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A Comprehensive Review of Fabry Disease

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ABSTRACT

Fabry disease (FD) is a lysosomal storage illness brought on by mutations in the GLA gene that result in insufficient α-galactosidase enzymatic activity.Hypohidrosis, acroparesthesias, heat intolerance, angiokeratomas, ocular opacities, cardiac arrhythmias, left ventricular hypertrophy, proteinuria, renal insufficiency, and cerebrovascular accidents are among the disease's clinical signs.A high level of clinical suspicion, a thorough physical examination, organ-specific testing, and the confirmation of low enzyme assays in homozygous males and gene typing in heterozygous females are required for the diagnosis of Fabry's disease have symptoms ranging from very mild to severe .Insufficient lysosomal α-galactosidase activity causes globotriaosylceramide to gradually accumulate inside lysosomes, which is thought to set off a series of biological activities. While dialysis or renal transplantation are options for people with end-stage renal failure, conventional therapy includes pain reduction with analgesic medications, nephroprotection (angiotensin converting enzyme inhibitors and angiotensin receptor blockers), and antiarrhythmic medications.Vital organ systems gradually deteriorate with ageing, and eventually, organs may cease to function.In certain situations, chaperones can also be used as treatment. Since the specific treatment can alter the prognosis of the disease, it is believed that it should be started as soon as a diagnosis is made.

INTRODUCTION:

One of the genetic conditions collectively referred to as lysosomal storage disease is Fabry's disease. Various enzyme deficiencies lead to substrate accumulation within lysosomes, which is the cause of lysosomal storage diseases. There are currently forty (40) recognised lysosomal storage diseases, with Fabry's being the only one that is X-linked[1].Mutations in the GLA gene, which encodes the lysosomal enzyme α-galactosidase A, cause Fabry disease.Patients with Fabry disease experience a wide range of progressive clinical symptoms, many of which appear in early childhood.GI issues, angiokeratomas, temperature intolerance, and burning sensations, especially in the hands and feet (acroparaesthesia) are some of these symptoms. Early adulthood and late adolescence are the times when end-organ failure and early death are most commonly linked to signs and symptoms. These include cardiac hypertrophy and arrhythmia, glomerulosclerosis and proteinuria, other cardiovascular diseases, and stroke[2].

Some Fabry disease patients may experience less pain, less lipid accumulation, and preservation of organ function with enzyme replacement therapy. Medication is frequently administered to manage the gastrointestinal distress and pain that come with Fabry disease, but it does not cure the illness. For adults with Fabry disease who possess a specific genetic mutation, the U.S. Food and Drug Administration (FDA) has authorised migalastat, also known as Galafold, as an oral medication. Blood pressure medications can slow the loss of kidney function in patients with Fabry disease, and anti-platelet medications can help prevent strokes. Some people might need dialysis or kidney transplants[3].

Untreated men's life expectancy is about 20 years shorter than the 50-year life expectancy of the general population, and survival rates sharply decline after 35 years[4].Because of the low expected post-commercialization profits and the high difficulty of organising clinical trials, their individual low incidence has discouraged active treatment search[5].Regardless of the particular substrate involved, studies concentrating on immune system abnormalities in lysosomal storage disorders have demonstrated that substrate deposits in lysosomes fuel multiple pathogenic cascades that ultimately result in an inflammatory response[6].Patients can receive two clinically available treatments: oral molecular chaperone therapy and intravenous enzyme replacement therapy. There are now mouse and, more recently, rat models available to test novel therapies and clarify the pathophysiology of disease[7].Approximately 1:7700 births were reported to have a combined incidence of LSD;

however, when all LSD are taken into account, this number may rise to 1:5000 births. The majority of LSD patients have normal birth appearances but experience severe, progressive pathology[8].

