Fabry disease: integrative aspects from diagnosis to treatment

Doença de Fabry: aspectos integrativos desde o diagnóstico até o tratamento

DOI:10.34119/bjhrv7n1-563

Recebimento dos originais: 25/01/2024
Aceitação para publicação: 26/02/2024

Paulo Cézar Gregório
PhD in Microbiology, Parasitology and Pathology
Institution: Universidade Federal do Paraná, Setor de Ciências Biológicas
Address: Av. Cel. Francisco H. dos Santos, 100, Jardim das Américas, Curitiba - PR,
CEP: 80531-980
E-mail: paulocezargregorio@gmail.com

Regiane Stafim da Cunha
PhD in Microbiology, Parasitology and Pathology
Institution: Universidade Federal do Paraná, Setor de Ciências Biológicas
Address: Av. Cel. Francisco H. dos Santos, 100, Jardim das Américas, Curitiba - PR,
CEP: 80531-980
E-mail: regidacunha@ufpr.br

Carolina Amaral Bueno Azevedo
Master in Microbiology, Parasitology and Pathology
Institution: Universidade Federal do Paraná, Setor de Ciências Biológicas
Address: Av. Cel. Francisco H. dos Santos, 100, Jardim das Américas, Curitiba - PR,
CEP: 80531-980
E-mail: carolina.amaral1@ufpr.br

Marlene Antônia dos Reis
Doctorate in Human Pathology
Institution: Universidade Federal do Triângulo Mineiro
Address: Rua Frei Paulino, 30, Abadia, Uberaba - MG, CEP: 38025-180
E-mail: mareispatologia@gmail.com

Andréa Emília Marques Stinghen
Doctorate in Health Sciences
Institution: Universidade Federal do Paraná, Setor de Ciências Biológicas
Address: Av. Cel. Francisco H. dos Santos, 100, Jardim das Américas, Curitiba - PR,
CEP: 80531-980
E-mail: andreastinghen@ufpr.br
ABSTRACT
Aim: identify the main aspects of Fabry disease (FD) from clinical suspicion to diagnosis, its vascular and cellular effects, in addition to treatment. Methods: This study is an integrative review of the literature supported by the search for articles in databases, PubMed, Lilacs, Scielo, journals, and websites, with the following descriptors “Fabry disease”, “Fabry Disease treatment”, “Agalsidase-β”, “Agalsidase-α”, “Migalastat”, “inflammatory biomarkers” and “oxidative stress”, using original research articles and reviews between the years 1991 and 2023. This bibliographic survey was carried out in the period 01/10/2022 to 20/04/2023. Results: From a total of 340 articles found, 85 articles were selected. Discussion: The natural history of FD appears to be very complex, with multisystemic involvement and phenotypic variability. The analysis of FD symptoms is essential to the early diagnosis, aiming for greater success in therapy and prognosis, ensuring better patients’ quality of life and survival. Conclusion: This review addresses the diagnosis and main therapeutic approaches to guide health professionals and researchers, and to stimulate the development of research on FD.

Keywords: fabry disease, fabry disease treatment, lysosomal storage disorder.

RESUMO

Palavras-chave: doença de fabry, tratamento da doença de fabry, distúrbio de armazenamento lisossomal.

1 INTRODUCTION
Fabry disease (FD) is one of the main lysosomal storage disorders, affecting 1:117,000 births (MEIKLE et al., 1999). It is a rare disease with an X-linked inheritance pattern, characterized by mutations in the GLA gene (Xq22.1), which results in a partial or total...
deficiency of the enzyme α-galactosidase (α-GAL). Therefore, α-GAL deficiency leads to the lysosomal accumulation of glycosphingolipids, especially the metabolites globotriaosylceramide (Gb3) and the deacetylated form of Gb3, globotriaosylsphingosine (lyso-Gb3). Sphingolipids accumulation in FD results in cellular and tissue damage, mainly affecting the cardiovascular system, the kidneys, and the central nervous system, which leads to a reduction in the life expectancy of Fabry patients (ARENDS; HOLLAK; BIEGSTRAATEN, 2015; DESNICK, 2015; GERMAIN, 2010). As an X-linked disorder, the clinical manifestation of FD uses to be more evident in hemizygous men. While heterozygous women, due to random inactivation of the X chromosome, can present a wide spectrum of manifestations and severity of the disease, from asymptomatic to severe cases (MACDERMOT; HOLMES; MINERS, 2001a; VELOSO et al., 2017).

