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FABRY DISEASE AND TREATMENT-AN OVERVIEW

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ABSTRACT

Fabry disease (FD) is an X-linked, hereditary, lysosomal storage disease caused by deficiency of enzyme α-galactosidase A (α-Gal A), which results in accumulation of neutral glycosphingolipid globotriaosylceramide(Gb3) in walls of small blood vessels, nerves,dorsal root ganglia, renal glomerular and tubular epithelial cells and cardiomyocytes. Males are mostly affected whereas women mainly act as carriers. Onset of FD symptoms depends upon its clinical type which vary from neuropathic pain, hypohidrosis, gastrointestinal symptoms, and angiokeratomas, chronic kidney disease, cardiomyopathy and cerebral events as seen in adults to severe mental retardation as seen in infantile form which drastically affects the quality of life and reduces life span of affected individuals. Enzyme replacement therapy (ERT) with intravenous infusions of recombinant human α-galactosidase A is approved by FDA for treating FD. Alternative treatments under investigation include substrate reduction therapy (SRT), chaperons, stem cell transplant and gene therapy.The aim of present study is to review pathophysiology, clinical manifestations, diagnosis, treatment of FD.

Key Words: Fabry disease, Globotriaosylceramide, α –galactosidaseA, Chaperones, Enzyme replacement therapy

INTRODUCTION

Lysosomal storage diseases (LSDs) result from a deficiency of a particular lysosomal protein/activity or, in a few cases, from non-lysosomal activities that are involved in lysosomal biogenesis or protein maturation. They comprise a group of at least 50 distinct genetic diseases which characterized by the accumulation of excessive quantities of certain glycolipids in various tissues of the body.These diseases are named according to the identity of the storage material.[1]

Fabry disease was first describedby Johannes Fabry and William Anderson in 1898 as a hereditary, X-linked lysosomal storage disease.Lysosomesknown as suicidal bags of the cell, are the main organelles responsible for breakdown and recycling of various substrates including sphingolipids. In Fabry disease function of lysosome is disrupted causing deficient or altered activity of lysosomal enzyme α-Galactosidase A (α-GAL A), due to mutation of*α-Gal A* gene located at Xq22 on the long arm of the X chromosome. This results in the accumulation of globotriosyceramide (Gb3) in various tissuesleading to multi-organ pathology which seriously affects cardiac, renal and cerebrovascular systems[2].

EPIDEMIOLOGY

Fabry disease is the second most common of the LSDs, after Gaucher disease. The reported epidemiological data are likely to be underestimates, due to missed diagnoses of these rare disorders.The majority of reports of FD are in Caucasians, but isolated cases have been reported in Asian populations. The results of a survey in Japan estimated the frequency of Fabry disease to be 1 in 200 000. In a study conducted by Fuller M et al., renal failure was detected in 43% of Fabry patients over the age of 30 years, while cardiac disease was

present in 60% of patients over the age of 40 years. Two point mutations have been described in Chinese patients with Fabry disease.[3]

GENETIC INHERITANCE OF FD

The genetic defect responsible for Fabry disease is located on the X chromosome. Men usually have one X and one Y chromosome, which can pass either one to their children. If a man with FD passes his X chromosome (with the defective gene) to a child, the child will be a daughter (XX) and the daughter will have the defective gene. If he passes his Y chromosome to a child, the child will be a son (XY) and will not have Fabry disease (since FD is X-linked disease). Therefore, men with FD have a 100% chance of passing the defective gene to their daughters and a 0% chance of passing it to their sons. All the daughters and none of the sons of a man with Fabry disease have a chance of developing symptoms of Fabry disease.

Women have two X chromosomes, they always pass an X chromosome to their children. A woman with FD has a 50% chance of passing the defective gene to each daughter and son. If a woman with FD passes the X chromosome with the defective gene, her child (son or daughter) may develop symptoms of Fabry disease. If she passes normal X chromosome, then her child (son or daughter) will not have FD.

