# Fabry disease in adults

## KEY QUESTIONS

### Multidisciplinary Iberian document


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With the Scientific Endorsement of the Spanish and Portuguese Societies:

SEMI Sociedad Española de Medicina Interna. La visión global de la persona enferma

Con el aval científico de Sociedad Española de Nefrología

SEN Sociedad Española de Neurología

SPMI Sociedade Portuguesa de Medicina Interna

SPN Sociedade Portuguesa de Nefrologia

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# When should I suspect a case of Fabry disease (FD)?

## A. Clinical suspicion of FD in adults

FD is an X-linked lysosomal storage disorder, caused by mutations in the gene that encodes the lysosomal enzyme alfa-galactosidase A (the *GLA* gene).

Mutations in the *GLA* gene cause reduced or absent activity of the α-galactosidase A (α-Gal A) enzyme which results in the progressive accumulation of globotriaosylceramide (GL3 or Gb3) and its deacylated form, globotriaosylsphingosine (lyso-GL3 or Lyso-Gb3), in plasma, urine and a wide range of cells throughout the body. This accumulation is most relevant in vascular endothelial cells, podocytes, cardiomyocytes, arterial smooth muscle cells and other cell types in the kidneys, nervous system, and other organs (1).

FD is clinically heterogeneous and slowly progressive. This disease can be divided into a classical phenotype, most often seen in men without residual enzyme activity, and into a non-classical phenotype, also known as late onset phenotype (Table 1). Patients with classical FD usually present characteristic FD signs and symptoms with onset in childhood or adolescence, such as neuropathic pain, cornea verticillata, and angiokeratoma; although more non-specific, they also frequently present gastrointestinal (GI) symptoms and other disturbances related with the peripheral nervous system (sweating abnormalities). Long–term **classical FD** and late-onset FD manifest in adults with progressive renal failure, hypertrophic cardiomyopathy, heart rhythm disturbances, and stroke. Men with **non-classical FD** typically have residual enzyme activity and lower levels of lyso-Gb3. This late-onset FD is characterized by a more variable disease course, in which disease manifestations may be limited to a single organ. This is even more true for female patients in whom, due to the lyonization phenomenon, the disease spectrum ranges from being asymptomatic or having mild, later-onset phenotypes to the severe classical phenotype (as observed in male patients) (2,5-7).

Thus, **adult patients with FD** are often identified in screening studies of individuals with stroke, chronic kidney disease or hypertrophic cardiomyopathy.

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## Table 1. Criteria for phenotypic classification of FD.

*Source*: adapted from Arends M, Wanner C, Hughes D, et al., Characterization of classical and nonclassical Fabry disease: a multicenter study, J. Am. Soc. Nephrol. 28 (2017) 1631-1641 (2).

| Phenotype | Men | Women |
|---|---|---|
| Classical FD | | |
| | • A mutation in the GLA genea.<br>• One or more of the following characteristic FD symptoms: Fabry neuropathic pain, angiokeratoma, and/or cornea verticillata.<br>• Severely decreased or absent leukocyte aGAL activity (<5% of the normal mean). | • A mutation in the GLA gene[a]<br>• One or more of the following characteristic FD symptoms: Fabry neuropathic pain, angiokeratoma, and/or cornea verticillata |
| Nonclassical FD | | |
| | A mutation in the GLA gene and not fulfilling the criteria for classical FD | |

aGAL, α-galactosidase A. [a]In this paper (2), certain genetic variants (A143T*, P60L, D313Y, R118C*, T385A, IVS0-10>T, and the complex haplotype IVS0-10C>T/IVS4-16A>G/IVS6-22C>T) were considered non-FD (neutral variants). In patients in whom classification on the basis of these criteria was not feasible, the final judgement was made by the treating physician.
*Pathogenicity of these variants is still contradictory in the literature: for example, A143T results in a variant of uncertain significance (VUS) in a recent paper (3); R118C is described as pathogenic in a recent publication (4).

Indications for screening for Fabry nephropathy are, according to the ERBP guidelines 2012 (8):

- Male patients with chronic kidney disease (CKD) under 50 years of age in whom a reliable renal diagnosis is absent (ungraded statement).
- Females with unexplained CKD, irrespective of age, with other unexplained symptoms potentially associated with FD (ungraded statement).

Arterial hypertension should not be an exclusion criterion as more than 50% of FD patients have mild-to-moderate hypertension, especially when the estimated glomerular filtration rate (eGFR) is < 60 ml/min/1,73 $m^2$ (9-11).

Given the above, if we focus on adults, clinical suspicion tends to appear linked to kidney and/or cardiac and/or central nervous system (CNS) symptoms, which cannot be explained by the most prevalent diseases or by common

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risk factors. Also, the finding of characteristic classical phenotype signs and symptoms should raise suspicion (1,12) (see the summary).

## B. Family suspicion

When the diagnosis of a new patient with FD appears, clinical and genetic screening of the at-risk members of his/her family is of critical importance. The X-linked nature of FD inheritance renders cascade screening of families efficient and of high diagnostic yield over, on average, three generations surrounding an index case (13). One pedigree review study found that, on average, there were at least five family members diagnosed with FD following the diagnosis of a proband (14). These family members may be diagnosed relatively early in the disease process. There are web-based tools that facilitate the building of a pedigree. The pedigree nomenclature of the National Society of Genetic Counselors (NSGC) should be used (15).

Also, genetic counseling must be provided to address all related personal, cultural or ethics issues (10,13). Once a genetic diagnosis has been made, patients should undergo a full clinical evaluation and appropriate management (1).

**SUMMARY:**
**clinical suspicion should be raised in adult patients with any of these signs and symptoms**

- Left ventricular hypertrophy of unknown etiology, arrhythmia (suspicion should be raised even in hypertensive patients).
- Chronic kidney disease of unknown etiology, microalbuminuria, proteinuria (suspicion should be raised even in hypertensive patients).
- Cryptogenic stroke in young adults.
- Angiokeratomas.
- Pain in the extremities (differential diagnosis of rheumatic disorders, fibromyalgia) (16).
- Cornea verticillata.
- GI symptoms of unknown etiology (Diarrhea-predominant irritable bowel syndrome (IBS) is a differential diagnosis).

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# 2 How do I confirm a diagnosis of FD?

In males, the primary test for the diagnosis of FD is the **activity of the α-Gal A enzyme**. α-Gal A activity testing alone is diagnostic for male patients, if it is < 5% of the normal range. Otherwise, even in male patients, ***GLA* gene sequencing** should be performed to confirm diagnosis (Figure 1) (12). Confirmation of the disease-causing *GLA* mutation is important to help establish the disease phenotype and to rule out benign polymorphisms that cause reduced levels of α-Gal A activity (1).

In female patients, evidence of the presence of a disease-causing mutation in the *GLA* gene is required as the enzyme activity is often found within the normal range (12).

Enzymatic activity is usually measured in plasma, dried blood spot (DBS) testing or leukocytes. This last one is considered the gold-standard to measure alfa-Gal A activity (1).

Molecular studies of *GLA* variants have identified a remarkable variety of variants (more than 1000) underlying the phenotypic heterogeneity of this genetic disorder (3).

For patients with a *GLA* variant of unknown significance (VUS), clinical, biochemical or histopathological evidence of FD is required to determine the pathogenic nature of the mutation, particularly when the clinical signs are nonspecific and alternative or additional diagnoses are under consideration. The finding of increased **plasma and/or urinary GL3**, or **plasma and/or urinary lyso-GB3** and its analogues in the evaluation of male or female patients with a VUS and normal (in female patients) or lowered α-Gal A activity provides additional diagnostic information but the role of biomarkers in such patients still requires validation (1). Normal plasma or urine GL3 or plasma lyso-Gb3 levels in these cases do not rule out the disease (6,18,19).

Evidence of lysosomal GL3 accumulation in **skin, renal or cardiac biopsies,** though invasive, may be required when the interpretation of genetic *GLA* mutation is challenging and of unknown pathogenic significance (20-22). Identification of **typical lysosomal inclusions** in tissue biopsy specimens (referred to as ***zebra bodies***, in electron microscopy) (Image 5) has been suggested as the gold standard of

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Fabry disease diagnosis. However, it should be noted that inclusions are not specific to FD. They may occur in other lysosomal storage diseases such as GM2 gangliosidosis and Niemann-Pick disease and have also been demonstrated in silicon nephropathy. In addition, various drugs including amiodarone, chloroquine and hydroxychloroquine may also mimic phospholipidosis of Fabry disease (23). Conversely, the Gb3 level may be increased in the absence of lysosomal inclusions. **Tissue Gb3** elevation can be demonstrated by immunohistochemistry in a tissue biopsy specimen using the anti-Gb3 antibody or using mass spectrometry (24).

