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Fabry disease in women: beyond the role of "carriers"

Miguel-Ángel Barba-Romero[1], Rosario Sánchez-Martínez[2]

[1]Internal Medicine Department, Albacete University General Hospital, School of Medicine of Albacete, Castilla-La Mancha University, Albacete 02006, Spain.
[2]Internal Medicine Department, Miguel Hernandez University, Alicante Institute for Health and Biomedical Research (ISABIAL), Alicante 03010, Spain.

Correspondence to: Miguel-Ángel Barba- Romero, Internal Medicine Department, Albacete University General Hospital, School of Medicine of Albacete, Castilla-La Mancha University, 37th, Hermanos Falcó, st. Albacete 02006, Spain. E-mail: mabarbar@sescam.jccm.es

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Abstract

Fabry disease (FD) is a rare X-linked lysosomal storage disease resulting from a deficiency of the lysosomal enzyme alpha-galactosidase A, caused by mutations in the *GLA* gene. This leads to the accumulation of glycosphingolipids, mainly globotriaosylceramide and its deacylated derivate globotriaosylsphingosine. Such non-metabolized substrates accumulate in cells and tissues throughout the body, resulting in significant morbidity, predominately in the kidneys, heart, and nervous system, and impaired quality of life. While FD was initially considered to predominantly affect men, women with this condition may manifest a wide array of clinical symptoms and, in some cases, a significant multi-systemic pathology similar to men. This has been mainly attributed to skewed X-chromosome inactivation, which causes different enzyme activity levels within tissues and organs. The diagnosis of FD in women is often delayed due to the initial non-specificity of presenting symptoms and the heterogeneity of clinical manifestations. The enzyme activities in the leukocytes of a significant number of women with this condition fall within the normal range. Therefore, genetic analysis for mutations in *GLA* has become the gold standard for the diagnosis of FD in women. Unlike men, the current criteria proposed to start specific treatment for women with this condition can underestimate the appropriate time to do so and impede women from obtaining the benefits of early initiation. In addition, there is some evidence that women with FD are still at risk of being undertreated, unlike male patients.

Highlights

Fabry disease is an X-linked lysosomal storage disease

Similar to men, women may manifest a wide array of clinical symptoms

In some cases, organ damage is as severe as that observed in men

Skewed lyonization of the X-chromosome may cause this clinical heterogeneity

Genetic analysis for *GLA* mutations is necessary for diagnosis in women

Current guidelines indicate that women may be at risk of undertreatment

Follow-up and treatment criteria for women may require revision

Keywords: Fabry disease, women, *GLA* gene, X-chromosome inactivation, diagnosis, clinical manifestations, follow-up, treatment

INTRODUCTION

Fabry disease (FD, OMIM #301500) is an X-linked inherited lysosomal disease associated with mutations in the *GLA* gene, which encodes the enzyme alpha-galactosidase A (alpha-Gal). Total or partial loss of enzyme function leads to lysosomal accumulation of complex glycosphingolipids, mainly globotriaosylceramide (Gb3) and its deacylated form, globotriaosylsphingosine (lyso-Gb3). Subsequent damage to various cell types, particularly those of the kidney, heart, and nervous system, results in cellular dysfunction, inflammation, and progressive organ damage[1].

FD causes significant morbidity and mortality in affected men, with cardiovascular, cutaneous, renal, ocular, central, and peripheral nervous system manifestations[2]. Clinically, two phenotypes can be distinguished: classical (defined by multi-systemic manifestation, early onset, and absence of alpha-Gal activity) and non-classical (late onset with some detectable alpha-Gal activity). Thus, FD comprises a clinical continuum, with a broad spectrum of clinical phenotypes[1] usually found in men being more complex in women.

The clinical presentation in female patients may be more variable due to random X-chromosome inactivation, ranging from asymptomatic to severe, as is typically seen in classically affected male patients[2]. The presence of symptoms in women depends on several factors, including genotype, phenotype, and percentage of affected X-chromosomes in tissues. Therefore, not all clinical manifestations should be assumed to be infrequent or less severe in women.

The variability of clinical manifestations in women makes follow-up more complex. This could lead, as reported in several studies, to women being undertreated compared to men[3-5], considering the current treatment guidelines[6].

Both sexes differ significantly in terms of clinical manifestations conditioned by phenotype, age at onset[2,7], and certain clinical manifestations, such as cardiomyopathy. Their diagnosis and follow-ups are also different. For instance, plasma lyso-Gb3 and alpha-Gal activity are less determinant in women than in men. Moreover, in the absence of ventricular hypertrophy, cardiac magnetic resonance imaging (MRI) is recommended for women during cardiac follow-up to evaluate cardiac replacement fibrosis[8]. These

differences in clinical expression determine phenotypic and sex-specific therapeutic recommendations[6].

Similar to other rare diseases, understanding the natural progression of FD is difficult owing to the paucity of longitudinal clinical information, particularly in heterozygous women. Most of our current knowledge is based on data extracted from registries[9,10]. This study aimed to describe the pathophysiological, clinical, diagnostic, and therapeutic features of women with FD based on knowledge derived from the current literature.