History:

In 1898, dermatologists William Anderson and Johannes Fabry published the first description of "angiokeratoma corporis diffusum" (Anderson, 1898; Fabry, 1898)[9].The first postmortem results from two affected brothers who passed away from renal failure were published by Pompen et al. in 1947. The presence of aberrant vacuoles in blood vessels throughout their bodies was the most important finding[10]. Hashimoto et al.'s 1965 electron microscopy study identified bodies in the endothelial, smooth muscle, fibrocyte, and perivascular cells of Fabry disease patients. He described these structures as "extremely overcrowded lysosomes" and came to the conclusion that a genetic abnormality was causing a disruption of lysosomal enzymes[11]. The disease's specific cause was identified as α-galactosidase A enzyme deficiency in 1970.The commercial introduction of Fabrazyme, a specific enzyme replacement therapy for Fabry's disease, occurred in Europe in 2001 and in the USA in 2003[12].

Causes:

1.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. The majority of cases are genetic, and newly discovered mutations are uncommon[13].Alpha-galactosidase A (Gal A), an enzyme that breaks down fatty compounds like Gb3 and lyso-Gb3, is active in lysosomes, the cell's recycling centre. The GLA gene codes for the production of Gal A. Mutations in GLA cause the activity of the Gal A enzyme to be missing or significantly reduced, which causes Gb3, lyso-Gb3, and other similar compounds to accumulate toxically inside lysosomes. Damage to tissues and organs results from this toxic accumulation. Fabry disease is therefore categorised as a lysosomal storage disease[14].

2.Inheritance:

There is a 50% probability that a female carrying the Fabry gene will pass on her faulty X chromosome to her offspring, and a 50% chance that she will pass on her normal X

chromosome. This indicates that every daughter and son born to a female who carries the Fabry gene has a 50% probability of inheriting the X chromosome that is afflicted and carrying the Fabry gene[14].While Fabry's disease is strongly associated with a positive family history, de novo or spontaneous mutations have also been reported, so the absence of a family history does not rule out the condition[1].

3.Sex difference:

A individual must inherit one mutant copy of the GLA gene from the X chromosome in order to have Fabry disease, which is inherited in an X-linked dominant way[14].Therefore, the normal gene on the other X chromosome can mask or diminish illness features on the X chromosome in females with X-linked disorders, such as Fabry disease. More specifically, one X chromosome is effectively "turned off" in each cell of a female since only one functional X chromosome is needed in men and females (random X-chromosome inactivation). This normally occurs in an unpredictable sequence. This indicates that in X-linked illnesses, the mutant "Fabry" gene will be active on the X chromosome in some cells. The percentage of cells in the tissue or organ where the X chromosome with the GLA gene mutation is active, but with no or noticeably decreased function, determines the symptoms and severity of organ involvement in Fabry disease. This partially explains why the disease severity in females varies more than in their affected male relatives. Males only have one X chromosome, so if a guy has the GLA gene mutation on that X chromosome, he will have the condition[15].

Pathogenesis:

The primary metabolic abnormality is a lysosomal alpha-galactosidase A (alpha-Gal A) deficiency. It is necessary for the breakdown of globotriaosylceramide (Gb3) to release the terminal galactose.Gb3 builds up in a variety of cells and tissues as a result, including the skin, kidney, heart, brain, and peripheral nervous system. Vascular occlusion, ischemia, and infarction are possible outcomes of vascular accumulation brought on by increased endothelial proliferation. The vertebrobasilar arteries are the most frequently dilated vascular sites, with smaller cerebral vessels coming in second. Young individuals with Fabry disease who present with stroke have low thrombomodulin (TM) levels and high plasminogen activator inhibitor (PAI) levels, which may indicate that the disease is prothrombotic. Theories concerning the causes of stroke in young Fabry disease patients have been connected to aberrant endothelial nitric oxide synthase (eNOS) activity, nitric oxide-

dependent endothelial proliferation and dilatation, and both. Other areas that frequently experience Gb3 accumulation are the renal glomerular, tubular, autonomic ganglia, interstitial cells, cardiac muscle cells, vascular smooth muscle cells, valvular fibrocytes, cardiac conduction fibres, and renal glomerular[16].

