

Fabry disease: genetics, pathology, and treatment

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SUMMARY

Fabry disease (FD) is a recessive monogenic inheritance disease linked to chromosome X, secondary to mutations in the GLA gene. Its prevalence is estimated between 1:8,454 and 1:117,000 among males and is probably underdiagnosed. Mutations in the GLA gene lead to the progressive accumulation of globotriaosylceramide (Gb3). Gb3 accumulates in lysosomes of different types of cells of the heart, kidneys, skin, eyes, central nervous system, and gastrointestinal system, and may lead to different clinical scenarios. The onset of symptoms occurs during childhood, with acroparesthesia, heat intolerance, and gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and neuropathic pain. Subsequently, symptoms related to progressive impairment appear, such as angiokeratomas, cornea verticillata, left ventricular hypertrophy, myocardial fibrosis, proteinuria, and renal insufficiency. The latter being the main cause of death in FD. The gold standard for diagnosis is the genetic analysis in search of mutation, in addition to family history. In homozygous patients, the enzyme activity can also be used. Once the diagnosis is confirmed, the patient and their family should receive genetic counseling. The treatment, in turn, currently focuses mainly on replacing the enzyme that is absent or deficient by means of enzyme replacement therapy, with the purpose of avoiding or removing deposits of Gb3. Chaperones can also be used for the treatment of some cases. It is considered that the specific treatment should be initiated as soon as a diagnosis is obtained, which can change the prognosis of the disease.

KEYWORDS: alpha-Galactosidase. Fabry Disease. Renal Insufficiency Chronic. Proteinuria. Enzyme Replacement Therapy.

INTRODUCTION

Fabry disease (DF) is an inborn error of metabolism that causes partial or total inability of catabolizing lipids. It is caused by mutations in the gene that codifies the lysosomal enzyme α -galactosidase A (α -GAL), leading to the progressive accumulation of glycosphingolipids, especially globotriaosylceramide (Gb3). Gb3 accumulates in lysosomes of different types of cells and can affect the heart, kidneys, skin, eyes, central nervous system, and gastrointestinal system. It has a progressive nature and may lead to organ failure¹⁻⁴.

The process of lysosomal involvement is likely to begin as early as in the fetal stage; however, the first symptoms usually appear after 3 years, or before in males, since it is an inheritance linked to the chromosome X. The manifestation of the disease in heterozygous women can vary from asymptomatic to a condition as serious as in males¹⁻⁴.

In 1898, the first reports of the disease were made by two dermatologists, William Anderson and Johannes Fabry, who described patients with “angiokeratoma corporis diffusum” in independent studies.

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However, it was only in 1947, after the finding of abnormal vacuoles in the blood vessels of two patients who died of kidney failure, that the condition was classified as a deposit disease. In 1967, the relationship between the deficiency of the α -GAL enzyme and the etiology of the disease was established⁵⁻⁸.

EPIDEMIOLOGY

The estimated prevalence of FD varies from 1:8,454 to 1:117,000 in males, and it has been described in various ethnic groups, with no predilection identified to date^{2,9,10}. It should be noted that recent studies in newborns found a high incidence, ranging from 1:3,100 in newborns in Italy to 1:1,550 in newborns of Taiwan. Therefore, it is likely that the disease had been underdiagnosed^{11,12}.

There are reports of FD prevalence of 0.019% and 0.017% in dialysis record programs in Europe and in the United States, respectively¹³. In Brasil, few studies have assessed the prevalence of FD in the dialysis population. In studies carried out between 2007 and 2008 in a small number of patients, the prevalence ranged from 0.36% to 0.57%¹⁴⁻¹⁶. In a more recent study, conducted in Bahia with 2,583 male patients on hemodialysis, the prevalence rate of FD was 0.12%¹⁷.

GENETIC

FD is a monogenic, recessive inheritance disorder linked to the X chromosome, secondary to a mutation in the GLA gene. This gene is responsible for encoding the α -GAL enzyme and is located on the long arm of the X chromosome at the Xq22 position. Most cases are hereditary, and cases of *new* mutations are rare^{1,18,19}. Over 900 different mutations have been described as the cause of the disease²⁰.

α -GAL has approximately 429 amino acids and is responsible for breaking Gb3 into galactose and lactosylceramide in the lysosomes. Therefore, in patients with FD, GB3 is accumulated in different tissues. It has a predilection for the vascular endothelium and smooth muscle cells of the cardiovascular system and for kidney podocytes, which explains the predominance of clinical manifestations affecting these organs²¹⁻²⁴.