EPIDEMIOLOGY

FD has an estimated incidence of 1:40,000 to 1:60,000 in men[1]. Recent newborn screening studies in Italy, Taiwan, Austria, Spain, and the United States that screened more than 500,000 male and female newborns found the incidence of FD mutations to be between 1:2445 and 1:8454[11-14]. Late-onset forms may be particularly common, with up to 1:4600 in one study[12].

In particular, the published epidemiology of FD in women describes the prevalence of FD carriers as 1 in 339,000 in the UK[15]. The prevalence in newborn screenings is reported as 1 in 129,591 in the Czech Republic[16], 1 in 40,844 in Taiwan[11], and 1 in 11,578 in Austria[17].

PATHOLOGY OF FABRY DISEASE IN WOMEN

Variability in the clinical involvement of X-linked inherited diseases in women heterozygous for X-linked mutations has been previously recognized[18]. The alpha-Gal A gene (*GLA*) is differentially expressed in female cells according to the principles of random X-chromosome inactivation (XCI)[19]. This phenomenon was also observed at the locus coding for alpha-Gal some years ago[20]. The result is a mosaic in which some cells show normal expression of the enzyme and others show little to no expression[21].

Clinical symptoms in carriers of X-linked diseases depend mainly on the levels of major proteins in the affected tissues. In addition, the enzyme activity thresholds required for normal enzyme functionality may differ between cells and tissues[22]. While other mechanisms have been hypothesized to explain the clinical expression of FD in women - such as gene mutations on both alleles, loss of one X-chromosome as in Turner Syndrome, or uniparental disomy - XCI skewing remains the most controversial[23]. Increased unbalanced inactivation of the X-chromosome with preferential inactivation of the non-mutated allele could explain the final phenotypic expression of FD in an individual patient. This phenomenon tends to increase with age and show tissue differences.

However, surprisingly, the results of different published studies on the effect of XCI on FD severity in women (generating balanced or unbalanced expression of the different *GLA* alleles) do not show concordance. Cohort and family case studies have shown that women with unbalanced XCI ratios and preferential expression of the mutated allele have a more severe phenotype. Additionally, they are more likely to develop organ damage and have accelerated disease progression[24,25]. However, other studies have failed to demonstrate the impact of XCI on the clinical phenotypes of affected women[26,27].

These contradictory results depend on several factors[23]. These include the analysis of non-homogeneous groups, absence of control groups, age of patients (younger patients may develop clinical symptoms later in life), lack of identification of the allele carrying the mutant gene, or use of different cut-off values for skewed XCI. The possibility of chromosomal cross-over effects is also a notable factor[28].

However, with a few exceptions, most published studies have used a single type of assay to evaluate XCI patterns and have generally done so in a single tissue, which may limit the interpretation of the results obtained. The XCI pattern in leukocytes may not reflect that of other cells with different embryogenic origins[27]. Therefore, a combination of different methods to study XCI, *GLA* expression, and enzyme activity has been proposed to obtain more accurate results[28]. Furthermore, the different embryological origins of tissues analyzed in different studies could also explain the lack of correlation observed between skewed XCI and the clinical expression of the disease, especially when using clinical tools such as the Mainz Severity Score Index (MSSI).

Unbalanced XCI-mediated methylation of the X-chromosome inactivation center can influence the clinical expression of FD[29]. Moreover, allele-specific DNA methylation of the *GLA* promoter may impact the expression levels of the mutated allele, thus affecting the onset and outcome of FD. Future prospects include the study of ultra-deep methylation of *GLA* to identify epigenetic signatures capable of predicting symptom development in pre-symptomatic female carriers, supporting timely therapeutic interventions[30]. The influence of the methylation status of wild-type *GLA* alleles on other processes, such as autophagy, deserves particular attention[31].

In heterozygous women with FD, the contribution of alpha-Gal activity from normal cells may result in a normal range of overall measured (serum or leukocytes) enzyme activity; however, some of these patients still manifest substrate storage and clinical features. This implies that in vivo cross-complementation by enzymes from normal cells is unlikely, as in Hunter disease, which is another X-linked disease. Recently, Najafian *et al.* showed that this lack of cross-complementation in female patients with FD occurs in the renal tissues of FD heterozygotes[32]. They developed and validated a novel method to measure the mean inclusion volume of Gb3 in podocytes, independent of mosaicism in women with FD and classical mutations. Using this method, they found that Gb3 accumulation and injury in the Fabry podocytes progressed with age in women. Importantly, Gb3 accumulation in women was similar to that in men, which is consistent with the absence of significant podocyte cross-correction or residual circulating enzyme effectiveness. One explanation for this phenomenon is suggested by the results of cell culture experiments performed by Fuller *et al.*[33]. Their results indicate that, unlike in Hunter syndrome, unaffected cells primarily secrete the mature 46 kDa form of the enzyme rather than the mannose-6-phosphorylated form. These mature forms lacking mannose 6-phosphorylated residues may not be readily taken up by other cells and cannot complement the activity in cells lacking enzyme expression. Another hypothetical reason could be the toxic effect of accumulated substrates, which are known to inhibit normal alpha-Gal enzyme activity and stimulate cardiomyocyte growth, as it happens with plasma lyso-Gb3[34,35].