In addition, **family history** can predict pathogenicity for a *GLA* VUS. The advice of an expert in genetics and the management of Fabry disease should be sought for interpretation of the pathogenicity of any VUS (1).

Characteristic patterns of neuropathic pain, angiokeratomas and/or cornea verticillata can support a FD diagnosis (1).

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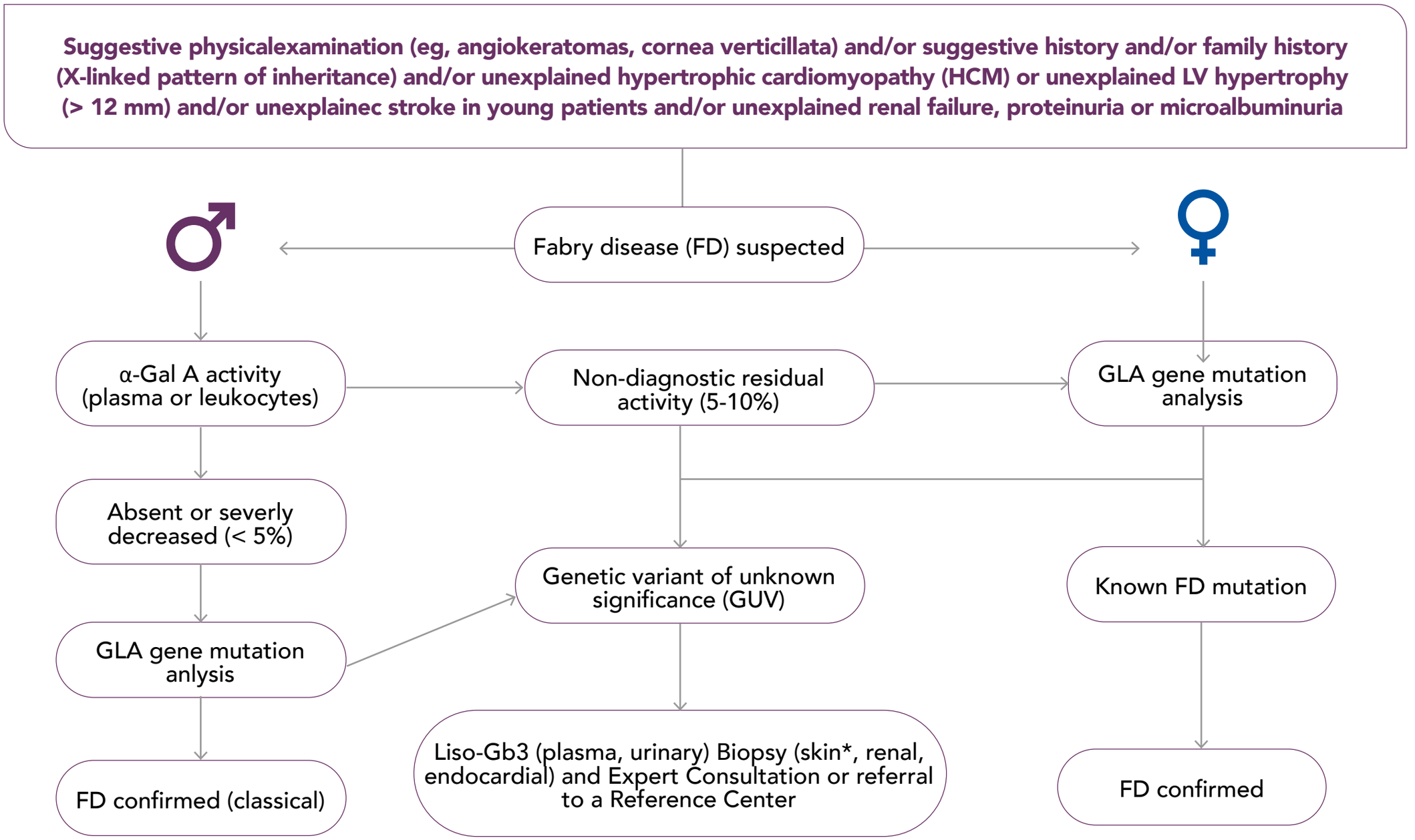
# How do I confirm a diagnosis of FD?




*Punch biopsy, taken from proximal (thigh: 15 cm above the patella) and distal (leg: 10 cm above the lateral malleolus) hairy skin sites or from other lesions to evaluate Gb3 deposits, and for other histopathological evaluations.

**Figure 1. Updated diagnostic algorithm for FD.**

*Source*: adapted from Vardarli I, Rischpler C, Herrmann K, et al. Diagnosis and Screening of Patients with Fabry Disease. Ther Risk Manag. 2020 Jun 22;16:551-8 (17).

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# When should I start specific treatment for FD in adults?

It has become increasingly clear that comprehensive and timely treatment of adult patients with FD should be directed toward the prevention of (further) progression to irreversible tissue damage and organ failure. Care should include specific treatment and adjunctive therapies to treat symptoms that arise due to tissue injury and prevent non-specific progression of tissue injury. Treatment and follow-up assessments to evaluate treatment responses should ideally be supervised by a physician experienced in the management of patients with FD, with input from sub-specialists who also have FD experience, as part of a multidisciplinary clinical team that ideally should include a neurologist, a nephrologist, a cardiologist, a internist, a ophthalmologist, a dermatologist, a medical geneticist, a genetic counselor, a psychologist, a nurse and a pharmacist (1, 25).

In 2015, an article was published with the recommendations of a group of European experts about the initiation of enzyme replacement therapy (ERT) (26). The group agreed that a differentiation should be made between male and female patients, and between patients with classical and non-classical FD. Later in 2018, another group of international Fabry experts published a new document with recommendations specifically for the adult patient, reaching similar conclusions (1). Based on these last recommendations for males with classical FD, treatment with specific treatment may be considered even if they have no symptoms or clinical signs of organ involvement. For classical cases in females, specific treatment is warranted when symptoms are present. For the rest of females (classic without symptoms and later-onset FD), and for later-onset FD males, as well as for patients with VUS, a specific treatment should be considered if there is laboratory, histological or imaging evidence of injury to the kidney, the heart or the CNS, even in the absence of typical Fabry symptoms. The abnormalities should be attributable to Fabry disease, after other causes have been excluded (see Table 2) (1).

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## Table 2. Recommendations for initiation of specific treatment in adult Fabry patients.

*Source*: adapted from Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Managment and treatment recommendations for adult patienst. Mol Genet Metab. 2018 Apr;123(4):416-27 (1). Used under CC BY. Licensed under CC BY by Dr. Patricio Aguiar, Dr. Miguel F. Gago, Dr. María Guedes Marques, Dr. Álvaro Hermida, Dr. Raúl Jesús Noguera Torregrosa, Dr. Tomás Pérez-Concha, Dr. José F. Rodríguez Palomares.

| Adult patient population | Recommendation for the initiation of specific treatment |
|---|---|
| **Classical Fabry mutation** | |
| Classical Fabry mutation. | • Specific treatment should be considered and is appropriate in all patients at any age of presentation. |
| Female patient, symptomatic. | • Signs/symptoms suggesting major organ involvement, warranting initiation of specific treatment:<br>– Neuropathic pain, pain crises, Fabry disease neuropathy.<br>– Proteinuria/albuminuria NOT attributable to other causes, evidence of renal impairment (may require renal biopsy if isolated).<br>– Stroke or TIA.<br>– Symptomatic cardiac disease not due to other causes (dyspnea, palpitations, syncope, chest pain).<br>– Recurrent diarrhea, chronic, disabling GI dysfunction (excluding alternative causes).<br>– Exercise intolerance and impaired sweating. |
| Female patient, asymptomatic. | • Specific treatment should be considered if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS:<br>– Renal disease: decreased GFR (< 90 ml/min/1.73 $m^2$ adjusted for age > 40 years (GFR category ≥ G2), persistent albuminuria > 30 mg/g [albuminuria category A2 or A3]), podocyte foot process effacement or glomerulosclerosis on renal biopsy, moderate or severe GL3 inclusions in a range of renal cell types.<br>– Silent strokes, cerebral white matter lesions (on brain MRI).<br>– Asymptomatic cardiac disease (cardiomyopathy or arrhythmia, cardiac fibrosis on contrast cardiac MRI). |

*(Continues on the next page)*

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## Table 2. Recommendations for initiation of specific treatment in adult Fabry patients (cont.).

| Adult patient population | Recomendación de inicio del tratamiento específico |
|---|---|
| **Later-onset Fabry mutation or missense *GLA* VUS** | |
| Male and female patients. | • Specific treatment should be considered and is appropriate if there is laboratory, histological or imaging evidence of injury to the kidney, heart or the CNS, as detailed above, even in the absence of typical Fabry symptoms. The abnormalities should be attributable to Fabry disease; this may require histological assessment or biochemical evidence of GL3 accumulation.<br>• The advice of an expert in genetics and management of Fabry disease should be sought for interpretation of the pathogenicity of any VUS. |

TIA: Transient Ischemic Attack; MRI: Magnetic Resonance Imaging; VUS: Variant of Uncertain Significance.

