Rare presentation and wide intrafamilial variability of Fabry disease: A case report and review of the literature 🎞

Sebastian Militaru, Robert Adam, Lucian Dorobantu[1], Paolo Ferrazzi[1], Maria Iascone[2], Viorica Radoi[3], Ismail Gener[4], Bogdan A. Popescu, Ruxandra Jurcut
Department of Cardiology, The Expert Center for Rare Genetic Cardiovascular Diseases, Euroecolab, Emergency Institute for Cardiovascular Diseases "Prof. Dr. C.C. Iliescu"; Bucharest-*Romania*
[1]Centre for Hypertrophic Cardiomyopathy and Valvular Heart Disease, Monza Clinical Hospital; Bucharest-*Romania*
[2]Medical Genetics Laboratory, Hospital Papa Giovanni XXIII; Bergamo-*Italy*
[3]Department of Medical Genetics, Carol Davila University of Medicine and Pharmacy; Bucharest-*Romania*
[4]Department of Nephrology, Fundeni Clinical Institute; Bucharest-*Romania*

Introduction

Fabry disease (FD) is an X-linked genetic disease caused by mutations in the *GLA* gene, which encodes α-galactosidase A, leading to an intralysosomal accumulation of globotriaosilceramide (Gb3) in a wide variety of cells. Thus, FD usually presents with multiorgan damage: cardiac (hypertrophic cardiomyopathy), renal (chronic kidney disease, proteinuria), neurological (stroke, acroparesthesia), cutaneous (angiokeratoma), and ophthalmic (cornea verticillate) (1). Although FD is X-linked, women with specific mutations are not only carriers, as it was previously expected, but most of them develop manifestations somewhat later in life than men (2, 3), due to a mosaic inactivation of the X chromosome. It is of the utmost importance to follow the FD diagnosis with a complete family screening, which can lead to timely diagnosis in other family members.

The present case report demonstrates how following the red flags of clinical suspicion for FD can lead to a correct final diagnosis in the index patient, even in case of a rare phenotypic presentation, while also highlighting the large intrafamilial variability of systemic FD manifestations.

Case Report

A 49-year-old woman was referred for evaluation with a diagnosis of hypertrophic obstructive cardiomyopathy (HOCM) established 6 years before, to discuss management options. The patient complained of dyspnea with moderate exertion, and she did not tolerate β-blockers as she developed severe bradycardia even at low doses. From the patient's personal history, we noted acroparesthesia during adolescence, which was no longer present in adulthood, as well as the history of a cryptogenic transient ischemic attack at the age of 46.

The clinical examination revealed the presence of a few dark-colored macules on the edge separating the skin and the lip's mucosa (Fig. 1a). The patient's family history revealed that one of her sisters a nephew had both died while on hemodialysis, aged 54 and 27, respectively (Fig. 2). The patient had an apparently healthy son who, however, complained of severe acroparesthesia since childhood and had many angiokeratomas in the inguinal area, as well as his on the lips and fingertips (Fig. 1b).

Lab workup showed mild renal impairment (estimated glomerular filtration rate of 73 mL/min/1.73 m^2) and mild proteinuria (300 mg/day); BNP of 105 pg/mL; and a slight increase in troponin (hs-TnI=0.024 ng/mL).

During the complete cardiological workup, the electrocardiogram showed sinus rhythm with a short PR interval (110 ms) (Fig. 3). The transthoracic echocardiography showed biventricular hypertrophic cardiomyopathy, with a significant dynamic gradient reaching up to 48 mm Hg at the Valsalva maneuver; the anterior mitral valve exhibited systolic anterior motion associated with moderate mitral regurgitation and turbulent flow in the left ventricular (LV) outflow tract. We also noted a normal LV ejection fraction, but with LV systolic longitudinal dysfunction characterized by low tissue velocities (septal S' 5 cm/s, septal e' 3 cm/s) and a mildly decreased global longitudinal strain (GLS) of −17.8% (Fig. 4, Video 1).