CLINICAL MANIFESTATIONS

Although FD is an X-linked inherited disease, both men and women may experience different clinical manifestations depending on their age and phenotype. This fact, together with the X-chromosome lyonization phenomenon, causes women to present with delayed onset of symptoms and a varied clinical spectrum. In fact, some initial series in the early 2000s indicated that most women are either asymptomatic or have mild symptoms[36]. However, it is now known that women with pathogenic variants of FD, regardless of the type of variant, are prone to develop disease symptoms. These symptoms vary in type and tend to increase in severity with age, leading to a poorer quality of life (QoL) and shorter life expectancy compared to the general population[2,4,5,37-39].

In a survey by Wilcox *et al.* based on the Fabry registry[2], the median age at symptom onset in women was 13 years, compared to 9 years in men ($P < 0.0001$). Women experienced symptoms and received a diagnosis

substantially later than men (24 years in men and 31 years in women, with a median delay of 11 years for both). The earliest initial symptoms in women were ophthalmologic (12.5%) and cutaneous (17.8%), followed by gastrointestinal manifestations (18.5% in men and 11.9% in women). The first findings indicative of vital organ involvement in women were as follows: renal in 10.6% (mean age 30.9 years), cardiovascular in 10.0% (mean age 33.4 years), and cerebrovascular in 4.2% (mean age 31.2 years). These observations are crucial for planning follow-up care in women.

A series of published studies analyzed the overall clinical involvement of women with FD, regardless of phenotype[2,4,5,37,38]. Results showed that 69% of women exhibited signs or symptoms of the disease, 43% displayed severe symptoms, and 20% manifested major cerebrovascular, cardiac, or renal events. The mean age of onset was 46 years[2]. The most frequently involved systems were the peripheral nervous system (38%-53.6%), cardiovascular system (10%-59%), renal system in the form of decreased glomerular filtration rate (GFR) or albuminuria (15.8%-49%), central nervous system (CNS) (4.2%-16%), ophthalmologic system (12.5%-61%), and dermatologic system (11%-39%). The wide ranges observed in the studies may be attributed to the type of mutations harbored by each female, and other factors previously mentioned. In a Spanish study of Fabry in women[5], the symptoms were analyzed by genotype and phenotype. Although a higher frequency of systemic symptoms was observed in the classical phenotypes (with a significant difference in cardiac, peripheral, and CNS manifestations, along with typical signs of the disease), women with non-classical phenotypes also had multiorgan involvement in 52% of cases (49.5% cardiac, 38.3% ophthalmic, 32.5% peripheral nervous system, and 15.8% renal). This underscores the fact that women with pathogenic variants of FD, regardless of the variant type, are likely to develop disease symptoms. Table 1 shows the main differences in the natural history of the primary clinical manifestations according to sex and phenotype.

Cardiac involvement in women with FD

According to data from the Fabry Outcome Survey (FOS), cardiac involvement was present in 59% (147/248) of female patients with FD, with onset at 33.5 years of age[37]. In the classic phenotype[40], major cardiovascular events have been described in 14% of women (with the first event occurring at 54 years of age), acute coronary syndrome in 10% (at 51 years), atrial fibrillation in 16% (at 58 years), and hospitalization for heart failure in 6% (at 69 years). In general, heart disease in women appears 10 years later than in men and is usually less severe[40], although it is the most frequent cause of death in women with FD, reported in 57% of women with a median age of 66 years[41,42].

Unlike in men, the loss of myocardial function and development of fibrosis in women with FD may occur in the absence of left ventricular hypertrophy (LVH). Thus, in contrast with the current recommendations, initial cardiac staging and follow-up should be preferentially based on replacement cardiac fibrosis rather than LVH assessment in female patients with FD[8].

Kidney involvement in women with FD

Globally defined as a decrease in GFR of less than 60 mL/min, reduced GFR was observed in 19% of women and proteinuria in 39% (with 7.5% exceeding 3.5 g/d), although without any correlation with age. Dialysis or transplant was required in 2.2%-4.8% of female patients[2,5,37]. Rapid progression of Fabry nephropathy was more prevalent among men than women. In the Schiffmann study[39], fifty-seven patients had end-stage renal disease (ESRD), and of these, 28 out of 279 men and 5 out of 168 women underwent kidney transplants. However, the mean age at dialysis initiation was the same in both sexes.