On the other hand, for the late onset subgroup, treatment should not be started in individuals with no demonstrable Fabry disease-related tissue pathology or clinical symptoms, particularly in heterozygous female patients. These patients should be monitored regularly by a multidisciplinary care team (1).

In addition, considerations for stopping or not starting specific treatment were discussed in the European Fabry Working Group consensus document (26) (see Table 3) (26). However, it should be noted that the clinical consequences of treatment cessation, compared with treatment continuation, remain to be clarified (1).

Treatment decisions in patients with advanced cardiac disease should be made on an individual basis, since there is no evidence to establish objective criteria that justify the discontinuation or non-initiation of treatment.

Finally, individuals with well characterized benign *GLA* polymorphisms should not be treated (1).

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## Table 3. Recommended criteria for stopping or not starting specific treatment in adult Fabry patients.

*Source*: adapted from Biegstraaten M, Arngrimsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. Orphanet J Rare Dis. 2015 Mar 27;10:36 (26).

| Stop criteria |
|---|
| • Non-compliance*.<br>• Failure to report regularly (according to local guidelines) to follow-up visits.<br>• Persistent life-threatening or severe reactions that do not respond to prophylaxis, e.g. anaphylaxis**.<br>• Patient request.<br>• End stage FD or other comorbidities with a life expectancy of < 1 year.<br>• Severe cognitive decline of any cause.<br>• Lack of response for 1 year when the sole indication for specific treatment is neuropathic pain while receiving maximum supportive care (except for classical males). |
| **Criteria for not initiating specific treatment** |
| • End stage FD or other comorbidities with a life expectancy of < 1 year.<br>• Severe cognitive decline of any cause. |

*Based on the criteria of each physician, since there is no objective evidence for established criteria of non-compliance; **An alternative therapeutic approach may be considered.
NOTE: Migalastat is not recommended in patients with eGFR below 30 ml/min/1.73 $m^2$;
FD: Fabry disease.

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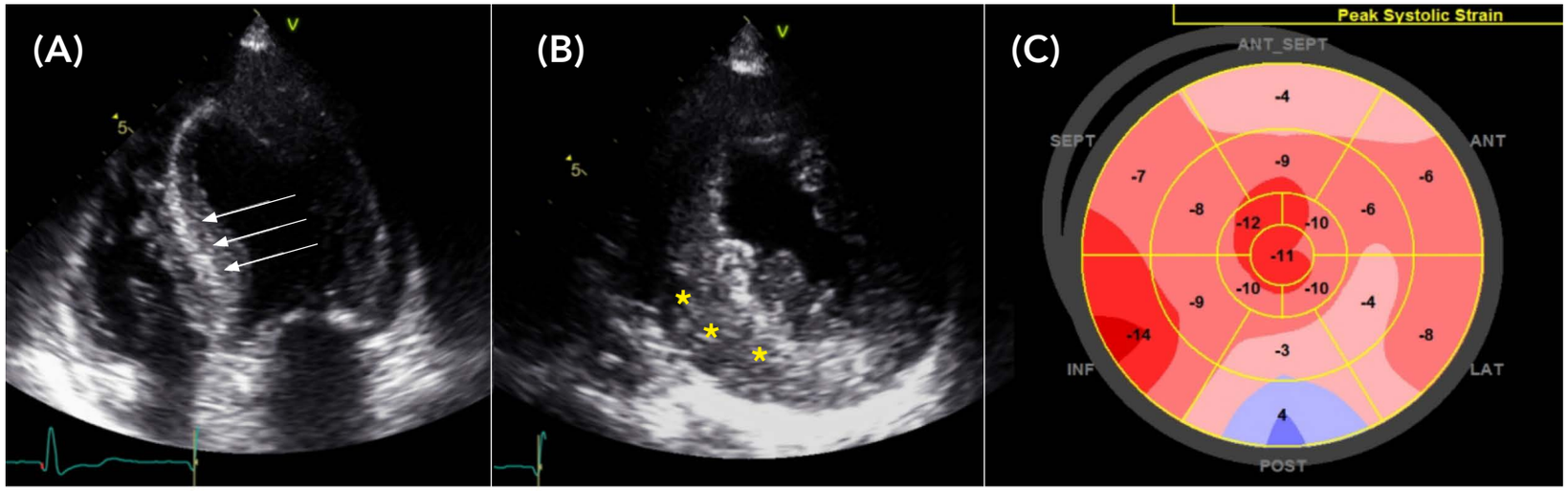
# 4 How can I demonstrate cardiac involvement in FD?

Clinical evidence of Fabry cardiac involvement may include dyspnea, palpitations, syncope or angina, depending on the cardiac tissue involved. These symptoms appear normally in advanced cardiac disease as a consequence of tissue damage accumulated over time. The challenge is to identify signs of cardiac disease prior to the onset of symptoms or to demonstrate that the symptoms are due to Fabry disease (27,28).

**Left ventricular hypertrophy (LVH)** is the hallmark of FD, detected both by **electrocardiography** (**ECG**) (LVH voltage criteria) and imaging techniques (echocardiography [Image 1], cardiac magnetic resonance imaging [CMR]) (29,30). Histologically, hypertrophy is characterized by the absence of myofibrillar disarray, lysosomal inclusions within myofibrils and vascular structures, and a variable degree of fibrosis depending on the stage of the disease (31,32).

**IMAGE 1** Echocardiographic images of a patient with PE.

*Source*: image courtesy of Dr. José Rodríguez Palomares (author).




(**A**) Apical 4-chamber plane showing the presence of septal hyperrefringence compatible with the septal binary sign (arrows). (**B**) Infero-lateral hyperrefringence compatible with fibrosis at this level (*). (**C**) Bull's-eye representation of strain values in an advanced stage with more marked strain alterations at the inferior-lateral level, in the area of greatest fibrosis (blue area).

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## ECG abnormalities

A short PR interval without evidence of an accessory pathway, repolarization abnormalities and signs of LVH (voltage criteria and repolarization abnormalities – 'strain' pattern) are early ECG features which precede the development of overt structural abnormalities in the heart. In older patients, sinus bradycardia and progressive conduction disease in the atrioventricular (AV) node/bundle of His and distal conduction system are common and are an adverse prognostic marker. ST-segment depression and T-wave inversion may be associated with the presence of fibrosis (28).

Palpitations and arrhythmias are common complaints in patients with Fabry disease. The most frequently encountered rhythm abnormalities include supraventricular tachycardias, atrial fibrillation and flutter. Ventricular arrhythmias were found mostly in very advanced stages of the disease. Symptomatic patients should undergo 24-hour Holter monitoring to rule out ventricular arrhythmias and the need for an implantable cardioverter defibrillator (33).

Syncope may occur in patients with Fabry disease. Cardiac causes of syncope include high degrees of AV blockade or, more rarely, severe dynamic obstruction of the LV outflow tract (33).

Patients with Fabry disease have a significantly reduced coronary flow reserve (34,35). Most patients with Fabry disease who are examined for chest pain have patent large coronary arteries.

Although pulmonary valvular involvement has been reported, valvular changes are found almost exclusively in the left heart valves, probably due to the higher hemodynamic stresses in the left side of the heart (33,36). This results in valvular thickening and deformation. Valvular regurgitant lesions are usually mild to moderate and only rarely require surgical correction (3 cases out of 752 patients in FOS).

## Cardiovascular magnetic resonance imaging (CMR)

Is an important tool to evaluate cardiac involvement in FD, not only to assess LV mass with accuracy, but for additional and valuable information through (28):

### Late gadolinium enhancement (LGE) (Image 2)

With the use of gadolinium contrast agents, CMR can visualize myocardial fibrosis typically distributed in the mid-myocardial layer of the posterolateral wall (28). In some patients, particularly females, areas of replacement fibrosis are de-

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tectable before development of significant LVH. Detection of fibrosis makes it possible to identify patients who are at higher risk of adverse cardiac events (37), namely ventricular arrhythmias, and is associated with a worse prognosis, even during disease-specific treatment (28).

