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A RUN-THROUGH ON FABRY'S DISEASE

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ABSTRACT

Fabry disease (FD) is an X-linked lysosomal storage illness characterised by a progressive, life-threatening multisystem disease caused by intracellular glycosphingolipids accumulation (mostly globotriaosylceramide [Gb3]). This is caused by a deficiency in α-galactosidase A (GLA/AGAL) function. Its incidence rate estimated over 1 in 1000 to 9000 people. Caused by mutation in GLA gene and Fabry disease is a monogenic, recessive inheritance disorder linked to the X chromosome that leads to lack of α -galactosidase A (α-GAL A) activity. it is classified into two types classic (symptoms start at age 2) and atypical type (symptoms start at age thirty-five or above). Disease pathology includes organ specific or secondary changes that reflect organ abnormalities and dysfunction. It cause Gb3 to accumulate in various cells and tissues that include skin, eyes, kidney, heart, brain and peripheral nervous system that lead to profuse symptoms such as burning sensation, dark red skin patches, cloudiness of the eyes etc. diagnosed through enzyme assay, genetics & screening in new born. Present treatment plans for Fabry disease is enzyme replacement therapy (ERT), chaperone therapy and palliative & adjunct therapy.

KEYWORDS: Alpha-galactosidase A (α-GAL A), heart failure, Acroparesthesia, angiokeratoma, genetics, ceramide trihexosides, epigastric pain.

INTRODUCTION

In 1898, dermatologists William Anderson and Johannes Fabry published the first description of "angiokeratoma corporis diffusum" (Anderson, 1898, Fabry, 1898). Initially identified as a systemic vascular illness, it was subsequently identified as a lipid storage condition (Pompen et al., 1947) (Hornbostel and Scriba, 1953). In 1963, Sweeley and Klionsky discovered the build-up of the glycolipids ceramidetrihexoside (now known as globotriaosylceramide, or GL- 3) and galabiosylceramide in a range of distinct cell types. Furthermore, in certain people, blood group antigens B, B1, and P1 also rise. A few years later, the deficiency was identified as inadequate activity of the ceramidetrihexosidase enzyme, which is responsible for the hydrolytic cleavage of the terminal galactose molecule from Gb3 (Brady et al., 1967). In 1970, Kint identified the anomeric specificity of α-galactosidase A, also known as ceramidetrihexosidase. In 1965, it was discovered that the illness was X-linked (Opitz et al., 1965).[1]

DEFINITION

Fabry disease (FD) is an X-linked lysosomal storage disorder that results in a progressive, life-threatening multisystem disease due to intracellular build-up of glycosphingolipids (mostly globotriaosylceramide [Gb3]). This is caused by a defect in α-galactosidase A (GLA/AGAL) function.[2]

Since lysosomal involvement is inherited and connected to chromosomal X, the process is believed to start as early as the foetal stage; however, symptoms typically manifest after three years, or earlier in males. In heterozygous women, the disease's manifestation might range from subclinical to as severe as in males.[3]

This page aims to provide a concise summary of Fabry's disease.

EPIDEMOLOGY

An estimated 1 in 1,000 to 9,000 people have the fibrillation illness. The classic, severe form of the illness is probably less prevalent than the milder, late-onset varieties. [4] It has been associated with a wide range of prevalence in white male populations, from about 1:17,000 to 1:117,000. Atypical presentations are linked to roughly 1:1000 to 1:3000 males and 1:6000 to 1:40,000 females with classical Fabry disease mutations observed in roughly 1:22,000 to 1:40,000 males.[5]

ETIOLOGY

Genetic mutations in the GLA gene (Xq21.3-q22) cause a lack of alpha- galactosidase A (α-GAL A) activity, resulting in lysosomal build-up of glycosphingolipids, particularly cerebroside trihexosides. Glycosphingolipids accumulate diffusely and abnormally in all organs, causing edema and endothelial cell

proliferation.[6] This may result in heart disease, strokes, early mortality, and renal failure in the third or fourth decade of life. These mutations are linked to the classic Fabry phenotype, which manifests as multisystem involvement. Missense mutations in milder instances are limited to heart problems.[5]

TYPES OF FABRYS DIEASES

The ages at which symptoms first manifest are reflected in the forms of Fabry disease. Types consist of

Classic type: Children or teenagers may experience the symptoms of classic Fabry disease. As early as age 2, you may detect a typical disease symptom, which is a severe burning feeling in your hands and feet. Over time, the symptoms develop worse and worse.