Table 1. Main differences in the natural history of primary clinical manifestations by sex and phenotype in women with FD

	Differences between sexes	Differences between phenotypes in women	Differences with women in the general population
Cardiovascular	Later onset than in men (10 years later) Loss of cardiac function and development of fibrosis not always associated with left ventricular hypertrophy in women	Difference by sex and phenotype More frequent and early manifestations in women with classic phenotype than late onset	Cardiovascular death/arrhythmias/heart failure/events more frequent and earlier than women of the general population
Renal	Later onset than in men and less frequent Frequent proteinuria but renal failure slightly higher than the general population Podocyte damage in the absence of analytical or clinical alterations	No differences by phenotypes in women	Renal failure slightly higher than the general population
Central nervous system	No differences by sex: increased incidence of stroke and white matter lesions in both sexes	No difference by phenotype in both sexes	Early onset and increased prevalence than the general population for both sexes
Others	Chronic and acute pain: common in women Gastrointestinal manifestation: early and frequent in women, with impact on quality of life	Peripheral nervous system: early clinical manifestation in women with classic phenotypes, with impact on quality of life	Worse quality of life than women in the general population

FD: Fabry disease.

Renal involvement appears to progress in a similar manner in both phenotypes[7], wherein lyso-Gb3 levels and podocyturia could be early markers of renal damage in women.

Although the prevalence of stroke and cardiac disease is similar between men and women with FD, that of chronic kidney disease appears to be far lower in heterozygotes than in age-matched hemizygotes. This is partially explained by the findings of Najafian *et al.*[32]. As mentioned earlier, their study showed that female podocytes do not exhibit cross-correction of enzyme activity, and their Gb3 load eventually reaches similar levels to that of male podocytes. Cellular mosaicism originating from X-chromosome inactivation could delay this accumulation. Additionally, in some registries and clinical trials, the mean age of the enrolled women is younger than that of the men, which decreases the likelihood of significant kidney damage in these women.

Central nervous system involvement

The prevalence of FD in cryptogenic strokes ranges from 0.6% to 11.1%, with similar rates reported in both sexes and a mean onset age of 38-51 years[43]. In women, CNS involvement has been described in 5.5%-25% of cases, manifesting as a stroke or transient ischaemic attack, with a mean onset age of 38.8 years[5,37]. Up to 46% of cases showed the presence of white matter lesions[44]. Such patients appear to have a similar risk of progression to stroke regardless of sex (20.7% in men and 23.1% in women)[44].

Other manifestations in women

Gastrointestinal involvement is frequent in women with FD, with abdominal pain in 60%, diarrhea in 41%, and early onset in 11.4% (mean onset age of 9.5 years)[45]. QoL of such patients is highly affected[46], as is also evident with pain[37], where chronic pain has a prevalence of 32% (mean onset: 20.7 years) and acute intermittent pain occurs in 57% (mean onset at 16.6 years). In general, despite the great variability in the clinical expression of FD in women, its progression associated with age results in a high disease burden with a significant impact on QoL[45,46].

Cornea verticillata is described in 61.5% and hypoacusia in 20.5% of women with classical FD[5].

MacDermot *et al.*[15] described in their study that the frequency of angiokeratoma is most likely underestimated in women, manifesting as patches in the dermatome distribution on the upper chest and upper or lower limbs. Hypohidrosis was reported in 32.8% of women and tinnitus in 25%, often accompanied by dizziness. Disabling joint and muscle pain, diagnosed as fibromyalgia, was present in 7% of carriers aged between 45 and 55 years. It was associated with reduced mobility, constant pain, and inability to work. Regarding emotional health, a third of the sample admitted to being depressed, anxious, tired, and frustrated some of the time; 15.8% were tired all the time; 5.7% were frustrated; and 5.4% were suicidal most of the time.

REPRODUCTIVE ISSUES IN WOMEN WITH FABRY DISEASE

Recently, there has been increasing interest in the influence of FD on the reproductive health of affected women. Thus, Hauser *et al.*, in a small study involving 13 patients with FD (six of them women), evaluated the sexual hormonal profile of patients. They found unaltered hormonal function and a normal fertility rate in both male and female patients compared with the control population[47].

In an analysis using data from 131 women included in the FOS registry, Hughes *et al.* documented a mean age at menarche (SD) of 12.9 (1.6) years in women with FD. No significant differences were observed between those who received enzyme replacement treatment (ERT) (12.8 ± 1.6 years) and those who did not (13.1 ± 1.5 years)[48]. These findings are similar to those reported in an ethnically diverse population in the USA (12.2 ± 1.6 years)[49]. Furthermore, in the FOS survey, early cessation of ovarian function was not evident in women, and the mean (SD) age of menopause was 48.7 (6.8) years, irrespective of ERT status.

Data indicating whether women with FD experience more menstrual pain than those without FD are limited. In a study by Bouwman *et al.* involving 63 women with FD and 52 age-matched controls, no significant difference was found in the prevalence of premenstrual and menstrual symptoms or age at menarche. However, a higher incidence of libido loss was reported in women with FD, which may be explained by the challenges of having a chronic disease rather than FD itself[50].