The gene that encodes α -GAL has approximately 12 kb and seven exons. FD can be caused by several types of molecular mutations in this gene: missense

(57%), nonsense 11%), partial deletions 6%), insertion (6%), and defects in the processing of RNA, which lead to abhorrent splicings (6%). The correlation between genotype and phenotype is complex, since the same mutation may determine different clinical manifestations. This could be attributed both to environmental factors and the blood group. Patients of blood groups AB or B may have more severe disease presentations since they have an additional accumulation of glycosphingolipids in the membrane of erythrocytes of blood group B²⁵.

CLINICAL FINDINGS

Patients with FD can present a spectrum of clinical manifestations, ranging from classic FD in males, to the asymptomatic disease in females, with several variants between these two extremes. The clinical signs and symptoms are subtle at first, which can hinder or delay the diagnosis, especially if there is no family history^{1,26,27}.

The classical presentation of FD is the more severe phenotype and occurs predominantly in men, with activity absent or minimal residual activity of the α -GAL enzyme. The onset of symptoms occurs during childhood or adolescence, with acroparesthesia, heat intolerance, and gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain. Between the third and fourth decades of life, the symptoms related to the progressive systemic impairment appear, i.e., changes in cardiac, renal, and cerebral function^{1,3,4,26,27}.

The cutaneous involvement is characterized by the presence of angiokeratomas, small telangiectasias, usually in the buttocks and thigh region. The impairment of the nervous system, in addition to the acroparesthesias, is characterized by hypohidrosis and cerebrovascular accidents. Ocular alterations are secondary to the Gb3 deposits in the cornea, causing an opacity called cornea verticillata^{1,3,4,26,27}.

Cardiac alterations increase with age, which possible left ventricular hypertrophy, fibrosis of the myocardium, valve regurgitation (mainly mitral), arrhythmias, and even coronary disease. The mild phenotype of FD is characterized primarily by cardiac alterations and is compatible with residual activity of about 5-10% of the α -GAL enzyme^{1,3,4,26,27}.

The presentation in women is highly variable, ranging from asymptomatic patients to scenarios very similar to classic FD. Ocular lesions are com-

mon, and cornea verticillata may be the only sign in asymptomatic women^{1,3,4,26,27}.

Kidney failure is the main cause of death. The most prevalent change is proteinuria, which occurs in 80% of men left untreated in the fourth decade of life. In addition, patients can develop end-stage kidney disease (ESKD)^{1,3,4,26,27}.

Renal involvement usually starts with microalbuminuria, followed by proteinuria in the second or third decades of life. Its progression is similar to diabetic nephropathy and contributes to the progression of chronic kidney disease. When patients are left untreated, it evolves to ESKD, usually between the fourth and the fifth decade of life. In general, the severity of the renal condition correlates with the residual enzyme activity^{1,28-30}. In a previous study, when enzyme activity was lower than 1%, renal disease was diagnosed at age 22 and, when the activity was between 1% and 12%, at age 47³⁰.

The study by Brandon et al. allowed a better understanding of the renal involvement; however, it is important to emphasize that in it, no patient survived beyond 60 years. A total of 82.5% of the patients developed proteinuria, and 22% developed chronic kidney disease. The onset of proteinuria was, on average, at around 34 years of age. Nephrotic proteinuria occurred only in 18% of patients, but nephrotic syndrome was not a common finding. In addition, urinary protein electrophoresis showed that proteinuria was of glomerular origin (albuminuria $\geq 50\%$), regardless of the degree of proteinuria^{2,30}.

Another highlight of this study was establishing that, in FD patients with renal involvement, the average time of progression to ESKD was four years. That is a very rapid progression, with an estimated annual decrease in glomerular filtration rate of approximately 12.2 ml/min. Even when compared to other causes of chronic kidney disease, such as diabetes and hypertension, this rate of decline is very high³⁰.

FD may cause Gb3 deposits in the tubules, particularly in the distal tubules, causing distal renal tubular acidosis and isosthenuria. However, there are also reports of the involvement of the proximal convoluted tubule, causing Fanconi syndrome^{1,28}.

Due to this broad renal involvement, many patients develop ESKD, requiring renal replacement therapy. Considering that renal transplantation is the best therapy, it can and should be performed in these patients, since it increases their survival. Although

there is a deposit of Gb3 in the transplanted kidney, patients do not develop graft dysfunction. The deposits appear to be insufficient to cause impairment of renal function. Recent studies have demonstrated that renal transplantation normalizes only the urinary levels of α -GAL, not the plasma levels. Thus, renal transplantation has no effect on the progression of non-renal manifestations of FD^{30,31}.