The classical phenotype of FD results from the total absence or low residual activity of α-GAL, characterized by acroparesthesias, angiokeratomas, hypohidrosis, and gastrointestinal symptoms that begin in childhood. The development of proteinuric chronic kidney disease, heart diseases, such as left ventricular hypertrophy (LVH) and conduction disturbances, as well as cerebrovascular disease, occurs throughout adult life (DESNICK et al., 2003; GERMAIN, 2010; LINHART et al., 2007). On the other hand, the non-classical phenotype of FD, also known as late-onset, is related to a greater residual activity of α-GAL, with clinical manifestation usually beginning in adulthood and with a more variable progression of the disease (ARENDS et al., 2017). In the late-onset phenotype, a target organ is affected, most commonly the heart or kidneys, defining the cardiac or renal variants of DF, respectively.

The diagnosis is based on the identification of a pathogenic variant in the GLA gene, and the consequent reduced enzymatic activity of α-GAL, as well as the elevated levels of Gb3 and lyso-Gb3, associated with clinical manifestations (CHIEIA et al., 2010; DESNICK et al., 2003). It is worth noting, however, that women with the disease may have normal or slightly reduced α-GAL activity, and genetic testing is recommended for the diagnosis (Silva et al., 2022).

FD treatment is mainly based on enzyme replacement therapy (ERT), with one of the currently available formulations, agalsidase-α (0.2 mg/kg/e.o.w) or agalsidase-β (1.0 mg/kg/e.o.w). Early ERT treatment is related to an attenuation of FD progression, including delaying the renal function decline and improvement of left ventricular hypertrophy (EL DIB et al., 2017; FELLGIEBEL et al., 2014; GERMAIN et al., 2013, 2015; ORTIZ et al., 2016; WARNOCK et al., 2012). More recently, the pharmacological chaperone migalastat was approved for patients with migalastat-amenable GLA pathogenic variants. In such patients, α-
GAL with abnormal protein folding is produced, which is prevented by the pharmacological chaperone by binding and stabilizing endogenous α-GAL, facilitating its transport to lysosomes, and restoring its enzymatic activity (FELDT-RASMUSSEN et al., 2020; GERMAIN et al., 2016). Furthermore, the concomitant use of medications for associated symptoms and illnesses, such as pain and gastrointestinal manifestations, may be necessary.

This study aimed to investigate the main clinical aspects of FD, elucidating its clinical manifestations, and vascular and cellular effects, in addition to treatment. Therefore, we hope this study can help understand the pathophysiology of FD and the different clinical conditions of this disease.

2 METHODS

This study is an integrative review of the literature that is supported by the search for articles in databases, Pub Med, Lilacs, Scielo, journals, and websites, with the following descriptors “Fabry disease”, “Fabry Disease treatment”, “Agalsidase-β”, “Agalsidase-α”, “Migalastat”, “inflammatory biomarkers” and “oxidative stress”, using original research articles and reviews between the years 1991 and 2023. This bibliographic survey was carried out in the period 01/10/2022 to 20/04/2023. A total of 340 works were found after applying the inclusion criteria: articles that fell within the scope of the review, such as original research articles and reviews between the years 1991 and 2023, written in Portuguese, English, or Spanish. Furthermore, the article by Ortiz et al. (2017) was used as methodological support for this work. Exclusion criteria: works published before the established dates, with incomplete content, without the description of the methodology, and outside the scope of the research. 85 scientific articles that were within the objective of this review were selected. Through descriptive analysis, the studies were evaluated for subsequent identification and extraction of relevant data. Figure 1 demonstrates the steps followed to select the articles used in this work.
Table 1 references the main scientific articles used in this integrative review and presents the title of the articles, year of publication, and publication journals. The articles listed best fit the criteria and contributed to the understanding and resolution of the guiding question of the present study.

