement, as opposed to his uncle, who was diagnosed much later in life.

Conclusion

Awareness and active search for cardiac and systemic 'red flags' both in cardiomyopathy patients as well as their pedigree allow for a correct diagnosis of rare diseases. This led to the finding of a new and rare type of mutation in FD. A complete positive diagnosis can improve the patients' prognosis through proper treatment for index patients and family members.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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