

Fabry's Disease — A comprehensive review on pathogenesis, diagnosis and treatment

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Abstract

Fabry's is a progressive, destructive and life threatening disease which reduces significantly life expectancy of the affected individual.

It is a genetic disorder of X-linked inheritance caused by deficiency of lysosomal enzyme α -galactosidase A resulting in progressive accumulation of glycosphingolipids within different body cells. Fabry's deposits are defined histopathologically as lamellate membrane like structure called myeloid or Zebra bodies.

Clinical manifestations of disease are hypohidrosis, acroparesthesias, heat intolerance, angiokeratomas, corneal opacities, cardiac arrhythmias, left ventricular hypertrophy, proteinuria, renal insufficiency and cerebrovascular accidents.

Diagnosis of Fabry's need a high clinical suspicion, good physical examination, organ specific tests and is confirmed by demonstrating low enzyme assays in homozygous males and gene typing in heterozygous females.

Specific therapy for Fabry's disease is enzyme replacement with recombinant human α -galactosidase A. If started early it has a promising role in renal and cardiac disease however beneficial role is not yet defined in CNS involvement.

Keywords: Fabry's disease, Review, Genetic disorder.

Introduction

Fabry's disease is one of the genetic disorders grouped together as lysosomal storage disease. The lysosomal storage diseases are caused by various enzyme deficiencies that result in substrate accumulation within lysosomes. Over forty (40) lysosomal storage disorders are already known and among these Fabry's is the only one which is X-linked.¹ Fabry's disease is also known as Anderson Fabry's disease, Angiokeratoma Corporis

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diffusum universal and Morbus Fabry. Estimated incidence of Fabry's range from 1 in 40000 to 1 in 117000 live male births.² Fabry's is a progressive, destructive and life threatening disease which reduces life expectancy by an average of 15 years in female patients and 20 years in male patients.^{3,4}

History

It was for the first time in 1898 that skin lesions of Fabry's was reported by Johann Fabry and William Anderson from Germany and England respectively.^{5,6} In 1947, Pompen et al further described it to be a generalized storage disorder because of abnormal vacuoles found in virtually all cells of the affected individuals.⁷ In 1963, the material that accumulates in the cells of Fabry's patients was identified as neutral glycosphingolipid.⁸ In 1967, Brady et al found that the disease is caused by deficiency of an enzyme galactosidase, required for glycosphingolipid metabolism.⁹ In 1970, Kint reported the anomeric configuration of terminal galactoside linkage to be alpha.¹⁰ In the late 1980, the full length cDNA was isolated and the entire gene sequence of α -galactosidase was determined.^{11,12}

Genetics

The enzymatic defect is linked to mutation in the gene encoding¹³ the enzyme located on the long arm of X-chromosome in region q21, 22. The gene encodes a 429 amino acid polypeptide and is 12 kilo base long and contain 7 exons. The defect that causes Fabry's is heterogeneous. To date more than 400 mutations of α -galactosidase gene have been recorded in human mutation database. Most families have private mutations which may explain the variations in clinical presentation of Fabry's disease.¹⁴

Inheritance

Fabry's disease is an X-linked disease. Heterogenous mothers with each conception have a 50% chance of passing the defective gene to all offspring. Sons who inherit defective gene will have Fabry's disease; daughters once thought to be asymptomatic carriers but may in fact develop disease manifestations from mild to severe because of X inactivation. Although a positive family

history is a strong indicator of Fabry's disease, de novo or spontaneous mutations have been documented, thus absence of family history does not rule out Fabry's disease.

Pathogenesis

In Fabry's Disease deficiency of lysosomal enzyme α -galactosidase A⁹ results in progressive accumulation of neutral glycosphingolipids with terminal α -galactosyl residue (ceramide di and tri hexoside) in lysosomes of endothelial, epithelial, smooth muscle cells, myocardial cells, nephrons, reticuloendothelial cells, connective tissue, corneal epithelial cells, ganglia and perineural cells of autonomic nervous system. Progressive accumulation of globotriaosyl ceramide within vascular endothelium leading to narrowing and tortuosity of vessels and occlusion ultimately leading to ischaemia and infarction in the organ involved resulting in various clinical manifestations of the disease. Other than vascular occlusion a prothrombotic state has also been one of proposed mechanism for ischaemic injury as described in a study on twenty-five (25) Fabry's patients published recently.¹⁵

Classification

Clinically Fabry's patients could be divided into three main groups based on their presentation and plasma α -galactosidase level.

Classical Fabry's.

Heterozygous females.

Atypical or cardiac variant.

