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AN INTEGRATIVE REVIEW ON FABRY DISEASE: FROM ITS MOLECULAR MECHANISM TO MODERN THERAPIES

Ms. P. Devika*, Ms. D. Jayashree, Ms. S. Sapna Banu, Mrs. S. Sathiya Priya, Ms. T. Yathika, Ms. A. Mumtaj Begum*

M. Pharm., Assistant Professor in the Department of Pharmacology at P.S.V. College of Pharmaceutical Science and Research, Krishnagiri – 635108.

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***Corresponding Author**

Ms. A. Mumtaj Begum

M. Pharm., Assistant Professor in the Department of Pharmacology at P.S.V. College of Pharmaceutical Science and Research, Krishnagiri - 635108.

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ABSTRACT

Fabry disease is a rare X-linked lysosomal storage disorder caused by pathogenic mutations in the GLA gene, resulting in deficient activity of the enzyme α-galactosidase A. Reduced enzymatic function leads to progressive intracellular accumulation of glycosphingolipids, primarily globotriaosylceramide (Gb3) and its deacylated metabolite lyso-Gb3, which disrupt cellular homeostasis and promote multisystem involvement. The disease predominantly affects the kidneys, heart, nervous system, and vascular endothelium, contributing to significant morbidity and reduced life expectancy. Advances in diagnostic strategies, including enzyme activity assays, molecular genetic testing, and biomarker assessment, have improved early disease identification and clinical monitoring. Current therapeutic approaches, such as enzyme replacement therapy, pharmacological chaperone therapy, substrate reduction strategies, and emerging gene-based interventions, aim to correct the underlying metabolic defect. However, treatment effectiveness is frequently limited by immune-mediated reactions, short biological half-life, and inadequate penetration across the blood–brain barrier. Recent progress in nanotechnology-based drug delivery systems has demonstrated potential to enhance therapeutic stability, tissue targeting, and overall clinical efficacy. This review provides a comprehensive overview of Fabry disease pathogenesis, diagnostic developments,

and evolving treatment strategies, highlighting future directions toward improved, personalized, and more durable disease management approaches.

KEYWORDS: Anderson‑Fabry Disease, GLA gene mutation, alpha-galactosidase A deficiency, globotriaosylceramide (Gb3) accumulation, lyso-Gb3 biomarker, X-linked lysosomal storage disorder, endothelial dysfunction.

1. INTRODUCTION

Fabry's disease is also known as Anderson-Fabry's disease, alpha-galactosidase A deficiency, angiokeratoma corporis diffusum, and ceramide trihexosidase deficiency. An insufficient amount of α-galactosidase A (AGAL) resulting from mutations in the α-galactosidase A gene (GLA) is the basis for Fabry disease (FD). It is an uncommon X-linked lysosomal storage disease. Glycosphingolipids, particularly globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3, the deacylated form) accumulate in the lysosomes and cause a multisystemic disease that significantly reduces the life expectancy of afflicted patients by causing progressive renal failure, cardiomyopathy with potentially malignant cardiac arrhythmias, and strokes.[1] Its incidence ranges from 1 in 40,000 to 1 in 1,70,000, and it primarily affects men. With an incidence of 1 in 3200 babies, including those with late-onset variations, some studies, however, indicate a higher prevalence.[2] Fabry's disease is one of the fifty recognized lysosomal storage disorders, primarily resulting from mutations in the GLA gene found on chromosome Xq22.[3]

Hemizygous males usually have minimal or absent α-galactosidase A activity, whereas heterozygous females demonstrate a broad spectrum of clinical severity due to random X-chromosome inactivation, potentially presenting with neurological pain, cutaneous angiokeratomas, renal involvement such as proteinuria and kidney failure, cardiac manifestations including cardiomyopathy and arrhythmias, cochlear-vestibular disturbances, and cerebrovascular events such as transient ischemic attacks and strokes. Insufficient lysosomal α-galactosidase activity Globotriaosylceramide gradually builds up inside lysosomes as a result, which is thought to set off a series of biological processes. The most reliable way to diagnose hemizygous males is to show a significant α-galactosidase A deficiency. Molecular testing (genotyping) of females is required because enzyme analysis can occasionally aid in the detection of heterozygotes but is frequently inconclusive due to random X-chromosomal inactivation. Other potential causes of pain in children, like

"growing pains" and rheumatoid arthritis, must be ruled out. Multiple sclerosis is occasionally taken into consideration in maturity.[4]

