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CASE REPORT
Inherited cardiac conditions/cardiomyopathies

Fabry disease due to D313Y variant with renal failure and possible cardiac involvement: a case report

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Background This is a case report of a patient with Anderson–Fabry disease (AFD) due to the D313Y variant on the a-galactosidase A (*GLA*) gene on migalastat treatment and severe chronic kidney disease referred to our unit to assess possible cardiac involvement.

Case summary A 53-year-old man with chronic kidney disease due to AFD and a medical history of revascularized coronary artery disease, chronic atrial fibrillation, and arterial hypertension was referred to our unit for evaluation of possible cardiac involvement in the context of AFD. Biochemical evaluation reported reduced serum alpha-galactosidase A activity and borderline abnormal serum lyso-Gb_3 enzyme activity. The patient had also history of acroparesthesias, dermatological presentation of multiple angiokeratomas, severe kidney impairment with an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73m^2 by the age of 16, and microalbuminuria that cumulatively set the diagnosis of AFD. Transthoracic echocardiogram showed left ventricular concentric hypertrophy with left ventricular ejection fraction of 45%. Cardiac magnetic resonance showed findings in keeping with ischaemic heart disease (IHD), i.e. akinesia and subendocardial scarring of the basal anterior and the entirety of the septum and the true apex; in addition, there was severe asymmetrical hypertrophy of the basal anteroseptum (max 18 mm), evidence of low-grade myocardial inflammation, and mid-wall fibrosis of the basal inferior and inferolateral wall, suggesting a cardiomyopathic process–myocardial disease which could not be explained solely by IHD or well-controlled hypertension.

Discussion This is the first case of possible cardiac involvement in a patient with AFD due to the D313Y variant. This case demonstrates the diagnostic challenges of cardiac involvement in AFD, especially in the presence of a concomitant underlying pathology.

Keywords Case report • Fabry disease • D313Y mutation • Myocardial involvement

ESC Curriculum 2.3 Cardiac magnetic resonance • 6.5 Cardiomyopathy

Learning points

- Cardiac involvement in Anderson–Fabry disease (AFD) due to the D313Y variant has not been previously reported.
- Screening of AFD patients with the D313Y variant for possible cardiac involvement may be of value.
- The combination of advanced cardiac imaging and genetic testing can be used to reach the diagnosis of AFD cardiomyopathy.

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Introduction

The prevalence of Anderson–Fabry disease (AFD) in patients with unexplained left ventricular hypertrophy (LVH) is nearly 1%. Most patients present mainly with renal and neurological symptoms and signs, while few of them may develop cardiac manifestations of the disease. The D313Y variant has been considered as a variant of uncertain significance (VUS), and there is paucity of evidence for its pathogenicity and clinical relevance.[1] There are reports of renal and nervous system involvement[2] in patients with AFD due to the D313Y variant on the a-galactosidase A (*GLA*) gene, but there has been no report of cardiac involvement.[3]

Timeline

Month 1	Diagnosis of chronic kidney disease
Month 6	Diagnosis of Anderson–Fabry disease with renal involvement due to the D313Y variant on the GLA gene
Month 7	Start of migalastat treatment
Month 19	Presentation to our unit for cardiac evaluation after 12 months on migalastat treatment. Electrocardiogram and transthoracic echocardiogram revealed findings compatible with Fabry disease
Month 20	Cardiac magnetic resonance showed a large transmural ischaemic scar in the left anterior descending artery (LAD) territory, but also severe left ventricular hypertrophy, low-grade myocardial inflammation, and mid-wall fibrosis compatible with AFD

Case presentation

A 53-year-old man with a medical history of coronary artery disease (single-vessel coronary artery bypass grafting that was performed 15 years ago), chronic atrial fibrillation, and arterial hypertension was referred to our unit for further evaluation due to severe left ventricular hypertrophy (LVH). He had a past medical history of acroparesthesias, angiokeratomas, severe kidney impairment with an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73m^2 by the age of 16, and microalbuminuria. Genetic testing had shown carriage of the D313Y variant in the GLA gene (ChrX(GRCh37):g.100653420C>A) (Supplementary material). Specialized blood testing of a-galactosidase A (a-GalA) activity had shown reduced activity and in turn serum lyso-Gb_3 enzyme activity that was found borderline abnormal. At the time of the evaluation, the patient was under migalastat treatment. He was also treated with aspirin 100 mg o.d., isosorbide mononitrate 60 mg o.d., atorvastatin 10 mg o.d., ezetimibe 10 mg o.d., nifedipine 40 mg b.d., spironolactone 25 mg o.d., torasemide 10 mg, o.d., apixaban 2.5 mg b.d., febuxostat 80 mg o.d., and folic acid 5 mg o.d.