<table>
<thead>
<tr>
<th>TITLE</th>
<th>YEAR</th>
<th>JOURNAL</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>An Asymptomatic Heterozygous Female with Fabry Disease: Implications for Enzyme Replacement Therapy</td>
<td>2005</td>
<td>Journal of Nippon Medical School</td>
<td>(INAGAKI et al., 2005)</td>
</tr>
<tr>
<td>Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation</td>
<td>2012</td>
<td>Nephrology Dialysis Transplantation</td>
<td>(WARNOCK et al., 2012)</td>
</tr>
<tr>
<td>Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease</td>
<td>2015</td>
<td>Journal of Medical Genetics</td>
<td>(GERMAIN et al., 2015)</td>
</tr>
<tr>
<td>Lyso-Gb3 activates Notch1 in human podocytes</td>
<td>2015</td>
<td>Human Molecular Genetics</td>
<td>(SANCHEZ-NIÑO et al., 2015)</td>
</tr>
<tr>
<td>Time to treatment benefit for adult patients with Fabry disease receiving agalsidase β: data from the Fabry Registry</td>
<td>2016</td>
<td>Journal of Medical Genetics</td>
<td>(ORTIZ et al., 2016)</td>
</tr>
<tr>
<td>The kidney in fabry disease: More than mere sphingolipids overload</td>
<td>2016</td>
<td>Journal of Inborn Errors of Metabolism and Screening</td>
<td>(TRIMARCHI, 2016)</td>
</tr>
<tr>
<td>Oxidative Stress and Cardiovascular-Renal Damage in Fabry Disease: Is There Room for a Pathophysiological Involvement?</td>
<td>2018</td>
<td>Journal of Clinical Medicine</td>
<td>(RAVAROTTO et al., 2018)</td>
</tr>
<tr>
<td>Enzyme replacement therapy clears GB3 deposits from a podocyte cell culture model of Fabry disease but fails to restore altered cellular signaling</td>
<td>2019</td>
<td>Cellular Physiology and Biochemistry</td>
<td>(BRAUN et al., 2019)</td>
</tr>
</tbody>
</table>
3 RESULTS AND DISCUSSION

3.1 DEFINITION AND GENETIC ASPECTS

FD is characterized by the absence or deficient activity of the α-GAL enzyme, which causes the accumulation of metabolites, such as Gb3. The α-GAL enzyme is coded by the GLA gene, which is 12 kb in size, has seven exons, and is in position q22.1 of the X chromosome (CHIMENTI et al., 2004; FELLGIEBEL et al., 2014). More than a thousand variants of this gene have been described that can cause the silencing or defective synthesis of α-GAL, and, therefore, may be related to the development of FD. Due to the high allelic heterogeneity of the GLA gene, Germain et al. (2022) highlighted that one of the greatest challenges is identifying whether the variant contributes to the disease, especially with a late-onset phenotype (GERMAIN et al., 2022). Currently, GLA gene variants are classified as pathogenic, probably pathogenic, of uncertain significance, probably benign or benign, with the first two being associated with the development of FD (Germain et al., 2022).

Due to the x-linked inheritance pattern, FD has high penetrance in men because they are homozygous. Heterozygous women carrying pathogenic variants of the GLA gene can also develop FD, with different degrees of severity, due to the random inactivation of the X chromosome that leads to the formation of the Barr body (high condensed X chromosome) (SVENSSON; FELDT-RASMUSSEN; BACKER, 2015; WANG et al., 2007). According to Lyon’s hypothesis, this X inactivation occurs randomly, which results in only one transcriptionally active X chromosome, providing a dose compensation mechanism to the double genetic load of the X chromosome present in women.
Figure 2 – Fabry disease in women. Fabry Disease (FD) is caused by a pathogenic variant in the GLA gene, which is located on the long arm of the X chromosome (Xq22). Random X inactivation that occurs via chromatin condensation forming the Barr body, resulting in cells with or without functional α-GAL in the same organism. Women with FD present a wide phenotypic variation, from asymptomatic to developing the classic phenotype. FD, Fabry disease.

Women with Fabry Disease

Studies have shown that the same genotype can present great phenotypic heterogeneity, while different genotypes can have similar phenotypes, which indicates that the genotype-phenotype relationship is still controversial. Phenotypic variability can be explained, at least in part, by phenotype-modifying factors, such as epigenetic factors (CAMMARATA et al., 2015). The classic phenotype of FD is associated with pathogenic variants that result in total loss or deficient residual function of the enzyme, generally due to nonsense and missense mutations, the latter occurring in the exchange of amino acids at the active site or in key residues of the enzyme (GERMAIN et al., 2022). Furthermore, pathogenic variants can be specific to descendants of the same family (ORTIZ et al., 2016; ROZENFELD et al., 2006). In women with FD, mosaicism can be observed due to the random inactivation of the X chromosome, which directly affects the clinical manifestations of the disease (MAUER et al., 2014).

α-GAL deficiency causes the progressive accumulation of its metabolites, mainly Gb3, which causes damage to the metabolism of glycosphingolipids in lysosomes. This accumulation causes damage to the most diverse cell types, including podocytes, tubular, mesangial, and interstitial cells of the kidneys, cardiomyocytes, fibroblasts, endothelial, and nerve cells (DESNICK, 2015; GERMAIN, 2010). Thus, FD is a multisystemic disease, affecting irreversibly and progressively the kidneys, heart, and nervous system, with clinical...
manifestations that can appear over lifetime, from childhood to adulthood, unlike other lysosomal diseases (Nakao et al., 2003; Park et al., 2011). Figure 3 illustrates the lysosomal accumulation of Gb3 in the absence of α-GAL or its malfunction.