## T1 mapping (Image 3)

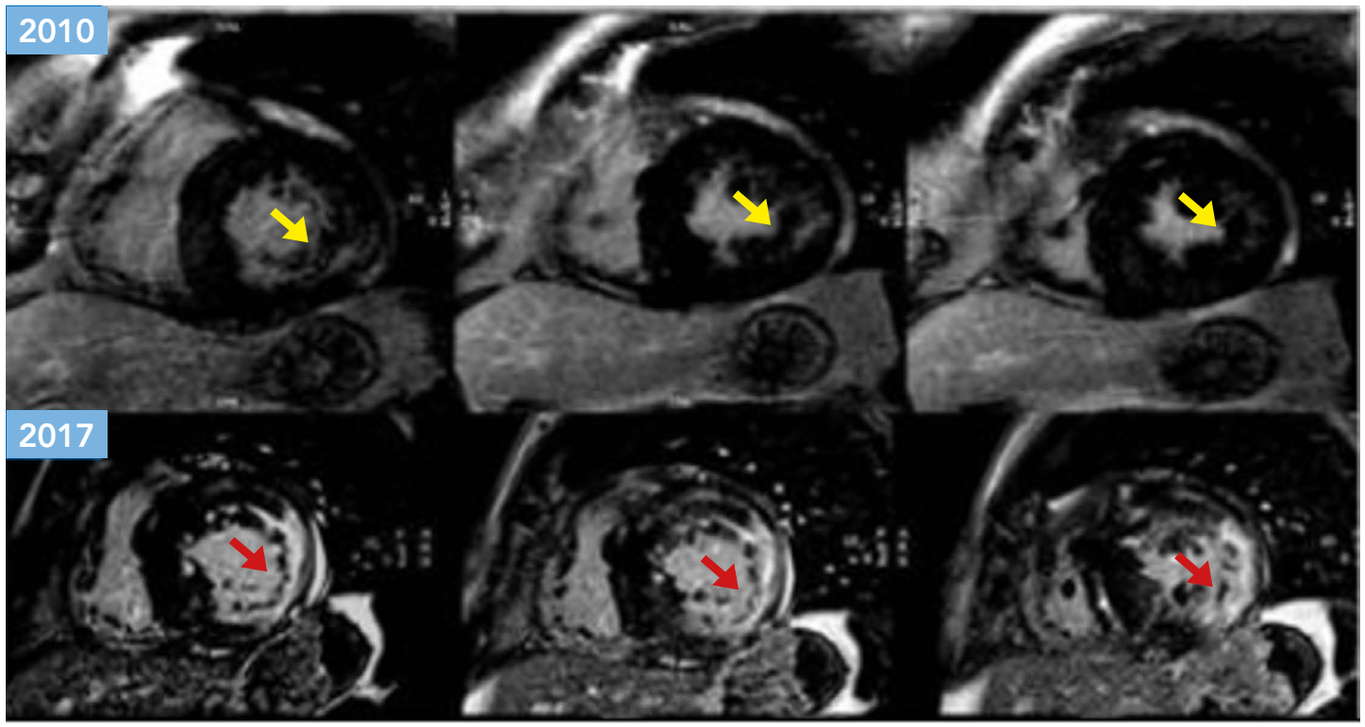
To identify early stages of the disease (38,39). Native T1 values are significantly decreased in early Fabry disease (40). Fat is known to possess a very low T1, so myocardial glycosphingolipid storage may be detected before the development of LVH (28,38).

## T2 mapping

It has demonstrated its relevance in Fabry disease since it allows to identify the presence of myocardial edema and inflammation that could be one of the possible etiologies of myocardial fibrosis in FD. Upon analyzing these sequences, we observed the presence of an increase in native T2 compared to controls (41).

**IMAGE 2** Short-axis late enhancement images of a patient with FD.

*Source*: image courtesy of Dr. José Rodríguez Palomares (author).




Presence of concentric hypertrophy and presence of late gadolinium enhancement at the level of the infero-lateral aspect (yellow arrows). Patient evolution from 2010 to 2017. The presence of increased fibrosis and wall thinning stands out (red arrows).

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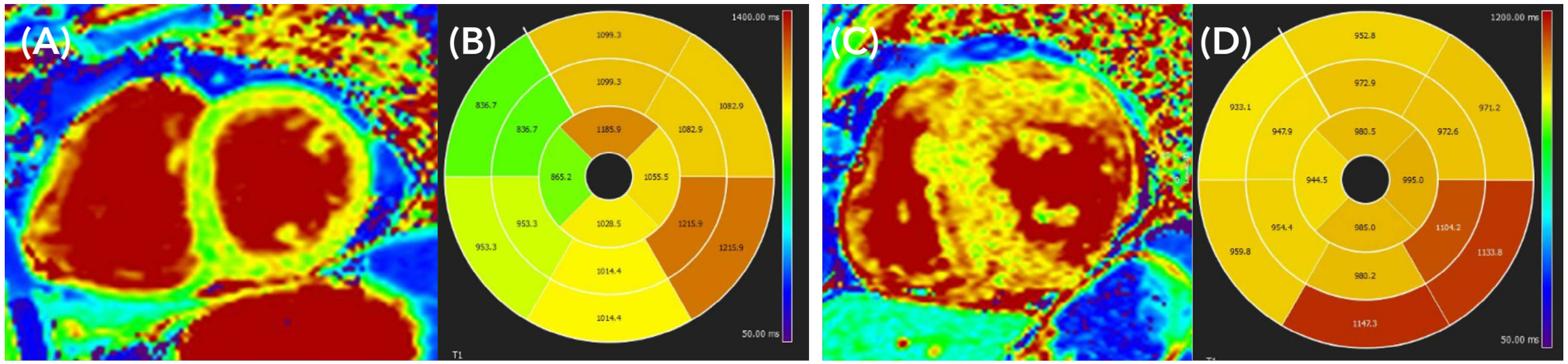
**IMAGE 3** Sequences of T1 mapping in two patients with FD at different stages.

*Source*: image courtesy of Dr. José Rodríguez Palomares (author).




Maps (**A** and **C**) and porthole representation (**B** and **D**). Images **A** and **B** show a patient in an initial stage, without LVH. The presence of low T1 values (green color) at the septal level and high T1 values (brown) at the inferolateral level stand out. Images **C** and **D** correspond to a patient in an advanced stage of the disease. The pseudonormalization of T1 values at the septal level (from green to yellow) and an increase in inferior-lateral fibrosis (dark brown) are observed.

## Tissue Doppler Imaging (TDI) and speckle tracking strain

May be potentially useful in the detection of subclinical disease (i.e., before the development of LVH):

- Systolic and diastolic tissue Doppler velocities at the mitral annulus are decreased in cases with LVH but may overlap with normal ranges in early stages of the disease (28). TDI has also been shown to identify early stages of various cardiomyopathies including FD (42).
- It was found that myocardial strain and strain rate were reduced in FD patients compared with those in normal control patients (43). Myocardial strain and strain rate are usually abnormal in patients with LVH, particularly in the posterolateral basal LV segment, sometimes with post-systolic thickening (Image 1). These findings may, in some cases, precede the development of significant LVH and may correlate with functional limitation (28).

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## Cardiac troponins

Are well-validated biomarkers of cardiomyocyte injury. Two studies, evaluating the performance of troponin I as biomarker of FD cardiomyopathy have shown that this analyte was elevated (≥ 0.04 ng/ml) in 21-37% of the patients, with a very high diagnostic accuracy for LVH or LGE in CMR (44,45). High-sensitivity troponin T was evaluated in a large cohort of 75 patients and found to be elevated (> 14 ng/L) in 40% of the cohort, 97% of whom had evidence of LGE in CMR (LGE-positive myocardial volume was the only factor independently associated with troponin elevation in multivariate logistic regression analysis). However, hs-troponin is not a useful biomarker of early involvement of the heart in FD cardiomyopathy, as it only increases in the advanced stages of FD cardiomyopathy (46).

## Plasma N-terminal pro B-type natriuretic peptide (NT-proBNP)

Has an established role in determining the diagnosis and prognosis of heart failure (47,48). NT-proBNP was evaluated as a biomarker of early cardiac involvement in FD in two relatively large cohorts of 89 and 117 FD patients. In both studies, a significant correlation was found between NT-proBNP and parameters of diastolic dysfunction and LV wall thickness; moreover, it has good diagnostic accuracy in predicting abnormal echocardiographic findings and may be a sensitive marker in detecting early changes in cardiac involvement, such as diastolic dysfunction (49,50). Other studies showed that NTproBNP is significantly higher in patients with LGE in CMR, in comparison with those without and that there is a significant correlation between NT-proBNP measurements and the amount of LGE (51,52).