On initial assessment, the clinical examination of respiratory, cardiovascular system was normal, but he presented with skin pigmentation and angiokeratomas. Electrocardiogram showed atrial fibrillation with slow ventricular response, high QRS voltages, and negative inferolateral T waves (*Figure 1*). Echocardiogram showed impaired left ventricular (LV) ejection fraction (45%), LV concentric hypertrophy (basal segments of 16–18 mm), and a dilated left atrium (*Figure 2*). Given the known AFD, to confirm/exclude myocardial involvement, a cardiac magnetic resonance (CMR) was ordered which showed normal LV volumes with severely increased LV wall thickness (maximum wall thickness of 18 mm at the basal anteroseptum) and akinesia of the basal anterior and the entirety of the septum and the true apex, due to a large subendocardial scar (>50% of wall thickness) in the LAD territory (*Figure 3*). Interestingly, there were low T1-mapping values in the interventricular septum suggestive of lipomatous metaplasia of the ischaemic scar in the periinfarct region, while remote myocardial segments had normal to high native T1 (1045–1097 ms)

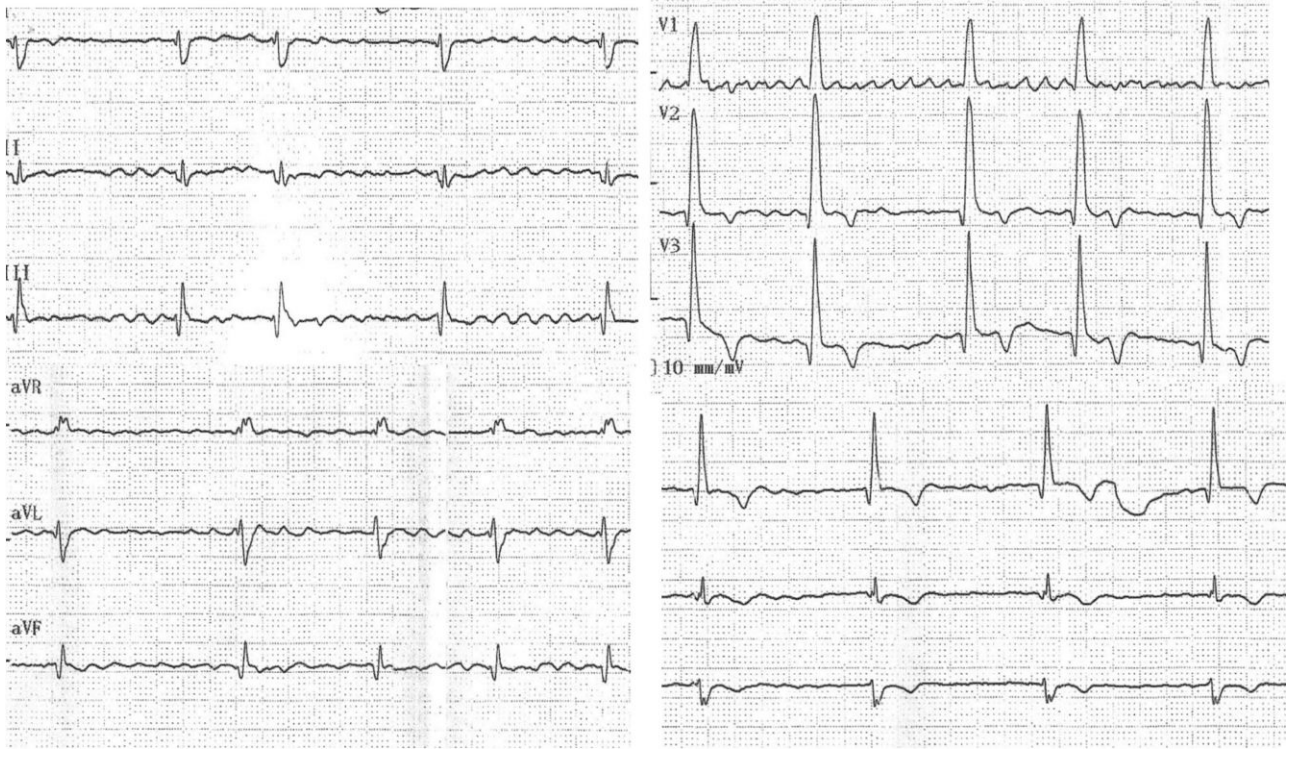

Figure 1 Patient's electrocardiogram showed atrial fibrillation with slow ventricular response, high QRS voltages, and negative inferolateral T waves.