Based on the association of HOCM with short PR interval, proteinuria, perioral angiokeratoma and acroparesthesia, and
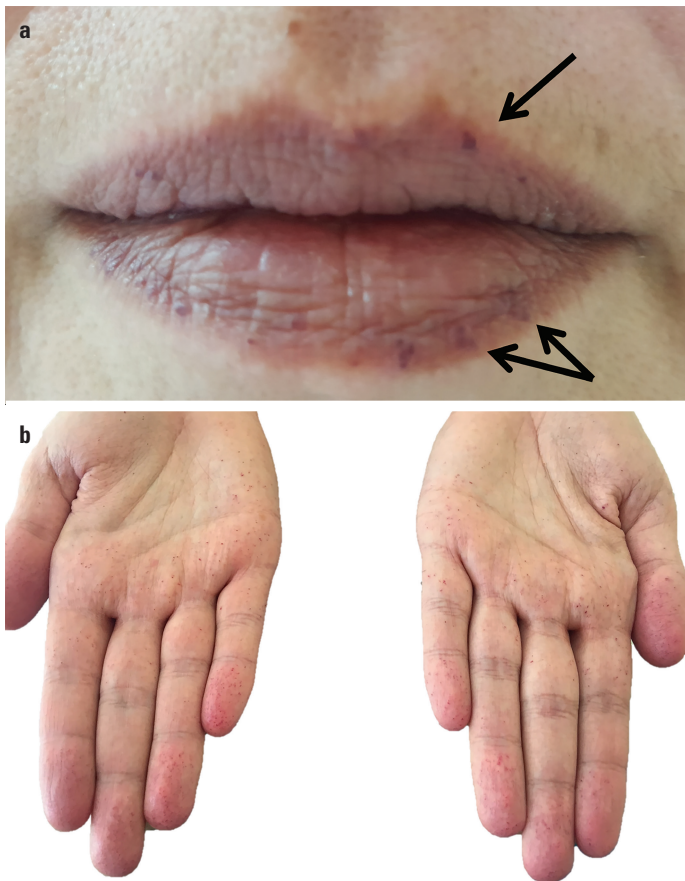
Figure 1. (a) Perioral angiokeratomas in the index patient (arrows). (b) Palmar angiokeratomas in the patient's son
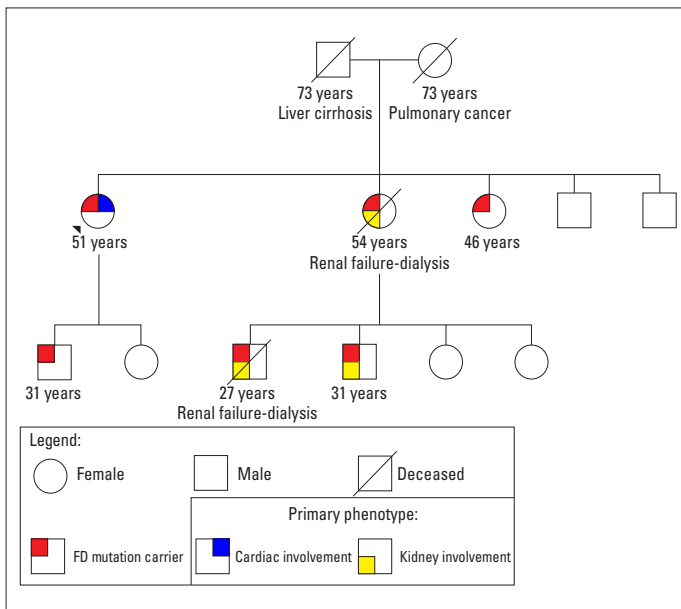

Figure 2. Family pedigree: the index patient is marked with the arrowhead. Her son has neurological symptoms. One of her sisters and her son died as they had kidney disease at the dialysis stage, while her second son has chronic kidney disease. Another sister is mutation positive, but phenotype negative. Patient subtext: current age/age at the time of death and assumed cause of death
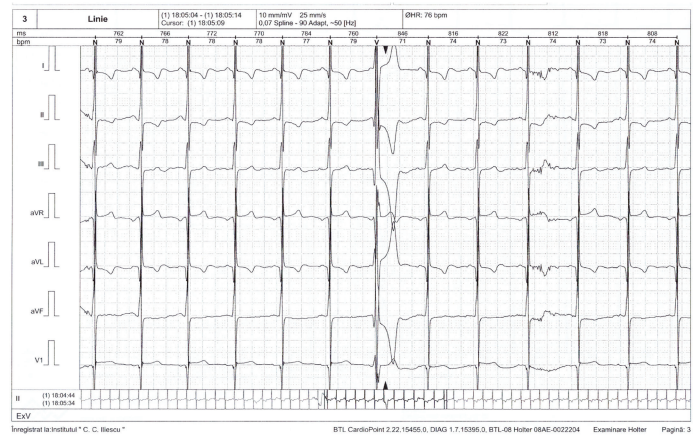

