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*Case Report*

# Diagnosis of Fabry Disease in a Patient with a Surgically Repaired Congenital Heart Defect: When Clinical History and Genetics Make the Difference

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**Abstract:** Fabry disease (FD) is a multiorgan disease, which can potentially affect any organ or tissue, with the heart, kidneys, and central nervous system representing the major disease targets. FD can be suspected based on the presence of specific red flags, and the subsequent evaluation of the α-Gal A activity and GLA sequencing, are required to confirm the diagnosis, to evaluate the presence of amenable GLA mutation, and to perform a cascade program screening in family members. An early diagnosis is required to start an etiological treatment and to prevent irreversible organ damage. Here, we describe a case of a 37-years-old patient, with a surgically repaired congenital heart defect in his childhood, who had a late diagnosis of FD based on the clinical history and targeted genetic evaluation. This case highlights the importance to perform a correct phenotyping and definite diagnosis of FD, to start an early and appropriate treatment in the index patient, and a cascade clinical and genetic screening to identify other family members at risk, which may benefit from specific treatment and/or a close follow-up.

**Keywords:** Fabry disease; congenital heart defect; clinical markers; enzyme replacement therapy; migalastat; cascade program screening

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## 1. Introduction

Fabry disease (FD) is a rare X-linked lysosomal storage disorder, caused by a mutation in GLA, that results in lower activity of α-galactosidase A (α-Gal A) enzyme and progressive accumulation of globotriaosylceramide (Gb3) and its deacylated form, globotriaosylsphingosine (lysoGb3), potentially affecting any organ or tissue [1]. Clinical manifestations are extremely heterogeneous, depending on the patient's sex and type of GLA mutation, which influences the degree of α-Gal A deficiency [2,3]. In adulthood, the main involved

organs are represented by kidneys, heart, and central nervous system, and this condition is suspected based on the presence of clinical markers, or red flags, which help to guide the subsequent investigations [4,5], such as the evaluation of the α-Gal A activity and GLA sequencing. Genetic analysis is mandatory to confirm the diagnosis, it is required to perform a cascade program screening in family members [6], and it is indicated to evaluate the presence of amenable GLA mutation [7].

This case report exemplifies the importance of the clinical markers in performing diagnosis of FD, to start an early and appropriate treatment in the index patient and a cascade program screening to identify other family members at risk, which may benefit from specific treatment and/or a close follow-up.

## 2. Case Report

A 37-year-old man was referred to the Inherited and Rare Cardiovascular Diseases Clinic of the University of Campania "Luigi Vanvitelli", Naples, Italy, for evaluation of left ventricular hypertrophy, in absence of hypertension or aortic valve stenosis, identified at echocardiography in a previous cardiological evaluation.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli". Informed consent was obtained from all subjects involved in the study.

The patient has been followed since birth from the Division of Pediatric Cardiology and subsequently from the Division of Adults with Congenital Heart Defects of our Department following the neonatal diagnosis of a partial atrioventricular septal defect. At 6 months old, he underwent surgical repair (the approximation of the edges of the valve cleft with interrupted nonabsorbable sutures and the closure of the interatrial communication with bovine pericardial patch) and at 14 years old he underwent reoperation (left valve repair) for severe left atrioventricular valve regurgitation. At 21 and 22 years old, he experienced two transient ischemic attacks (TIAs) manifested with left arm weakness and speech difficulty.

Thus, he underwent a comprehensive diagnostic work-up to identify the possible cause of the TIAs. In detail, he underwent complete laboratory investigations, including complete blood count, electrolytes, coagulation, renal function, glucose and homocysteine levels, screening for autoimmune diseases and thrombophilia, non-contrast brain computerized tomography (CT) and magnetic resonance imaging (MRI), carotid Doppler ultrasound, 12-lead electrocardiogram (ECG), repeated 24-h ECG monitoring, transthoracic and transesophageal echocardiography. However, no underlying cause of TIA was identified, thus the episodes were labeled as "idiopathic TIAs". At 36-years-old, he experienced a third TIA. The echocardiographic evaluation showed the presence of a mild concentric left ventricular hypertrophy, which was considered unrelated to the congenital disease and/or other potential causes, and the patient was referred to our clinic for further evaluation.