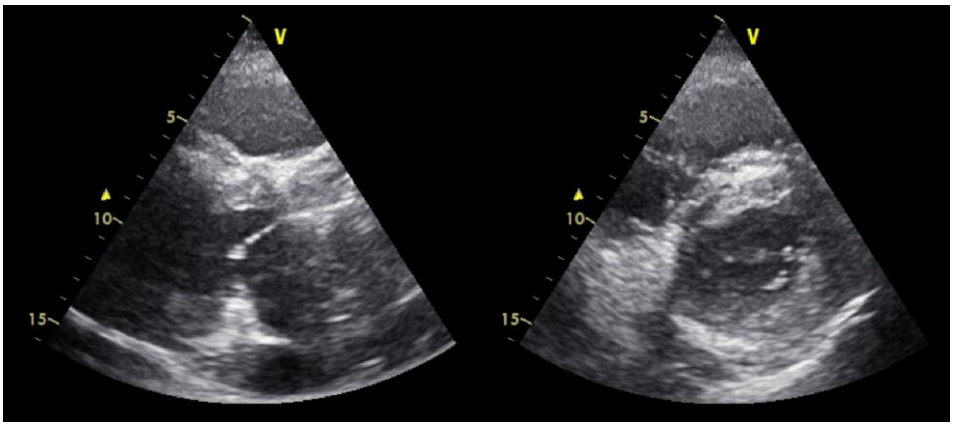

Figure 2 Left ventricular hypertrophy (basal segments up to 18 mm) and left atrium dilation, as shown in echocardiogram.

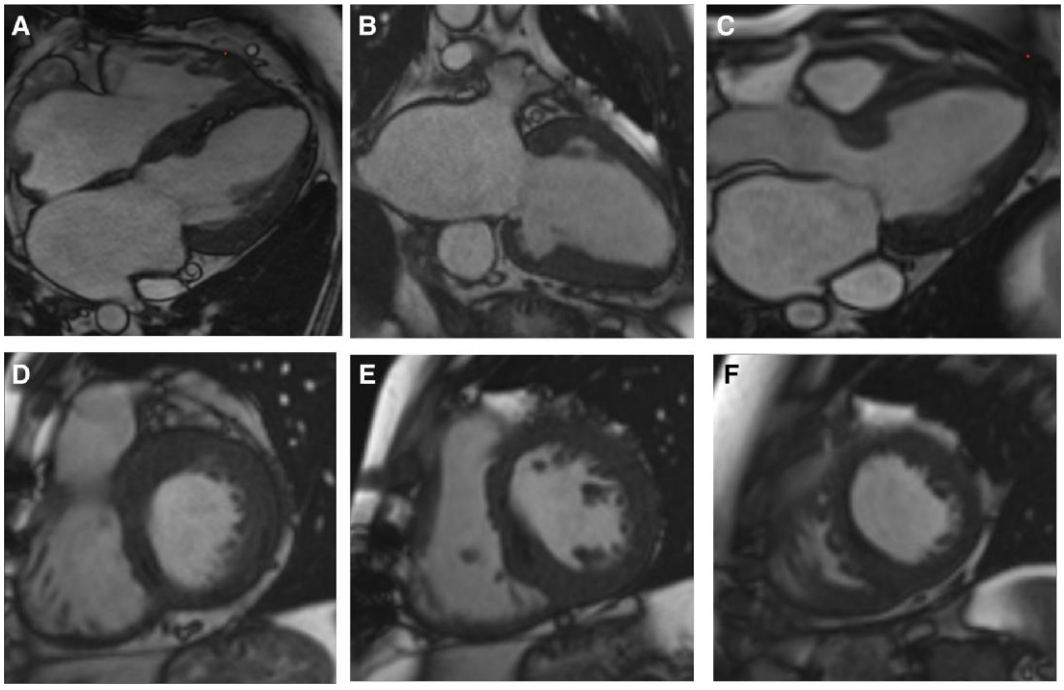

Figure 3 Balance steady-state free precession (bSSFP) cine images by cardiac magnetic resonance (CMR). End-diastolic frames from long axis (*A*–*C*) and basal-mid-apical short axis (*D*–*F*) are shown.

suggesting diffuse fibrosis and pseudo-normalization of native T1 values in the context of Fabry disease (*Figure 4A*). In addition, there was evidence of low-grade myocardial inflammation (i.e. increased values in myocardial T2 on T2 mapping, *Figure 4B*) and mid-wall fibrosis in the basal inferior and inferolateral wall of non-ischaemic origin (*Figure 5*), findings that could not be explained by either well-controlled arterial hypertension or ischaemic heart disease.