Figure 3. Electrocardiogram: the sinus rhythm, a short PR interval (~110 ms) without the delta wave, left ventricular hypertrophy criteria with secondary repolarization changes, and a ventricular extrasystole
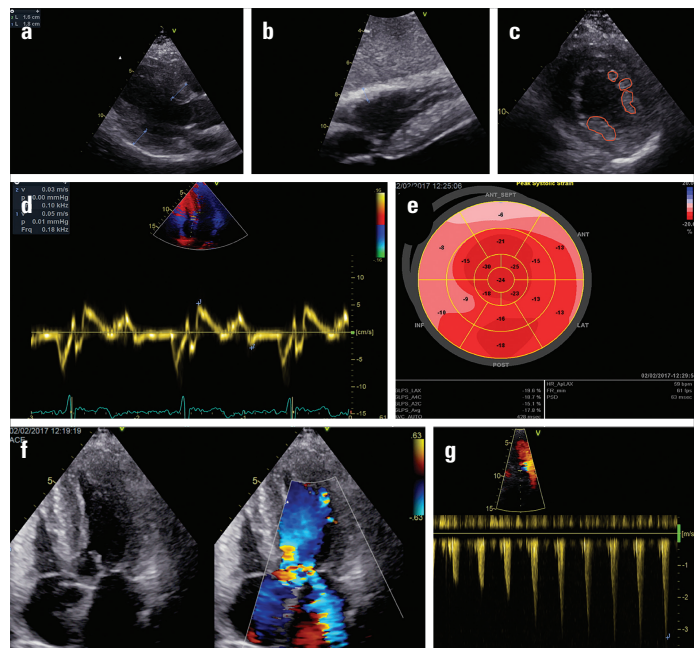

Figure 4. Transthoracic echocardiography. (a) Parasternal long-axis view: asymmetrical LV hypertrophy (interventricular septum, 20 mm; posterior wall, 17 mm); (b) Subcostal view focused on the right ventricle (RV) indicating mild RV hypertrophy (RV-free wall thickness, 7 mm); (c) Parasternal short-axis view: hypertrophic and supranumerary papillary muscles marked by red contour. (d) Pulsed-wave tissue Doppler (septal site) showing reduced myocardial velocities: S'=5 cm/s, e'=3 cm/s. (e) Speckle tracking echocardiography showing the LV longitudinal strain map ("bull's eye"): mild global impairment (GLS=−17.8%) with a predominant decrease at the septal and anterior wall level. (f) Systolic anterior motion of the anterior mitral leaflet with turbulent flow in the LVOT and moderate mitral regurgitation. (g) Continuous-wave Doppler interrogation of the LVOT, showing a peak resting gradient of 10 mm Hg, increasing up to 48 mm Hg during the Valsalva maneuver