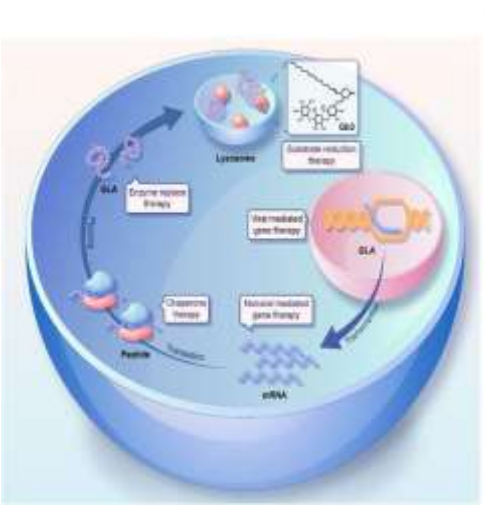
Atypical/late-onset: Individuals with late-onset Fabry disease do not exhibit symptoms until they reach the age of thirty-five or beyond. Heart disease or renal failure could be the first sign of an issue.[8]

GENETICS

Due to a mutation in the GLA gene, FD is a monogenic, recessive inheritance condition associated with the X chromosome. This gene, which is found at the Xq22 location on the long arm of the X chromosome, codes for the α-GAL enzyme. Rarely do new mutations occur; most cases are inherited. There are more than 900 distinct mutations that have been identified as the illness's cause.

Gb3 is broken down into galactose and lactosylceramide in the lysosomes by α- GAL, which has about 429 amino acids. GB3 is therefore accumulated in several tissues in FD patients. It prefers to target renal podocytes, smooth muscle cells in the cardiovascular system, and the vascular endothelium, which explains why these organs are the primary target of clinical symptoms.

The α-GAL gene is composed of seven exons and roughly 12 kb. Multiple molecular variants in this gene have been linked to FD: missense mutations (57%), nonsense mutations (11%), partial deletions (6%), insertions (6%), and errors in RNA processing that result in aesthetically offensive splicings (6%). Because a single mutation can cause a variety of clinical symptoms, the relationship between genotype and phenotype is complicated. Both the blood type and environmental variables may be to blame for this. Because blood group AB or B patients have an extra build-up of glycosphingolipids in their erythrocyte membranes, they may present with more severe illness symptoms.[3]



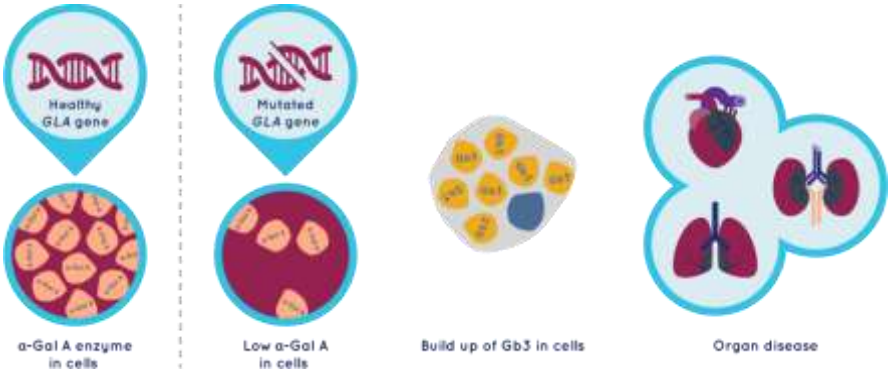
PATHOLOGY

Pathologic abnormalities can be classified as disease-specific or secondary changes that reflect organ abnormalities and dysfunction.[1]

The major metabolic abnormality is a lack of lysosomal alpha-galactosidase A (alpha-Gal A). It is essential to break down the terminal galactose in globotriaosylceramide (Gb3). It causes Gb3 to accumulate in a variety of cells and tissues, including the skin, eyes, kidney, heart, brain, and peripheral nervous system.

Vascular accumulation triggered by raised endothelial proliferation may result in vascular obstruction, ischemia, or infarction. The vertebrobasilar arteries were the most prominent site for vascular dilatation, followed by smaller cerebral vessels. Young individuals with stroke associated with Fabry disease had low levels of thrombomodulin (TM) and higher levels of plasminogen activator inhibitor (PAI), implying that the illness is prothrombotic. Stroke mechanisms in young individuals with Fabry disease have been correlated with nitric oxide- and non-nitric oxide-dependent endothelial proliferation and dilatation, as well as aberrant endothelial nitric oxide synthase (eNOS) activity. Other typical sites of Gb3 accumulation include autonomic ganglia, dorsal root ganglia, renal glomerular, tubular, interstitial cells, cardiac muscle cells, vascular smooth muscle cells, valvular fibrocytes, and cardiac conduction fibres.

Globotriaosylceramide (Gb3) aggregates in the kidney primarily in the glomerulus, followed by deposits in the distal tubule. The predilection for Gb3 deposits in these areas is linked to the development of early proteinuria and polyuria. The mechanism of renal sinus cyst development linked with Fabry disease is poorly known.[4,10,11]



CLINICAL SIGNS AND SYMPTOMS

People with Fabry disease experience varying effects. Often, childhood is when the first symptoms manifest. In some situations, the individual doesn't experience any symptoms till a later age.