In 2017, Laney *et al.* published the results of a multicenter study on infertility problems in 376 North American patients with FD, of whom 242 were women[51]. They found that women with FD had, on average, more living biological children (1.8) than men with FD (1.1), which exceeded the average of men in the general US population (0.9). In addition, approximately 20% of women with FD reported infertility problems and nearly 14% sought an infertility evaluation to address specific issues. The number of women with FD who reported infertility problems was somewhat higher than that in the general population, but equivalent to the number of women in the general population who requested an infertility evaluation. Finally, 12.4% of female patients sought infertility services to attempt a pregnancy.

Gb3 deposition has been observed in placental tissues of both maternal and fetal origin, which may increase the possibility of vascular alterations in the placental circulation. The potential risks include the development of ischaemic phenomena[52-54].

In the aforementioned study by Bouwman *et al.*[50], 32 women with a history of 89 pregnancies were described. Compared to the small control group, women with FD showed a higher incidence of proteinuria, whereas the incidence of preeclampsia, preterm delivery, hypertension, miscarriage, and intra-uterine death did not differ.

In contrast, a retrospective study of 102 pregnancies in 41 women[55] found a higher frequency of hypertension in pregnant women with FD than in the general population; however, no differences were found in the incidence of eclampsia. At the same time, certain FD-related symptoms, such as gastrointestinal issues, acroparaesthesia, and proteinuria, were found to worsen during pregnancy. However, women with FD did not have a higher incidence of miscarriages than women in the general population.

In a study of patients from the FOS registry[48], data were retrospectively obtained from 98 pregnancies in 73 women, 53 of whom did not undergo ERT. In summary, 91.3% of pregnancies in treated women and 96.0% of pregnancies in non-treated women had normal outcomes, and no miscarriages occurred. When comparing treated and non-treated women from before to after pregnancy, no significant differences were observed in the mean changes in the estimated glomerular filtration rate (eGFR), mean urinary protein, left ventricular mass index (LVMI), or Brief Pain Inventory (BPI) pain severity scores.

Recently, Haninger-Vacariu *et al.* reported the results of 70 pregnancies and deliveries in 32 women with FD in Austria[56]. Women with low pain burden before pregnancy showed no increase in pain during pregnancy, whereas those with moderate pain before pregnancy experienced an increased pain burden. Approximately 87% of pregnancies had a successful outcome, 8.6% had a miscarriage, and 4.3% were terminated by induced abortion. Preeclampsia occurred more frequently (11.5%), and neonates were more often preterm (20.3%), had a lower birth weight (20.3%), and were more frequently small for gestational age (28.1%) compared to the overall data and the general Austrian population. Moreover, risk factors for poor maternal and fetal outcomes during pregnancy were overrepresented in the cohort compared with the general population, and included hypertension (16.4%), proteinuria (27.9%), and smoking (39.3%).

DIAGNOSIS OF FABRY DISEASE IN WOMEN

The diagnosis of FD in women is often delayed owing to the initial non-specificity of the presenting symptoms. Some young heterozygotes are essentially asymptomatic, and manifestations in women are heterogeneous. Most worrisome, in addition to this, is the lack of awareness of female presentations common among physicians. This leads to delayed and complicated diagnoses, exposing women to the risk of irreversible damage caused by the disease.

Pedigree analysis of X-linked disorders predicts approximately twice as much prevalence of this disease in women than in men. However, data from observational studies such as the FOS and Fabry Registry suggest near parity in disease ascertainment, implying that many women with FD remain undiagnosed or unreported[2,57].

After detailed anamnesis, including the collection of family history, the physical examination of a female patient with a classic phenotype may reveal skin lesions compatible with angiokeratomas, which can suggest a possible case of FD. Similarly, observation of typical keratopathy (cornea *verticillata*) due to Gb3 deposition in the cells of the basal corneal epithelium can be of great help in identifying women with little symptomatology. On the other hand, although some studies have demonstrated Gb3 deposits in renal tissues[58] and the myocardium[59], in a comprehensive study of 57 women with FD, Gupta *et al.* demonstrated a paucity of Gb3 deposits in vascular endothelial cells. These deposits were somewhat higher in the perineurium but had no relationship with clinical features[60].

Homozygous men have low alpha-Gal enzyme activity and can be diagnosed quickly and easily. For heterozygous women suspected of FD, alpha-Gal activity in the peripheral blood or plasma leukocytes is variable, depending on lyonization skewing[61,62]. Approximately 40%-60% of women with a confirmed diagnosis of FD show a normal range of enzyme activity in leukocytes[63,64].

Therefore, genetic analysis for mutations in *GLA* has become the gold standard for the diagnosis of FD in women[65]. This is straightforward when family history and knowledge of the mutation facilitate targeted evaluation[61], but presents potential difficulties in female index cases and in screening studies, where full sequence analysis is necessary. However, in some cases, gene sequencing may fail to detect significant deletions or duplications, large gene rearrangements, and cryptic splice-site mutations[66]. Notably, *GLA* contains a significant number of Alu repeat elements, and in cases of FD heterozygous patients, Alu-Alu recombination events may not be detected through sequencing, leading to negative results[67]. In such cases, multiplex ligation-dependent probe amplification and, if necessary, alpha-Gal mRNA expression analysis should be performed on the patient's fibroblasts to provide evidence of defects in transcriptional regulation.