Enzyme replacement therapy (ERT), gene therapy, and chaperone therapy are some of the preclinical and clinical methods used to treat Fabry's disease.[5] Even though these therapy approaches are effective, each one has its drawbacks. For example, the short half-life of the recombinant enzyme, the development of antidrug antibodies, and the enzyme's incapacity to pass the blood-brain barrier restrict the clinical effectiveness of ERT.[6] These recent, quick developments in nanotechnology and nanoscience have opened new possibilities for getting around the challenges of existing treatments.[7] The production of therapeutic medications with acceptable pharmacokinetic properties, such as adequate blood retention, good bioavailability, and potent immune-evasion capabilities, is made possible using biomaterials and nanotechnology.[8] For example, preclinical and clinical research has shown that a polyethylene glycol-modified approach can enhance the therapeutic result of ERT.[9] Crucially, spatiotemporal control of drug distribution is made possible by the development of focused techniques in nanoscience, which may lead to increased therapeutic efficacy and a lower risk of side effects. In this review, we first examine and talk about recent mechanistic studies on Fabry disease, with an emphasis on lysosomal function, autophagy, and lipid metabolism, along with how these are related. The advancements in the development of therapeutic modalities for Fabry disease, including ERT, gene therapy, and chaperone therapy are then sequentially summarized part from the methods for delivering therapeutic medications to specific locations using nanotherapeutics active or passive targeting. Specifically, each therapeutic approach's advancements and ongoing difficulties are also discussed. Lastly, we discuss the therapeutic approaches that show promise for treating Fabry disease. In general, we estimate that this study will enrich our knowledge of the mechanisms behind Fabry disease development and provide new perspectives on present and future possibilities for the disorder's therapy.

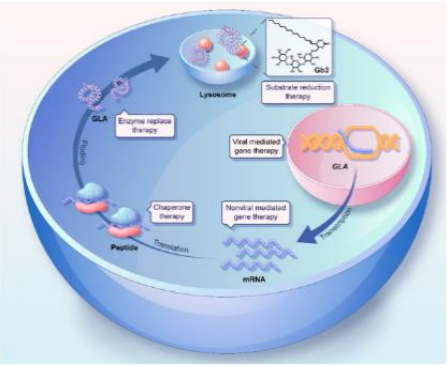

Figure 1: Diagrammatic representation of the GLA synthesis process and various Fabry disease treatment approaches.

1.1. TYPES

1. CLASSICAL VARIANT

The classical phenotype has an early onset and is associated with extensive multisystem involvement. It is characterized by little or low (<1%) α-Gal-A activity.

2. ATTENUATED (OR) LATE-ONSET VARIANT

The attenuated variant appears later in life and has different symptoms depending on the levels of α-Gal-A activity. It is characterised by α-Gal-A activity having (>1%).[10]

2. AIM AND OBJECTIVES

AIM

To provide a comprehensive overview of Fabry disease, focusing on its pathophysiology, clinical manifestations, diagnostic methods, and current strategies for symptom management and complication prevention.

OBJECTIVES

- To explain the genetic basis and enzyme deficiency involved in Fabry disease.
- To describe the early and progressive symptoms associated with Fabry disease.
- To outline the multi-organ complications, including cardiac, renal, neurological, and dermatological involvement.
- To highlight current diagnostic approaches for early detection.
- To review the available treatment options, including symptomatic management and enzyme replacement therapy.
- To emphasize the importance of early diagnosis and intervention to improve patient outcomes.

3. ETIOLOGY

3.1. GENETICS: Fabry disease is a monogenic, hereditary disorder linked to the X chromosome that results from a mutation in the GLA gene. This gene is located at Xq22 on the α-GAL enzyme, which is encoded by the long arm of the X chromosome. Newly detected mutations rarely occur, and the majority of cases are genetic.[11] The cell's recycling center, known as lysosomes, is home to the enzyme alpha-galactosidase A (Gal A), which degrades fatty compounds like Gb3 and lyso-Gb3. Gal A is produced by the GLA gene. Gb3, lyso-Gb3, and other similar chemicals build up toxically inside lysosomes due to mutations in GLA that result in the absence (or) significant reduction of Gal-A enzyme activity. This poisonous buildup causes damage to organs and tissues. Thus, Fabry disease is classified as a lysosomal storage disorder.[12]

3.2. INHERITANCE: A female with the Fabry gene has a 50% chance of transmitting her defective X chromosome to her progeny and a 50% chance of passing on her normal X chromosome. This means that every daughter and son born to a woman with the Fabry gene has a 50% chance of inheriting the affected X chromosome and carrying the Fabry gene.[12] Where a positive family history is strongly linked to Fabry's disease, de novo or spontaneous mutations have also been documented; therefore, the disorder cannot be ruled out in the absence of a family history.[13]