RENAL PATHOLOGY

The accumulation of Gb3 occurs in virtually all types of kidney cells: endothelial, tubular, mesangial, and podocytes, with a predilection for the latter. Therefore, FD can cause tubular, vascular, and glomerular disorders^{1,30}.

The definitive diagnosis of renal involvement due to FD is made by renal biopsy. It is an important tool in the diagnosis and, according to some, the evaluation of treatment efficacy. The Gb3 deposits are found both in the vascular and glomerular compartments, as well as in the interstitial-tubule. These deposits are correlated with the severity of the morphological and functional renal changes^{2,29,30}.

Using optical microscopy, it is possible to observe vacuolizations in the cytoplasm of cells, especially of podocytes (Figures 1a and 1b), with subsequent impairment of mesangial and endothelial cells. With the progression of the disease, there may be an increase in the mesangial matrix associated with glomerular sclerosis, in addition to interstitial fibrosis and tubular atrophy. Using immunofluorescence, deposits of immune complexes are generally not found^{29,30}.

Whereas using electronic microscopy, deposits of Gb3 strongly stained with blue are found inside the cells (Figure 1c). The deposits inside the lysosomes are electron-dense structures intercalated with electron-lucid lamellas, forming "myelin figures" or "zebra bodies" (Figure 1d). The cell with most deposits is the podocyte. The deposits of Gb3 affect the structure of its cytoskeleton, promoting erasure of pedicels, and, thus, altering its permeability and leading to the loss of proteins^{29,30}.

Diagnosis and biomarkers

The diagnosis of FD usually takes some time, especially in the pediatric population, since the symptoms are often nonspecific, and the disease is not widely known. In addition, renal and cardiac dysfunction appear only in more advanced stages of the

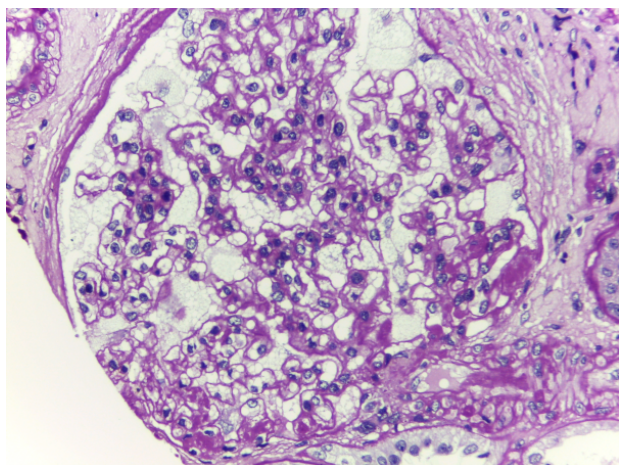


FIGURE 1A - Optical microscopy showing podocyte vacuolization SBP – (400x).

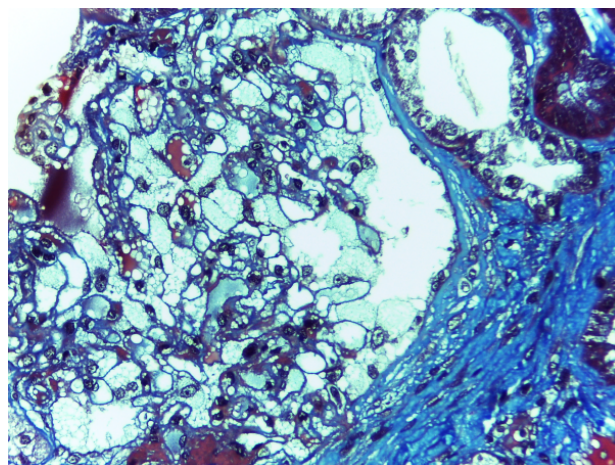


FIGURE 1B- Optical microscopy showing vacuolated podocytes Masson's trichrome – (400x).

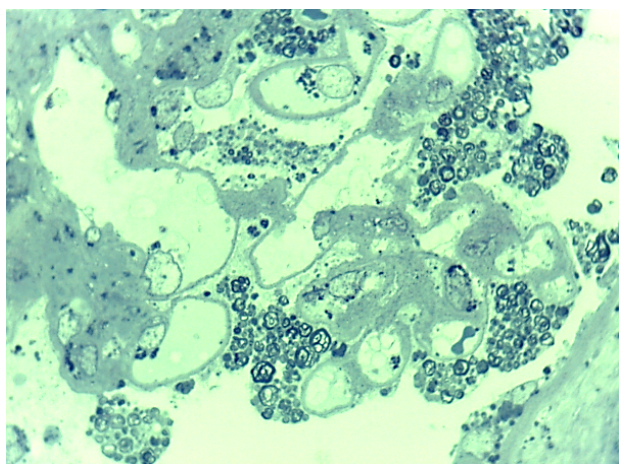


FIGURE 1C - Optical microscopy with semi-thin planes showing corpuscles of inclusion in podocytes, endothelial, and mesangial cells Toluidine Blue – (1,000x).