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## Table 4. Summary of cardiac tests useful in FD cardiomyopathy.

*Source*: own elaboration.

| Test | Utility | Finding |
|---|---|---|
| Echocardiography (conventional). | Gold standard to assess cardiac morphology and function. | • Presence of LV hypertrophy (IVS > 12 mm) without a secondary cause and "binary"* aspect of the myocardium.<br>• Elevated LV filling pressures as assessed by E/e' ratio are associated with unfavorable prognosis (53). |
| Tissue Doppler Imaging (TDI). | Cardiac function. | Presence of septal and/or lateral Sa < 10 cm/sec high sensitivity and specificity to identify patients with a positive mutation even without LVH. The presence of septal Ea < 8 cm/sec and lateral < 10 cm/sec high sensitivity and specificity to predict cardiac involvement (54). |
| Speckle tracking strain and strain rate (echocardiography). | Cardiac function. | Strain < -12.5% → is associated to fibrosis by CMR using LGE with a 90% sensitivity and 97% specificity (55). |
| CMR + LGE. | Morphology and function. | Concentric LVH with infero-lateral fibrosis (LGE) (56). |
| T1 mapping (CMR). | Tissue characterization. | Low native T1 value at the septal level and generally elevated at the inferior-lateral level (fibrosis zone) (38). |
| T2 mapping (CRM). | Tissue characterization. | Predominantly lateral elevated native T2 value (edema/inflammation) (41). |
| Troponin. | Cardiac injury. | Elevated plasma concentrations in intermediate or advanced stages (46). |
| NT-proBNP. | Cardiac dysfunction. | Elevated plasma concentrations in advanced stages and/or with marked diastolic dysfunction (47). |
| ECG. | Cardiac conduction. | Short PR-interval (early).<br>LVH signs.<br>ST depression.<br>T wave inversion (57). |

IVS: interventricular septum; Sa: systolic velocities; Ea: early diastolic velocities; *binary sign: the binary sign is characterized by a bright endocardial layer and adjacent hyperechogenicity of the intraventricular septum.

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# How can I demonstrate kidney involvement in FD?

Kidney involvement follows Gb3 deposition in all types of renal cells and is characterized by a progressive disease that usually leads to end-stage renal disease.

Other than histologic findings, albuminuria, followed by proteinuria (usually under the nephrotic range) and reduction of GFR are the only markers of renal dysfunction in FD and the most important predictors of renal disease progression in adult Fabry patients (58). Inclusions in kidney cells lack prognostic value, while nonspecific lesions, like glomerular sclerosis and tubule-interstitial fibrosis, are associated with the worst prognosis, even in treated patients. Therefore, unfortunately, specific treatment is commonly delayed until proteinuria or even overt organ involvement occurs, when the reversibility of renal damage is difficult to achieve, and the prognosis is poor (26,58-60).

## Albuminuria

Remains as the best existing marker to detect early renal involvement. In the case of patients at risk of FD, any albuminuria, should be considered suspect (8). **Proteinuria** progresses and correlates with the decline in renal function, e.g. male Fabry patients with a proteinuria > 1 g/24 h had a greater yearly decline in renal function (-6.9 ml/min/1.73 $m^2$) than patients with proteinuria between 0.1 and 1 g/24 h (-2.2 ml/min/1.73 $m^2$) and patients with proteinuria <0.1 mg/24 h (-0.6 ml/min/1.73 $m^2$). Therapy with antiproteinuric drugs like angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) should be added to specific Fabry treatment, since the reduction of proteinuria is one main objective and does not respond quickly (or does not respond at all) to specific treatment for FD (8).

## GFR

The CKD-EPI creatinine equation (2009) is the recommended equation for estimating GFR in adults with FD (61-63).

Treatment is, at best, only effective in CKD Stage 1 or 2, before the deterioration of renal function or onset of overt proteinuria, as it does not reduce proteinuria per se (8).

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## Urine microscopy

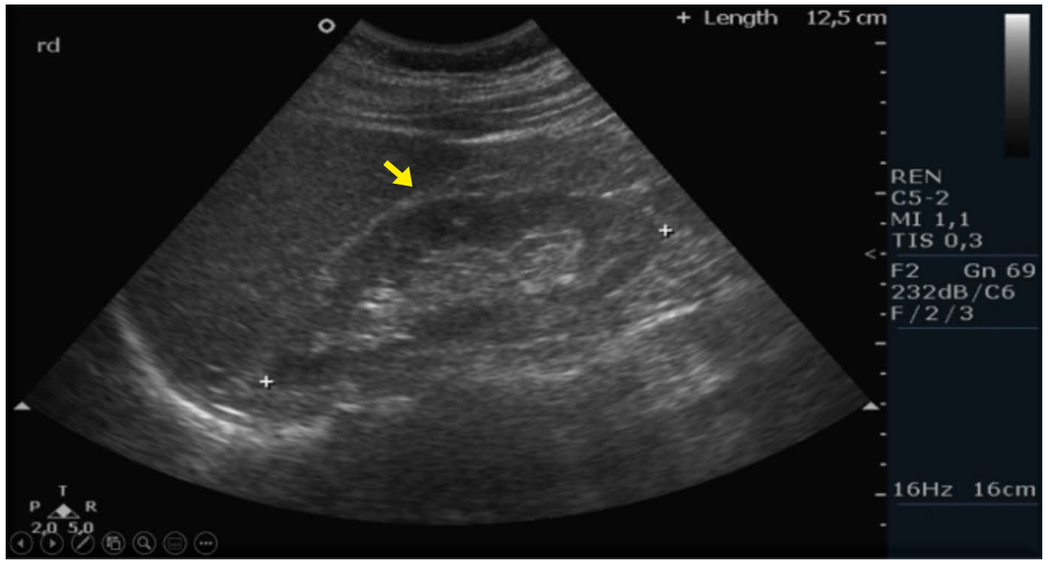
Has some limitations because its diagnostic value is not well established in patients with attenuated phenotypes (mainly in females), most of the findings are not pathognomonic of FD, and its prognostic value needs further evidence (64). However, **mulberry cells** with characteristic "**Maltese cross bodies**" can be detected in the urinary sediments of Fabry patients under a polarized microscope (65). **Podocyturia** could be an important and early biomarker of renal disease in Fabry patients. However, it lacks laboratory standardization, so currently it is only used with research purposes (64).

## Parapelvic cysts

The presence of **parapelvic cysts** (Image 4) has been linked to FD and reported in the literature as a possible characteristic of its renal involvement (66,67). The actual knowledge about it suggests that although to date parapelvic cysts cannot be considered a pathognomonic sign of FD, their presence should alert both nephrologists and radiologists to consider the diagnosis of FD, especially in subjects with an unclear family history of renal disease and when other stigmata of the disease are evident (64).

**IMAGE 4** Parapelvic cysts in a case of FD.

*Source*: imagen courtesy of Dr. María Guedes Marques (author).




## Kidney biopsy (Image 5)

Indications for kidney biopsy include:

- Confirm the diagnosis of FD: it helps us to confirm the pathogenicity of an ISV.
- In patients already diagnosed with FD, it allows us to rule out that renal involvement is due to other causes and to show early involvement by FD even in the absence of albuminuria, since the effacement of the pedicels of the podocytes precedes the pathological albuminuria.

