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A Review on Fabry Disease

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Abstract: *Fabry disease is the most common of the lysosomal storage disorders and results from deficient activity of the enzyme alpha-galactosidase A (α-Gal A), leading to progressive lysosomal deposition of globotriaosylceramide and its derivatives in cells throughout the body. The classic form, occurring in males with less than 1% α-Gal A enzyme activity, usually has its onset in childhood or adolescence with periodic crises of severe pain in the extremities (acroparesthesia), the appearance of vascular cutaneous lesions hyperhidrosis), characteristic corneal and lenticular opacities, and proteinuria. Gradual deterioration of renal function to end-stage kidney disease (ESKD) usually occurs in men in the third to fifth decade. In middle age, most males successfully treated for ESKD develop cardiac and/or cerebrovascular disease, a major cause of morbidity and mortality. Heterozygous females typically have milder symptoms at a later age of onset than males. Rarely, females may be relatively asymptomatic throughout a normal life span or may have symptoms as severe as those observed in males with the classic phenotype. In contrast, late-onset forms occur in males with greater than 1% . Alpha Gal A activity. Clinical manifestations include cardiac disease, which usually presents in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy, arrhythmia, and proteinuria; kidney failure, associated with ESKD but without the skin lesions or pain; or cerebrovascular disease presenting as stroke or transient ischemic attack.*

Keywords: Fabry disease.

I. INTRODUCTION

Fabry disease is an X-linked genetic disorder resulting from decreased activity of a-galactosidase A. Consequently, the enzyme substrate globotriaosylceramide accumulates in various organs, including the kidneys. Recently, enzyme replacement therapy (ERT) has been introduced; however, whether ERT is able to improve renal function is a matter of debate . Appropriate measurement of the glomerular filtration rate (GFR) is of paramount importance for the assessment of renal function. In this article we give a short overview of the methods used to examine renal function, in particular those methods used in clinical trials of ERT. These data will highlight the problems associated with the routinely used measurements or estimates of GFR in patients with Fabry disease.[1,2]

Clinically, Fabry disease can be divided into a classical form, later onset variants and female heterozygotes. The classical form usually has onset in childhood or adolescence with acroparesthesia, angio keratomas, anhi drosis, corneal lenticular opacities, abdominal pain and proteinuria, followed by gradual deterioration of renal function to end-stage renal disease (ESRD), cardiovascular and/or cerebrovascular complications. Males who present later in life typically have a more attenuated disease course, while females range from being relatively.[3]

Fabry disease (FD) is a progressive, X-linked inherited disorder of glycosphingolipid metabolism because of deicient or absent lyposomal alpha-Galactosidase A (a-Gal A) activity . At the time of this writing, there exist various articles which evaluate the efficacy of different enzyme replacement therapy (ERT) regimens. Some of these reports include patients with classic mutations observed concomitantly with late-onset mutations and even, possibly, some polymorphisms with no pathologic signiicance.

Fabry disease (FD) is a rare and highly debilitating lysomsomal storage disorder that results from a deficiency of α-galactosidase A (α-Gal A) due to mutations in the GLA gene located on the X chromosome (1). The deficiency in α-Gal A causes accumulation of globotriaosylceramide (GL-3; also abbreviated Gb3) within the lysosomes of multiple cell types throughout the body. [4]

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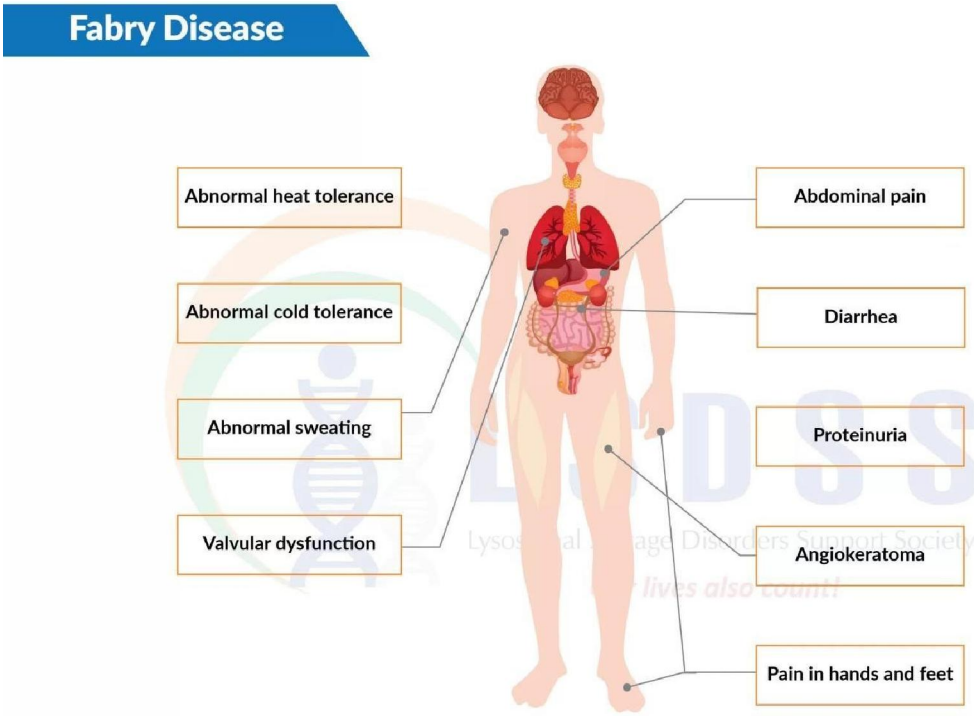

