WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 4, 493-499. Review Article ISSN 2277– 7105

FABRY DISEASE: AN EXPENSIVE ENZYME REPLACEMENT THERAPY

Pramod Singh Khatri*, Babra Javaid[1], Satyender Mathur[1], Sonam Pandey[1]

*Assistant Professor and Program Coordinator, Dept of Clinical Research, Amity Medical School, Amity University, Gurgaon.

[1] MSc Clinical Research, Amity Medical School, Amity University, Gurgaon.

Article Received on
29 Jan 2016,
Revised on 22 Feb 2016,
Accepted on 15 Mar 2016
DOI: 10.20959/wjpr20164-5850

***Correspondence for Author**
Pramod Singh Khatri
Assistant Professor and Program Coordinator, Dept of Clinical Research, Amity Medical School, Amity University, Gurgaon.

ABSTRACT

Fabry's is a destructive, progressive and life threatening disease which lessens survival of influenced individual. It is a genetic disorder of X linked inheritance caused by deficiency of lysosomal enzyme a-galactosidase, resulting in accumulation of glycosphingolipids inside different body cells. Fabry's depositare characterized histopathologically as lamellate membrane like structure known as myeloid or Zebra bodies. Clinical indications of disease are hypohidrosis, acroparesthesias, heat intolerance, angiokeratomas, corneal opacities, cardiovascular arrhythmias, left ventricular hypertrophy, proteinuria and renal insufficiency. Diagnosis of Fabry's require a high clinical suspicion, physical investigation, organ specific tests and is affirmed by demonstrating low enzyme assay in homozygous males and gene typing in heterozygous females. Specific treatment for Fabry's disease is ERT with recombinant human a-galactosidase A. If the treatment is started early it has a promising role in renal and heart disease, however valuable role is still not characterized in CNS involvement. Management of Fabry disease consist of pain relief with analgesic drugs, nephroprotection (angiotensin converting enzyme inhibitors and angiotensin receptors blockers) and antiarrhythmic agents, while dialysis or renal transplantation are accessible for patients encountering end-stage renal failure. With age, vital organ degrades, and at some point these organs might stop working. End-stage renal disease and life threatening cardiovascular complications limit life expectancy of untreated males (20 years) and females (10 years). While there is investigational proof that long term ERT can stop disease progression, the significance of adjunctive treatments ought to be accentuated

and the possibility of developing an oral dose drives research forward into active site specific chaperones for effective treatment of Fabry disease.

KEYWORDS: glycosphingolipids, hypohidrosis, acroparesthesias.

INTRODUCTION

Fabry disease (FD) is an X-linked inherited disorder of glycosphingolipid metabolism because of deficiency of lysosomal a - galactosidase A activity. FD has a frequency of 1 in 100,000 population.[1] Traditionally influenced hemizygous males, with a-galactosidase A activity might show all the characteristic neurological pain, angiokeratoma, proteinuria, kidney failure, cardiomyopathy, arrhythmia, cochleo-vestibular and strokes indications of the disease while heterozygous females have side effects ranging from mild to severe. Deficient activity of lysosomal a-galactosidase A leading to amassing of globotriaosylceramide inside lysosomes, which can trigger a course of cellular mechanism.[2-3]

Fabry disease is also alluded as

- Fabry's disease,
- Anderson-Fabry disease,
- Angiokeratoma corporis diffusum, and
- Alpha-galactosidase A deficiency

Identification of a-galactosidase A deficiency is the confirmatory method for hemizygous male patients. Enzyme identification might occasionally identify heterozygotes but are mostly inconclusive because of random X-chromosomal inactivation that's why genotyping of females is obligatory.[4] With the help of prenatal diagnosis, DNA testing in chorionic villi or in amniotic cells is carried out for male fetuses (table:1).