Owing to advances in high-throughput next-generation sequencing, gene panels incorporating *GLA* can now be used to screen high-risk patients. These screenings can detect multiple *GLA* variants of unknown significance, necessitating complementary clinical and biochemical testing. However, recent research has raised controversy regarding the possible influence of specific single nucleotide polymorphisms, especially those located in noncoding regions, making case-by-case decisions necessary[68].

To overcome the potential setbacks imposed by the frequently uninformative results derived from enzyme activity assays in women with suspected FD, new biomarkers have emerged to assist in the diagnosis based on the measurement of Gb3 and its deacylated product, lyso-Gb3.

In women with FD, it is common to find elevated urinary excretion of Gb3[69,70], which is up to ten times higher than that in women without the disease. However, plasma concentrations of Gb3 vary and may even be within the normal range[71,72]. In contrast to Gb3, plasma concentrations of lyso-Gb3 are usually found to be increased, independent of Gb3 levels[73]. Thus, plasma lyso-Gb3 has become a more reliable biomarker for the diagnosis of FD in women, with a potential role not only in diagnosis but also in differentiating between classic and late-onset phenotypes[74].

With the development of more sensitive liquid chromatography-mass spectrometry techniques, several lyso-Gb3 analogs and isoforms have been found to be excreted at higher levels in the urine of patients with FD compared to the overall level of total lyso-Gb3. This provides a more informative assessment[75,76].

Two recent studies combined the use of alpha-Gal activity and plasma lyso-Gb3 to improve the effectiveness of FD diagnosis in women using dried blood spots as test samples[77,78]. In a study by Baydakova *et al.*[77], the alpha-Gal activity/plasma lyso-Gb3 ratio demonstrated a sensitivity of 100% in distinguishing a group of 35 female patients from controls (n = 140). This ratio was significantly different between symptomatic and asymptomatic patients. The measurement of alpha-Gal and plasma lyso-Gb3 alone showed sensitivities of 8.6% and 74.4%, respectively. Furthermore, a cut-off value of 2.5 demonstrated a sensitivity and specificity of 100%.

Similarly, in a study by Balendran *et al.*[78] involving 11948 women with suspected FD, enzyme activity together with lyso-Gb3 concentration in dried blood spots substantially improved the diagnostic detection of FD compared with enzyme activity alone. Abnormal values for both were highly suggestive of FD [a 97%

positive predictive value (PPV), similar to that in men]. In cases with abnormal biochemical values, elevated lyso-Gb3 was a much more important indicator than low enzyme activity (39% *vs.* 6% PPV). Patients with negative results for both biochemical parameters were unlikely to have FD, even in clinically suspicious cases. Additionally, the researchers suggested that the use of a biochemical strategy combining alpha-Gal activity and plasma lyso-Gb3 levels drastically decreases the number of unnecessary genetic testing in women. This strategy prevents the identification of benign variants that are carried by women at a high rate[6]. However, it cannot be used as a standalone test for families with an index patient. Plasma lyso-Gb3 concentrations may be low in pre-symptomatic female relatives and in young individuals with suspected FD; therefore, genetic testing is necessary to avoid misdiagnosis[78].

FOLLOW-UP

As FD is a progressive multi-systemic disease with reduced life expectancy, early diagnosis and treatment are essential. In the absence of early markers of organ involvement, structured follow-up of patients could be a strategy for the early detection of organ damage associated with the disease.

It is highly advisable to perform an initial baseline evaluation in individual patients regardless of their sex and phenotype, with subsequent modifications in the intensity and periodicity of follow-up. These modifications can be made according to the phenotype, specific therapeutic status, and approximate age at the onset of each organic condition. In this sense, knowledge of the natural history of the disease based on phenotype and sex would be useful for scheduling individualized follow-ups. In the absence of early markers of organ damage, structured follow-up could be useful, especially for women, as the disease development is more heterogeneous than in men. This approach may enable the early detection of clinical and analytical alterations, indicating the need for early initiation of specific treatment.

Other specific considerations for follow-ups in women with FD include the use of Cardiac MRI for cardiac evaluation[8], even in the absence of ventricular hypertrophy on echocardiography. Cardiac MRI is useful in detecting fibrosis and decreased T1 mapping. Additionally, tracking the evolutionary trends of lyso-Gb3 levels and the alpha-Gal activity/plasma lyso-Gb3 ratio may prove useful in monitoring disease evolution in women[77].

Patient monitoring depends on the rate of disease progression and severity. The clinical goals of optimal monitoring are early diagnosis and timely initiation of therapy to prevent progression to irreversible tissue damage and organ failure. Several factors are important for routine clinical assessment, particularly the type of variant, distorted XCI, predominant expression of the mutant allele, and whether the patient is symptomatic or asymptomatic. The proposed multidisciplinary follow-up plan for patients with FD is presented in Table 2.