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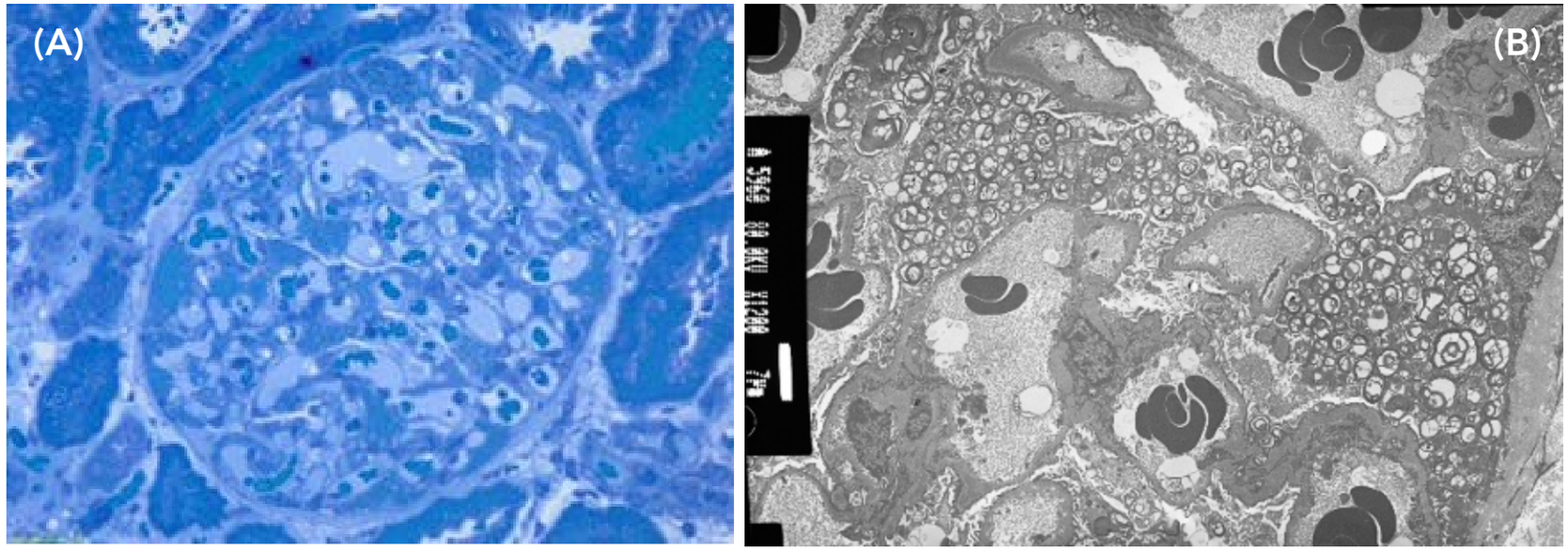
# How can I demonstrate kidney involvement in FD?

- In treated patients it is useful in the event of an unexpected and unsatisfactory response to the specific treatment of the disease and to identify a possible renal comorbidity if there is a sudden decrease in renal function, a rapid increase in proteinuria or a clinical nephrotic syndrome.

Kidney biopsies performed by skilled practitioners with modern radiological guidance are becoming increasingly safe in routine practice. It is advisable to assess whether the benefits of this invasive procedure outweigh the risks (1).

**IMAGE 5** Renal biospias of FD.

*Source*: image courtesy of Rita Theias Manso, Department of Pathological Anatomy, Hospital Professor Doutor Ferrado Fonseca (Portugal).




(**A**) Histological view of inclusions by toluidine blue staining by light microscopy. (**B**) Histological view of lamellar bodies (or zebra bodies) by electron microscopy.

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## Table 5. Summary of renal tests useful in FD nephropathy.

*Source*: own elaboration.

| Test | Utility | Finding |
|---|---|---|
| Albumin normalized for creatinine on a fresh morning urine sample. | Diagnostic value. | Elevated (over 30 mg/day) (8). |
| Proteinuria. | Prognostic value. | Levels of proteinuria correlate with GFR decline, poor renal outcome is expected with levels over 1 g/24 h (8). |
| Serum creatinine. | Prognostic value. | Reflects renal function (eGFR CKD-EPI creatinine 2009) (63). |
| Glomerular filtration rate. | Prognostic value. | Treatment is at best only effective in CKD Stage 1 or 2, before the deterioration of renal function (8). |
| Gb3 deposits in renal cells (biopsy). | Diagnostic value. | Presence of inclusions in light or electron microscopy (lamellar "*zebra*" bodies) (64). |
| Urine microscopy. | Diagnostic value. | Mulberry cells and Maltese cross (64). |
| Parapelvic cysts (Image 4). | Diagnostic value. | Their detection has been associated to FD nephropathy (64). |

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# How can I demonstrate neurological involvement in FD?

In brain tissue, Gb3 storage primary occurs in endothelium and vascular smooth muscle cells (68), but it is also responsible for glial deposition and neuronal ballooning in cortical regions and deep nuclei (69-71). In the peripheral nervous system, glycolipid accumulation in the dorsal root ganglia, the spinal and sympathetic ganglia or the endothelial cells of the blood vessels supplying the nerve fibers have been reported (72,73).

Central nervous system (CNS) symptoms can vary from very mild to severe, including manifestations related to acute and/or chronic cerebrovascular events in anterior and posterior vascular territories, posterior circulation alterations, along with neuropathic pain, cochleovestibular dysfunction and a varying degree of cognitive impairment and psychiatric symptoms (74).

## Small vessel microangiopathy

This is the most common expression of cerebral vasculopathy in FD. It manifests as either subcortical stroke or, more frequently, as asymptomatic **cerebral white matter hyperintensities** (**CWMH**) (Image 6). In fact, up to 80% of patients show a varying degree of periventricular, deep and/or subcortical white matter (WM) involvement (75,76).

WM lesion (WML) burden in FD begins sooner when compared with the general population (76,77). In a large natural history cohort of 203 FD patients with late-onset FD due to p.F113L mutation (78), WML presents early, before 30 years of age, affecting 11.1% of males and 26.9% of females under 30 years of age (Image 6), and increases progressively thereafter, becoming a universal finding in males and females over 70 years of age, mirroring another late-onset FD cohort with p.N215S mutation (79). This further emphasizes the importance of insidious brain damage from a young age and the importance of early treatment.

WM hyperintensities (WMH), are defined as hyperintense signal abnormalities surrounding the ventricles and in the deep white matter on FLAIR- and T2-weighted images without hypointense center (80), not referable to focal acute cerebrovascular accient, and can be silent in the absence of focal neurologic signs (81).

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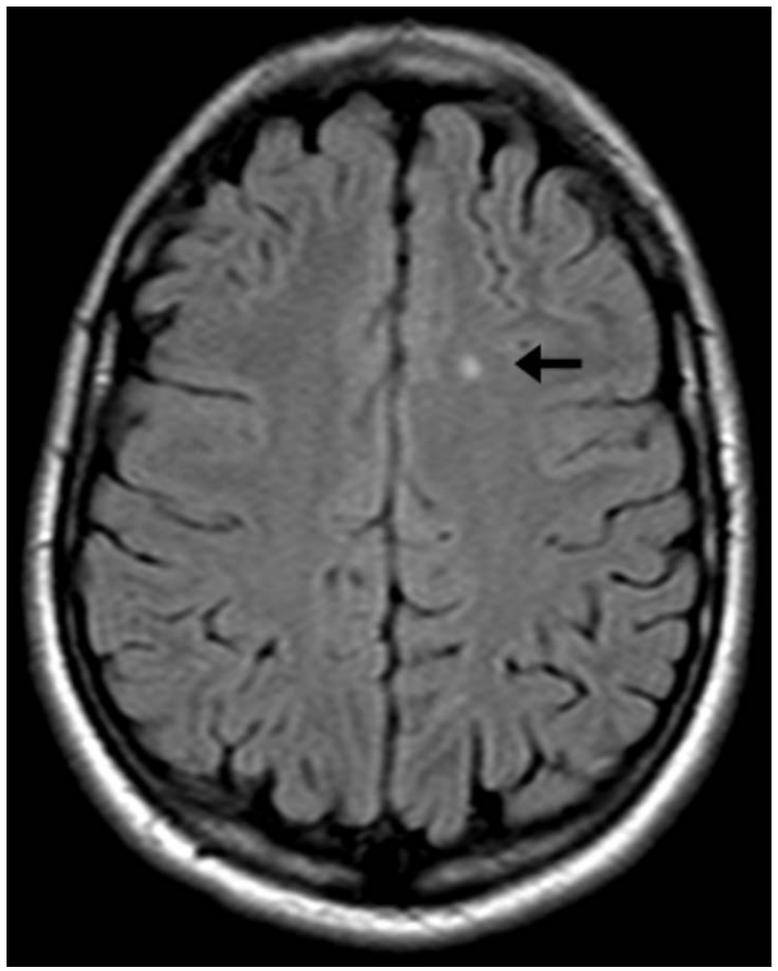
**IMAGE 6** **Brain MRI showing WML lesions (T2 and FLAIR left semi-oval center hyperintensity, without translation in T1 and without restriction in diffusion) in a young female with FD, in the absence of cardiovascular risk factors or other morbidities.**

*Source*: image courtesy of Dr. Miguel Gago (author).



Thus, **brain magnetic resonance imaging** (**MRI**) is the standard imaging technique to evaluate the CNS involvement in FD (82).Quantitative semi-automated volumetric MRI assessment methods have been used to perform volumetric analysis of WML (76), making the objective progressive assessment of CNS burden in the natural history of FD, its clinical guidance and therapeutic management critical.

The once-considered characteristic **T1-weighted hyperintensity of the pulvinar**, originally thought to be pathognomonic of the disease, should be considered as a very rare neuroradiological finding in FD patients (82). Its real incidence has been recently settled in around 3% of FD cases, with a clear predilection for males with impaired renal function (83), while a positive pulvinar sign has only been anecdotally reported in female FD patients (84).