Figure 3 – Cellular dysfunction is caused by the accumulation of Gb3 resulting from total or partial deficiency of the α-GAL enzyme. Mutations in the GLA gene can cause the absence or defective synthesis of α-GAL, the enzyme responsible for cleaving globotriaosylceramide (Gb3) in lysosomes. Total or partial α-GAL deficiency, characteristic of Fabry disease (FD), leads to lysosomal accumulation of Gb3 and cellular damage.

Source: created by the author.

3.2 EPIDEMIOLOGY OF FD

FD has an estimated incidence of 1:117,000 live births, however, these data may be underestimated due to the diversity of symptoms that can lead to incorrect diagnoses (GERMAIN, 2010; MEIKLE et al., 1999; TURKMEN et al., 2016). It is estimated that, among lysosomal storage disorders, FD is the second most common disease, only behind Gaucher disease. Otherwise, Fabry disease neonatal screening studies indicate that its incidence may be higher. Spada et al. (2006) found an incidence of 1:3,100, in which the proportion of classic phenotype and late-onset phenotype was 1:11 (SPADA et al., 2006). In another study, Sawada et al. (2020) screened 599,711 newborns, among which 57 individuals were reported with 26 variants of the GLA gene, 15 of them pathogenic, whereas 11 were variants of unknown significance (Sawada et al., 2020). Hence, it is important to keep mind that one of the challenges when it comes to detecting GLA gene variants is determining whether the variant is pathogenic.
or benign, while several variants of unknown significance have been identified (Germain et al., 2022).

Due to renal impairment in FD, several clinical studies have screened patients with kidney disease for the diagnosis of Fabry by evaluating the enzymatic activity of α-GAL and genetic testing. Turkmen et al. (2016) evaluated 313 patients with CKD not receiving renal replacement therapy, and identified three carriers of FD and, subsequently, eight more carriers through family screening (TURKMEN et al., 2016). Recently, Mallett et al. (2022) also carried out screening for the diagnosis of FD in a cohort of 3,000 patients with CKD, in which three new Fabry cases were identified (MALLET et al., 2022). Yalin et al. (2019) evaluated 5,657 patients who received kidney transplants and found 17 people with FD. Furthermore, family screening identified 43 new cases among 71 relatives of the index cases (YALIN et al., 2019). This highlights the importance of correct diagnosis to adopt appropriate therapies to mitigate the progression of the disease, cascade family screening as well as appropriate genetic counseling (Yalın et al., 2019). Other epidemiological studies have evaluated the presence of FD in groups considered to be at high risk, such as patients with hypertrophic cardiomyopathy or cryptogenic stroke. Brouns et al. (2010) reported that FD may be responsible for approximately 1% of cerebrovascular diseases of unknown origin in young patients (BROUNS et al., 2010). Azevedo et al. (2020) demonstrated that the prevalence of FD, in a cohort of 780 patients with hypertrophic cardiomyopathy, was 0.9% (Azevedo et al., 2020). Sadasivan et al. (2020) identified a 2% prevalence of FD in a cohort of 266 patients with left ventricular hypertrophy of unknown origin (SADASIVAN et al., 2020). Therefore, the prevalence of FD is higher in patients on renal replacement therapy, with early stroke, and with left ventricular hypertrophy of unknown origin compared to the general population, and screening for investigation of FD is indicated in these groups (Germain, 2010).

In Brazil, data on the prevalence of FD are scarce. Sodré et al. (2017) analyzed 36,442 patients with kidney disease treated in 854 dialysis centers in Brazil, of which 8,087 were tested for α-GAL enzymatic activity and genetic testing, resulting in the detection of 71 FD carriers. The general prevalence was 0.19%, but after algorithm optimization, the general prevalence was updated to 0.87% (SODRÉ et al., 2017). In addition, the screening of family members (n=1,214) of the index cases allowed the diagnosis of 115 new cases (SODRÉ et al., 2021). Recently, the Rare Diseases Committee (Comdora) of the Brazilian Society of Nephrology (SBN) published the Brazilian FD consensus to standardize diagnostic, case tracking, and treatment recommendations. According to the consensus, family screening is recommended based on index cases and in groups that present renal, cardiac, and neurological changes or
clinical symptoms/signs suggestive of FD, which does not have a defined etiology (Silva et al., 2022).