3.3. SEX DIFFERENCE: Fabry disease is inherited in an X-linked dominant manner and requires the inheritance of one mutant copy of the GLA gene from the X chromosome.[12] As a result, in females with X-linked conditions like Fabry disease, the normal gene on the other X chromosome may conceal or reduce disease symptoms on the X chromosome. Since only one functional X chromosome is required in both males and females, one X chromosome is essentially "turned off" in each female cell (random X-chromosome inactivation). This usually happens in a random order. This suggests that some cells with X-linked diseases will have the mutant "Fabry" gene activated on the X chromosome. The symptoms and degree of organ involvement in Fabry disease are determined by the proportion of cells in the tissue or organ where the X chromosome with the GLA gene mutation is active but has no or significantly reduced function. It helps to explain why females' disease severity differs more than that of their male relatives. Since men only have one X chromosome, an individual is susceptible to the disorder if he has the GLA gene mutation on the X chromosome.[14]

4. SIGNS & SYMPTOMS

4.1. CLASSICAL TYPE

- Onset: Symptoms usually begin in childhood or adolescence, more severe in males.[15]
- Cause: Glycolipid buildup in kidneys, heart, and blood vessels leads to progressive organ damage.

KEY SYMPTOMS

1. Acroparaesthesia: Burning pain in hands and feet; triggered by fever, stress, or activity.[16]

2. Anhidrosis/Hypohidrosis: Reduced or no sweating, leading to heat intolerance.

3. Angiokeratomas: Dark red/blue skin rashes, often in genital or lower trunk areas (common in males).

4. GI Issues: Diarrhoea, abdominal pain, especially after large meals.

5. Corneal Dystrophy: Whorl-like eye changes; vision usually unaffected but vessels may appear twisted or enlarged.

Other Symptoms of Type 1 Fabry Disease

- Persistent fatigue
- Headache
- Dizziness
- Generalized weakness
- Vomiting and/or nausea
- Postponed puberty
- Insufficient or minimal hair growth
- Malformation of the joints (rare, particularly in the fingers)
- Lymphedema (foot or leg swelling brought on by lymph buildup)

4.2. ATTENTUATED (or) LATE ONSET

It commonly arises in the 3rd–7th decades.

GENERAL FEATURES

- Milder or absent childhood symptoms
- Less severe neuropathic pain
- Hypohidrosis

- Intermittent GI symptoms.

4.3. CARDIAC VARIANT

- Left ventricular hypertrophy (LVH)
- Hypertrophic cardiomyopathy
- Conduction abnormalities
- Arrhythmias
- Exercise intolerance
- Dyspnoea on exertion
- Chest pain.[17]

4.4. RENAL VARIANT

- Proteinuria
- Isosthenuria
- Progressive chronic kidney disease
- End-stage renal disease in certain persons
- 0.2–0.5% of dialysis patients have FD
- Hypertension
- Edema.[18]

4.5. SIGNS OF PROGRESSIVE ORGAN INVOLVEMENT

4.5.1. Renal Dysfunction

- GL-3/Gb3 buildup in endothelial cells, smooth muscle cells, and podocytes causes progressive renal decline.[19]
- In type 1 classic males and females, renal cellular and vascular damage appears from childhood/adolescence.[20]

4.5.2. Cardiovascular Disease

- GL-3/Gb3 deposits in valves, cardiomyocytes, nerves, and coronary vessels.
- Leads to heart failure, arrhythmias, cardiac enlargement, and LVH progressing to HCM.
- LVH occurs in ~20% of both men and women.[21]
- Type 1 males: early mitral insufficiency and arrhythmias in their 20s, later LVH → HCM
- Type 2 males: often detected in cardiac clinics with LVH/HCM, presenting at older ages.[22]

4.5.3. Cerebrovascular Complications

- Gb3 accumulation in small cerebral vessels and heart-related atrial fibrillation can cause ischemic/haemorrhagic strokes in ~7% of men and ~4% of women with type 1 disease, usually after age 40.[23]

4.5.4. Respiratory Abnormalities

- Glycosphingolipid accumulation leads to interstitial lung disease and fibrosis.
- Involves alveoli and bronchi, causing restrictive, obstructive, or mixed airway disease.[24]