This accumulation results in inflammation, ischemia, hypertrophy, and the development of fibrosis ultimately resulting in cellular damage and progressive organ dysfunction. Many cell types are involved in Fabry disease pathology, including vascular cells (endothelial and smooth muscle cells), cardiac cells, a variety of renal cells (tubular and glomerular cells, and podocytes), and nerve cells (2–5).

Gastrointestinal symptoms are some of the most frequently reported symptoms in patients with Fabry disease.

The most common complaints – abdominal pain, bloating, diarrhea, constipation, recurrent nausea and vomiting.

In Fabry disease, globotriaosylceramide accumulates within the vascular epithelium, kidneys, cornea, heart, and other tissues, causing renal failure, painful acroparaesthesias, typical angiokeratoma, hypohydrosis, and cardiac failure.1 The disease usually causes death in adult life from renal, cardiac, or cerebrovascular complications of vascular disease.[5]

The incidence of stroke together with vessel ectasia is about 40% in hemizygous male individuals; young people seem to be most affected. Although stroke is generally regarded as a disease of elderly people, its importance is not negligible in younger adults, and even in children. The worldwide incidence of stroke in young adults (aged 16–55 years) is estimated to be nine to 14 per 100 000 people.2 About 27% of ischaemic strokes are judged to be cryptogenic (ie, no specific cause can be identified), and cryptogenic stroke is more common in young rather than old patients.3 We aimed to measure the frequency of Fabry disease in a cohort of more than 700 young white adults aged 18 to 55 years with acute strok.[7]

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by a deficiency of the enzyme - galactosidase . FD causes glycolipids, such as globotriaosylceramide (Gb3), to accumulate in the vascular endothelium of several organs, including the skin, kidneys, nervous system, and heart, thereby triggering inflammation and fibrosis. These processes generally result in organ dysfunction, which is usually the first clinical evidence of FD.[8]

As FD is an X-linked disorder, heterozygous women had long been thought to be ‘only gene carriers’. This was explained by X-chromosome inactivation (Lyon hypothesis). However, it is now generally accepted that also heterozygous women may develop clinically manifest organ involvement. Moreover, women in particular are known to develop variants of FD characterized by very severe involvement of a specific vital organ such as the heart. [9]

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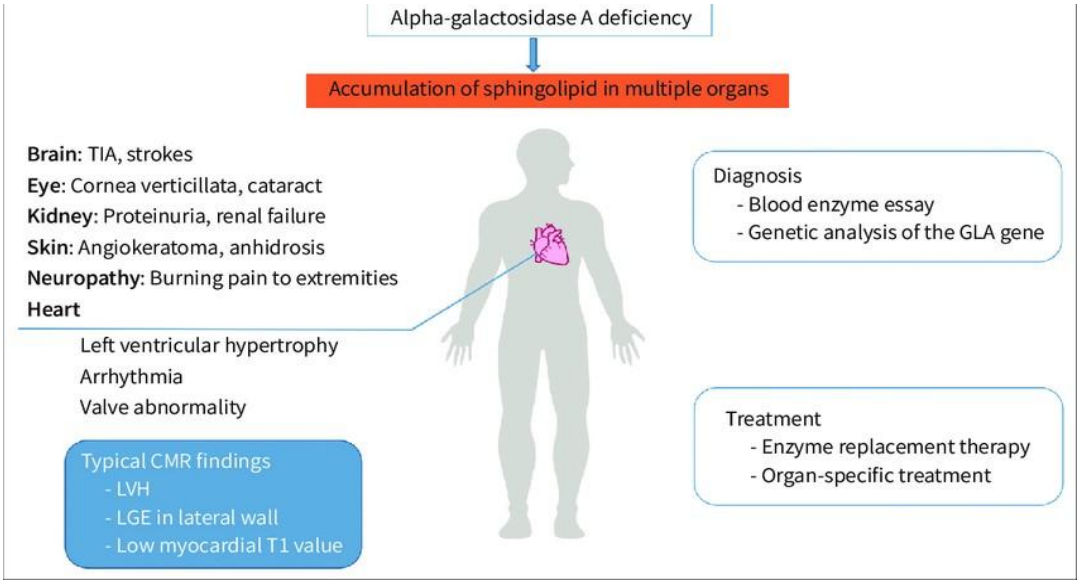