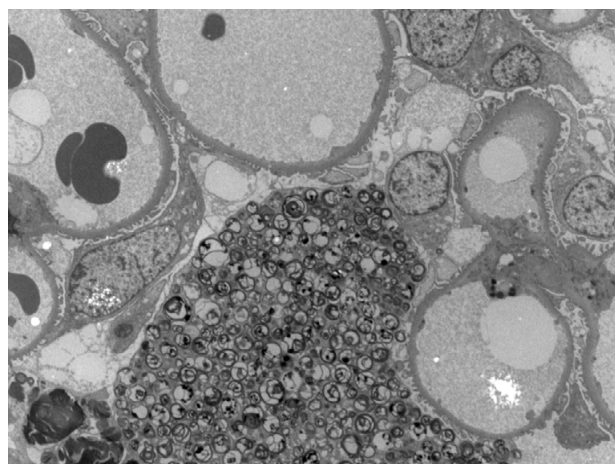


FIGURE 1D - Electronic microscopy showing lamellar inclusions in a podocyte, endothelial cell, and visceral epithelium (3,000x).

disease. Recent data suggest delays of up to 15 years in the diagnosis¹.

Genetic investigation and family history are crucial for the diagnosis. In the absence of such information, the suspected diagnosis is based on clinical information, such as the presence of angiokeratomas or opacity of the cornea. The finding of cornea verticillata has increasingly contributed to the diagnosis, as it can be observed since childhood and even in patients with normal enzyme dosage of α -GAL^{1,32-35}.

The images can be used to document areas of ischemia or cerebral vasculopathy. An echocardiogram is useful in the search for hypertrophy of the left ventricle, and an electrocardiogram can be used to evaluate arrhythmias. However, if the clinical examination raises suspicion of FD, the biochemical examination and genetic confirmation are required^{1,32-35}.

In homozygotes, the enzyme activity can be used

for diagnosis. The levels of α -GAL usually are low, and a finding of activity <15% constitutes a diagnostic of the disease. However, in female patients and in some variants in males, it is common to have false-negative results^{1,32-35}.

Another form of diagnosis uses the dosage of Gb3 in urine and blood. If high values are found, these are suggestive of the disease. Some women test normal for enzyme activity, but have high levels of Gb3 in urine, with that it is possible to distinguish a patient who has the condition from one who does not^{1,32-35}.

However, the genetic analysis in search of mutations in the α -GAL gene is the gold standard test to confirm the diagnosis of FD in both sexes. The sequencing of the coding region of the gene can detect a mutation that causes the disease in more than 97% of the patients. However, this analysis has a high cost, which hinders its widespread use^{1,32-35}.

Therefore, a new biomarker was sought to assist in the diagnosis and monitoring of the therapy. The answer found was to measure the product of Gb3 degradation, the globotriaosylsphingosine (lysoGb3). In a prospective study with 124 patients, the levels of lysoGb3 were correlated to the clinical condition, type of mutation, as well as to changes in imaging examinations, proving to be a reliable predictor of the disease. In another study, a high level of lysoGb3 was found even in women with the normal activity of α -GAL who, subsequently, had a clinically significant presentation of the disease, thus showing advantages in relation to the direct measurement of GB3. In addition, it was demonstrated that the levels of lysoGb3 decrease with enzyme replacement therapy (ERT). Thus, lysoGb3 has been accepted as a more accurate marker of disease activity. However, long-term data still need to be analyzed^{36,37}.

The prenatal diagnosis is also possible, since the accumulation of Gb3 starts early, still in intrauterine life. When there is a XY fetus, it is possible to demonstrate low α -GAL activity through a biopsy of the chorionic villi or amniotic cell cultures^{1,32-35}.

Biopsies of different tissues of FD patients can also suggest the disease. Using optical microscopy, the presence of cytoplasmic vacuoles containing the lipids can be seen. Using electronic microscopy, lysosomal inclusions are seen, with the lamellar configuration. When these findings are not conclusive, immunoelectron microscopy can be used to search for anti-Gb3 antibodies^{1,32-35}.