5. PATHOPHYSIOLOGY

The primary metabolic abnormality is an imbalance in lysosomal alpha-galactosidase A (alpha-Gal A). It is necessary for the breakdown of globotriaosylceramide's terminal galactose (Gb3). The skin, eye, kidney, heart, brain, and peripheral nervous system are among the cells and tissues where it causes Gb3 to build up.[25] Vascular blockage, ischemia, and infarction are possible manifestations of vascular accumulation triggered by enhanced endothelial proliferation. Smaller cerebral vessels are the next most prevalent location of vascular dilatation, after the vertebrobasilar arteries. Low levels of thrombomodulin (TM) and high levels of plasminogen activator inhibitor (PAI) are indicative of the prothrombotic character of Fabry disease in young stroke patients. Nitric oxide and non-nitric oxide-dependent endothelial proliferation and dilatation, as well as insufficient endothelial nitric oxide synthase (eNOS) activity, have been proposed as causes for stroke in young Fabry disease patients. Various common locations of Gb3 deposits include autonomic ganglia, dorsal root ganglia, renal glomerular, tubular, and interstitial cells, as well as cardiac muscle cells, vascular smooth muscle cells, valvular fibrocytes, cardiac conduction Fibers, and the cornea.[26]

The kidney often deposits globotriaosylceramide (Gb3) in the glomerulus, which is followed by accumulation in the distal tubule. Early proteinuria and polyuria are linked to the predilection for Gb3 deposition in these areas. It is unclear how renal sinus cysts linked to Fabry disease arise.[27]

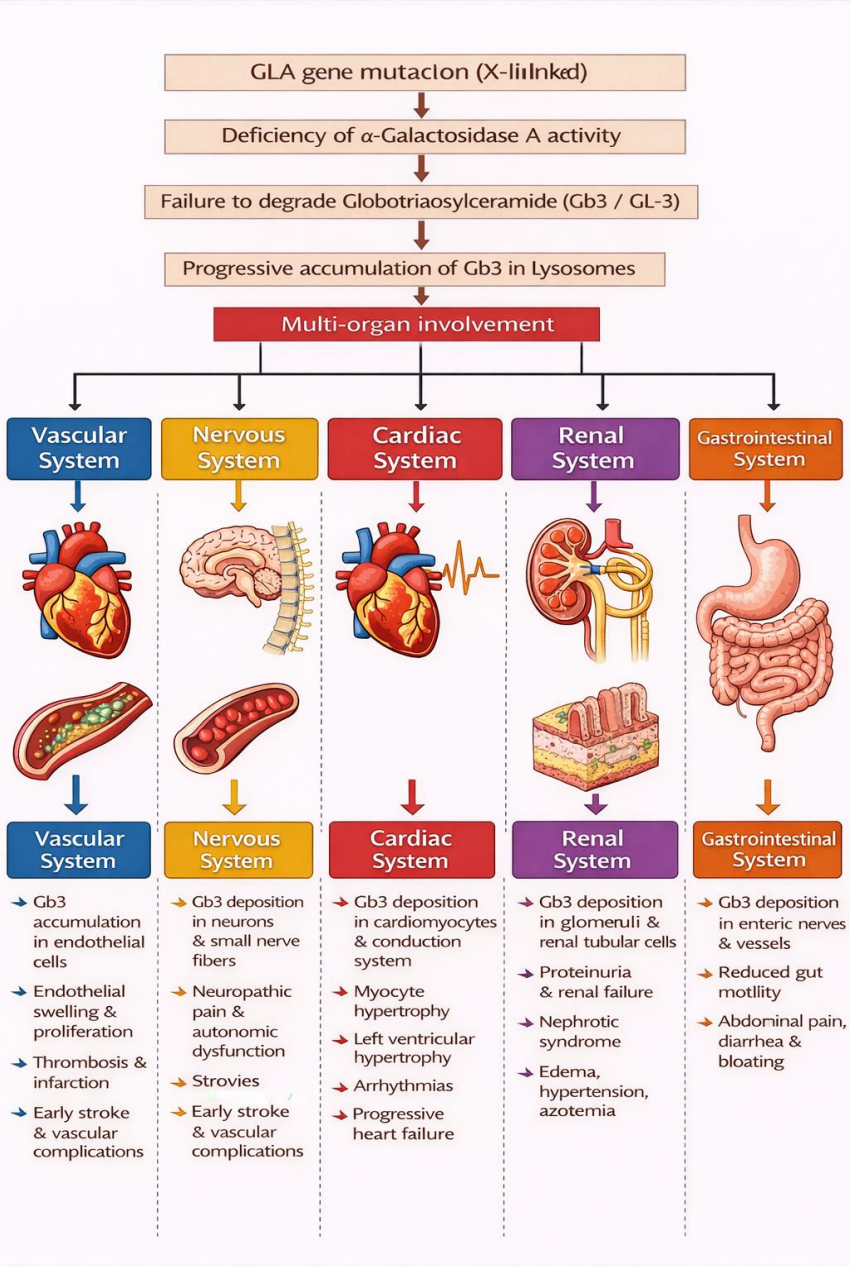

Figure 2: Molecular Pathogenesis of Fabry Disease.