TREATMENT

The therapeutic goals of FD include: (1) reduction of symptoms; (2) delaying/preventing the progression of organ manifestations; (3) improvement in QoL; and (4) normalization of life expectancy. There are concomitant medications to achieve several of these objectives that should be used according to the clinical manifestations of patients with FD. These include pregabalin and duloxetine for neuropathic pain; platelet aggregation inhibition for stroke; renin-angiotensin system blocker, aldosterone antagonist drugs, and sodium-glucose linked transporter 2 inhibitors for patients with eGFR reduction and albuminuria/proteinuria; diuretics, renin-angiotensin system blocker, pacemaker, or implantable cardioverter defibrillator (if indicated) in patients with symptomatic heart disease. Platelet aggregation inhibition or anticoagulants may also be used if indicated for cardiac involvement[79].

Table 2. Proposed multidisciplinary follow-up in patients with FD

Coordination consultation: annual/6 months/on demand	Clinical evaluation at each visit. Blood and urine analysis (*) with plasma Lyso-Gb3 (basal and annual). Biobank (if available) Periodic audiometry as required Baseline and periodic ophthalmology examination according to symptomatology Baseline and periodic spirometry every 2 years (minimum) according to clinical symptoms Others according to symptoms: Densitometry, annual SF36 questionnaire, FIPI Index, pain questionnaire for adults (BPI) (**), and psychiatric consultation if necessary
Nephrology: annual/6 months	If albuminuria-proteinuria or alteration in the GFR: optimization treatment hypertension and proteinuria.
Cardiology: annual	Echocardiogram every 12-24 months Cardiac MRI (T1 mapping) and Holter, depending on age and phenotype
Neurology	If neurological symptoms: annual follow-up with brain MRI If no neurological symptoms: baseline brain MRI from 30 years of age/neurosonographic studies

FD: Fabry disease; FIPI: Fabry International Prognostic Index; GFR: glomerular filtration rate; MRI: magnetic resonance imaging; (*) including GFR, urinary albumin-creatinine ratio, N-terminal pro-B-type natriuretic peptide, and troponin T; (**) Pain 2014 Nov;155(11):2301-5.

Symptomatic treatment has shifted to a more integrated therapeutic approach using FD-specific treatments. These include three molecules for ERT (Agalsidase alfa at a dose of 0.2 mg/kg biweekly, Agalsidase beta at 1.0 mg/kg biweekly, and Pegunigalsidase alfa at 1.0 mg/kg biweekly or 2.0 mg/kg monthly - not approved at this dose in Europe) and the pharmacological chaperone Migalastat, which has been approved for use and is currently available[80]. Specific treatment of FD must correct or ameliorate defects in the altered metabolic pathway, preventing rather than treating the various complications of FD. When initiated early, it might alter the natural course of the disease, allowing its stabilization or even reducing the disease burden and improving the QoL of patients[79].

Multiple studies have shown that biweekly intravenous infusions effectively reduce plasma and tissue Gb3 accumulation; improve anhidrosis, peripheral nerve function, pulmonary gas exchange, gastrointestinal symptoms, and acroparesthesia; and stabilize renal function[79]. Although relatively few women were included in the pivotal trials, ERT appeared to benefit them. Both treatments (Agalsidase alfa and Agalsidase beta) have shown improvements in different aspects of the disease, particularly in women[10,81].

In a direct comparison study of the effectiveness of Agalsidase alfa, involving 172 men and 78 women from the FOS registry after 4 years of treatment, women started treatment significantly later than men - women, 48.6 years (28.3-66.5) *vs.* men, 33.9 years (21.5-48.3). Disease severity (FOS-MSSI) was similar between both sexes, with comparable responses to Agalsidase alfa, suggesting that there should be no differences in the criteria for treatment evaluation between women and men[82].

According to current recommendations for women, regardless of the phenotype, it is necessary to demonstrate signs or symptoms of FD (ruling out other causes) before starting treatment[6]. The initiation of ERT in men with FD is clinically well established, as patients often suffer from organ involvement typical of FD and/or abnormal biomarkers (low or absent alpha-Gal activity and elevated plasma lyso-Gb3 values). However, the age at which ERT is initiated in men with classical asymptomatic FD is not clearly established. In contrast, the optimal time to initiate ERT in women with FD, often misclassified as “only” asymptomatic or mildly symptomatic carriers, remains unclear, as the manifestations and progression of the disease as well as the levels of biomarkers are diverse and heterogeneous. Owing to this heterogeneous clinical and biochemical picture, the optimal time for initiating ERT in women remains controversial.