3.3 ENDOTHELIAL DYSFUNCTION

Clinical and experimental studies have raised the hypothesis that endothelial dysfunction may underlie macro and microvascular complications in FD. The combination of acroparesthesia, arteriopathy, albuminuria, and Gb3 deposits in glomerular endothelial cells may indicate a more severe phenotype (GERMAIN, 2010). Further, it suggested an association between Gb3 accumulation and reduced NO bioavailability, atherogenesis, thrombosis, and impaired vasodilation (KANG et al., 2013; SHEN et al., 2008), in addition to an increased ROS production in endothelial cells (Shen et al., 2008).

Gb3 accumulation in the endothelium was associated with NO depletion, reducing endothelium-dependent NO vasodilation in isolated aortic rings (J. L. Park et al., 2008). Park et al., (2008), demonstrated endothelial dysfunction caused by the accumulation of Gb3 in GLA gene knockout mice. The study also found a decrease in eNOS expression in endothelial cells and, consequently, endothelium-dependent vasodilation was negatively affected (PARK et al., 2008). Furthermore, Kang et al., (2014), suggested that the uncoupling of the eNOS enzyme in a GLA knockout murine model in mesenteric arteries may, in part, contribute to endothelial dysfunction (KANG et al., 2013). Accumulation of Gb3 is frequently observed in endothelial cells in patients with FD, which results in organ perfusion impairment (SATOH, 2014). Choi et al., (2014), demonstrated that Gb3 modulates the expression of calcium-dependent potassium channels (KCa 3.1) in endothelial cells through a clathrin-dependent process. This mechanism directly implicates endothelial dysfunction in patients with FD. Thus, the authors demonstrated that Gb3-induced degradation of KCa 3.1 channels plays a crucial role in endothelial dysfunction in an animal model and humans with FD (CHOI et al., 2014).

Histopathological findings demonstrated that lysosomal deposits in FD occur predominantly in the endothelium, in the middle layer of small vessels, renal tubules, glomeruli, cardiac muscle, conducting fibers, autonomic ganglia, and brain structures (MacDermot et al., 2001a, 2001b). Furthermore, clinical data demonstrated renal, cardiac, and nervous system involvement found in these patients. Therefore, lipid accumulation in cells triggers a progressive cascade of processes that lead to changes in cellular structure, tissue injury, and consequent organ failure (SEYDELMANN et al., 2015). Also, the accumulation of glycosphingolipids in the vascular endothelium can increase the risk of stroke due to the thickening of small vessels with subsequent occlusion and due to the endothelial dysfunction...
generated (MOORE et al., 2001). Segura et al. (2013) showed a significant increase in the expression of sVCAM-1, C-reactive protein (CRP) and tumor necrosis factor-α TNF-α (SEGURA et al., 2013). Other studies also show an increase in sVCAM-1, sICAM, P-selectin, E-selectin, and PAI (GELDERMAN; SCHIFFMANN; SIMAK, 2007), suggesting that the local process in the vessel wall may be the main responsible for ischemic lesions in patients with SCD (ROMBACH et al., 2010).

The establishment of new biomarkers is necessary to advance the diagnosis and treatment of FD. Syndecan-1, also called CD138, is a transmembrane heparan sulfate proteoglycan expressed in endothelial cells, stromal fibroblasts, and inflammatory cells (CAVALCANTE et al., 2016). It is considered a biomarker of endothelial glycocalyx damage. Interestingly, syndecan-1 is an early marker of acute kidney injury in pediatric patients undergoing cardiac surgery (CAVALCANTE et al., 2016; NIEUWDORP et al., 2005). Another important biomarker that has been studied in heart patients is GDF-15, a member of the TGF-β (transforming growth factor-β) superfamily of cytokines, which is weakly expressed under normal conditions (SUN et al., 2018). Recently, it was observed that GDF-15 levels increased in response to tissue ischemia, such as cardiovascular injury and kidney disease progression (HO et al., 2013; NAIR et al., 2017). Furthermore, GDF-15 is associated with increased risks in patients with acute myocardial infarction (KEMPF; WOLLERT, 2009). The inflammatory profile found in patients with FD may corroborate the increased levels of syndecan-1 and GDF-15 (GREGÓRIO et al., 2022).

3.4 SYMPTOMS

The lysosomal accumulation of glycosphingolipids due to the dysfunction of α-GAL is the initial pathological event in FD and begins in the intrauterine phase in classically affected patients (VEDDER et al., 2006). Therefore, the most common clinical manifestations of classic FD generally begin in childhood or adolescence. Skin lesions, called angiokeratomas, are typically located on the torso, scrotum, and periumbilical region but can also be found on the hands, feet, and face. The main clinical consequence of FD emerges from the progressive accumulation of Gb3 in the vascular endothelium leading to ischemia and infarction, especially in the heart and brain. Furthermore, it can affect the coagulation system, activating prothrombotic factors. The involvement of different types of cells in different organs and systems explains the multisystemic nature of this disease. Thus, Gb3 deposition in podocytes is related to proteinuria and, in cardiomyocytes, to hypertrophy and cardiac changes (ARENDS; HOLLAK; BIEGSTRAATEN, 2015; BARSAGLINI; SANCHES, 2015). Ischemia caused by
Gb3 deposition in the vascular endothelium and mitochondrial dysfunction may play an important role in cardiac involvement in these patients (CORREIA et al., 2011). The deposition of Gb3 in endothelial, podocyte, and mesangial cells can be observed in Figure 4.