6. DIAGNOSIS

6.1. DIAGNOSTIC CHALLENGES

- Diagnosis is straightforward in classic males, but more complex in females and individuals with GLA genetic variants.[28]
- A complete history, family history, clinical exam, biochemical tests, genetic testing, and imaging are recommended for accurate diagnosis.
- Symptoms such as acroparesthesia, angiokeratomas, and cornea verticillata are considered highly indicative of Fabry disease.[29]

6.2. ENZYME ACTIVITY TESTING

- In suspected males, α-Gal A activity must be measured.
- Classic FD is strongly suggested when activity <1%.[29]
- In females, α-Gal A levels may be normal or variable despite symptoms due to X-linked mosaicism.[30,31]

6.3. GENETIC CONFIRMATION

- GLA gene testing is essential in both males and females.[29]
- GLA mutations may represent classic FD, variant FD, or a GVUS (genetic variant of uncertain significance).[29]
- Testing for migalastat (pharmacological chaperone) amenability is performed using a GLP-validated HEK cell–based in vitro assay, the only approved method for this purpose.[32,33]

6.4. BIOMARKERS (LYSO-GB3)

- Lyso-Gb3 is a strong biomarker with high diagnostic and clinical value.[34]
- Useful in GVUS cases to determine whether a mutation is pathogenic.[35]
- Helps distinguish classic vs. variant FD, even before symptoms, and is especially helpful in females with heterogeneous phenotypes.[36]

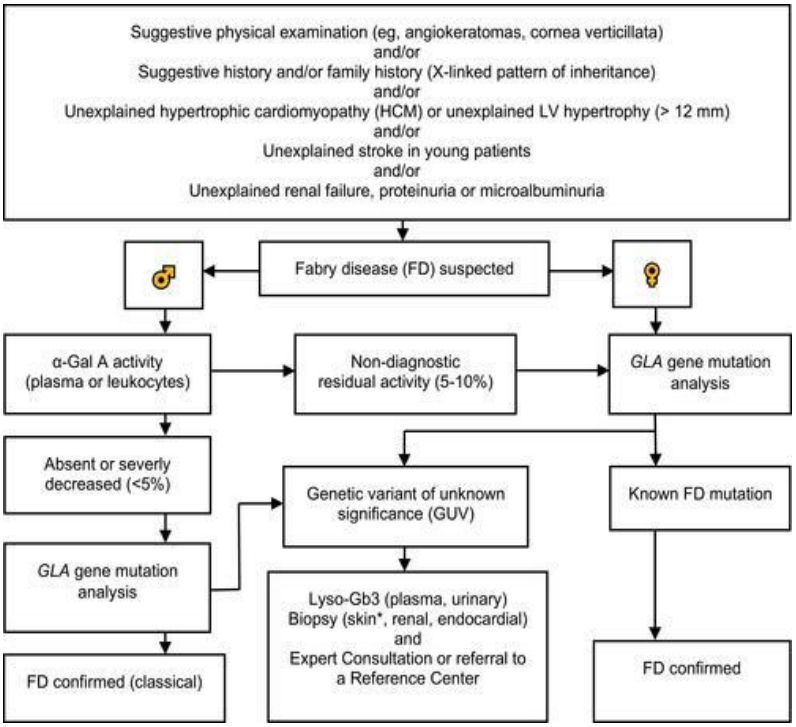

Figure 3: Diagnostic algorithm for fabry disease.

6.5. DIAGNOSIS OF CARDIAC INVOLVEMENT

6.5.1. ECHOCARDIOGRAPHY

- First-line test for Fabry cardiomyopathy.
- Typical findings: concentric LVH, markedly thickened papillary muscles, diastolic dysfunction.
- Ejection fraction (EF) usually preserved until late-stage disease

6.5.2. ADDITIONAL CARDIAC EVALUATION

All suspected FD patients should undergo:

- Echocardiography
- 24-hour Holter ECG
- Cardiac MRI (CMR) for structural and functional assessment.

6.5.3. CMR & ADVANCED IMAGING

- LGE-CMR: Gold standard for detecting cardiac fibrosis.
- T1 mapping: Helps differentiate Fabry disease from other LVH causes; native T1 values are typically low in FD.
- Myocardial mapping: Highly sensitive and specific for FD.
- PET-MR (Nappi et al.): Detects early myocardial inflammation, even in non-hypertrophic stages.