PATHOPHYSIOLOGY

α-Gal A gene is located at Xq22 on the long arm of X chromosome.FD results from inherited mutations, rather than from new mutations, most of the patients have blood relatives who are either affected males or carrier females. [5]Mutations in *α-Gal A* gene causes marked deficiency of α-Gal A activity leading to accumulation of Gb3 in all tissues stimulating proliferation of endothelial cells.[6,7]Abnormal reactivity of endothelial cells causes change in blood flow which is the critical cause for multi organ damage the most prominently affected being brain, heart and kidneys.Disturbances in the intraluminal pressure and alterations in the angioarchitecture especially in the small arteries cause narrowing, occlusion and formation of infarcts at multiple sites.Decrease in levels of thrombomodulin and increase in levels of plasminogen activator inhibitor suggests the prothrombotic state causing stroke in FD patients.[8]

CLINICAL MANIFESTATIONS

Depending upon activity of enzyme FD can be classified clinically into Classic FD and Atypical FD.[8]

I. Classic FD

The individuals exhibiting less than 1% α-Gal A activity and exhibiting full spectrum of symptoms is grouped under classic FD. Based upon the incidence of symptoms classic FD is again categorized as early and late manifestations.

a. Early manifestations

These begins in childhood or adolescence.[10,11] They include:

- Acroparathesia
- Gastrointestinal symptoms
- Neuropathic pain
- Anhydrosis/Hypohidrosis
- Angiokeratomataies
- Corneal and lenticular opacities

Acroparathesia and neuropathic pain

The pain and acroparathesia in fabry disease is caused by the lysosomal accumulation of Gb3 in peripherial nerves,dorsal root ganglia and spinal cord, atropy of smallunmyleniated nerves involved in pain and temperature sensation. Extreme pain attacks are referred as Fabry pain crisis, which are accompained by low grade fever, body pains and fatiguesometimes involving large joints.[12,13] Hypohidrosis and acroparathesia is more pronounced in the presence of pulmonary disease. The acroparathesia is typically resistant to treatment with conventional analgesics such as acetaminophen or ibufropen.Acute painful crises are treated with narcotic analgesics such as codeine, meperidine, morphine and Carbamazepine.[14]Chronic pain in FB is treated with phenytoin,amitriptyline or gabapentin.[15]

Gastrointestinal symptoms

GI manifestations of FD is due to deposition of Gb3 in small vesselsand the autonomic gangliaof the intestine.GIT symptoms begins in the chilhood or adolescenceand worsen with age.Chronic abdominal pain followed by multiple bowel movements,diarrhea,nausea and vomitingare common in FD. GIT symptoms can be treated with loperamide or bismuthsubsalicylate, Histaminergic (H_2) blockers.[16]

Angiokeratomata

Weakening of capillary wall and vascular ectasiawithin the epidermis and dermis causes angiokeratomata. These symptoms manifest at the age of 5-13 years,initially these lesions appear small,slightly raised and purplish red.The number and size of these lesions increases with age. Anhidrosis or hypohidrosisis caused due to the accumulation of lipid in the eccrine cells of sweat

glands and dysfuctioning of autonomic nervous system. Angiokeratomata is also seen on the skin of scrotum and penis.Biopsy specimens of lesions typically show vacuolation of the capillary endothelial cells and smooth muscle cells. Lesions are treated with series of liquid nitrogen treatment prior to laser therapy.[17]

Corneal manifestations

These are reported in 70-90% of patients.The occular symptom is whitish spiral streaks in the corneal epithelium known as cornea verticillata. This causes structural changes in cornea, lens , retina and conjunctiva. They cause severe impairment of vision and is difficult to treat.[8]

Anhidrosis or hypohidrosis

FD patients experience decreased or absent sweat production (hypohidrosis or anhidrosis) and discomfort (heat intolerance) in warm temperatures, with exercise, or fevers.

b.Late manifestations:

***Impaired Renal Function*[16,20]**

Impairment in renal function is due to Gb-3 deposition in renal endothelium and other kidney cell types. Proteinuria, albuminuria may be apparent in adolescence and early adulthood.Progression of disease is marked by proteinuria,increase in serum creatinine levels and reduction in glomerular filtration rate (GFR). Braton and co-workers report has shown that 50% patients had proteinuria by the age of 35 and had renal disease by age 47. Intially proteinuria is treated with angiotension receptor blockers, in later stages long term hemodialysis and renal transplantation is only the treatment for renal failure.[16]

Cardiac Arrhythmias and Left Ventricular Hypertrophy

Cardiac arrythmias and conduction defects are common. The disease is associated with progressive left ventricular hypertrophy,which may aggravated by arterial hypertension.As the condition advances,progressive impairment of diastolic filling causes decreased cardiac output and early death.Damage to the coronary vascular bed may lead to anginapectoris and myocardial infarction. Failure of left ventricular hypertrophy respond well to Enzyme Replacement therapy in some patients.[8,16]

Transient Ischemic Attacks and Stroke

A high frequency of FD has been reported in patients with cryptogenic stroke,which affects predominantly the vertebrobasilar circulation. Decreased levels of thrombomodulin and increased plasminogen activator inhibitor causes stroke in patients.[8,16]

II.Atypical FD

The individuals with residual enzyme activity and exhibiting symptoms limited to one or few organs are grouped under atypical FD. The symptoms are not found during their childhood but appear later in life.

DIAGNOSIS [8,16]

Measurement of α-Gal A

Identification of FD in affected males is relatively easy, by carrying out pedigree analysis and measurement of α-GalA activity in plasma, serum, leukocytes or tissue biopsies. The identification of carrier females is more difficult because many of them have normal levels of α-Gal A.[18] The increased concentration of Gb3 in urine sediment serves as a diagnostic parameter for the diagnosis of FB.

Tissue biopsies

Increased lipid content in the biopsies skin cells suggests FD.Lung biopsy and sputum analysis evaluates the progression of disease in Lungs.

Renal evaluation

Renal function markers such as BUN, creatinine, protein, urinary GB3 levels are measured. Also renal biopsy is suggested for atypical cases of FD to differentiate from other renal disorders.

DNA analysis

DNA isolated from blood or biopsy specimens are used for the analysis ofα-Gal A gene sequence to identify disease causing mutations.Hence DNA testing served as a preferred method for identifying FD and it also determines the carrier status in females.

Imaging studies

Magnetic Resonance Imaging (MRI), Positron emission tomography (PET) scanning and Plethysmography demonstrates the progression of the disease in various affected organs.

***Eletrocardiography*[19]**

Abnormal ECG findings which include sinus bradycardia, nonspecific ST segment changes, shortening of PR interval, P-wave inversion will be usually observed in FD patients.

Other Tests

Complete Blood Picture,Serum electrolyte level measurement and lipid profile.

TREATMENT

Enzyme Replacement Therapy[21,22]

Enzyme Replacement therapy (ERT) for FD is approved by FDA in United States in 2003 .The goal of ERT is to reverse the metabolic and pathological abnormalities in the cells and tissues. In ERT the infused enzyme is taken up into lysosomes through specific receptors located on the surface of target cells. Agalsidasealfa and agalsidase betaare the versions of α-galactosidase that are produced by recombinant DNA techniques. Agalsidasealfais produced by gene activation of human cell lines and agalsidase beta is produced from chinese hamster ovary cells.Compared with agalsidase alpha,agalsidase beta contains higher proportion of the mannose-6-phosphate residues that are required for cellular uptake of exogenously administered enzyme and is taken more readily by cultured fibroblasts. The recommended doses of agalsidase alpha is 0.2mg/kg and agalsidase beta is 1.0mg/kg biweekly by slowintravenous infusion. ERT with either drug is very expensive,costing approximately $250 000 per year for an average adult with the disease. ERTto FD patients soon after diagnosis prevents irreversible organ damage. ERT has shown marked improvement in acroparathesia**,** GI symptoms**,** hypohidrosis**,** **s**tabilization of deteriorating renal function, cardiac functionand reduction in stroke frequency**.** ERT has shown decreased levels of Gb-3 in plasma,urine,endothelial cells and in various organs like heart,kidneys and skin.