Discussion

AFD is an X-linked inherited lysosomal storage multisystem disease caused by pathogenic mutations in the *GLA* gene, leading to a decrease in a-GalA activity and accumulation of glycolipids–primarily globotriaosylceramide (Gb3) and lyso-Gb3 in peripheral tissues and vital organs, including the kidney, the heart, and the nervous system. More than 900 mutations on the *GLA* gene have been reported to date.[4]

There are two phenotypical subtypes of AFD: the early- and late-onset AFD. The former, also called the classical type, has an early age onset (in childhood or adolescence), and its main manifestations are angiokeratomas, acroparesthesias, corneal opacities, and hypohidrosis. In this subtype, cardiac involvement is also present and it is characterized by LVH accompanied by typical ECG changes. The late onset AFD, also known as atypical variant, has a later age onset and typically a milder clinical phenotype due to a residual a-GalA activity.[5] However, cardiac manifestations in atypical variants have been reported,[5] which usually present in the 6th to 8th decade.

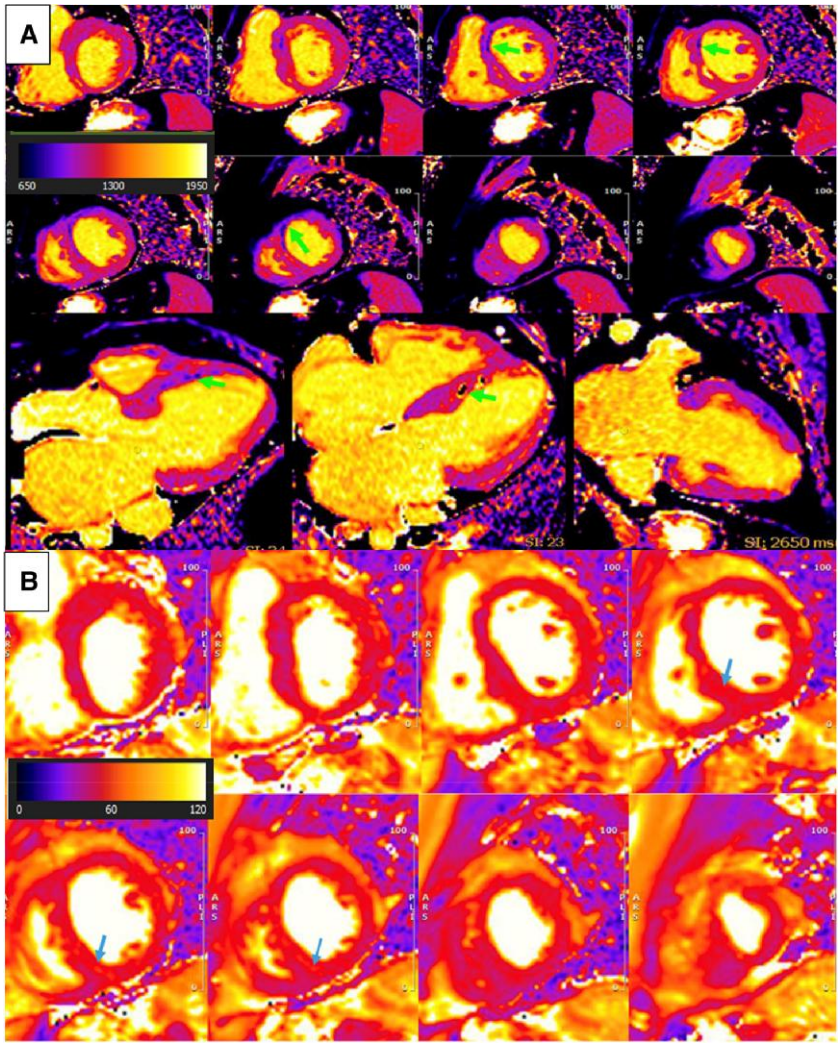

Figure 4 (*A*) Native T1 mapping (short axis stack and long axes) showing low myocardial T1 values in the ischaemic scar of the LAD territory (T1 910 ms), in keeping with lipomatous metaplasia of the scar, and increased values in remote myocardial segments (up to 1097 ms at 1.5 T). (*B*) Myocardial T2 mapping showing increased values (up to 62 ms) in the basal inferior wall and the inferoseptum, suggestive of myocardial oedema (inflammation).