Intracellular accumulation of Gb3 and/or exposure of Gb3 or lyso-Gb3 to various blood cell types may also trigger other pathogenic pathways, including changes in autophagy or mitochondrial function or innate immunity. With time, various tissues, primarily the kidney and heart, will experience fibrosis due to this ongoing inflammatory state, which will result in the accompanying clinical symptoms. Furthermore, different pathogenic mechanisms may be involved based on the exposed tissue or type of cell. When there is renal involvement, podocyte injury from Gb3 or lyso-Gb3 accumulation exposure seems to be the first step in triggering various pathogenic mechanisms that could lead to the development of nephropathy. These are permanent conditions brought on by ischemia, and they will eventually result in end-stage renal disease. Various studies have demonstrated the involvement of certain mediators in these mechanisms in FD[17].Furthermore, it has been noted that FD tissues, such as the heart, have infiltrated with lymphocytes and macrophages, indicating a potential role for inflammation in tissue damage. It's possible that oxidative stress and chronic inflammation in FD cause organ damage[18].Uncertainty surrounds the cellular mechanisms underlying renal dysfunction in Anderson-Fabry disease. Necroptosis is one of the pathways leading to programmed necrotic cell death that appears to be important in kidney injury[19].

Classification of fabry disease:

According to their presentation and plasma levels, Fabry's patients might be classified into three primary groups clinically. Level of galactosidase[1].

Classification of fabry disease
• Classical fabrys disease
• Heterozygous females
• Atypical or late onset variants of fabry diseases

1.Classic fabry disease:

Individuals with classical Fabry disease exhibit symptoms and indicators that impact many organ systems. The first ten years of life are when symptoms of classical Fabry disease initially appear in afflicted patients[20]. It has been revealed that about 965 mutations in the GLA gene cause Fabry syndrome. However, different mutations have varying effects on the production of Gal A, thus patients will not all have the same amounts of the enzyme. The majority of Gb3 cannot be eliminated by the body in patients with mutations that produce little to no Gal A activity, which is defined as less than 3% of normal activity. Thus, from an early age, this fat molecule accumulates in most tissues, leading to the most severe symptoms of the illness[21]. Classic Fabry disease symptoms usually start to show up in infancy or adolescence. 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[22]. The first symptoms appear in the first or second decades of life and include symptomatic organ complications (e.g., progressive renal disease leading to renal failure and left ventricular hypertrophy (LVH) linked to arrhythmias, strokes, and myocardial fibrosis). usually first appear in people who are young adults and ultimately cause an early death[23].

2.Heterozygous female:

Although reports of disease symptoms in female heterozygotes exist, they are thought to be uncommon and often mild. About 70% of people have asymptomatic corneal dystrophy, which is helpful for heterozygote diagnosis and manifests as cornea verticillata and posterior lenticular cataract. About 10% of women experience sporadic episodes of neuropathic pain, while about 30% have mild angiokeratomas. Though confirmed cases of severe and early cerebrovascular illness, strokes, and renal failure have been reported in female heterozygotes, the incidence of these significant symptoms was estimated to be less than 1%. Since this is an X-linked condition, unbalanced X inactivation was the explanation for these severe manifestations in females[24]. While some female carriers show no symptoms and have normal α-Gal A concentrations, others have more severe disease signs. This variation is believed to be partially caused by Lyonization, a process that causes one X chromosome in some or all of the female embryo's cells to be randomly inactivated[25]. Men are primarily affected, while carrier (heterozygous) women may experience severe illness symptoms. According to estimates, the incidence of Fabry disease in men is 1:117,000 births; however, screening investigations on newborns have revealed a significantly higher frequency[26].