Current guidelines and recommendations for FD suggest the initiation of ERT in women after the onset of the first renal, cardiac, and/or CNS complication typical of FD, or in the setting of a rapidly progressive

disease[6]. According to Biegstraaten *et al.*[83], ERT should be considered in women with classical and non-classical phenotypes if there is albuminuria/proteinuria, eGFR < 90 mL/min/1.73 m^2, cardiac hypertrophy, signs of rhythmic disturbances, cerebral white matter lesions, transient ischaemic attack or stroke, and other symptoms of the peripheral nervous system, such as pain or gastrointestinal symptoms related to FD. However, because ERT is assumed to be most effective when initiated early, before the onset of fibrosis or other irreversible tissue damages[10], this strategy could be suboptimal.

These factors have been highlighted in reports from Spain and other countries documenting the undertreatment of women with Fabry disease according to published recommendations. Evidence from the literature suggests that women are referred less frequently for diagnostic interventions and treated less aggressively than men[3-5]. This real-life sex-specific disparity in treatment initiation has been consistently identified. Sánchez *et al.*[5] reported in their series of 99 Spanish women that according to the European treatment guidelines, 56.6% of the untreated patients could be candidates for treatment. Barba-Romero *et al.*[3], in a study of Spanish women from the FOS registry, found that 76.7% of women who did not receive specific treatment met one or more criteria for initiating ERT (30% neuropathic, 43.3% renal, and 23.3% cardiac criteria). Lenders *et al.*, in a study that included 224 German women with FD, reported that while 55% of the women received treatment, 1/3 of those not treated had at least one clinical manifestation subsidiary to specific treatment[4].

Although no studies have directly compared the long-term effectiveness of ERT between men and women, observational studies based on the FOS registry using Agalsidase alfa have found no significant differences[82,84]. Early initiation of ERT is associated with better performance of specific treatments. In a study by Hughes *et al.*, early ERT start was defined as treatment onset after less than 24 months since diagnosis or at the detection of the primary symptoms; reduced cardiovascular or renal events were seen in these patients of both sexes compared with those with later ERT[84]. On the other hand, the risks of cardiovascular or renal events have been shown to be significantly higher[81] in patients who already have LVH and/or eGFR < 90 mL/min/1.73 m^2 at the start of treatment; however, female sex was shown in multivariate analysis to be associated with a reduced risk of renal events. All these findings of a decrease in events under these circumstances have also been confirmed in the Fabry registry with Agalsidase beta[10], in addition to beneficial effects on cardiac hypertrophy specifically in women[85]. Similar outcomes have been observed with Migalastat[86] in patients with amenable mutations, with a significant LVMI decrease in both men and women. Considering these data, analysis of the factors that determine whether women are treated less aggressively than men is crucial. Addressing these disparities is essential for avoiding the loss of the therapeutic window that could allow women to obtain the most optimal benefits with specific treatments.

CONCLUSIONS

The development of ERT and the need for comprehensive clinical evaluation of potential candidates for its administration, together with the implementation of postmarketing registries for the drugs used, have reshaped the understanding of FD in women. It is clear that female heterozygosity for mutations in *GLA* can present with an array of biochemical and clinical consequences of alpha-Gal deficiency. Women have a wide spectrum of clinical manifestations of FD, with both 'classical' and 'non-classical' phenotypes, and greater phenotypic heterogeneity than hemizygous men. Women may be apparently asymptomatic throughout their lives; however, a non-negligible proportion may develop typical disease involvement, mainly cardiac and cerebrovascular, albeit with a delay in onset of approximately 10 years, compared to men. This variability, both in the extent and severity of organ involvement, correlates positively with patient age, which has a significant impact on their QoL. It has been postulated that unbalanced inactivation of the X-chromosome could explain, at least in part, the different clinical manifestations of FD in women.

Nevertheless, the early and accurate diagnosis of FD in women remains challenging. Owing to frequently uninformative results derived from enzyme activity assays, genetic analysis of mutations in *GLA* has emerged as the gold standard for the diagnosis of FD in women. Recent studies have suggested that the use of a biochemical strategy combining alpha-Gal activity and plasma lyso-Gb3 analyses could decrease the number of unnecessary genetic tests in women and avoid the identification of benign variants that are carried by women at a high rate. Women diagnosed with this condition should be thoroughly assessed to the same extent as male patients. A tailored strategy for follow-ups in women with FD is highly advisable. It should be designed to consider the genotype of the patients and other clinical and analytical biomarkers of early organ damage. Current recommendations for the initiation of ERT in female patients may underestimate the appropriate time. This could impede women from obtaining the benefits of early ERT initiation. In addition, there is some evidence that women with FD are still at risk of being undertreated, unlike men.

DECLARATIONS

Authors' contributions

Preparation of the article and the bibliographic review: Barba-Romero MA, Sánchez-Martínez R

Availability of data and materials

Not applicable.

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Conflicts of interest

Rosario Sánchez-Martínez received fees on advisory boards, speaking fees or travel support, and participated in clinical trials and registries sponsored by Shire, Takeda, Amicus Therapeutics, Sanofi-Genzyme, Eusa Pharma, Alnylan, Chiesi, Pfizer, and Bayer.

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Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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