The D313Y variant is currently classified as a variant of unknown significance (VUS) with residual a-GalA activity, but there is growing evidence suggestive of its pathogenicity. For example, Koulousios *et al.*[4] have published convincing evidence of the renal involvement in the context of the D313Y *GLA* variant. However, cardiac involvement was not systematically examined by this study.

In our case, there were features in favour but also features against cardiac involvement of Fabry disease due to the D313Y variant. The patient's symptomatology with acroparesthesias and angiokeratomas along with the severe kidney impairment, microalbuminuria, and the low a-GalA activity pointed to a diagnosis of AFD with renal involvement. The CMR images showing mid-wall fibrosis in the basal inferolateral and inferior walls—a typical site of cardiac involvement in AFD—along with the patient's LVH, the degree of which was inconsistent with the patient's history of well-controlled hypertension, support the possibility of cardiac involvement. Moreover, the low-grade myocardial inflammation, a finding consistent with cardiac AFD, could not be explained by either ischaemic heart disease or arterial hypertension. However, the presence of asymmetric LVH, non-specific mid-wall fibrosis, and borderline lyso-Gb3 levels posed a diagnostic challenge. The T1-mapping values could be interpreted as pseudo-normalized in the setting of advanced disease with replacement fibrosis. The borderline lyso-Gb3 activity is a finding in keeping with AFD in the context of the D313Y variant. These patients often demonstrate a high a-GalA residual activity and may even present with normal lyso-Gb3 levels.[4] Endomyocardial biopsy would have helped to establish the diagnosis of Fabry cardiomyopathy, but since the patient was already under migalastat treatment, this was considered as a diagnostic step that would not change the treatment decisions. Altogether, these findings were deemed suggestive of possible myocardial involvement in the context of the D313Y variant.

In conclusion, AFD disease is a multisystem disorder with a wide range of clinical manifestations and variable degrees of phenotypic expressions. The D313Y variant is currently classified as a VUS, but our case provides first clinical evidence for the possibility of not only renal disease but also cardiac involvement in carriers of the D313Y variant.

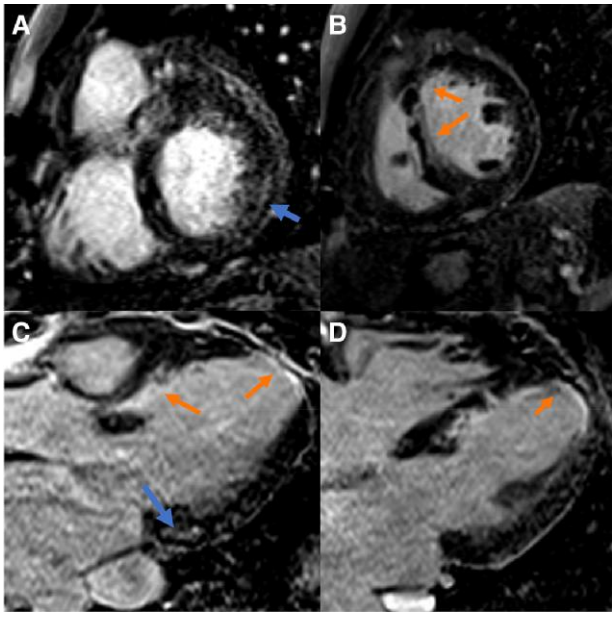

Figure 5 Late gadolinium enhancement (LGE) showing transmural ischaemic scar (orange arrows)*(B-D)* in the left anterior descending artery territory as well as mid-wall fibrosis (blue arrows) *(A, C)* in the basal inferolateral and inferior walls.

Lead author biography

Dr. Evangelia Bei is a cardiologist with a special interest in cardiomyopathies and sports cardiology. She has graduated from Medical School of Athens and finished her specialty training in cardiology in the First Department of Cardiology of Athens University at Hippokration Hospital. Currently, she is a PhD Candidate in Medical School of Athens.

Supplementary material

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

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None.

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

Consent: We report that the patient gave their consent for the material presented about themself to appear in this publication in accordance with COPE guidelines. It was explained to them that this material has educational and scientific value and that the publication may help to improve the care that others will receive in the future. Identifying information has been excluded from written descriptions, photographs, and pedigrees, while patient data weren't altered or falsified in order to attain anonymity.

Conflict of interest: None declared.

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Data availability: Data identifiers are present in the manuscript.

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