Fig 2. A schematic diagram for fabry disease

This is explained by the differences in inactivation patterns even between different organs. On the other hand, there are a few genetically confirmed Fabry women who went very old without developing any clinical manifestations of FD. This clinical variability highlights the crucial role of organ-specific staging in the context of disease progression in Fabry women.

Lysosomes are organelles that perform a vital function in the catabolism and recycling of cytosolic compounds (Luzio et al., 2007; Boustany, 2013). Deficiencies in proteins with physiological functionalities can lead to lysosomal storage disorders (LSDs) (Schultz et al., 2011; Platt et al., 2018), with over 70 lysosomal enzyme deficiencies causative of LSDs having been identified to date (Martina et al., 2020).

Fabry disease is associated with the reduced activity of lysosomal galactosidase A (GLA), an enzyme involved in the catabolism of globotriaosylceramide (Gb3). GLA deficiency in patients with Fabry disease results in abnormal glycosphingolipid metabolism and the progressive accumulation of Gb3 (Aerts et al., 2008; Kang et al., 2019). With disease progression.

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.[10]

TYPES OF FABRY DISEASE

1. Classic Fabry Disease

Onset: Early childhood to adolescence

Cause: Severe deficiency or complete absence of alpha-galactosidase A enzyme activity

Symptoms: Symptoms typically start during childhood or adolescence and progress over time. These include:

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Pain (acroparesthesia): Episodes of burning pain, particularly in the hands and feet, are common. These may be triggered by stress, physical activity, fever, or temperature changes.
Angiokeratomas: Small, dark red or purple spots that appear on the skin, especially around the lower abdomen, thighs, and buttocks.
Hypohidrosis: Reduced ability to sweat, which can lead to overheating.
Corneal opacities: Clouding of the cornea, which can sometimes be detected in an eye exam but typically does not affect vision.[11]
Gastrointestinal issues: Some people experience abdominal pain, diarrhea, or nausea.
Kidney involvement: Progressive accumulation of Gb3 in the kidneys can lead to proteinuria (excess protein in urine), reduced kidney function, and eventually kidney failure.
Heart problems: Enlarged heart, arrhythmias (irregular heartbeat), and heart valve abnormalities can develop over time.
Hearing loss: Tinnitus (ringing in the ears) and progressive hearing loss can occure

2. Late-Onset (Atypical) Fabry Disease
Onset: Adulthood
Cause: Partial deficiency of alpha-galactosidase A enzyme activity
Symptoms: The symptoms of late-onset Fabry disease are generally milder compared to the classic form. They may only affect certain organs, particularly the heart or kidneys, and appear later in life, typically in adulthood. Some key features include:
Cardiac variant: Some individuals may primarily develop heart-related symptoms, such as left ventricular hypertrophy (thickening of the heart muscle), arrhythmias, or valve abnormalities. Heart failure may develop as the disease progresses.[13]
Renal variant: Others may experience primarily kidney-related symptoms, such as proteinuria and progressive loss of kidney function, eventually leading to kidney failure.
Cerebrovascular variant: Stroke or TIAs due to vascular involvement in the brain may be the first sign of Fabry disease in some cases.
Other systemic features: Patients may experience milder or fewer systemic symptoms compared to the classic form, and pain or skin manifestations may be less prominent or absent.

Other Types or Considerations
While the classic and late-onset forms are the main subtypes, some variations in severity or organ involvement may occur within these categories. For example, some patients may have intermediate phenotypes or exhibit only mild symptoms throughout their lives.

Gender Differences
Males: Since Fabry disease is X-linked, males are more severely affected than females, particularly in the classic form. Males typically develop symptoms early in life and experience more severe progression.

Females: Female carriers may still develop symptoms due to X-chromosome inactivation, but their symptoms are generally milder and appear later in life. However, some females can experience symptoms as severe as males, especially in the late-onset form.[14]

Mechanism
1. Autophagy
Lysosomes are tightly associated with the degradation and recycling of cellular components, including lipids, proteins, and nucleic acids. The inability to digest Gb3 in lysosomes may lead to the activation of several signaling pathways aimed at reducing the levels of accumulated Gb3, eventually resulting in multiple cellular pathologies (Biancini et al., 2012; Hsu et al., 2019). Autophagy plays a critical role in degrading lysosomal substrates (Festa et al., 2018). Several

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studies have demonstrated that autophagy is upregulated in response to Gb3 accumulation. Gb3 accumulation can activate autophagy pathway to degrade Gb3, alleviating intracellular stresses simultaneously.