Table:1 Molecular Genetic Testing Used in Fabry Disease

Gene	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	
			Affected Males	Carrier Females
GLA	Sequence analysis	Sequence variants	~100%	<100%
	Targeted mutation analysis	c.427G>C	100% for the targeted variant	
	Duplication/deletion analysis 10	Partial and whole-gene deletions		

GLA has approximately13 kb of gDNA and usually have seven exons; the cDNA has 1290 bases and encodes a polypeptide of 429 amino acids along with a 31-amino acid signal peptide.[5] FD is inherited in about 50 genetically distinct, biochemically related LSDs. Every disorder is brought on by an IEM because of a monogenetic defect resulting in deficiency of lysosomal enzymes. The clinical sign of FD has neuropathic pain and lipid accumulation due to degeneration of nerve fibers in the dorsal root ganglion cells. The accumulation of glycosphingolipid starts in the lysosomes, leading to inflamed cells, tissue hypertrophy, apoptosis and organ failure. Lipid deposits are noticeable in the endothelium, renal tubules and glomeruli, heart muscle, autonomic ganglia, and in particular cortical and brain stem structures.[6] These histopathological investigations have clarified that the clinical appearances of the cardiomyopathy, and renal failure can lead to premature death. Attributable to IEM defect, multiple disease manifestation can affect such patients in light of the fact that Gb3 accumulation is found in most non-neuronal tissues and body fluids. Clinical data on the frequency and severity of FD manifestation would be useful if carried at large cohort level and assessment of ERT treatment for such patient in order to identify safety and efficacy level of the drugs available.[7] Hypohidrosis likewise happens at a youth age, while the vascular difficulties demonstrate a moderate progression, with a clinical presentation of organ failures from the third, fourth or fifth decade.(table:2) The analysis of Fabry disease is carried out by clinical sign and symptoms, which are neuropathic pain, Fabry crisis, angiokeratomas.[8]

Table 2: Early signs and symptoms of Fabry disease

Organ system	sign &symptoms
Nervous System	Acroparesthesias
	Heat intolerance
	Nerve deafness
	Hearing loss, Tinnitus
Gastrointestinal tract	Nausea,Vomiting, Diarrhoea
	Difficulty gaining weight
	Postprandial bloating and pain, early satiety
Skin	Angiokeratomas
	Hypohidrosis
Kidneys	Microalbuminuria, Proteinuria
	Impaired concentration ability
	Hyperfiltration
	Increased urinary Gb3 excretion
Eyes	Corneal and lenticular opacities
	Vasculopathy (Retina, Conjunctiva)
Heart	Arrhythmias

	Mild Valvular insufficiency
	ECG abnormalities (shortened PR interval)

Prenatal diagnosis

Prenatal diagnosis is feasible for pregnant women who are carrier for FD. The standard procedure is to identify fetal sex by conducting chromosome investigation in CVS (performed between 10 to 12 weeks) or amniocentesis (15 to 18 weeks gestation). On the off chance that the karyotype is 46,XY, then α-Gal A enzyme activity is calculated in fetal cells.[9] And if the family has a history of GLA mutation, then the clinical finding might be affirmed by genotyping of fetal DNA. For male fetuses who are at risk for Fabry disease, enzyme investigation or DNA mutation investigation can be performed from CVS or amniocentesis.

Genotype/Phenotype Correlations

Fabry disease is considered very penetrant in male patients albeit variable in its appearance. In influenced male patients, the clinical determination is affirmed by alpha-gal A insufficiency. Male patient with Fabry disease have missing or low enzyme activity (1–2% of typical) and traditional phenotype with various disease manifestations (figure:1). Male patients with clinical components of Fabry disease have remaining alpha-gal A enzyme activity (1–10%) Several male patients were portrayed with higher residual enzyme activity, roughly 3–10% of typical, and seemed to have milder expression of Fabry disease.[10] These patients were determined to have Fabry disease sometime later in life after cardiomyopathy of obscure etiology was found.

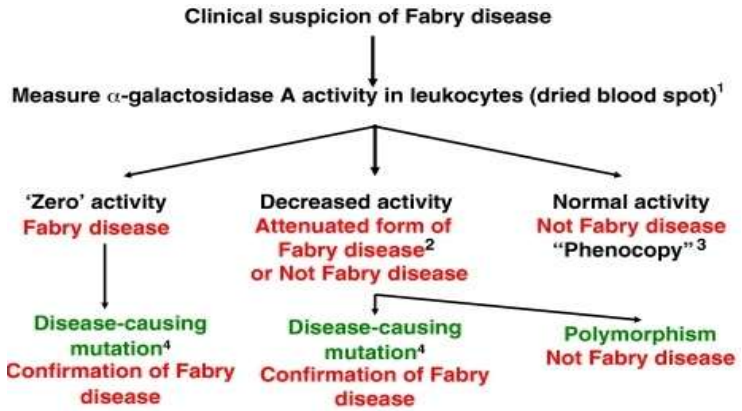

Figure: 1 Diagnosis of Fabry disease in males

Around 70% of females heterozygous for a Fabry disease transformation have some disease indications, and roughly 10% of these heterozygous females have extreme manifestations,

like the phenotype in male patients (figure:2). Enzyme activity is not unswerving for deciding female carrier status in light of the fact that ladies who are obligate carriers have variable levels of alpha-gal A that can overlap with enzyme levels found in healthy controls.[11]