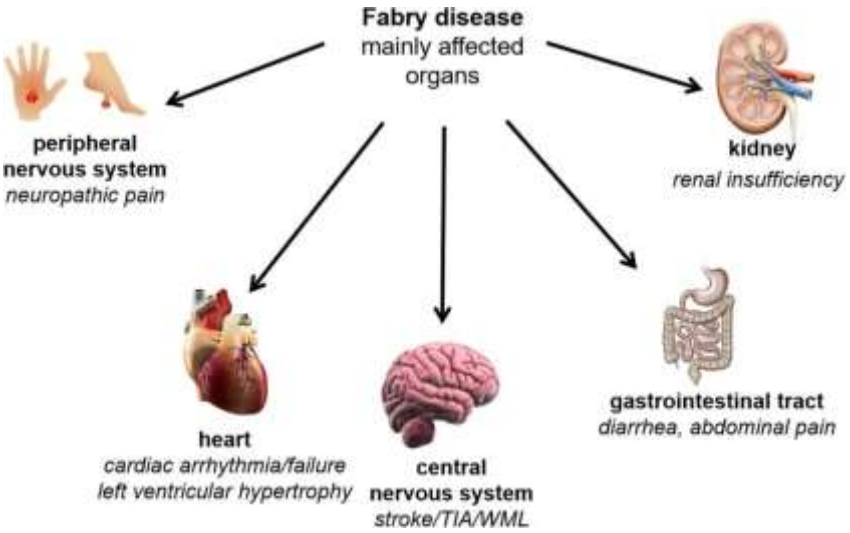
Early-life pain is frequently the initial indication of Fabry disease. It could be disregarded and written off as "growing pains."

Among the other typical symptoms in youngsters are

- Burning sensation, particularly in the hands and feet clusters of tiny,
- Dark red skin patches
- Cloudiness of the eyes
- Digestive issues, such as constipation, diarrhoea, and discomfort hearing issues

Other symptoms that adults may have include

- Headaches or light-headedness
- Excessive or insufficient perspiration tinnitus, or ringing in the ears
- Renal issues
- Cardiac issues[12]



DIAGONSIS

Males with conventional FD may have an easy diagnosis, while females and those with genetic variations may have a difficult diagnosis.

It is advised to use a diagnostic strategy that includes a thorough history, family history, physical examination, clinical and biochemical results, genetic testing, several imaging modalities, and expert opinion. Acroparesthesia, angiokeratoma, and corneal verticillate are a few examples of clinical symptoms and findings that may have a high specificity.[13]

Measurements of α-Gal A activity should be made in males suspected of having FD. When the Alpha Gal A activity is less than 1%, it strongly suggests the diagnosis of classical FD. The α-Gal A activity varies and can be within the normal range in females even when there are clinical symptoms. The majority of these girls experience clinically serious illness.[14]

Examinations to identify Fabry disease, including as

Enzyme assay: This examination gauges blood alpha-GAL enzyme activity. When the measurement is 1% or less, illness is present. Only men and individuals who identify as AMAB may trust this test; women and those who identify as AFAB cannot use it.

Genetic: To determine the GLA gene mutation, medical professionals employ genetic testing (DNA sequencing)

on males and individuals AFAB with Fabry disease, as they may have normal levels of alpha-GAL enzyme activity.

Screenings for newborns: A few states examine infants for lysosomal storage diseases, including Fabry disease.[15]

TREATMENT OF FABRY'S DIEASES

A inherited lysosomal storage disorder that worsens with age and has no known treatment is called Fabry disease. The illness is brought on by a lack of the enzyme α-galactosidase A, which causes globotriaosylceramide—also known as ceramide trihexosides, Gb3, or GL-3—to accumulate in the cells. The function of the blood arteries, tissues, and organs is eventually compromised by the accumulation of these glycolipids.[16]

The present treatment plans are

- Enzyme Replacement Therapy (ERT)
- Chaperone Therapy
- Palliative and Adjunct Therapy(2)(17)

Enzyme Replacement Therapy (ERT)

The mainstay of treatment for Fabry disease is enzyme replacement therapy (ERT), which involves intravenous infusion of synthetic enzyme made by recombinant DNA technology.[18] Fabry disease presently has no known treatment. Nonetheless, there are authorized drugs that function by increasing alpha-galactosidase A enzyme activity, reducing organ damage, and enhancing patients' quality of life.[19] At present, there are two ERTs that are Galactosidase beta (Fabrazyme) and Agalsidase alpha (Replagal).[15]