6.5.4. ECHOCARDIOGRAPHIC ALTERNATIVE

- Speckle-tracking echocardiography (STE) useful when CMR is contraindicated (e.g., pacemaker, end-stage renal disease).

6.5.5. BIOMARKERS

hs-Troponin T (hsTNT)

- Best biomarker for FD cardiac involvement.
- Values >14 ng/mL strongly suggest LGE-positive fibrosis.
- Rising hsTNT correlates with EF decline and fibrosis progression.

NT-PROBNP

- Increased in FD with cardiac involvement.
- Correlates with echocardiographic changes, not with fibrosis or disease progression.

6.5.6. TREATMENT MARKER

- Initiation of ERT recommended once organ involvement appears—e.g., when LGE becomes detectable.

6.5.7. ENDOMYOCARDIAL BIOPSY

- Limited role today because biochemical markers, imaging, and genetic testing provide adequate diagnostic accuracy.[36]

6.6. DIAGNOSIS OF RENAL INVOLVEMENT

6.6.1. BLOOD TESTS

- Serum creatinine to assess baseline kidney function[37]
- Measured GFR for accurate renal assessment[37]
- Combined GFR calculation using creatinine + cystatin C, recommended for better accuracy[38]
- Serum cystatin C is more sensitive than creatinine for detecting early renal impairment[34]

6.6.2. URINE TESTS

- 24-hour urine protein (ideal)
- Spot urine protein/creatinine ratio
- Spot urine albumin/creatinine ratio[37]
- Proteinuria and albuminuria are the earliest markers of kidney damage; require regular monitoring[33]
- Microalbuminuria screening
- Measurement of albumin-creatinine ratio in spot urine is strongly recommended[37]
- Urine lyso-GB3 shows no correlation with renal damage in FD[39]

6.6.3. FUNCTIONAL INDICATORS

- Glomerular hyperfiltration
- Defined as age-corrected eGFR > 130 mL/min/1.73 m^2
- May indicate early renal involvement[40]

6.6.4. IMAGING

- Kidney ultrasound to assess renal structure and detect abnormalities.[40]

6.6.5. RENAL BIOPSY

- Indicated in persistent albuminuria and/or proteinuria
- Helps evaluate extent of renal tissue damage.[41]

6.7. DIAGNOSIS OF NEUROLOGICAL INVOLVEMENT

6.7.1. No Blood Markers

- No specific blood tests are available to detect neurological involvement in FD.

6.7.2. When to Suspect

Suspicion based on symptoms like:

- Burning pain or sensory loss
- Hypohidrosis or anhidrosis
- Tinnitus or hearing loss
- Dizziness, nausea, abdominal cramps, post-meal diarrhoea

6.7.3 Diagnostic Tools

- Brain MRI: Shows white matter changes, dolichoectasia, infarcts
- Audiometry: Assesses hearing-related symptoms.[46]

6.8. DISEASE SCREENING TECHNIQUES

- Screening identifies asymptomatic individuals who may have FD and need further diagnostic confirmation. Effective screening should enable early diagnosis, reduce morbidity/mortality, and be cost-effective.[47]
- Recommended mainly for high-risk groups and family members of affected patients.[48,49]
- Neonatal screening is not widely applied due to practical and economic issues.[50]

6.8.1. SCREENING METHODS

- α-Gal A activity and lyso-Gb3 levels are useful initial screening tools in males.[51]
- Enzyme assays are unreliable in females; molecular testing is preferred.
- Retinal vascular changes may serve as an additional screening indicator.
- High-Risk Group Screening

1. Individuals with unexplained LVH (>12 mm) or HCM
2. Patients on dialysis, kidney transplant recipients, or those with unexplained proteinuria
3. Individuals aged 15–55 years with unexplained stroke.

- Screening often identifies people with GLA mutations or GVUS, some of whom show reduced enzyme activity but not the pattern seen in classic FD.