Figure 4: kidney biopsy specimen, osmicated, epoxy-embedded tissue, stained with Toluidine blue under Light microscopy (a and b) and Electron microscopy (c and d). a and b: glomerulus with Gb3 deposits stained in dense, dark blue granules in the cytoplasm of different cells, endothelial cells (EC), mesangial cells (MC) and especially in enlarges podocytes (P). c and d: glomerulus with electron dense multi-lamellated concentric layers Gb3 deposits in lysosomes in Endothelial Cell (EC), Mesangial Cell (MC) and especially in Podocytes (P). RBC: red blood cell; BM – basal membrane. (Original magnification: a: 63x; b: 100x; c and d: 3,000x).

Source: created by the author.

A decrease in the glomerular filtration rate (GFR) has been detected in patients with FD, which may be associated with non-nephrotic range proteinuria. Patients may have a progressive loss of renal function and hypertrophic cardiomyopathy, with severe clinical outcomes including end-stage renal disease, stroke, arrhythmias, and premature death (BOUWMAN, 2012; GERMAIN, 2010; SVENSSON; FELDT-RASMUSSEN; BACKER, 2015). The main clinical characteristics in classic FD patients, regardless of age, are: (I) intermittent acroparesthesia and severe attacks of acral and abdominal pain (Fabry crisis); (II) disseminated cutaneous angiokeratomas; (III) hypohidrosis and (IV) cornea verticillate that do not interfere
with vision (CHIEIA et al., 2010; PORTO et al., 2021). In an observational study involving 20 patients with FD, Whybra et al. (2001) detected, in addition to dermatological symptoms, several other symptoms related to the disease, including renal failure, cerebrovascular disease, and gastrointestinal and cardiac disorders (WHYBRA et al., 2001). Furthermore, studies show that patients with FD who reach the end-stage kidney disease have an increased risk of involvement of other organs, presenting a higher incidence of cardiovascular and cerebrovascular problems (ORTIZ et al., 2010). Germain et al. (2002) observed progressive hearing loss, with a significantly higher prevalence in patients with renal failure or cerebrovascular lesions (GERMAIN et al., 2002). According to the literature, around 10% of heterozygous women develop kidney failure (INAGAKI et al., 2005; WARNOCK et al., 2015).

3.5 DIAGNOSIS

FD is difficult to diagnose in clinical practice, due to its rarity and lack of knowledge of the symptoms by most clinicians. However, the diagnosis is clinical and is supported by laboratorial and molecular analyses that confirm the proper diagnosis. In addition to the classic symptoms of the disease, the diagnosis must be based on measuring the enzymatic activity of α-GAL and demonstrating the presence of the mutation in the GLA gene. The manifestations of the disease in childhood are diverse and nonspecific, affecting several organs, and can easily be confused with other pathologies, including rheumatic diseases (ROZENFELD, 2009). Therefore, these patients take an average of 10 years to confirm the diagnosis of the disease, which is generally made by a multidisciplinary team. After the identification of an index case, a new cases of FD may be detected among the family members (ROZENFELD et al., 2006). In men, after suspicion of the disease, confirmation is made by demonstrating the low activity of the α-GAL enzyme and the presence of the pathogenic variant in the GLA gene. In women, the diagnosis should not be based solely on enzymatic activity, as they may have normal α-GAL activity values. In this case, the appropriate diagnosis must be made based on sequencing studies, finding the pathogenic variant in the gene, in the Xq22 region (Neumann et al., 2013; Seydelmann et al., 2015).