The patient was asymptomatic, the physical examination showed a systolic heart murmur, the ECG showed sinus rhythm, normal atrioventricular and interventricular conduction, and repolarization abnormalities in the inferior leads (Figure 1). The echocardiogram confirmed the presence of concentric left ventricular hypertrophy with the maximal wall thickness of 13 mm at the level of the anterior interventricular septum and showed papillary muscles hypertrophy, normal ejection fraction (EF, 65%), and mild reduction of global longitudinal strain (GLS, −18.2%) (Figure 1). Thus, he underwent a cardiac MRI that evidenced basal inferolateral late gadolinium enhancement (LGE) and reduced cardiac native T1 time (Figure 1).

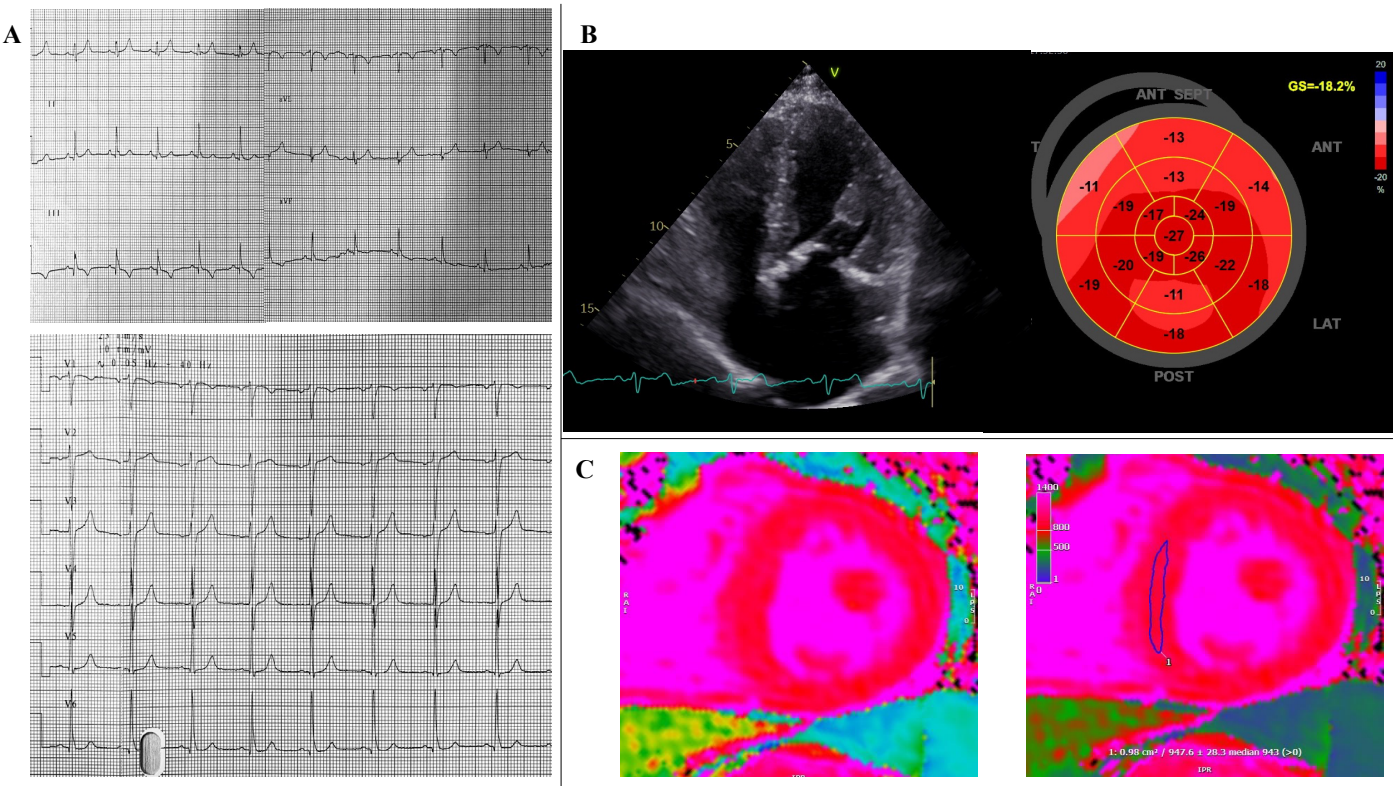


**Figure 1.** Electrocardiography (**A**), apical 4 chamber view showing left ventricular hypertrophy and global longitudinal strain at echocardiography (**B**) and native T1 mapping at cardiac magnetic resonance (**C**) of the proband (III-1).