6.8.2. FAMILY SCREENING

- Requires pedigree analysis and genetic counselling.
- At-risk relatives should undergo genetic testing.[51]

7. TREATMENT

1. Enzyme replacement therapy
2. Chaperon therapy
3. Gene therapy
4. Therapy for substrate reduction
5. Proteostasis regulator
6. activating the GLA promoter
7. Nutraceuticals

7.1. ENZYME REPLACEMENT THERAPY

- For Fabry disease (FD), ERT is a recognized and successful therapy[52]
- Clinical studies show improvements in Gb-3 levels, cardiac anomalies, and neuropathic discomfort.
- Although the effectiveness of agalsidase-α and agalsidase-β is comparable, their different glycosylation patterns may affect their safety and response profiles.
- Fabrazyme® and Replagal® are examples of recombinant α-GAL-A enzymes that successfully lower Gb-3 buildup and alleviate clinical symptoms.
- ERT has been shown to enhance renal function and lessen neurological symptoms in animal models and patient investigations.
- In FD patients, ERT is often safe and well tolerated.[53] Mannose-6-phosphate receptor-mediated routes are the main means of enzyme absorption.
- Intravenous infusion is used to provide both agalsidase-α and agalsidase-β.
- In males with classical FD, ERT significantly minimizes Gb-3 and can restore normal levels.[54]

7.2. CHAPERON THERAPY

- Migalastat is used in chaperone treatment to improve enzyme activity and trafficking by stabilizing misfolded α-GAL-A in patients with susceptible mutations. It provides an oral substitute for ERT and has advantages in Gb-3 reduction, cardiac, and renal outcomes. Its effectiveness varies depending on the mutation.
- Approved by the FDA (2018) and EMA (2016).[55]

7.3. GENE THERAPY

Gene therapy for Fabry disease involves either ex-vivo alteration of patient cells or in-vivo transfer of a functional gene to restore α-GAL-A activity. Viral vectors (such as AAV or lentivirus), non-viral techniques (lipid nanoparticles), or mRNA treatment that generates the enzyme can all be used. A possible therapeutic method was highlighted by Marina et al., who demonstrated that siRNA targeting the A4GALT gene may inhibit Gb-3 production and that their lipid nanoparticle formulation provided efficient gene suppression in vitro without hurting cells.[56]

7.4. SUBSTRATE REDUCTION THERAPY

By lowering the synthesis of Gb-3, the material that accumulates in cells, substrate reduction treatment can treat Fabry disease. Instead of raising the α-GAL-A enzyme, it functions by inhibiting the enzymes that produce Gb-3. Gb-3 levels in the body can be lowered by medications such as lucerastat and venglustat.[56]

7.5. PROTEOSTASIS REGULATOR

Small chemicals known as proteostasis regulators can enhance protein folding or encourage the breakdown of misfolded proteins. They restore the function of mutant α-GAL-A in Fabry disease. When protease inhibitors are combined with 1-deoxygalactonojirimycin, lyso-Gb3 is reduced and α-GAL-A activity is increased by repressing proteasome activity and elevating GLA expression. Verapamil and diltiazem are the drugs that improves enzyme folding.[57]

7.6. ACTIVATING THE GLA PROMOTER

By attaching to the GLA promoter in the cell nucleus, small-molecule promoter activators increase the synthesis of target proteins. This results in increased production of the mutant α-GAL-A enzyme and enhances GLA transcription in Fabry disease. In order to lessen substrate buildup, the increased enzyme levels enhance trafficking to lysosomes and increase

functional GLA within lysosomes. This method presents a possible way to supplement current Fabry disease treatments.[57]

7.7. NUTRACEUTICALS

Products generated from food that provide health benefits, such as disease prevention and treatment, are known as nutraceuticals.Curcumin has been investigated as a potential therapy for Fabry disease. In 80% of the examined mutant genotypes in cell models, curcumin increased α-GAL-A activity. Additionally, it worked in combination with pharmacological chaperones like galactose or 1-deoxygalactonojirimycin, which helped most of the mutations under investigation. Long-term treatment of certain mutants, including L300F, enhanced lysosomal function and Gb-3 clearance. These findings highlight the need for customized approaches in the management of FD and demonstrate curcumin's potential as a supportive drug.[57]

7.8. NANOTECH BASED DRUG DELIVERY

- By addressing the main issues with traditional medicines, like degradation of enzymes, limited circulation time, and immunological responses, nanotechnology-based delivery devices provide a prospective advance for the treatment of Fabry disease.
- Therapeutic enzymes are protected by these nano-carriers, which also improve their penetration into cells and aid in their more precise delivery to the afflicted organs. To increase their stability in the circulation and enhance their ability to target, their surfaces can be altered using polyethylene glycol (PEG), aptamers, or antibodies.
- Certain renal and vascular endothelial tissues overexpress αvβ3 integrins in Fabry disease, which makes them perfect targets for RGD peptides, particularly the stable cyclic RGDfk form that improves enzyme delivery.
- Furthermore, effective use in various lysosomal storage diseases indicates the potential of ICAM-1-directed administration employing anti-ICAM-functionalized carriers. When taken as a whole, these nanotechnological methods provide a highly focused, stable, and refined alternative that can enhance Fabry disease treatment results.[58]

7.8. DRUGS USED IN FABRY DISEASE

Table 1: Drugs for fabry disease.