Although activating autophagy has beneficial effects on lysosomal stress responses in the short term, longterm activation of this pathway can also result in dysregulated autophagy, which accelerates disease progression and worsens pathogenetic changes. Impaired autophagic activity has been observed in peripheral blood mononuclear cells from patients with Fabry disease as well as in several in vitro models of Fabry disease (Chévrier et al., 2010; Liebau et al., 2013; Ivanova et al., 2019). For instance, Song et al. constructed a model of Fabry disease in human embryonic stem cells (hESCs) via the CRISPR/ Cas9- mediated knockout of the GLA gene (Song et al., 2019). [15]

The authors found that, compared with their wild-type counterparts, cardiomyocytes differentiated from these hESCs exhibited significantly increased cell size and Gb3 deposition, as well as impaired autophagic flux. These findings indicated that dysregulated autophagy resulting from GLA gene deficiency and consequent Gb3 accumulation plays a role in myocardial hypertrophy. In turn, impaired autophagy can further trigger secondary lysosomal deposition via the accumulation of damaged mitochondria and reduced protein degradation, which may further result in a pathogenic cascade and cellular damage. Xing et al. (Xing et al., 2022) demonstrated that impaired autophagic flux can induce myocardial ischemic/ reperfusion injury through the accumulation of damaged mitochondria. The restoration of myocardial autophagy improved cardiomyocyte survival in vitro and heart function in mice in vivo. Combined, these observations suggest that targeting autophagy may represent a potential therapeutic strategy for treating Fabry disease.[16]

2. Lysosomal

dysfunction The mechanism underlying the Gb3 accumulationinduced intracellular pathogenic cascades remains poorly understood and further studies exploring the link between autophagic disorder and upstream lysosomal functions are necessary. Vacuolar (H+)-adenosine triphosphatases (V-ATPases), which use ATP hydrolysis to pump H+ into the lysosome, play a central role in maintaining the acidic environment of this organelle (pH = 5.2–6.1) and normal lysosomal function. Lysosomal substrate accumulation in cells leads to increased expression of V-ATPase. AMP-activated protein kinase (AMPK) is also activated in response to depleted ATP levels, and AMPK phosphorylation was observed to be increased in Fabry cardiomyocytes in an in vitro model of the disease Chou et al. constructed in vitro Fabry disease models based on peripheral blood mononuclear cells derived from patients with the disorder They found that, compared with controls seahorse metabolic flux assay.[17]

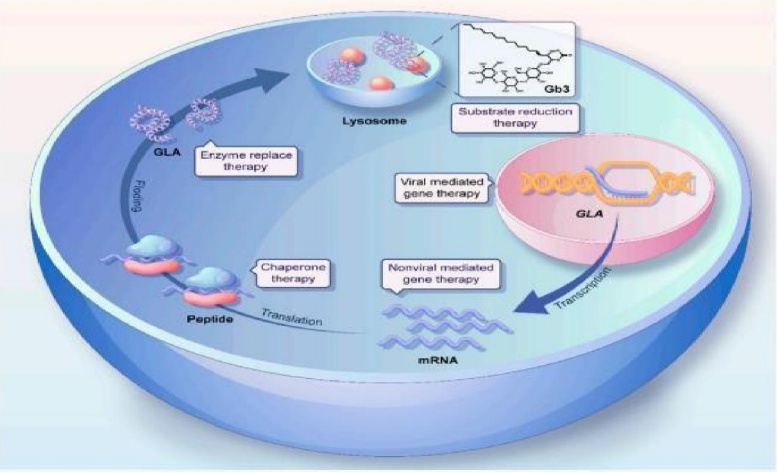

Fig 3 mechanism of fabry disease

Compared with control cells, total energy metabolism, including glycolysis and fatty acid oxidation, was significantly decreased in model cells. Meanwhile, energy metabolism was shifted toward glycolysis from fatty acid β-oxidation. These findings illustrate that GLA gene deficiency can induce AMPK activation and enhance glycolysis; however, further in vivo investigation is required and aberrant fatty acid metabolism in this disorder needs much deeper