the pedigree with severe renal disease cases, we had a high level of suspicion of FD, which was also based on the finding of cornea verticillate at ophthalmologic examination (Fig. 5) (4). Specific lab tests for FD found borderline α-galactosidase levels at 1.2 μmol/
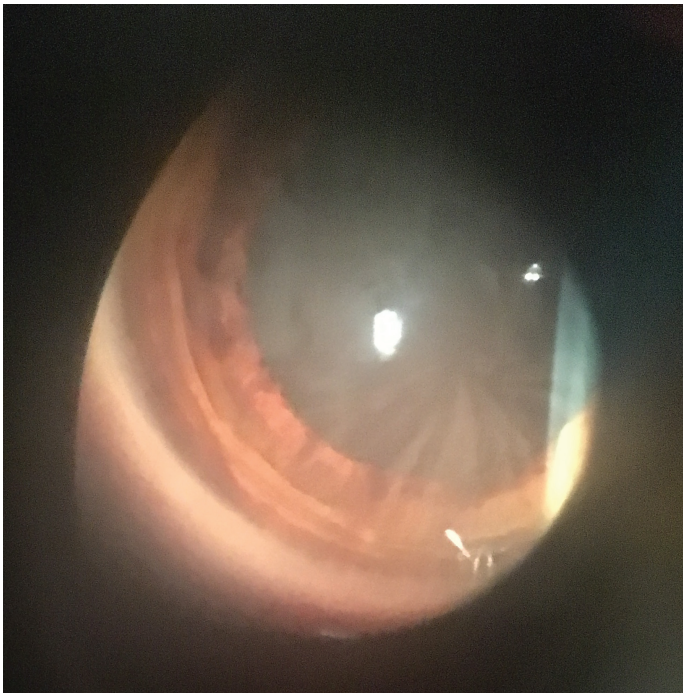
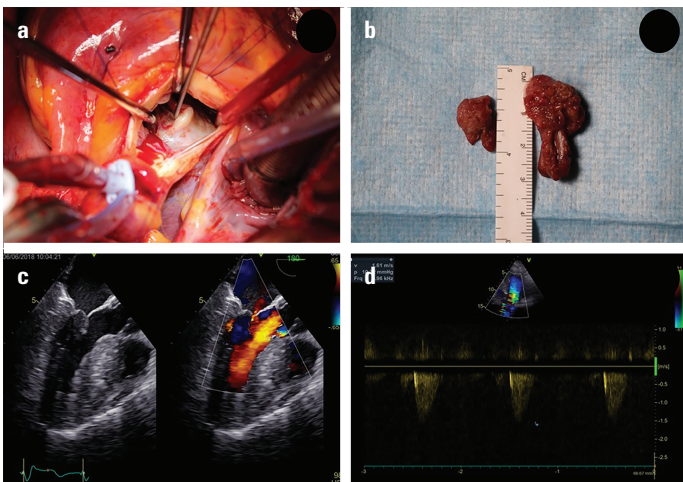**Figure 5.** Cornea verticillate at an ophthalmologic examination

Figure 6. Intraoperative aspects and postoperative echocardiography. (a) Transaortic approach that showed multiple secondary chordae at the level of the anterior mitral leaflet. (b) Two myectomy specimens, the larger one from the anterior septum and the smaller one from the inferior septum extended transaortic myectomy (dimensions of 3.4/1.3/0.6 cm and 2.0/1.0/0.4 cm, respectively). (c) A TEE midesophageal long-axis view in late systole showing residual mild mitral regurgitation, without turbulence in the LVOT. (d) TTE–continuous-wave interrogation of the LVOT with no residual gradient after surgery, neither at rest, nor with the Valsalva manuver

L/h (normal >1.2), increased lyso-Gb3 at 6.7 ng/mL (normal <3.5), and detected a previously described pathogenic missense mutation in the exone 5 of the *GLA* gene c[797A>C] (p[Asp266Ala]). As an obstructive form of hypertrophic cardiomyopathy is quite infrequent in FD, the patient was also tested for sarcomeric gene mutations by the next-generation sequencing gene panel, but no other mutation was detected.

Therapeutic management included an angiotensin receptor blocker for limiting proteinuria; enzyme replacement therapy (ERT) with agalsidase β was started at a dose of 1 mg/kgc every 2 weeks. The patient remained symptomatic, and after follow-up, the LVOT gradient had become more severe. Thus, we established the formal indication for invasive septal reduction therapy. The patient underwent surgical septal myectomy and mitral valvuloplasty (with careful mobilization of the papillary muscles and resection of several fibrotic secondary mitral valve chordae) (5), with good results (no residual obstruction or mitral regurgitation) (Fig. 6, Video 2) and an uneventful postoperative recovery. The pathologic specimen of myectomy only showed features specific to FD.