Fabrazyme

Sanofi Genzyme's Fabrazyme is the first medicine designed especially for Fabry disease. The U.S. Food and Drug Administration gave it its approval in 2003. The European Medicines Agency has approved the use of Fabrazyme in the European Union for the treatment of Fabry disease. Agalsidase beta is an artificially produced alpha-galactosidase A enzyme found in Fabrazyme. It assists individuals with Fabry disease in breaking down Gb3. It is exactly the same as the naturally occurring alpha-galactosidase A enzyme.(18) dose is 1.0 mg/kg/2 weeks.[7]

Chaperone Therapy

Recently, migalastat (Galafold®), a pharmacological chaperone molecule, has been made accessible for the treatment of familial diarrhoea (FD). It was licensed in 2016 as first-line therapy in the US and Europe for FD patients with susceptible GLA gene variations, but is now being used as second-line therapy in Korea.[16] In individuals with appropriate mutations, the medication helps the body's malfunctioning alpha-Gal A enzyme reach the lysosomes and function more regularly by stabilizing it. For some individuals with Fabry's disease, galafold is the first effective oral medication. The FDA has authorized galafold for use in these patients. To find out if Galafold can help a person with their faulty enzyme, a test is available.[19]

Dose in table 1 Table 1

ERT for children < 16 years with a confirmed diagnosis of FD and who meet the treatment starting criteria

Agalsidase alfa (Replagal®) 0.2 mg/kg in 100 mls of NaCl 0.9% IV over 40 minutes every other week OR Agalsidase beta (Fabrazyme®) 0.3-1.0 mg/kg in 500 mls of NaCl 0.9% IV over 4 hours (reducing to 90minutes as tolerated) every other week.

Oral therapy for children ≥12 years and ≥45kg with a confirmed diagnosis of FD and who have an amenable pathogenic variant to meet the treatment starting criteria for migalastat

Migalastat (Galafold®) 123 mg (1 capsule) once every other day by mouth at the same time of day.

Palliative and Adjunct Therapy

Palliative therapy is a therapeutic technique used to treat Fabry disease with the goal of improving the patient's quality of life and symptom relief. For Fabry patients, a number of palliative therapies are frequently employed, such as.

Pain management: Neuronopathic pain is a prevalent FD symptom that interferes with day-to-day activities. Analgesics and ERT, or pharmacological chaperone, work well together to relieve pain. Carbamazepine, gabapentin, pregabalin, and serotonin and norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine) are among the first-line options for pain treatment available today. It is ineffective to use nonsteroidal anti-inflammatory medications. The second line of treatment might include topical capsaicin patches, lidocaine, and tramadol. Using strong opioids ought to be a last choice.

Cardiac care: Heart failure may result from cardiac problems in patients with FD, such as LVH. In order to manage hypertension and heart failure, cardiac therapy may involve the use of beta-blockers, ACE inhibitors (ACEi), and diuretics. Consider permanent cardiac pacing if there is symptomatic bradycardia, chronotropic incompetence, or substantial AV conduction dysfunction. It is advised to take lifelong anticoagulation if atrial fibrillation is detected. In the event of a malignant arrhythmia, implanted cardioverter- defibrillators should be taken into consideration.

Renal care: Renal problems in patients with FD, such as proteinuria, can result in chronic kidney disease (CKD). To manage hypertension and chronic kidney disease (CKD), renal treatment may involve the use of ACEi, angiotensin receptor blockers (ARBs), and diuretics. A low-sodium diet is advised since a high-sodium diet reduces the effects of ACEi and ARBs.

Gastrointestinal medication: The symptoms of epigastric pain and delayed gastric emptying were relieved with metoclopramide and H-2 blockers. Patients with FD, particularly those with paediatric FD, often have dysmotility and diarrhoea. These symptoms can be controlled with medication and dietary modifications, such as increasing fiber intake and eating smaller, more frequent meals.

Hearing impairment: Cochlear implants and hearing aids are required.

Care for the lungs: It is strongly advised against smoking. Bronchodilators might be useful in easing blockage of the airway.

Physical treatment: Patients with Fabry disease may have less discomfort and an improvement in joint mobility and muscular strength with regular physical therapy sessions.

Occupational therapy: With occupational therapy, people with Fabry disease can become more independent and better at managing their everyday tasks.

Psychological support: Because of their condition and how it affects their day- to-day life, patients with FD may feel distressed on an emotional and psychological level. Therapy, support groups, and counselling are a few forms of psychological assistance.

It is crucial to remember that palliative care is not curative and that patients may require long-term monitoring and treatment. Additionally, the effectiveness of the medication may vary based on the particular mutation present in the patient as well as other circumstances. Furthermore, it's crucial to speak with an expert in the field before beginning any palliative care.[16]

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