Drug	Brand Name and Manufacturer	Type of Therapy	APPROVED BY	Route of Administration & Dose	Source
Agalsidase beta	Fabrazyme ®, Sanofi	ERT	US-FDA and EMA	IV,1.0mg/kg every two weeks	Ovary cells of Chinese Hamster
Agalsidase alpha	Replagal ®, Takeda pharmaceuticals	ERT	EMA	IV,0.2 mg/kg weekly	Human fibrosarcoma cells (HT-1080)
Pengunigalsidase alfa-iwxj	Elfabrio ®, Protalix	ERT	US-FDA and EMA	IV,1mg/kg every two weeks	Nicotiana tabacum cells (ProcellEx)
Migalastat	Galafold ®	Pharmacological chaperone	US-FDA and EMA	Oral ,123 mg every two days	Fermentation product of streptomyces lydicus (Strain PA-5726)

8. EPIDEMIOLOGY

Fabry disease, the second most prevalent lysosomal storage disease, is a relatively uncommon hereditary condition. It is brought on by mutations in the GLA gene, which result in poor or missing α-galactosidase A. This defect causes Gb3 to build up in cells, which over time damages several organs and causes inflammatory conditions and fibrosis in the body.

8.1. INCIDENCE AND PREVALENCE

- Approximately 1 in 40,000 males (global range: 1 in 8,454 to 1 in 117,000) have classic Fabry disease
- Late-onset Fabry disease is three to ten times more prevalent. The frequency is significantly greater (1 in 1500 to 1 in 4000) in regions like Taiwan and Italy.
- According to a UK Biobank investigation, 36 out of 200,643 individuals have GLA variants:
- Incidence of late-onset variant: 1 in 5732
- Incidence of Classical variant: 1 in 200,643

According to global surveillance statistics from 2022, 8098 Fabry patients are primarily from North America (40.3%) and EMEA (Europe, Middle East & Africa) (45.7%), with minor contributions from Latin America (5.9%) and JAPAC (Japan, Pacific & Asian

countries) (8.1%). The incidence of Fabry varies significantly by area, according to newborn screening programs.

1. Italy: The incidence varies between 1:3100 (2006) and 1:7879 (2021), with late-onset variations being more prevalent.
2. Taiwan: 2.5 times greater than Italy, with a much greater prevalence (~1:1250), mostly due to late-onset GLA mutations.
3. Japan: A number of distinct variations have been found, with an estimated prevalence of 1 in 7,683 overall and 1 in 11,854 particularly for pathogenic variants.

Overall, the prevalence of Fabry is greater in East Asian locations (particularly Taiwan), and the majority of cases seen are late-onset phenotypes that reflect variations in screening and genetics.

8.2. GENDER VARIABILITY

After a revision in 2007 to include all identified females regardless of symptoms, the Fabry Registry recorded 43.5% of males and 56.5% of female patients as of October 2022. Mutation in the GLA gene causes Fabry disease, which is X-linked. Males often have more severe symptoms since they only have one X chromosome. Due to unpredictable X-inactivation, females with two X chromosomes exhibit inconsistent symptoms, which frequently results in an underdiagnosis.[59]

9. CONCLUSION

Mutations in the GLA gene cause Fabry disease, an uncommon inherited lysosomal storage disorder that results in a lack of the α-galactosidase A enzyme and the buildup of dangerous lipids like Gb3 and lyso-Gb3 in critical organs like the kidneys, heart, brain, and skin. Due to X-linked heredity and random X-chromosome inactivation, this disease manifests in both classical and late-onset variants, with symptoms differing greatly across males and females. Early symptoms can include scorching pain in the hands and feet, decreased sweating, skin rashes, changes in the eyes, and gastrointestinal issues. These symptoms can lead to more serious complications such kidney failure, heart disease, strokes, and brain damage. Enzyme activity testing, genetic confirmation, biomarkers like lyso-Gb3, and sophisticated imaging methods are all necessary for an accurate diagnosis. Although there are still drawbacks including immunological reactions and restricted brain penetration, modern treatment alternatives include enzyme replacement therapy, chaperone therapy (migalastat), gene therapy, substrate reduction therapy, and supportive management have improved patient

outcomes. Recent advances in tailored medication delivery systems and nanotechnology offer encouraging prospects for overcoming these obstacles in the future. To slow the progression of the disease, avoid complications, and enhance the quality of life for those who have Fabry disease, early screening, prompt diagnosis, and suitable long-term treatment are essential.

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