Atypical or late onset variant fabry complaint:

The enzyme still acts kindly, or at roughly 30 of normal exertion, in colorful forms of Fabry complaint. These variations are appertained to as" latterly- onset Fabry complaint" or" atypical Fabrydisease. A person might stay until they're in their 40s, 50s, or indeed decades to seek medical attention for them. There are nevertheless negative consequences in these situations, constantly to the heart. Because of this, the illness is sometimes unintentionally set up in cases witnessing evaluation for unexplained cardiac issues(27). late onset Compared to the classic type, Fabry is three to ten times further current. It's also linked to a advanced degree of residual girl A exertion (3 to 15 of normal), which indicates that cases can still break down someGb3.Even so, the accumulation of adipose motes in apkins occurs vastly more sluggishly and to a lower extent, performing in milder symptoms that develop latterly in life(9). clinical instantiations, with the fourth and seventh decades of life being the normal times for the donation of cardiac and renal symptoms (similar as LVH and lower glomerular filtration rate, or GFR) (23). Late- onset hypertrophic cardiomyopathy or idiopathic left ventricular hypertrophy may be a significant causative factor in the cardiac interpretation of Fabry's complaint (1).

Organ specific manifestation:

1.Cardiac manifestations:

Over half of all Fabry patients experience cardiac involvement, or Fabry cardiomyopathy, with concentric left ventricular hypertrophy (LVH) being the most common type[28].Hemizygous men and heterozygous women with Fabry disease frequently experience cardiac involvement, which is one of the three main causes of morbidity and death. Numerous heart cells, including cardiomyocytes, conduction system cells, valvular fibroblasts, endothelial cells in all kinds of vessels, and vascular smooth muscle cells, store globotriaosylceramide[29].ECG abnormalities (signs of left ventricular hypertrophy, short PR interval or AV conduction abnormalities, deep T inversions in precordial leads) are the first clinical signs of Fabry-related cardiac disease in adults. Results from echocardiography and magnetic resonance imaging (MRI) show a gradually increasing left ventricular hypertrophy (LVH), which is clinically evident in the third decade for men and the fourth decade for women. LVH is typically concentric and diffuse, with prominent papillary muscles[30].

2.Renal involvement:

ECG abnormalities (signs of left ventricular hypertrophy, short PR interval or AV conduction abnormalities, deep T inversions in precordial leads) are the first clinical signs of Fabry-related cardiac disease in adults. Results from echocardiography and magnetic resonance imaging (MRI) show a gradually increasing left ventricular hypertrophy (LVH), which is clinically evident in the third decade for men and the fourth decade for women. LVH is typically concentric and diffuse, with prominent papillary muscles[31].According to registry data and clinical trials, patients who begin enzyme replacement therapy (ERT) at a younger age and start taking agalsidase alpha at 0.2 mg/kg or agalsidase beta at1.0 mg/kg every other week (EOW) will benefit the most from ERT and have better long-term renal outcomes[32].Important indicators of Fabrizy nephropathy include a urinary concentration defect, microalbuminuria, and eventually overt proteinuria as well as a progressive decline in the glomerular filtration rate (GFR).Patients may first experience glomerular hyperfiltration at a pace akin to that of diabetic nephropathy[33].

3.Skin involvement:

Fabry disease initially presents with soft-tissue and dermatological symptoms, including lymphoedema, acroparaesthesia, angiokeratomas, and abnormal sweating (hypo- and hyperhidrosis).It is essential to identify these symptoms in order to diagnose and treat Fabry disease as soon as possible[34].Patients with Fabry disease typically present with telangiectases organised as superficial angiomas or angiokeratomas, which are distinctive cutaneous lesions. These typically manifest between the ages of 5 and 13, though they can also happen in infancy. In a thorough investigation by Ries and associates, the Fabry disease affected two out of every three male and one out of every three female children[35].