Upon further family screening, the patient's 27-years-old son was also diagnosed as genotype positive, with no residual enzymatic activity, presenting with acroparesthesia, numerous angiokeratomas, and anhidrosis, but without cardiac or renal impairment, and was started on ERT. The patient's other sister was also a carrier, without cardiac, neurologic, or renal impairment, even while displaying a low residual enzymatic activity (0.4 µmol/L/h) with high lysoGb3 (10.7 ng/mL), and was followed yearly to determine the ERT indication. However, her second nephew (the other son of the patient's deceased sister) presented with severe renal involvement (eGFR of 27 mL/min/1.73 m² at diagnosis), angiokeratoma, acroparesthesia, and mild cardiac hypertrophy (possibly of mixed origin - FD and hypertensive heart disease). Even if he was granted ERT rapidly, his renal failure quickly progressed, and he was put on hemodialysis a few months later.

Discussion

The present case illustrates several caveats of the FD diagnosis. First, the main reason for presentation can be less typical, since most FD patients exhibit non-obstructive, concentric hypertrophic cardiomyopathy; however, red flags found during workup should always be taken into consideration. Second, the same mutation can have various clinical expressions in different family members, as was the case in this family: the index patient had severe cardiac disease, her son had mild neurologic features, one sister and her two sons had severe renal disease, whereas her second sister of similar age is a healthy carrier.

Cardiac involvement is one of the main mortality causes in FD. Generally, cardiac involvement is manifested by LV hypertrophy, which occurs rarely in children and is detected on average in men around the age of 40 and later in women (3). The hypertrophy is generally concentric, but in some cases, asymmetric septal hypertrophy can be seen, the obstructive form being rare, but possible (6). Multimodality imaging used in the cardiac evaluation of FD range from two-dimensional and strain echocardiography to cardiac magnetic resonance (CMR), cardiac scintigraphy, and positron emission tomography (7). Imaging red flags for the FD diagnosis include concentric non-obstructive LVH with possible posterior wall basal thinning, prominent hypertrophy

of the papillary muscles (8), low longitudinal strain, involving basal posterolateral segments (9); late gadolinium enhancement, mostly distributed to the posterolateral basal level; and decreased T1 and extracellular volume by T1 mapping at CMR (10). The electrocardiogram (ECG) can be very useful in detecting early heart involvement in FD. Namdar et al. analyzed the ECG of a group of 30 patients diagnosed with FD and found four parameters that may indicate early cardiac damage: the short PQ interval and QRS duration, increased dispersion of repolarization, and a considerably reduced P-wave duration (11). In advanced stages of cardiac involvement, the ECG shows LV hypertrophy, which may be associated with the rhythm or conduction disorders: atrial fibrillation, sustained or non-sustained ventricular tachycardia, atrioventricular block of varying degrees, and intraventricular conduction blocks.

The renal involvement in FD is characterized by proteinuria and progressive decrease in renal function caused by the Gb3 accumulation, especially in the podocytes. Therefore, proteinuria might be the first manifestation of kidney damage in FD. A German study has shown the correlation between high levels of proteinuria and a rapid progression of renal dysfunction, with a cutoff value of the urinary protein/creatinine ratio >1.5 (2). Initial proteinuria, an initial low GFR, hypertension, and male gender are associated with a faster evolution of Fabry nephropathy (12).

The prognosis of patients with FD is affected, with a life expectancy significantly lower mainly in untreated patients, according to the Fabry International Registry (13). The progression of renal disease in patients treated with ERT is related, to some extent, to the severity of the disease prior to treatment. Thus, ERT initiation before the development of significant glomerulosclerosis and proteinuria is the key to preventing renal impairment (14). Regarding cardiac effects, the ideal treatment goal is to achieve the normalization of LV hypertrophy, but this is probably unachievable in most patients, particularly in those with myocardial fibrosis (15, 16). Therefore, a more realistic goal is to prevent the progression of LVH on the unproven assumption that this translates into an improved patient outcome (17). However, it is still not completely clear why some patients under ERT have a positive evolution, while others progress to renal, cardiovascular, and/or cerebrovascular dysfunction.