Gb3 concentration can be measured in urine and plasma, as it is usually elevated in FD. However, although it can be a useful non-invasive tool for diagnosis, it is not an ideal biomarker for monitoring response to ERT (LEPEDDA et al., 2013; MACDERMOT; HOLMES; MINERS, 2001b, 2001a). More recently, the Gb3 metabolism product, lyso-Gb3, has been described as a new biomarker for the detection and monitoring of FD. Lyso-Gb3 is a watersoluble molecule and is more easily found in urine (Nowak et al., 2017). The concentration of
lyso-Gb3 is increased in the plasma of patients with FD, and it is appreciated as a diagnostic tool that can help to differentiate men with classic and non-classic phenotypes (NIEMANN et al., 2014). Importantly, this biomarker may be useful in to differentiate pathogenic variants of the GLA gene from benign ones (BOUWMAN, 2012; BRAKCH et al., 2010; WALDEK; FERIOZZI, 2014). Furthermore, recently, studies have shown that podocyturia can be a good biomarker to assess early glomerular involvement in hereditary diseases such as FD since these cells appear in the urine before the development of proteinuria (TRIMARCHI, 2016).

Recently, the presence of urinary mulberry cells (MCs) and mulberry bodies (MBs) has been researched as an early diagnosis of FD. Urinary MCs and MBs are characteristic features of Fabry disease, being released from epithelial cells or podocytes with Gb-3 accumulation, reflecting the podocyte injury (SHIMOHATA et al., 2017; YONISHI et al., 2022). MBs can be distinguished from fat particles by their inner lamellar appearance (Shimohata et al., 2017). Shimohata et al. (2017) present a late-onset FD case, with no abnormal urinary findings except for urinary MCs and MBs. They were able to detect Fabry nephropathy before the presence of any renal clinical symptoms and, thus, could start the ERT before the presence of proteinuria and renal impairment. Because of this, the renal function of the patient seemed to remain stable during the ERT (SHIMOHATA et al., 2017). Yonishi et al. (2022) showed that urinary MBs excretion preceded proteinuria in most patients in a study with 51 FD patients. Also, urinary MBs were negatively correlated with the duration of ERT, showing that ERT reduces the excretion of MBs significantly (YONISHI et al., 2022). Nakamura et al. (2023) evaluated the accuracy of MBs/MCs testing in FD patients and found high sensitivity and specificity. In this study, urinary MBs/MCs were detected in most patients, including asymptomatic patients with normal renal functions. Also, all asymptomatic female carriers tested positive for MBs/MCs (NAKAMURA et al., 2023). Taken together, these findings suggest that the screening of MBs/MCs can be a strong ally for the early diagnosis and monitoring of FD patients.

3.6 TREATMENT

FD is a potentially treatable disease using commercially available ERT. Currently, there are two enzyme formulations for the treatment of FD: agalsidase-α (Replagal, Shire HGT, MA, USA) and agalsidase-β (Fabrazyme, Genzyme Corporation, MA, USA) which are based on enzyme preparations produced in human fibroblasts and in Chinese hamster ovary (CHO) cell culture, respectively (NEUMANN et al., 2013; ROZENFELD, 2009). Except for the oligosaccharide side structures, the amino acid sequences of these products are the same (FERVENZA; TORRA; WARNOCK, 2008). The dose varies depending on the preparation:
0.2 mg/kg of agalsidase-α and 1 mg/kg/dose of agalsidase-β (CHIEIA et al., 2010; TØNDEL et al., 2013). ERT must be administered intravenously every two weeks throughout life. This enzyme replaces the missing enzyme, being incorporated by cells and thus catabolizing lipid deposits. ERT has been used to stabilize disease progression (FELLGIEBEL et al., 2014; SEYDELMANN et al., 2015). Lysosomal enzymes are absorbed by tissues through cell surface receptors, which recognize the carbohydrate structure of these enzymes. The mannose-6-phosphate receptor (M6PR) and the mannose receptor (MR) are the two main contributors to the uptake of the administered enzyme. These receptors are expressed on many cell types, including macrophages, dendritic, endothelial, renal mesangial, and smooth muscle cells (SHEN et al., 2016). A recent study demonstrated that the agalsidase-β enzyme is associated with a lower incidence of renal, cardiovascular, and cerebrovascular events compared to the non-ERT group and even showed a lower incidence of cerebrovascular events compared to agalsidase-α (El Dib et al., 2017).