Based on the patient's sex, the history of TIAs, and the presence of the mentioned cardiological abnormalities, FD was suspected. Alpha-Gal A activity was significantly reduced and the sequencing of GLA identified the presence of the pathogenic variant c.1066C>T (p.Arg356Trp) for FD.

A multidisciplinary evaluation (i.e., genetic, neurologic, ophthalmologic, nephrological, dermatological, otolaryngological) failed to show other organ involvement. After a careful discussion about the risk/benefit balance of the available treatment options, the patient decided to refuse the intravenous enzymatic replacement therapy (ERT), and considering the presence of an amenable mutation, chaperone therapy with Migalastat was started. At 6-months of follow-up, echocardiographic parameters, including left ventricular mass, left ventricular EF, and GLS, remained stable.

After the identification of the disease-causing mutation in GLA, family members were invited to join the cascade program screening (Figure 2). The pathogenic mutation was identified in the mother, both the two sisters and the two daughters of the proband.

All the subjects underwent a comprehensive multidisciplinary evaluation and cardiological investigations, including ECG, echocardiography, and cardiac MRI. The mother (II-2) and the two daughters (IV-1 and IV-2) showed normal α-Gal A enzyme activity and no signs of organ involvement. The sister III-2 (33 years old) experienced a TIA when she was 13 years old and showed mild proteinuria, while the sister III-3 (37 years old) showed a significant elevation of lysoGb3 levels, in absence of any sign of organ involvement. No cardiac abnormalities were evidenced in these two patients (Figure 3).

Thus, a careful discussion was performed with both the sisters. Sister III-2, in consideration of cerebrovascular and renal involvement, started enzyme replacement therapy, while for sister III-3, no specific therapy was recommended, and a close follow-up was initiated.

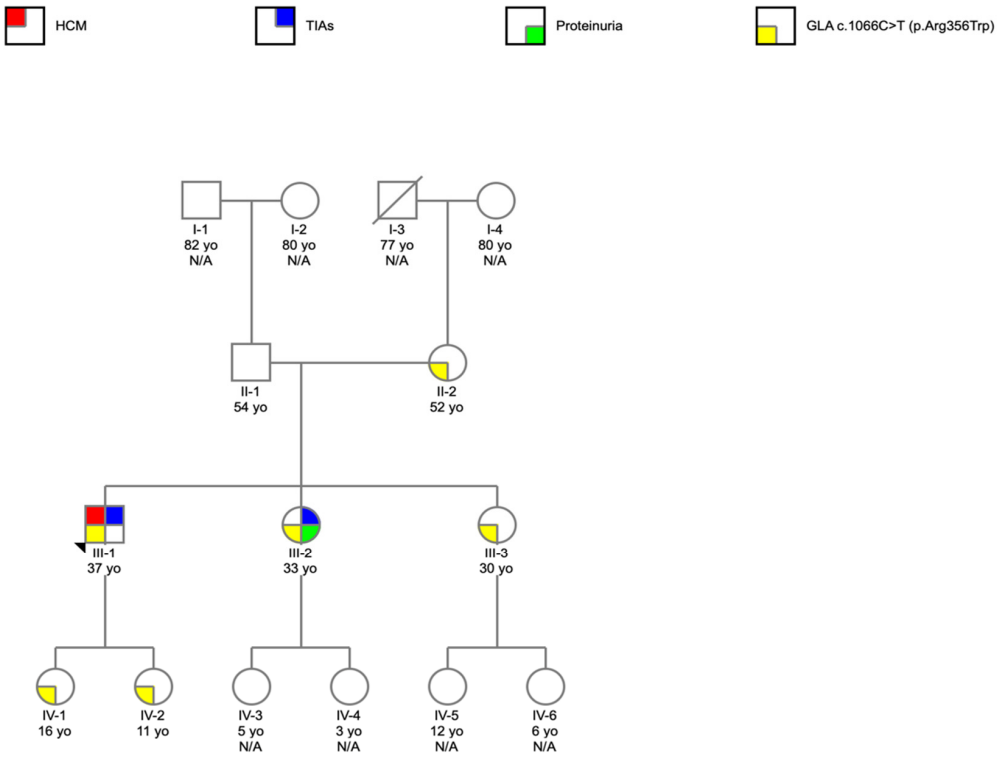


**Figure 2.** Pedigree of the members of the family studied and their phenotypic spectrum and genotype. The arrow indicates the proband (III-1). HCM, hypertrophic cardiomyopathy; N/A, not analyzed; TIAs, transient ischemic attacks.