Another important observation is the phenotypic variability of the disease in the same family. The heterozygous mutation detected in all living members of this family affected by FD (c.[797A>C] or p.[Asp266Ala]) is a missense mutation first described in 2013 by Tian et al. (18), but it maintains an uncertain significance in databases. However, based on the previous report and considering the fact that this mutation is present in all affected individuals in the family, we can classify it as likely pathogenic. Because our patient does not present other sarcomeric gene mutations, and the pathological result of the myectomy specimens was compatible with FD, it appears that HOCM was a rare phenotypic form of Fabry cardiomyopathy. Such phenotypic intrafamilial variability reminds us about the possible involvement of modulators in the FD pathophysiology, unrelated to α-GalA and Gb3 accumulation, such as genetic and

environmental factors. Several studies reported the association of single-nucleotide polymorphisms or mutations in inflammatory and coagulation factor genes, such as interleukin 6, endothelial nitric oxide synthase, the factor V, and the gene encoding the vitamin-K-dependent protein Z, with an increased risk of cerebral lesions and stroke in patients with FD (19-21). Of note, the residual enzymatic activity alone does not appear to be the main phenotype determinant (as the presymptomatic carrier appears to have lower enzyme levels and higher lysoGb3 than her affected sister).

The high variability in clinical manifestations of FD can also lead to delays between the symptom onset and correct diagnosis, and between the correct diagnosis and ERT initiation. Analyzing the Fabry Outcome Survey data, Reisin et al. (22) compared patients with FD pooling the time intervals 2001–2006 vs. 2007–2013 and found that, while the delay in diagnosis did not improve substantially, the delay in treatment onset improved in recent years. This is in contrast to the known fact that better outcomes may be observed when treatment is started at an early age prior to the development of organ damage, such as chronic kidney disease or cardiac fibrosis (23). This was also the case in the present family, as there was a large delay between the first presentation in the index patient (diagnosed with HOCM several years ago), as well as her relatives (two deaths while on hemodialysis without etiologic diagnosis).

Conclusion

This case presentation of a family with FD highlights several issues. First, in a systemic genetic disease, the diagnostic workup should take into consideration any possible multiorgan involvement based on a solid knowledge of disease markers, and without the preconception of one typical phenotype. Second, cascade genetic family screening is very important, as there can be a very wide variability in the clinical presentation. Early diagnosis is essential for a timely initiation of specific therapy.

Video 1. Preoperative transesophageal echocardiography–mid esophageal long axis view: interventricular septal hypertrophy, elongated anterior mitral valve with systolic anterior motion; right panel with color Doppler showing turbulence in the left ventricular outflow tract and moderate mitral regurgitation

Video 2. Postoperative transesophageal echocardiography–mid esophageal long axis view: after septal myectomy and mitral valvuloplasty we note a reduced thickness of the interventricular septum with no turbulence in the left ventricular outflow tract, as well as a shortened anterior mitral valve with good coaptation and minimal residual mitral regurgitation