WML has been linked to the risk of stroke, poor post-stroke outcome, and functional disability in aging adults (85-87). Therefore, periodic brain assessment is desirable in FD, detecting not only silent strokes but also quantifying WML, which may serve as a marker of disease progression and outcome of therapeutical interventions (77).

Alterations of the posterior circulation system include elongation, tortuosity, diffuse ectasia and/or focal aneurysmal dilatation of vertebral and basilar arteries (dolichoectasia), routinely detected with the use of a **time-of-flight** (**TOF**) **MRI angiography** (88).

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## Sensorineural deafness

In early and late onset FD is common, with FD patients presenting worse age-adjusted hearing thresholds in all analyzed frequencies compared to the normal population (2). Patients may develop progressive and accelerated sensorineural hearing loss, mainly in high frequencies, early in life, as early as 30 years of age (78).

## Neuropathic pain

Neuropathic pain (often referred to as **acroparesthesia**) is an early symptom of Fabry disease; it is common in male patients but has also been reported to occur in between 10 and 90% of female patients in various studies.

Two types of pain often co-occur in classical FD: chronic pain in the hands and feet and severe episodic pain attacks, also referred to as 'Fabry crises'. Fabry crises are characterized by severe burning pain originating in the extremities and radiating inwards to the limbs and may be precipitated by fever, exercise, fatigue, stress and rapid changes in temperature. The chronic pain is often described as burning, shooting or tingling pain, with a low to severe intensity.

The small-fiber neuropathy of Fabry disease is associated with an increased threshold of perception of cold and warm stimuli as well as heat pain (89). Large fiber functions (vibration and position sensation) are usually intact and, therefore, peripheral nerve conduction velocity is normal unless compression neuropathy develops (90).

There are various pain questionnaires developed for Fabry disease, which can be useful when managing the patient and even deciding the initiation of disease-specific treatment (91-93).

## Hypohidrosis

Is a common and early manifestation of Fabry disease, with a higher prevalence in males than in females. Hyperhidrosis is much less common in patients with Fabry disease than hypohidrosis and appears to be more common in females than males. It has been reported in 14.5% of females (36 of 248 patients) and 4.1% of males (12 of 291 patients) in the FOS database (89).

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## Table 6. Summary of Central and Peripheral Nervous System (CNS and PNS) tests useful in FD.

*Source*: own elaboration.

| CNS | Findings | Test |
|---|---|---|
| Cerebrovascular disease. | • Acute stroke.<br>• White matter hyperintensities.<br>• Microbleeds. | • Computed tomography in acute setting (94).<br>• MRI (T2-weighted and FLAIR sequences) (76).<br>• MRI (susceptibility-weighted imaging) (95). |
| Cerebral arteriopathy. | Dolichoectasia. | TOF MRI angiography (88). |
| **PNS** | **Findings** | **Test** |
| Neuropathy. | • Small fiber neuropathy.<br>• Pain assessment. | • Quantitative sensory testing (QST) (96).<br>• BPI (93), FPQ (91), FabryScan (92). |
| Sudomotor function. | Anhidrosis; hypohidrosis; hyperhidrosis. | Quantitative sudomotor axon reflex testing (QSART) Sudoscan (97). |
| Dysautonomia. | Dysautonomic. | Tilt test, Valsalva maneuver (II phase), deep breathing (98). |
| Auditory system. | Progressive sensorineural hearing loss. | Audiological test (99). |

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# 7 What other manifestations can add evidence of organ involvement by FD?

## Ocular manifestations

Ocular manifestations are among the first observable signs of the presence of the disease, even before birth (100), and are easily identified through a regular **slit lamp examination** performed by a trained eyecare professional. One prevalent feature is the presence of deposits in the cornea, with a whorl-shaped pattern. This keratopathy is known as **cornea verticillata** (101) (Image 7). It defines and is a hallmark of classical phenotype, being very uncommon in late-onset phenotypes (Image 7). Although less specific, a diffuse corneal haze can also be found in conjunction with corneal deposits (102). Neither manifestation is habitually associated with any loss of visual acuity.

**IMAGE 7** Cornea verticillata.

*Source*: image courtesy of Dr. Filipe Mira, Portugal.

## Lens opacification (Fabry's cataract)

Is less pathognomonic than cornea verticillata and its prevalence is also lower.  It appears as a sub-capsular opacity along the posterior lens suture lines, very similar to the cortisone-induced cataract or those following head trauma. This type of cataract becomes visually disturbing soon after its onset, and patients develop high light sensitivity and reduced visual acuity (103). A second cataract manifes-

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tation relates to the presence of a white, wedge-shaped, linear deposit on the anterior sub-capsular area of the lens (101), usually covering all quadrants. They are less associated with visual disturbance and may not be visible under slit lamp examination without pupil mydriasis.

## Blood vessel tortuosity

Appears as a consequence of the alteration of the vessels' natural architecture by substrate accumulation in the vascular endothelium (104). Hemizygotes are almost all affected by this clinical sign after age 30, while at least 50% of heterozygotes show similar manifestation (104). Tortuosity can be seen in the bulbar conjunctiva, in the retina, and on the external surface of the upper eyelid (105).

Substrate accumulation in the lachrymal gland fosters **eye dryness**, experienced by 50% of Fabry patients (107).

## Skin manifestations

### Angiokeratomas

Are benign vascular skin lesions characterized by the proliferation of dilated blood vessels in the upper dermis. They occur when the accumulation of Gb3 in dermal endothelial cells leads to vessel bulge and incompetence of the vessel wall, followed by secondary ectasia. They are the main cutaneous lesions found in classical phenotype patients with Fabry disease and may be the earliest physical sign of the disease, appearing in children between the ages of 5 and 15 years (mean age, 13.5 years) (108,109).

Although any region of the skin can be affected, lesions usually localize to the swimming trunk area (from the umbilicus to the upper thighs) (110).

## Lymphoedema

Anderson cited **lymphoedema** as a clinical sign of Fabry disease in the original description of the disorder. Lymphoedema also occurs in other lysosomal storage disorders, such as Kanzaki disease (α-N-acetylgalactosaminidase deficiency). In the absence of therapy, lymphoedema in Fabry disease can be complicated by erysipelas, with a risk of systemic infection (6).

## Gastrointestinal (GI) symptoms

Some early-onset signs appearing in childhood will usually remain present during adulthood and, among them, gastrointestinal involvement is a common, but under-appreciated, manifestation of FD. Patients may complain of abdominal pain (often after eating), diarrhea, nausea and

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vomiting, which are a significant cause of anorexia. These GI symptoms may be related to the deposition of Gb3 in the autonomic ganglia of the bowel and mesenteric blood vessels. Diarrhea-predominant irritable bowel syndrome (IBS) is a differential diagnosis (6).

## Skeletal involvement

Skeletal involvement has been confirmed in a large cohort of 53 patients in which osteopenia was present in approximately 50% of cases (6).

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# 8 What specific treatments are available for FD?

Specific treatment available for FD is based on enzyme replacement therapy (ERT) and on chaperone therapy with migalastat. ERT is available as agalsidase α and agalsidase β. Therapy with migalastat is indicated for patients with amenable *GLA* mutations, which are detailed in the product SmPC.

## Table 7. Available specific therapies for FD.

*Source*: own elaboration based on SmPC. See SmPC for complete information (111-113).

| | Agalsidase α | Agalsidase β | Migalastat |
|---|---|---|---|
| Therapeutic indications. | Indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency). | Indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency). Indicated in adults, children and adolescents aged 8 years and older. | Indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (see the tables in section 5.1 of SmPC) (113). |
| Contraindications. | Hypersensitivity to the active substance or to any of the excipients. | Life-threatening hypersensitivity (anaphylactic reaction) to the active substance or any of the excipients. | Hypersensitivity to the active substance or to any of the excipients. |

*(Continues on the next page)*

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## Table 7. Available specific therapies for FD (cont.).

| | Agalsidasa α | Agalsidasa β | Migalastat |
|---|---|---|---|
| Posology. | Administered at a dose of 0.2 mg/kg body weight every other week by intravenous infusion over 40 minutes. | 1 mg/kg body weight administered once every 2 weeks as an intravenous infusion. The initial infusion rate should be no more than 0.25 mg/min (15 mg/hour) to minimize the potential occurrence of infusion-related reactions. After patient tolerance is established, the infusion rate may be increased gradually with subsequent infusions. | 123 mg migalastat (1 capsule) once every other day at the same time of day. Food should not be consumed at least 2 hours before and 2 hours after taking migalastat. |
| Clinical efficacy and safety. | Assessed in two randomized, double-blind, placebo-controlled studies and open-label extension studies, in a total of forty adult patients. | Evaluated in two double-blind placebo-controlled studies, and one open-label extension study in both male and female adult patients. | Evaluated in adults in two randomized Phase 3 pivotal trials (one double-blind placebo-controlled and another one open-label active comparator [ERT]) and two open-label extension (OLE) trials. |