Patients with Fabry can be analyzed through a basic test that detect protein alpha-GAL is available in the blood or not. Whereas Female patients, might have Fabry regardless of the fact that they have normal levels of alpha-GAL. In this way, genetic testing, which dissects DNA, is expected to figure out if a female has Fabry disease or not.

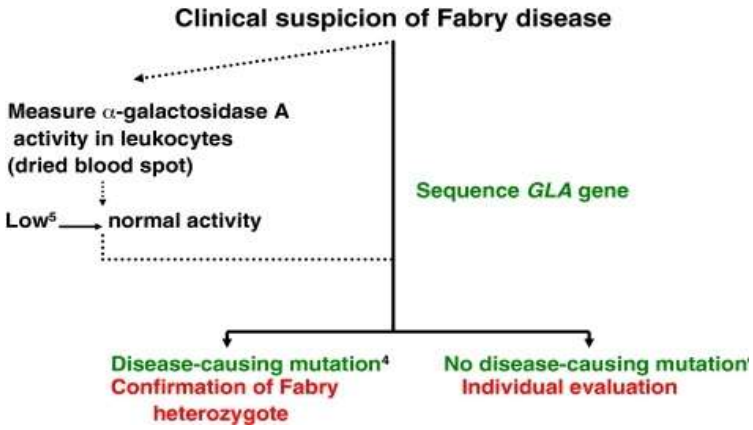

Figure: 2 Diagnosis of Fabry disease in females

Enzyme replacement therapy

Ordinary treatment does not address the fundamental imperfection of FD and the year 2001 saw the introduction of ERT utilizing recombinant human a-galactosidase A. From that point forward, long term efficacy and safety of replacement treatment have been researched and ERT has been accepted as disease specific therapeutic agent for patients influenced with FD. As an illustration, current protocol for beginning the ERT in patients vary from one nation to other nation and hence there remain a matter of civil argument particularly in heterozygous females and youngsters. In Europe, there are presently two ERT treatment for Fabry's Disease. i.e (Replagal), registered for infusion at a dose of 0.2mg/kg every other week, and (Fabrazyme), infused at 1.0 mg/kg fortnightly.[12] ERT is connected with a considerable abatement in neuropathic torment and peripheral nerve function in influenced patients. Alleviation of gastrointestinal symptoms is one of the soonest and most reliably beneficial impacts of ERT.Two distinctively produced ERT has been investigated in various phases of clinical trials for the treatment of Fabry disease: one developed by Chinese hamster ovary (CHO) cells with exemplary recombinant technology (Fabrazyme), and the other produced by

cultured human skin fibroblasts with an enacted promoter of the alpha - Gal A gene (Replagal). Both ERT treatment has reduced Lipid substrate in tissue biopsies. In spite of the fact that it had been recommended that alpha-Gal A mRNA experiences splicing, which may bring coproduction of an altered protein with a phe396-to-tyr mutation that may have a significant physiologic function found no sign for the presence of splicing at the protein or RNA levels in either recombinant GLA enzyme.[13]

Different treatment modalities are

- ✓ laser treatment for skin problems
- ✓ regular cardiac monitoring with ultrasound
- ✓ Preventive treatment for blood clots
- ✓ Kidney transplantation for serious loss of kidney function.

Closing Remarks

Fabry's is a progressive and life threatening disease which decreases life expectancy, so all endeavors ought to be made for an early diagnosis and initiation of Fabry's treatment. Enzyme replacement therapy has a favorable role in renal and cardiac disease but not beneficial for CNS involvement. ERT by intravenous infusion of recombinant human - galactosidase A delivered stamped improvement in acroparesthesias, pain and gastrointestinal disorders. However, renal function keeps on disintegrating, and the patient usually have small strokes, leading to diplopia and headache. Patient quality of life has marginally improved however will continue to encounter fatigability. If the ERT on these patients are started earlier then the development of irreversible secondary tissue and cellular damage can be prevented.

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