References

1. Mehta A, Widmer U. Natural history of Fabry disease. Fabry Disease: Perspectives from 5 Years of FOS. Mehta A, Beck M, Sunder-Plassmann G, editors. Oxford: Oxford PharmaGenesis; 2006.
2. Wanner C, Oliveira JP, Ortiz A, Mauer M, Germain DP, Linthorst GE, et al. Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry. Clin J Am Soc Nephrol 2010; 5: 2220-8.
3. Kampmann C, Linhart A, Baehner F, Palecek T, Wiethoff CM, Miebach E, et al. Onset and progression of the Anderson–Fabry disease related cardiomyopathy. Int J Cardiol 2008; 130: 367-73.
4. Rapezzi C, Arbustini E, Caforio ALP, Charron P, Gimeno-Blanes J, Heliö T, et al. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013; 34: 1448-58.
5. Ferrazzi P, Spirito P, Iacovoni A, Calabrese A, Migliorati K, Simon C, et al. Transaortic Chordal Cutting: Mitral Valve Repair for Obstructive Hypertrophic Cardiomyopathy With Mild Septal Hypertrophy. J Am Coll Cardiol 2015; 66: 1687-96.
6. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. Heart 2007; 93: 528-35.
7. Militaru S, Ginghină C, Popescu BA, Săftoiu A, Linhart A, Jurcuţ R. Multimodality imaging in Fabry cardiomyopathy: from early diagnosis to therapeutic targets. Eur Heart J Cardiovasc Imaging 2018; 19: 1313-22.
8. Niemann M, Liu D, Hu K, Herrmann S, Breunig F, Strotmann J, et al. Prominent papillary muscles in Fabry disease: a diagnostic marker? Ultrasound Med Biol 2011; 37: 37-43.
9. Krämer J, Niemann M, Liu D, Hu K, Machann W, Beer M, et al. Two-dimensional speckle tracking as a non-invasive tool for identification of myocardial fibrosis in Fabry disease. Eur Heart J 2013; 34: 1587-96.
10. Kammerlander AA, Marzluf BA, Zotter-Tufaro C, Aschauer S, Duca F, Bachmann A, et al. T1 Mapping by CMR Imaging: From Histological Validation to Clinical Implication. JACC Cardiovasc Imaging 2016; 9: 14-23.
11. Namdar M, Steffel J, Vidovic M, Brunckhorst CB, Holzmeister J, Lüscher TF, et al. Electrocardiographic changes in early recognition of Fabry disease. Heart 2011; 97: 485-90.
12. Schiffmann R, Warnock DG, Banikazemi M, Bultas J, Linthorst GE, Packman S, et al. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrol Dial Transplant 2009; 24: 2102-11.
13. Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. Genet Med 2009; 11: 790-6.
14. Germain DP, Charrow J, Desnick RJ, Guffon N, Kempf J, Lachmann RH, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J Med Genet 2015; 52: 353-8.
15. Krämer J, Niemann M, Störk S, Frantz S, Beer M, Ertl G, et al. Relation of burden of myocardial fibrosis to malignant ventricular arrhythmias and outcomes in Fabry disease. Am J Cardiol 2014; 114: 895-900.
16. Beer M, Weidemann F, Breunig F, Knoll A, Koeppe S, Machann W, et al. Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. Am J Cardiol 2006; 97: 1515-8.
17. Wanner C, Arad M, Baron R, Burlina A, Elliott PM, Feldt-Rasmussen U, et al. European expert consensus statement on therapeutic goals in Fabry disease. Mol Genet Metab 2018; 124: 189-203.
18. Tian ML, Yan YL, Xiong JC, Liu XX, Yang Y, Hu ZX. [Genetic and clinical study of three Chinese pedigrees with Fabry disease]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2013; 30: 185-8.
19. Altarescu G, Chicco G, Whybra C, Delgado-Sanchez S, Sharon N, Beck M, et al. Correlation between interleukin-6 promoter and C-reactive protein (CRP) polymorphisms and CRP levels with the Mainz Severity Score Index for Fabry disease. J Inherit Metab Dis 2008; 31: 117-23.
20. Altarescu G, Moore DF, Schiffmann R. Effect of genetic modifiers on cerebral lesions in Fabry disease. Neurology 2005; 64: 2148-50.
21. Heltianu C, Costache G, Azibi K, Poenaru L, Simionescu M. Endothelial nitric oxide synthase gene polymorphisms in Fabry's disease. Clin Genet 2002; 61: 423-9.
22. Reisin R, Perrin A, García-Pavía P. Time delays in the diagnosis and treatment of Fabry disease. Int J Clin Pract 2017; 71. doi: 10.1111/ijcp.12914.
23. Germain DP, Elliott PM, Falissard B, Fomin VV, Hilz MJ, Jovanovic A, et al. The effect of enzyme replacement therapy on clinical outcomes in male patients with Fabry disease: A systematic literature review by a European panel of experts. Mol Genet Metab Rep 2019; 19: 100454.

Address for Correspondence: Ruxandra Jurcut, MD,
Department of Cardiology,
The Expert Center for Rare Genetic Cardiovascular Diseases,
Euroecolab, Emergency Institute for Cardiovascular Diseases
"Prof. Dr. C.C. Iliescu"; Sos Fundeni No 258 02232,
Bucharest-*Romania*
Phone: +4 072 450 64 34
E-mail: rjurcut@gmail.com