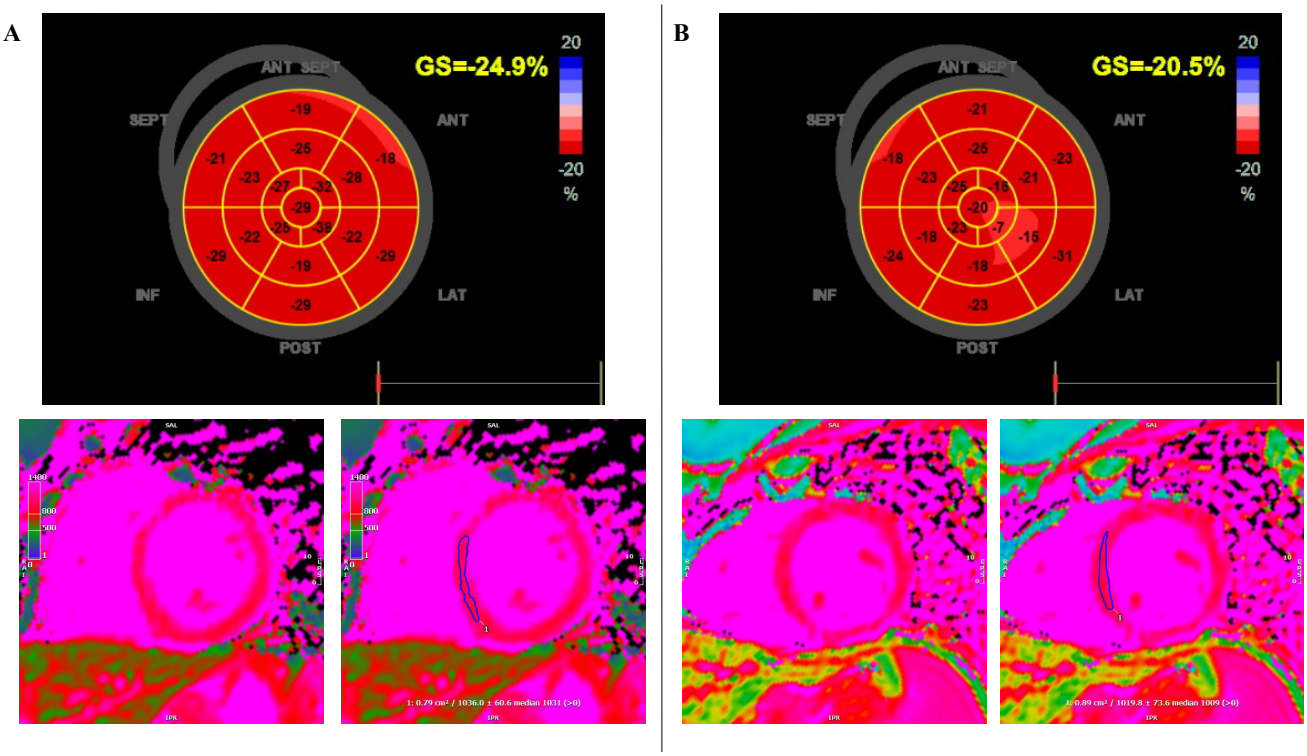


**Figure 3.** Global longitudinal strain at echocardiography and native T1 at cardiac magnetic resonance of the two sisters of the proband ((**A**): III-2; (**B**): III-3)) that showed no cardiac involvement.

## 3. Discussion

FD is a multiorgan disease, which can potentially affect any organ or tissue, with the kidneys, heart, and central nervous system representing the major disease targets [1]. The classic form of the disease manifests during childhood, and gastrointestinal disorders, neuropathic pain, hypohidrosis, and angiokeratomas are the most common manifestations of the disease [1]. In adulthood can appear signs and symptoms of heart, kidneys, and cerebral involvement, which is responsible for the increased mortality and morbidity in these patients [8]. On the contrary, males with the non-classic form or later-onset FD and female patients generally show mild clinical presentations and tend to have single organ involvement.