4.Ocular manifestations:

Ophthalmological abnormalities in Fabry's disease primarily affect the cornea, lens, and conjunctival and retinal vessels. They are associated with an increasing accumulation of glycosphingolipids within the structures of the eyes. The vessels in the conjunctiva and retina are twisted and may dilate aneurysmically[36].Hyperreflective intracellular inclusions at the level of the basal epithelial cells or the epithelial basement membrane are examples of corneal manifestations. In contrast to corneal involvement, there is no difference in conjunctival involvement between male and female patients. Round-shaped intracellular inclusions have been reported. In addition, general dilatation, microaneurysms, and vessel

tortuosity are examples of vascular abnormalities. The most prevalent types of cataracts are posterior subcapsular or anterior capsular cataracts. Because they occur so frequently, posterior subcapsular cataracts are also known as Fabry cataracts. Retinal vessel tortuosity is the most frequently observed finding. Discedoema is one of the other types of retinal vessel disease that have been reported[37].

Diagnosis:

After signs and symptoms appear, the diagnosis of Fabry disease is frequently made at least three years—and frequently more than twenty years—later. The condition's rarity (and the corresponding lack of awareness among clinicians) as well as the variety and non-specificity of presenting symptoms are the causes of this delay. A general practitioner or family doctor, dermatologist, ophthalmologist, paediatrician, geneticist, neurologist, cardiologist, or nephrologist may receive the initial presentation. An all-encompassing diagnostic algorithm that incorporates pertinent investigations based on the organ system involved[2].

Ultrasound role: The first-line non-invasive imaging method for determining cardiac involvement in FD is electrocardiography. Increased lethal ventricular wall thickness, which is typically progressive, concentric, and non-obstructive in FD, can be detected with ultrasounds. Nonetheless, in the most severe form of the illness, asymmetric hypertrophy can occasionally be seen along with posterior wall fibro tic thinning and septal thickening. Later on, right ventricular hypertrophy could appear and could eventually lead to right ventricle dilation[38].

Prompt diagnosis is necessary when FD signs and symptoms first appear, especially since ERT is readily available. However, there are a number of reasons why it could be difficult to identify the early signs in clinical practise. The symptoms can mimic those of more common diseases, the disease presentation is typically heterogeneous, and significant cardiac or renal dysfunction is rare in paediatric patients. Even in this day and age, patients frequently need to see multiple medical specialists before receiving the proper diagnosis, and diagnostic delays can still be significant. According to recent data, the mean time between diagnoses for both genders was approximately 15 years . The proper biochemical and/or genetic confirmation is required if the clinical examination [39].

Management:

Enzyme replacement theory:

In order to prevent or remove Gb3 deposits, the goal of treating FD patients mostly involves using ERT to replace the enzyme that is lacking or inadequate. Based on the finding that cells can absorb an enzyme from the extracellular medium and use it in their regular metabolism, the ERT that is currently in use. ERT is generally thought to be beneficial for all male patients affected by the classic presentation of FD. If there is a clinical manifestation, ERT should be given to women and patients with unusual presentations. It's also critical to emphasise that, because ERT can lessen neurological and cardiovascular problems, individuals who are currently receiving dialysis should still receive treatment. To manage symptoms, patients should have specialised care for the afflicted organs. Clinical research has revealed a drop in heart mass, the frequency of pain episodes, and Gb3 deposits in the skin and kidneys. In certain cases, renal function has even improved. Additionally, there is proof that ERT alleviates gastrointestinal symptoms and sudoresis. Still, no studies have been conducted to demonstrate the decline in mortality[13].