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exploration. Subsequently, activation of AMPK and V-ATPase can lead to the inhibition of mammalian target of rapamycin complex 1 (mTORC1), which is involved in a variety of signal transduction pathways, including the induction of autophagic activation and lysosomal biogenesis. Interestingly, mTOR activity has been reported to be decreased in Fabry podocytes. Combined, the results of these studies suggest that autophagic dysfunction likely results from the triggering of the activation of the AMPK-mTOR signaling pathway due to intracellular Gb3 accumulation. These observations further suggest that the targeting of processes upstream of lysosomes to modulate autophagy may represent an attractive therapeutic strategy for Fabry disease.[18]

3. Lipid metabolism

An increase in the number of lipid droplets is often seen in Fabry tissues and in vitro models of Fabry disease. Recently, Kim et al. generated GLA-mutant kidney organoids via CRISPR-Cas9 technology. Transmission electron microscopy and oil red O staining analysis showed greater lipid accumulation in Fabry disease model organoids compared with that in the controls suggesting that lipid metabolism may have been inhibited in the model organoids. However, the mechanism involved in lipid droplet formation in Fabry disease remains elusive, even in preclinical studies. Disordered fatty acid utilization may underlie the observed lipid droplet formation. First, lipid accumulation may indicate that fatty acid oxidation could be blocked. As discussed above, energy demand is mismatched with the decreasing fatty acid β-oxidation. Defects in carnitine palmitoyl transferase 1 (CPT1), a key enzyme in the transportation of fatty acids into mitochondria for β-oxidation, may lead to lipid formation and dysregulated fatty acid utilization. It has been suggested that increased malonyl-CoA synthesis by acetyl CoA carboxylase can block β-oxidation. Abnormal levels of substrate for fatty acid metabolism are also observed in other Fabry cells LC–MS/MS analysis of acylcarnitines isolated from Fabry disease model cells indicated that the levels of short-chain acylcarnitines and free carnitine were significantly elevated in Fabry cells, whereas those of medium- and long-chain acylcarnitines were decreased. The results of recent studies have confirmed that acylcarnitine accumulation leads to mitochondrial dysfunction and impaired fatty acid oxidation (McCoin et al., 2015; Nguyen et al., 2017). Taken together, these reports suggest that fatty
acid metabolism is altered in Fabry disease. However, whether CPT1 has a role in Fabry disease is unknown. Additionally, the link between lipid metabolism and Fabry disease phenotypes requires further elucidation in vivo. Secondly, lipid metabolism is strongly associated with autophagy. Under metabolic stress, lipid droplets can be exploited for energy production through autophagy (Rambold et al., 2015; Benador et al., 2019). Blocking autophagy impedes the flux of stored fatty acids from lipid droplets to mitochondria, thus reducing mitochondrial β-oxidation and energy supplementation. Another potential explanation for lipid droplets may be related to mitochondrial biogenesis. Peroxisome proliferator- activated receptor (PPAR) and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC1α) are the main regulators of mitochondrial biogenesis via gene transcription.[19]

4. Inflammatory

Inflammation is a series of adaptive biological responses triggered by several internal or external stimuluses. Controlling inflammatory responses can help restoring host homeostasis and adaptations, while dysregulated inflammatory responses could induce tissue injury and even tissue fibrosis Frontiers in Pharmacology 04 frontiersin.org Li et al. 10.3389/fphar.2022.1025740 (Medzhitov, 2008; Rozenfeld and Feriozzi, 2017). Progression of Fabry cardiomyopathy is associated with increased inflammatory responses, as demonstrated by elevated inflammatory biomarkers (Yogasundaram et al., 2018). Recently, Song and co-workers reported that pro-inflammation pathway are activated within the cells with Fabry pathology. While the inflammatory responses can be reversed using gene therapy, further confirming the correlation between inflammatory activation and Fabry pathology (Song et al., 2021). Several molecular pathways have been reported to be attributed to the inflammatory activation of Fabry disease, including the nuclear factor kappa B (NF-κB) pathway, oxidative stress, and transforming growth factor-β (TGF-β) pathway. It has also been found that inflammatory activation is closely related to autophagy (defective autophagic protein could enhance inflammasome activation) as well as sphingolipids homeostasis (Levine et al., 2011). Aflaki and co-workers demonstrated that inflammatory response in Gaucher disease is activated through disrupted autophagy (Aflaki et al., 2016). Another study shows that autophagy impairment in Fabry mice exacerbates the pathologies features of renal

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interstitial fibrosis. Sphingolipids elevate the inflammation responses in many diseases, such as obesity, myocardial infarction, and
Parkinson's disease (Chaurasia et al., 2016; Belarbi et al., 2020; Hadas et al., 2020). For example. Elevated sphingolipids levels (ceramide) were significantly upregulated after myocardial infarction, which triggered severe inflammatory responses and apoptosis of cardiomyocytes (Hadas et al., 2020). Nevertheless, detailed mechanism and consequences about inflammation responses in Fabry disease have not been fully understood. Therapeutic strategy targeting inflammatory to treat Fabry disease [20]