Several messages emerge from this case report:

1. The diagnostic delay that generally characterizes rare diseases;
2. The potential coexistence with other diseases (i.e., congenital heart defect) and the importance of identifying specific red flags that raise the possibility of the disease;
3. The importance of the cascade program screening to identify family members at risk;
4. The difficulty in the management of asymptomatic female patients or with mild clinical manifestations.

### *3.1. Diagnostic Delay and Clinical Markers in FD*

The high variability in clinical manifestations of FD, with different possible age and symptom onset, can lead to delayed diagnosis and treatment. Similar to patients with other rare diseases, also FD patients frequently had an initial misdiagnosis [9], and the diagnostic "odyssey" to which the patients are frequently subjected is negatively experienced. A recent study shows that the average diagnostic delay from symptom onset is 10.5 years in adults and 4 years in children [10]. The greater diagnostic delay in adults may probably be explained by the non-specific and milder clinical presentation than children. However, the early diagnosis is fundamental in FD since the organ damage, in particular, cardiac and renal injury is in large part irreversible [1,7].

In the classic form of FD, with a clear cardiovascular and renal involvement, the diagnosis is generally easy. Patients are referred to nephrologists for proteinuria or to cardiologists for (generally concentric, non-obstructive) hypertrophic cardiomyopathy, and the coexistence of the two conditions is a well-recognized "alarm bell" to promote further investigation [4,11]. The presence of additional cardiac (including short PR interval, atrioventricular blocks, reduced GLS with involvement of the basal inferolateral wall, hypertrophy of papillary muscles, mid-layer inferolateral LGE, low T1 time) or non-cardiac "red flags" (hearing loss, angiokeratoma, cryptogenic TIA or stroke) may be of help to suspect the diagnosis [4,5,12–14]. In the present case, the proband was followed for a repaired congenital heart disorder. Clinical history after the second operation included multiple, cryptogenic strokes. The coexistence of mild, concentric hypertrophy, with no evident clinical cause, was the primary reason for referral to our center, and the prompt to look for additional markers (i.e., papillary muscle hypertrophy, reduced longitudinal strain in inferolateral walls, reduced T1).

### *3.2. Genetic Diagnosis and Cascade Program Screening in FD, and Treatment in Females with FD*

Genetic testing is an indispensable tool in patients with cardiomyopathies and inherited cardiac conditions [15–24] to confirm the diagnosis and to perform a cascade screening in family members. Thus, after the identification of a disease-causing mutation in the index patient, family members should be invited to join the cascade program screening. This program consent to early identify patients at risk and to start early and appropriate management. In the present case, though the cascade screening, it was possible to identify a symptomatic female patient (with proteinuria and history of TIA) who started ERT, and an asymptomatic female patient (with very low enzyme activity and high lysoGb3), which may potentially benefit from etiological therapy in the future.

The etiological therapy shows the maximal benefit in terms of a decrease in incidence rates of adverse events in males; however, also female patients may benefit from a specific treatment [25,26]. In particular, a comprehensive systematic literature review showed that ERT in female patients was associated with significant reductions in plasma and urine GB3 accumulation, in those with elevated pre-treatment levels, and improvement of cardiac parameters and quality of life [25].

Although there appears to be a common consensus on the initiation of therapy in symptomatic female patients [7], its role in asymptomatic or mildly symptomatic patients is less clear. Thus, the decision to proceed to etiological treatment in these patients should be evaluated after a case-by-case discussion, considering the risk/benefit balance of the treatment and the patient's will.

## 4. Conclusions

FD is a multiorgan disease, which can potentially affect any organ or tissue, with the heart, kidneys, and central nervous system representing the major disease target. Based on clinical markers which should guide the suspect, the clinical and genetic diagnosis in the index patient and family members allows starting appropriate treatment to prevent irreversible organ damage.

**Author Contributions:** G.L. designed the study and supervised the writing project of the manuscript. M.R. and E.M. prepared the manuscript and wrote the draft together. M.C. designed the pedigree and managed genetic analysis. M.R., E.M. and M.C. prepared the figures. G.P., M.L., A.C. (Annapaola Cirillo), A.F., F.V., A.P., G.D. (Gaetano Diana), F.A., A.C. (Arturo Cesaro), G.D. (Giovanni Duro), B.S., M.G.R. and P.C. actively participated in the discussion and suggestions for the manuscript. All authors have read and agreed to the published version of the manuscript.

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