Reduction of left ventricular hypertrophy and stabilisation of heart wall thickness, amelioration of gastrointestinal complaints and neuropathic pain, improvement in sweating capacity, and stabilisation of kidney function or postponement of the development of terminal kidney failure. Because of the way the enzymes are made and used, ERT has drawbacks that make it difficult to use in routine clinical settings. Allergy-induced infusion responses, such as cephalalgia, paresthesis, hypotension, fever, chills, nausea, and exhaustion, can happen during infusion (particularly after infusions).Reducing the infusion rate and administering glucocorticoids, antihistamines, and/or non-steroidal anti-inflammatory medications can typically ease these effects[40]. The majority of patients who experienced these clinical advantages did so prior to the development of irreparable organ damage. According to several studies, women who had ERT initially experienced a decrease in heart mass. While cardiomyocytes and podocytes—two of the most seriously afflicted cell types in FD—take up very little recombinant enzyme, the majority of recombinant enzyme supplied is deposited in the liver[41].

Chaperone therapy

It has been demonstrated that FD patients with multiple missense mutations produce a mutant protein with normal αGAL A catalytic activity. The overall decrease in αGAL The

significantly decreased stability of the mutant protein has been linked to an enzymatic activity in patients with these GLA mutations. Protein misfolding and the ensuing early breakdown are the causes of this Chaperone therapy aims to increase the mutant protein's stability by promoting proper folding. Galactose was used in the initial in vitro investigations on the role of a chaperone in FD. The galactose analogue 1-deoxygalactonojirimycin (now known as Migalastat, Amicus Therapeutics), in which the oxygen is substituted with a nitrogen atom in the ring to produce an iminosugar, was mostly used in subsequent chaperone experiments [41].

For individuals with susceptible mutations, oral treatment using migalastat appears to be a practical substitute for intravenous ERT. Nonetheless, patients with varying amenable mutations will have varying clinical responses, in part because of the patient's unique increase in AGAL activity, the disease's severity at the beginning of treatment, potential comorbidities, and drug adherence[40].

Handling renal involvement in patients with Fabry disease:

FD is frequently linked to proteinuric chronic kidney disease, and it seems that FD can benefit from the same treatment approaches that have been shown to be successful in treating diabetes mellitus and other types of proteinuric renal disease. Patients with proteinuria can benefit from the use of angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEi) .A large number of FD patients with renal involvement may need kidney transplantation or dialysis [42]. It is crucial to diagnose Fabry's disease patients as soon as possible because ERT can enhance renal functions and glomerular structure by reducing kidney glycolipid deposits and attempting to stop further renal deterioration[1].

Management of cardiac involvement in fabry disease:

The clinical presentation determines the course of treatment for people with heart illness. When angina is present, it is best to rule out epicardial coronary artery disease before starting traditional antianginal therapy, which includes nitrates, β-blockers, calcium channel blockers, and antiplatelet medications. Antiarrhythmic medications can be used to help individuals with atrial fibrillation transition to sinus rhythm, however there isn't much data regarding how safe these medications are for people with Fabry disease. Patients with bradycardia that exhibits symptoms are fitted with pacemakers[43].

Pain management:

Avoiding situations that can cause acute pain attacks, such as intense physical activity and temperature fluctuations, may be beneficial for patients suffering with neuropathic pain[22].The current approaches to treating neuropathic pain are either based on clinical experience or adhere to international and national criteria. First-line therapies include tricyclic antidepressants (cave), gabapentin, pregabalin, carbamazepine, and serotonin and norepinephrine reuptake inhibitors (like duloxetine and venlafaxine).Strong opioids should only be regarded as third-line treatments; lidocaine, topical capsaicin patches, and tramadol are regarded as second-line choices. Currently, fourth-line therapies include tapentadol, botulinum toxin, methadone (which has both N-methyl-d-aspartate and opioid-receptor effects), and anticonvulsants with less evidence of efficacy (such lamotrigine and lacosamide).On the other hand, patients experiencing neuropathic pain ought to speak with a neurologist who specialises in FD[40].

Conclusion:

Fabry's is a progressive, destructive and life- hanging complaint which reduces life expectation significantly, so all attempts should be made for an early opinion of Fabry's as early launch of remedy is the only stopgap to arrest progression of complaint.

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