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 date2,9,10). 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 underdiagnosed11.12. There are reports of FD prevalence of 0.019% and 0.017% in in dialysis record programs in Europe and in the United States, respectively. 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%. In a more recent study, conducted in Bahia with 2,583 male patients on hemodialysis, the prevalence rate of FD was 0.12%.[21]

GENETIC FABRY DISEASE

It 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 rare1,18,19. 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 B2.[22]

COMPLICATION OF FABRY DISEASE

Fabry disease is a rare genetic disorder caused by the buildup of a type of fat called globotriaosylceramide (GL-3) in various organs and tissues due to a deficiency of the enzyme alpha-galactosidase A. This buildup leads to damage in different systems of the body. Complications of Fabry disease can be severe, especially if not diagnosed and treated early. Here's a detailed overview of its complications:

1. Kidney Complications

Progressive kidney disease (nephropathy): The accumulation of GL-3 in the kidneys can lead to progressive damage, causing proteinuria (protein in the urine) and a decline in kidney function.Chronic kidney disease (CKD): If left untreated, Fabry disease can lead to CKD, which may progress to end-stage renal disease (ESRD), requiring dialysis or kidney transplantation.

2. Cardiovascular Complications

Hypertrophic cardiomyopathy (HCM): GL-3 deposits in the heart muscle can cause the heart walls to thicken, leading to hypertrophic cardiomyopathy, which may lead to heart failure if untreated.

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Arrhythmias: Fabry disease may cause abnormal heart rhythms (arrhythmias), including atrial fibrillation, ventricular arrhythmias, or heart block.
Heart valve abnormalities: The buildup of GL-3 can cause thickening of the heart valves, which may result in valve dysfunction, such as mitral valve prolapse.
Heart failure: In advanced stages, heart failure can develop due to a combination of arrhythmias, cardiomyopathy, and valve disease.
Ischemic heart disease: Reduced blood flow to the heart, possibly due to GL-3 accumulation in blood vessels, can lead to angina or myocardial infarction (heart attack).

Neurological Complications
Pain crises: One of the earliest symptoms of Fabry disease is episodic pain in the hands and feet (acroparesthesias). These episodes are often triggered by stress, exercise, or temperature changes and can be severely disabling.
Stroke: GL-3 deposits in the blood vessels of the brain increase the risk of cerebrovascular disease and strokes, sometimes at a young age. Strokes are often a serious complication of Fabry disease.Transient ischemic attacks (TIA): Patients may experience mini-strokes (TIA), which are warning signs of future strokes.
Peripheral neuropathy: Damage to peripheral nerves causes chronic pain, tingling, and numbness in the extremities.[23]

3. Gastrointestinal Complications
Gastrointestinal pain: Patients often suffer from abdominal pain, bloating, and diarrhea due to the buildup of GL-3 in the gastrointestinal system.
Diarrhea and malabsorption: Chronic diarrhea is common and can lead to weight loss and malnutrition in some cases.
Nausea and vomiting: Digestive issues can be recurrent, contributing to poor quality of life.

4. Skin Complications
Angiokeratomas: Small, dark red to purple raised spots on the skin (often found around the umbilicus, buttocks, and upper thighs) are common in Fabry disease. These are caused by GL-3 deposits in small blood vessels.
Hypohidrosis: Many patients with Fabry disease experience reduced sweating (hypohidrosis), making them prone to overheating and discomfort, especially in warm environments.

5. Eye Complications
Corneal verticillata: A whorl-like pattern on the cornea is one of the characteristic signs of Fabry disease.
This doesn't typically affect vision but is a useful diagnostic marker.
Cataracts and retinal vessel abnormalities: Some individuals may develop cataracts or other eye complications affecting vision.

6. Hearing Complications Hearing loss:
Gradual sensorineural hearing loss, sometimes sudden, is associated with Fabry disease. Tinnitus (ringing in the ears) is also common.
Dizziness and vertigo: The inner ear may also be affected, leading to balance problems, dizziness, and vertigo.

7. Pulmonary Complications
Respiratory issues: Some individuals may experience respiratory problems, including shortness of breath or airway obstruction, related to the accumulation of GL-3 in the lungs and airways.

8. Psychological and Social Complications
Depression and anxiety: The chronic pain and frequent health problems associated with Fabry disease can lead to mental health issues, such as depression and anxiety.
Reduced quality of life: The cumulative impact of Fabry disease on the heart, kidneys, nervous system, and other organs can significantly reduce quality of life, especially without treatment.