Genetic counseling

Once the FD diagnosis is confirmed, the patient and their family should receive genetic counseling. Family screening is useful to identify additional cases. In addition, counseling is essential to inform about the risk of offspring inheriting the disease. All daughters of a homozygote father will inherit the disease since they will inherit the X from the father who has the mutation; none of the sons will inherit the disease, since they will receive only the Y chromosome from the father. Half of the children of a woman who carries the mutation will be affected, given that she has one normal X and one X with the mutation^{32,38}.

Treatment and prospects

The treatment of FD patients focuses mainly on replacing the enzyme that is absent or deficient by

means of ERT, with the purpose of avoiding or removing deposits of Gb3. The ERT currently used is based on the discovery that cells can incorporate an enzyme from the extracellular medium and use it in its normal metabolism^{1,39-41}.

In addition, patients should receive specific treatment for the organs affected to control symptoms. Some important measures include: nephroprotection with the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) to control proteinuria; pain control with the use of analgesics and opiates, avoiding the use of anti-inflammatory agents; and control of blood pressure, with a preference for the use of ACEI or ARB. Prophylaxis with anticoagulants and antiplatelet agents can also be considered in patients with a history of ischemia. Another very important factor is to instruct the change of habits and lifestyle, including cessation of smoking, reduction of sodium intake, and practice of physical activity^{1,39}.

In general, it is considered that all male patients affected by the classical presentation of FD should receive ERT. It should be started as soon as the diagnosis is made, regardless of whether or not there are clinical manifestations since the deposit of Gb3 starts as early as in intrauterine life. Women and patients with atypical presentations should receive ERT if there is a clinical manifestation. It is also important to stress that even patients who are already undergoing dialysis should be treated since ERT can reduce cardiovascular and neurological complications^{1,39,40}.

Two formulations of recombinant human α -GAL have been developed: algasidase alfa and algasidase beta. Both proteins appear to be equally effective and are administered intravenously every 15 days. There are no studies with a definitive recommendation for the duration of therapy, but it is believed that it is necessary for the entire life of the patient, since the amount of the enzyme in the plasma is rapidly depleted. The treatment is expensive. In 2005, for example, the estimated retail cost for the therapy with the first formulation for a year was US\$ 160,000 in Europe and \$206,000 in the United States. The tolerance to ERT is normally good, except for mild or moderate reactions associated with the infusion^{1,39,40}.

Clinical studies have found a decrease in the frequency of pain episodes, cardiac mass, and Gb3 deposits in the skin and kidneys, with even improvement of renal function in some patients. There is also evidence that ERT improves sudoresis and gastroin-

testinal symptoms. However, there are still no studies that prove the decrease in mortality. In addition, the formation of antibodies against the enzyme is described, which reduces its effectiveness in the long term^{1,39,40}.

There are other therapies under study. One of them included chaperones and would be useful to patients that have unstable variants of the mutant α -GAL. These variants are retained in the endoplasmic reticulum due to its defects but still maintain residual enzymatic activity. Small synthetic molecules that act as a chaperone are used to recover residual α -GAL, transporting it to the lysosomes and, thus, increasing its activity^{1,41,42}.

The drug already produced with this purpose is the migalastat, which is administered orally, thereby avoiding the need for fortnightly infusions. However, it can only be used in 30-50% of patients with FD that have specific mutations. A first randomized clinical trial on migalastat showed an effect comparable to that of ERT on renal function and cardiac outcomes. Another study analyzed the combination of this chaperone with ERT and showed promising results, with an increase from 1.2 to 5.1 times in enzymatic activity in comparison to ERT alone. Further studies are still needed to confirm these findings and evaluate long-term results⁴³.

Another option would be the use of reversible competitive inhibitors of α -GAL. These, from the inside of the cells, would determine an increase in the enzyme activity. In addition, these substances seem to accelerate the transportation, maturation, and stability of the mutant enzyme. Again, these would only be useful in

patients with residual enzymatic activity¹⁴².

Finally, FD seems to be a disease suitable for gene therapy. This technique aims to add a normal gene of α -GAL to the DNA of the patient, which would then start producing a normal enzyme. Thus, definitive treatment for the disease is proposed. This therapy is promising but is still under the testing of experimental models¹⁴⁴.

CONCLUSION

FD is a lysosomal storage disorder that generates a systemic and severe condition, with onset in childhood, and that should be promptly diagnosed since there is an effective treatment. Delays in diagnosis certainly contribute to high morbidity and mortality due to this disease, which should be more well known by health professionals. It stands out, finally, the extreme importance of genetic counseling in this type of disease. Future possibilities include the early diagnosis and perhaps even cure by means of gene therapy.

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PALAVRAS-CHAVE: α -galactosidase A. Doença de Fabry. Doença renal crônica. Proteinúria. Terapia de reposição enzimática.

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