Psychological Treatment [8]

Disease symptoms can be improved by professional counseling helps the patient in managing the difficulties of the disease and the lifestylechanges might be required.Special attention and care should be taken to overcome the signs of anxiety disorders,clinical depression and suicidal ideation.

FABRY DISEASE THERAPY IN FUTURE

Chaperones

Chaperones are small molecular ligands, which will bind and stabilize some mutant forms of α-Gal A in the endoplasmic reticulum.This binding and stabilization facilitates protein folding and allows for correct trafficking.The stable complex of mutant enzyme-Chaperone is transported to lysosome,where complex dissociates spontaneously under acidic condition,enzymatic activity of the mutant protein is rescued.Chaperone therapy served as a feasible strategy for the treatment of FD.[21,22]

Migalastat hydrochloride(1-deoxygalactonojirimycin hydrochloride) is an analog of terminal galactose of Gb3 that selectively binds and stabilizes the mutant forms of α-Gal A. Phase 2 clinical trials demonstrated increase in α–Gal A activity and reduction in levels of Gb3 in blood, skin and kidneys .The advantages of chaperones are they are non-invasive, orally available and having higher tissue distribution. Migalastat hydrochloride is under phase 3 clinical trial to evaluate the long term safety and efficacy of the drug.[21,22]

Substrate Reduction Therapy

Substrate reduction therapy is a new approach to treat FD by decreasing the synthesis of substrate Gb3, by inhibiting the enzyme which catalyses the first step in the synthesis of Glycosphingolipids and the subsequent molecules.[22]

Miglustat has shown positive outcomes in fabry mice in preclinical trials,but the inhibitory effect of miglustat is not specific for Glucosylceramide synthase. Gastrointestinal complaints and peripheral neuropathy are observed as symptoms,hence it is not yet approved clinically.

Another investigational product (Genz-6828452) is under clinical trial,in preclinical studies it has shown more specific inhibitory effect towards glucosylceramide synthase and decreased plasma levels in various tissues of mice.

Stem cell transplant

Several trials were carried out to treat FD using stem cell therapy. But its use is limited due to the requirement of matching donor and serious effects that arise from transplant rejection reactions. In addition the transplanted cells and their progeny could not meet the therapeutic enzymatic levels required.[22]

Gene therapy

It has been explored as a potential treatment for LSDs including FD. This involves replacing or altering the mutated gene with the gene of interest into the targeted cells using carriers known as “vectors”. The most commonly used vectors are recombinant viral vectors which include retroviral lentiviral, adenoviral and adeno-associated viral vectors. But their use is limited because of their potential to cause immunogenicity, carcinogenicity, limited DNA packaging capacity and difficulty in vector production. Now a days trials have been conducted using non viral vectors and the engineered nucleases to overcome the limitations of viral vectors. This is yet to be approved by FDA.[22]

CONCLUSION

FD is a heterozygous disease that causes impairment of major organ systems, resulting in a diminished quality of life, and a notable reduction in lifespan of

about 15-20 years. Early diagnosis helps in slowing down the progression of disease and worsening of the patient condition. Theonly FDA approved treatment is ERT,which has shown marked reduction of symptoms and improved the quality of life of the patient. But it is very expensive which decreases its affordability.Treatment with chaperons has a potential advantage over ERT because it can be administered orally,crosses the blood brain barrier, donot cause autoimmune response and its affordable price.Stem cell transplant and gene therapy also serve as an alternative treatment for FD with good therapeutic outcomes. Further studies are to be carried out for obtaining a potential mode of treatment, which provide a reliable cure and become a boon to the FD patients so that they can lead a quality life!

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