A phase 3 clinical study demonstrated that agalsidase-α was effective in attenuating the main clinical manifestations of the disease, reducing the accumulation of Gb3 in the kidneys, skin, and heart. Also, after 20 weeks of treatment, there was a reduction in Gb3 deposits in vascular endothelium (ENG et al., 2001). Preclinical studies have demonstrated decreased clinical severity after administration of purified α-GAL (CHIEIA et al., 2010). Treatment with ERT during childhood can positively impact the quality of life of individuals who started treatment early (Hopkin et al., 2016). Agalsidase-β reduces Gb3 levels in cardiac tissue, especially in vascular endothelial cells (CORREIA et al., 2011; WEIDEMANN et al., 2003). Fervenza et al., (2008) showed an increase in creatinine clearance after treatment with agalsidase-β in patients with nephropathy caused by FD (FERVENZA; TORRA; WARNOCK, 2008) Tondel et al., (2013) demonstrated a significant decrease in the accumulation of Gb3 in kidney cells after treatment with agalsidase-α, in standard or double-dose concentrations (0.2-0.4 mg/kg Every Other week) (TØNDEL et al., 2013) A study involving 21 male patients on agalsidase-β for 24 months found a reduction in the concentration of Gb3 in several cells of the body in most patients (LUBANDA et al., 2009). Another study involving 58 patients with classic FD showed a reduction in Gb3 accumulation in kidney cells after 54 months of treatment with agalsidase-β (Germain et al., 2007).

A cohort of 12 patients, aged between 7 and 33 years, underwent ERT for 5 years, using both commercially available enzymes, with kidney biopsies performed before and after treatment. The results showed that, after this time of ERT, a total clearance of endothelial and mesangial glomerular lipid inclusions occurred in all individuals and, those patients who
received the highest dose of the enzyme, had a significant (but not total) clearance of podocyte Gb3 inclusions. Furthermore, ERT starting during childhood can improve the quality of life and attenuate disease progression (HOPKIN et al., 2016). However, the reduction in Gb3 levels with ERT treatment does not necessarily prevent disease progression (WILCOX et al., 2004).

FD is associated with endothelial damage and decreased migratory and regenerative capacity of circulating angiogenic cells (CAC). ERT represents a potential therapeutic strategy, improving the regenerative capacity of CACs in SCD patients suffering from coronary artery disease and, therefore, may attenuate the development of cardiovascular disease in the long term (LORENZEN et al., 2012). Although in initial studies the main cause of death in SCD was renal dysfunction after the advent and advances in ERT, the main cause of death became cardiovascular disease (CVD). An increase in the quality and life expectancy of these patients has also been also observed (Cordeiro et al., 2007).

Currently, a new drug has been used in clinical practice to treat FD. Migalastat (Amicus Therapeutics, New Jersey, USA) is a pharmacological chaperone used in patients over 16 years of age who have a missense mutation of the α-GAL enzyme, the effect of which is to unfold the enzyme, leading it to the lysosomes (Gaggl & Sunder-Plassmann, 2016; ISHII, 2012; Markham, 2016). Benjamin et al. (2012) demonstrated in fibroblasts derived from patients with SCD the presence of Migalastat at a concentration of 10-1000 μmol/L, associated with an increase between 4.4 and 5.6 times in cellular α-GAL levels and a reduction in levels of Gb3 significantly. Furthermore, this drug increased the half-life of α-GAL in rats (BENJAMIN et al., 2012). A study carried out by Hughes et al., (2017), with 54 patients for 18 months, compared the effect of Migalastat versus ERT by evaluating renal and cardiac parameters, serum Gb3 levels, and patients’ reports of symptoms. There was no significant difference between the two approaches in all these parameters. This demonstrates that in patients with amenable pathogenic variants, it can be considered a first-choice drug (GERMAIN et al., 2019; HUGHES et al., 2017).

In addition to the specific treatments described above, in an attempt to alleviate the general symptoms of the disease, such as peripheral pain and gastrointestinal symptoms, medications such as analgesics, anti-inflammatories, carbamazepine, gabapentin, pregabalin, antispasmodics, antiarrheals, among others (DOS SANTOS JÚNIOR et al., 2023; NEUMANN et al., 2013; ROZENFELD et al., 2006).
4 CONCLUSIONS

FD is a rare multisystem disease, mainly affecting the cardiovascular system, kidneys, and nervous system. Therefore, early diagnosis and the attention of a multidisciplinary team are necessary for adequate treatment, including ERT. It is important to highlight that health professionals have little experience with these patients as it is a rare disease. Still, this knowledge must be disseminated so that these professionals can help FD patients, especially at the onset of symptoms. Early diagnosis directly contributes to greater therapeutic success and, consequently, to improving the patient's quality of life. Therefore, this review addressed the current perspectives on the disease, its diagnosis, and treatment, which can contribute to guiding health professionals and researchers in the area. Furthermore, the need for new studies to elucidate the pathological mechanisms of FD stands out, which can contribute to the development of new therapeutic approaches to improve the survival of FD patients.
REFERENCES


ROZENFELD, P. A. Fabry Disease: Treatment and diagnosis. IUBMB Life, v. 61, n. 11, p. 1043–1050, 1 nov. 2009.


WANG, R. Y. et al. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. *Genetics in Medicine*, v. 9, n. 1, p. 34–45, 2007.