*(Continues on the next page)*

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## Table 7. Available specific therapies for FD (cont.).

| | Agalsidasa α | Agalsidasa β | Migalastat |
|---|---|---|---|
| Summary of safety profile. (very common adverse reactions). | The most commonly reported adverse reactions were infusion-related reactions, which occurred in 13.7% of adult patients treated with agalsidase α in clinical trials. Most undesirable effects were mild to moderate in severity. Very common adverse reactions included headache, flushing, nausea, rigors, pyrexia, pain and discomfort, fatigue. Hypersensitivity, including anaphylaxis, has been reported. | Since agalsidase beta (r-hαGAL) is a recombinant protein, the development of IgG antibodies is expected in patients with little or no residual enzyme activity. Patients with antibodies to r-hαGAL have a greater potential to experience infusion-related reactions (IARs). Reactions suggestive of immediate (Type I) hypersensitivity have been reported in a small number of patients. Very common adverse reactions included chills, pyrexia, feeling cold, nausea, vomiting, headache and paraesthesia. 67% of the patients experienced at least one infusion-related reaction. Anaphylactoid reactions have been reported in the post-marketing setting. | The most common adverse reaction was headache, which was experienced by approximately 10% of patients who received migalastat. |
| Particularities. | IgG antibody response has been observed in approximately 24% of the male patients. | The majority of patients developed IgG antibodies to r-hαGAL, typically within 3 months of the first infusion with agalsidase β. | Not recommended in patients with GFR less than 30 ml/min/1.73 $m^2$. |

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# 9 How do I monitor the evolution of my patient with Fabry disease?

Being a disease that could involve several organs, they must all be thoroughly evaluated at diagnosis. Patients should be monitored at 12-month intervals, taking measurements of disease progression.  In severe patients, the monitoring could be more frequent (every 3-6 months), and should be dependent on each individual case (see Table 8).

In female patients, the correlation between genotype, phenotype and prognosis is not clear. Methods to assess the skewing of X chromosome inactivation is promising in this regard but is still a work in progress (7). In general, female patients should be assessed and monitored in a similar way to that recommended for men (i.e., a full baseline evaluation followed by annual assessments). Longer intervals between assessments for asymptomatic women can be considered, particularly when a skewed X chromosome inactivation profile with predominant expression of the wild type *GLA* allele has been demonstrated (7). Clinical vigilance and regular monitoring are essential, as an absence of symptoms at baseline or at follow-up assessment does not predict the progression of the disease or the development of organ complications. Although most female patients have uneventful pregnancies (114), signs such as proteinuria should be monitored closely by a specialist, as they may progress during pregnancy, and genetic counseling should be provided in line with current guidance (6,115).

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## Table 8. Check list for monitoring adult patients with FD.

*Source*: adapted from Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Managment and treatment recommendations for adult patienst. Mol Genet Metab. 2008 Apr;123(4):416-27 (1). Used under CC BY. Licensed under CC BY by Dr. Patricio Aguiar, Dr. Miguel F. Gago, Dra. María Guedes Marques, Dr. Álvaro Hermida, Dr. Raúl Jesús Noguera Torregrosa, Dr. Tomás Pérez-Concha, Dr. José F. Rodríguez Palomares.

| Organ/system | Assessment (s) | Monitoring schedule |
|---|---|---|
| General. | Complete history and physical examination. | Every clinic visit. |
| Renal. | • Glomerular filtration rate.<br>• Albuminuria and/or proteinuria. | Baseline (BL), annually if low risk, every 6 months if moderate risk, and every 3 months if high to very high risk. |
| Cardiac. | • Blood pressure and cardiac rhythm.<br>• ECG, 24-h Holter monitoring.<br>• Echocardiography: wall thickness, cardiac function (strain, TDI if possible).<br>• Cardiac MRI with gadolinium.<br>• Cardiac MRI with T1 and T2 mapping.<br>• NT-proBNP.<br>• Troponins (T, I). | • Every clinic visit.<br>• BL, Annually.<br>• BL, Annually.<br>• BL, As clinically indicated (at least less than 3 years desirable).<br>• If available in the center: basal and when clinically indicated (recommended at least every 3 years).<br>• BL, each follow-up visit.<br>• BL, each follow-up visit. |
| Cerebrovascular. | • Brain MRI (ordinal and/or automated quantitative methods).<br>• Angiography (by TOF MRI or CT imaging).<br>• CT imaging. | • BL, periodic evaluation, As clinically indicated.<br>• BL, periodic evaluation, As clinically indicated.<br>• In case of acute stroke or of MRI contraindication. |

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## Table 8. Check list for monitoring adult patients with FD (cont.).

| Organ/system | Assessment (s) | Monitoring schedule |
|---|---|---|
| PNS. | • Pain evaluation and history: pain measurement scale such as the Neuropathic Pain Symptom Inventory or Brief Pain Inventory.<br>• GI symptoms.<br>• Autonomic symptom evaluation by orthostatic blood pressure.<br>• Audiometry.<br>• Ophthalmological examination.<br>• Cold and heat intolerance (quantitative sensory testing, if available). | • BL, Annually.<br>• BL, Annually.<br>• BL, Annually.<br>• BL, Annually.<br>• BL, As clinically indicated.<br>• BL, As clinically indicated. |
| Quality of life. | General health questionnaires (SF-36, EQ-5D). | BL, Annually. |

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# What is stability or progression in FD?

FAbry StabilizaTion indEX (FASTEX) is a dynamic, simple and fast tool that directly determines disease stability or progression and might be suitable for the clinical routine, as well as for cohort studies aiming to analyze therapeutic effects. FASTEX is a validated and publicly-available tool with few items (seven) (116). It looks at three domains with a small number of items in each: the nervous system (pain and cerebrovascular events), the kidneys (proteinuria and glomerular filtration rate), and the heart (echocardiography and electrocardiograph parameters and New York Heart Association functional class). Because it does not include many factors that are unlikely to change over time (e.g. the presence of cornea verticillata or angiokeratoma), FASTEX may be more sensitive to changes in disease state than the MSSI or DS3.

FASTEX scores changed significantly for more than half of the participants in Lenders et al. 2020 (117). The researchers defined progression (sometimes referred to as having "unstable disease") as a change in at least 20% in FASTEX score. Based on this definition, 66% of participants experienced disease progression over the course of the year assessed. In all participants, no significant differences were observed in age, sex or treatment modality (including both types of ERT and treatment length), or in terms of heart and kidney involvement at the start of the year. Closer analysis of the unstable disease group revealed that the change in scores was driven primarily by changes in kidney parameters over the year.

Complementarily, in 2018, a European panel of experts collaborated to develop a consensus document that sets organ-specific therapeutic goals for Fabry disease (118). The main conclusions of this consensus can be summarized as follows:

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# 10 What is stability or progression in FD?

- Therapeutic goals for patients with Fabry disease should be individualized by considering patient characteristics, the disease variant and the stage.
- The reversal of symptoms or prevention of disease progression is the goal for most parameters associated with Fabry disease.
- Multidisciplinary input is vital at all stages of Fabry disease management and should be based on a comprehensive assessment of affected organs and regular monitoring.
- The timing of the therapy plays an important role in Fabry disease management; early initiation of disease-specific therapy can delay progression in patients with Fabry disease.
- Optimal Fabry disease management includes both disease-specific and adjunctive treatment and should consider the balance between anticipated clinical benefits and potential therapy-related challenges.

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# INTEREST CONFLICT

## Dr. Patricio Aguiar

Grant/research support from Takeda.
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## Dr. Miguel F. Gago

Received congress and travel/accommodation sponsorship from Takeda Pharmaceutical Company, Shire, Sanofi Genzyme.

## Dra. María Guedes Marques

None to declare.

## Dr. Álvaro Hermida

Received honoraria for presentations and board meetings from Amicus Therapeutics, Sanofi Genzyme, and Shire HGT.

## Dr. Raúl Jesús Noguera Torregrosa

Received honoraria as a speaker at meetings related to Fabry Disease from Takeda, Sanofi-Genzyme and Amicus. Paid by those companies to attend courses, meetings and congresses related to Fabry Disease.

## Dr. Tomás Pérez-Concha

Received honoraria from Amicus Therapeutics and Sanofi Genzyme.

## Dr. José F. Rodríguez Palomares

None to declare.

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