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9. Complications in Female Carriers

Female carriers of the gene mutation may also experience many of the same complications as males, although they often have a milder form of the disease. However, some women may still develop significant organ involvement, including kidney, heart, and neurological issues.

10. Treatment-Related Complications

Infusion-related reactions: Enzyme replacement therapy (ERT), the standard treatment for Fabry disease, can lead to allergic reactions during infusions, including chills, fever, and anaphylaxis.

Development of antibodies: Some patients may develop antibodies against the infused enzyme, reducing the effectiveness of the therapy.[24]

PREVENTION OF FABRY DISEASE

Fabry disease is a rare genetic disorder caused by mutations in the GLA gene, leading to the deficiency or malfunction of an enzyme called alpha-galactosidase A. This enzyme is responsible for breaking down a fatty substance called globotriaosylceramide (Gb3). As Gb3 accumulates in various tissues, it causes damage to organs such as the kidneys, heart, and nervous system.Since Fabry disease is inherited, there is no absolute way to prevent it. However, the following strategies can help manage and mitigate its effects:

Genetic Counseling and Testing

For Families with a History of Fabry Disease: Genetic counseling is crucial. Families can undergo genetic testing to identify carriers of the GLA gene mutation. If a person is identified as a carrier, they can discuss family planning options and reproductive technologies that may reduce the risk of passing the disease to offspring.

Prenatal Testing: For families at risk, prenatal testing can be performed during pregnancy to determine if the fetus has inherited the disease. Options include amniocentesis or chorionic villus sampling (CVS).

Preimplantation Genetic Diagnosis (PGD)

For Couples Undergoing In-Vitro Fertilization (IVF): PGD can be used to screen embryos for the GLA mutation before implantation. This allows the selection of embryos that do not carry the mutation, preventing the transmission of Fabry disease.

Early Detection and Screening

Newborn Screening: In some regions, newborn screening for Fabry disease is available. Early detection through such programs can allow for timely interventions that reduce the progression of the disease.

Family Testing: If one family member is diagnosed, it is recommended that other family members be tested, especially siblings, parents, and children, since Fabry disease is an X-linked disorder.[26]

Enzyme Replacement Therapy (ERT) and Chaperone Therapy

ERT: Although ERT is not preventive, early administration can slow down the progression of the disease. It works by replacing the missing or deficient enzyme with a synthetic form, reducing the accumulation of Gb3 in tissues.

Chaperone Therapy: Some patients have a form of the disease where the enzyme is present but misfolded. Drugs like migalastat (approved in some countries) can stabilize and restore the function of the enzyme, preventing the build-up of harmful substances.

Supportive Therapies

Cardiovascular Management: Preventing complications like heart attacks or strokes involves managing high blood pressure, arrhythmias, and other heart-related issues through medications and lifestyle adjustments.

Kidney Protection: Early interventions to prevent kidney damage include monitoring kidney function and using treatments like angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) to protect the kidneys.

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Pain Management: Neuropathic pain is common in Fabry disease, so managing it with medications such as anticonvulsants, antidepressants, or gabapentin can improve quality of life.[27]

Lifestyle Modifications

Healthy Diet and Exercise: Although not preventive in the traditional sense, maintaining a healthy lifestyle can improve overall well-being and help manage symptoms. A balanced diet low in sodium, along with regular exercise, can support cardiovascular and kidney health.

Avoiding Triggers: Some patients with Fabry disease may have specific triggers, such as temperature extremes or certain medications, that can exacerbate symptoms. Identifying and avoiding these triggers can reduce symptom severity.

Ongoing Research

Research is being conducted into gene therapy as a potential cure for Fabry disease. This approach aims to correct the underlying genetic defect and potentially prevent the disease entirely. Although still in experimental stages, gene therapy offers hope for future prevention strategies.

Routine Monitoring Regular Check-Ups: Patients with Fabry disease need regular monitoring of their kidney, heart, and nervous system functions. Early detection of organ involvement allows for timely interventions to prevent severe complications.[28]

DIGNOSIS AND TREATMENT OF FABRY DISEASE

Fabry disease is a rare genetic disorder caused by mutations in the GLA gene, which results in a deficiency or malfunction of the enzyme α-galactosidase A (α-Gal A). This enzyme is responsible for breaking down a fatty substance called globotriaosylceramide (Gb3 or GL-3). The accumulation of Gb3 in various organs and tissues leads to a wide range of symptoms affecting the kidneys, heart, skin, and nervous system.

Here's a detailed look at the diagnosis and treatment of Fabry disease:

1. Diagnosis of Fabry Disease

Diagnosing Fabry disease involves several steps and tests to confirm the condition and assess its severity.

Clinical Symptoms and Family History:Symptoms may include pain (especially in the hands and feet), angiokeratomas (small, dark red spots on the skin), hypohidrosis (reduced ability to sweat), corneal opacities, and progressive damage to the kidneys, heart, and nervous system.A detailed family history is critical since Fabry disease is an X-linked disorder, meaning males are typically more severely affected, but females can also experience symptoms due to random X-chromosome inactivation.[29]

Enzyme Activity Test: Measuring the activity of the α-Gal A enzyme in blood or white blood cells. Males with Fabry disease usually have very low or absent enzyme activity, while females may have normal, reduced, or absent activity, making this test less reliable for diagnosing women.

Genetic Testing: DNA sequencing of the GLA gene is the definitive method for diagnosing Fabry disease in both males and females. This identifies mutations in the gene that cause the condition.

Urine and Blood Tests: Testing for the presence of GL-3 (accumulated substrate) in the urine or plasma can be indicative of Fabry disease. Elevated levels of these substrates are often seen in affected individuals.

2. Treatment of Fabry Disease

There is no cure for Fabry disease, but various treatments can help manage symptoms, prevent complications, and slow the progression of the disease.

Enzyme Replacement Therapy (ERT):Agalsidase alfa (Replagal) and agalsidase beta (Fabrazyme) are two enzyme replacement therapies that aim to restore α-Gal A activity. These therapies help reduce the accumulation of GL-3 in tissues and organs.is given intravenously, typically every two weeks, and is the standard treatment to manage symptoms and slow disease progression.

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Chaperone Therapy: Migalastat (Galafold) is an oral treatment that works as a pharmacological chaperone to stabilize and enhance the function of α-Gal A in patients with amenable mutations. This treatment is used for individuals who have specific genetic mutations that allow the enzyme to fold correctly with assistance. Unlike ERT, migalastat is taken orally and does not require infusions.

Pain Management: Neuropathic pain associated with Fabry disease can be managed using medications like anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., amitriptyline), and other pain- modulating agents. Non-pharmacological interventions like physical therapy may also be beneficial.

Management of Heart and Kidney Disease: ACE inhibitors or ARBs (Angiotensin II Receptor Blockers) are often prescribed to slow the progression of kidney disease. Cardioprotective medications like beta- blockers or calcium channel blockers may be used for managing heart involvement (e.g., hypertrophic cardiomyopathy, arrhythmias).In advanced stages, dialysis or kidney transplantation may be necessary for patients with severe kidney damage, and pacemakers or defibrillators may be needed for heart arrhythmias.

Gene Therapy: Experimental treatments like gene therapy aim to correct the underlying genetic defect by introducing a functional copy of the GLA gene. Though not yet widely available, gene therapy is a promising area of research for treating Fabry disease.[30]

Supportive Care: Lifestyle modifications such as a low-sodium diet for patients with kidney issues and cardiac-friendly practices for those with heart involvement are recommended. Monitoring and managing complications related to stroke, cardiovascular disease, and kidney failure are critical to long-term management

Follow-up and Monitoring; Patients with Fabry disease require regular follow-up to monitor the progression of the disease and the effectiveness of therapy. This involves: Frequent blood tests to monitor enzyme levels and kidney function. Cardiac evaluations to check for heart involvement. assessments if there are signs of nervous system involvement. Genetic counseling is also advised, especially for families with a history of the disease.

Prognosis

The prognosis of Fabry disease varies based on the severity of symptoms, early diagnosis, and timely intervention. ERT and other treatments can significantly improve the quality of life and slow down disease progression. However, untreated, Fabry disease can lead to life-threatening complications such as kidney failure, heart disease, and strokes, particularly in middle-aged and older individuals.[31,32,33]

II. CONCLUSION

Fabry disease is a rare, inherited lysosomal storage disorder caused by mutations in the GLA gene, leading to a deficiency or malfunction of the enzyme alpha-galactosidase A. This results in the buildup of a fatty substance called globotriaosylceramide (GL-3 or Gb3) in various organs and tissues, leading to a wide range of symptoms.

Symptoms of Fabry disease can include severe pain, kidney dysfunction, heart issues, gastrointestinal problems, and skin abnormalities (angiokeratomas). As the disease progresses, it can cause serious complications, including kidney failure, heart disease, and stroke.

Early diagnosis and treatment are essential to manage the disease. Treatment options include enzyme replacement therapy (ERT) and chaperone therapy, which aim to reduce the buildup of GL-3 and alleviate symptoms. Additionally, supportive care and monitoring for organ complications are critical in managing the condition.

In conclusion, while Fabry disease is a serious and progressive condition, advancements in treatments have improved outcomes, especially when diagnosed early. Regular medical care and personalized management can help control symptoms and enhance the quality of life for affected individuals.

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