Classical Fabry's disease is the most studied group. Classical Fabry's are patients with less than 1% of normal plasma α -galactosidase activity and usually presents in childhood with pain, fever, hypohidrosis, fatigue, and exercise intolerance. However, symptoms often go unrecognized until adulthood when organ system damage has occurred. In general disease severity is inversely related with plasma enzyme activity and most of classical Fabry's patients are males however females can also have classical Fabry's disease.¹⁶

Heterozygous females are patients with 0-100% of normal plasma α -galactosidase activity. Once thought to be asymptomatic carriers may in fact develop disease manifestations from mild to severe because of X inactivation.¹⁶ A recent study of obligate carrier females found significant disease manifestations in 20 out of 60 females including 17 who had experience transient ischaemic attacks or cerebrovascular accident.³

Atypical variants are patients with 1-30% of normal plasma α -galactosidase activity.¹⁶ Because of low α -galactosidase activity these hemizygous have few or none of the hallmark symptoms of classical Fabry's disease. These patients present later in life at age of around 40 years and have manifestations predominantly in one organ system. Cardiac variant of Fabry's may be an important cause of idiopathic left ventricular hypertrophy or late onset hypertrophic cardiomyopathy.¹⁷

Organ Specific Manifestations and Diagnosis Skin Lesions

Skin lesions in Fabry's called Angiokeratomas are now recognized as characteristic features of the disorder and include red-purple maculopapular vascular non blanching lesions found in bathing trunk distribution of buttocks, groin, umbilicus, and upper thigh. These range in size from pin point to several millimeters and become larger and more numerous with age.^{18,19}

Eye Lesions

Corneal opacity seen with slit lamp examination in Fabry's patients is found universally among hemizygous and in majority of heterozygous. It is classically whorl like corneal rays emanating from a single vertex and a useful diagnostic indicator. The opacity may not affect the vision.²⁰

Cardiac Manifestations

Cardiac involvement in Fabry's is frequent and is more serious in hemizygotes. Deposits of neutral glycosphingolipids within cardiocytes lead to conduction abnormalities like short PR interval, AV blocks, supra ventricular and ventricular arrhythmias. Myocardial ischaemia in Fabry's has in most instances a functional origin due to endothelial dysfunction of coronary arteries and more oxygen demand of hypertrophic myocardium.²¹ Valvular fibrosis leading to valvular abnormalities frequently occurs, however involvement is generally mild and clinically insignificant.

Different diagnostic modalities used to assess cardiac functions in Fabry's are echocardiogram for conduction abnormalities, echocardiography for myocardial mass assessment, and magnetic resonance Imaging.²²

Renal Involvement in Fabry's

Renal involvement in Fabry's is known since original reports by Anderson and Fabry in late nineteenth century.^{5,6} Renal involvement is likely to begin at an early age of around 22 years and likely to be more severe in patients with α -galactosidase levels of less than 1% than in those with enzyme level detectable in whom renal

involvement is less severe and begins late at age of around 47 years. Urinary concentration defects, polyuria, proteinuria, and chronic renal insufficiency are known clinical renal manifestations of Fabry's. Concentration defects are the earliest functional manifestation. Proteinuria, often the cause for nephrology referral, may begin in teenage and becomes more frequent when patients reach their 20s and 30s. One fourth of patients may progress to chronic renal insufficiency without ever having nephrotic range proteinuria. Even patients with nephrotic range proteinuria may not have all manifestations of nephrotic syndrome.²³

Diagnosis of Fabry's is made by nephrologists in approximately 19% of cases suspected by urinary concentration defects or proteinuria or renal insufficiency in presence of neuropathic pains, hypohidrosis, or typical skin lesions. Urine cytology is a noninvasive, underutilized approach to diagnose Fabry's or for demonstrating renal involvement in Fabry's. Urine Cytology demonstrates presence of lipid laden cells or oval fat bodies in urinary sediment. Urinary detection of globotriaosylceramide (Gb3) is another way to diagnose renal involvement in Fabry's patient. Renal biopsy done for evaluation of proteinuria can diagnose Fabry's for its typical histopathological lesions. Here Fabry's inclusions can be identified with PAS or papanicolau stain demonstrating vacuolated epithelial cells on light microscopy and maltese cross pattern under polarized light or characteristic lamellar pattern on electron microscopy.

End stage renal failure was commonest cause of death in Fabry patients before advent of renal replacement therapy at mean age of 41 years. Reported average time from onset of renal insufficiency leading to end stage renal failure is between 1-13 years and is not affected by patients age at onset of renal insufficiency or magnitude of proteinuria.²⁴ The onset of CRI may begin as early as the second decade of life. The mean age of onset of clinical nephropathy has been reported as 27 years.²⁵ Thereafter the glomerular filtration rate decline is at mean rate of 12.2ml/min/year. Overall 13-23% of male Fabry's patients and 3% of female patients develop endstage renal failure.^{23,25} In NIH series, survival analysis has shown that 50% of patients developed CRI by 43 years of age.²⁶

CNS Involvement

Cerebral vasculopathy occurs commonly in Fabry's and leads to ischaemic cerebrovascular events in younger age. Acroparesthesias or acute burning and tingling pain in extremities with no apparent cause, hearing loss gradual or sudden, vertigo, hemi facial numbness, seizures, transient Ischaemic attack, hemiplegia, hemianaesthesia,

aphasia and cerebral haemorrhage, all of which are known clinical manifestations of cerebral Fabry's resulting from multifocal cerebral small vessel disease. Diagnosis of Fabry's should be considered whenever stroke is seen at a younger age.²⁷

Evaluation of cerebral involvement in Fabry's is done through detailed clinical examination, Magnetic Resonance Imaging can show asymmetric wide spread pattern of deep white matter lesions which are hyper intense on T2 and FLAIR weight images. Magnetic Resonance Angiography can show structural lesions and magnetic resonance spectroscopy can see altered biochemical and metabolic ratios in Fabry's patients. Recurrent cerebrovascular events are an important cause of morbidity and mortality in these patients and structural changes on MRI are found as early as 24 years of age, however cerebrovascular events are more common in middle age.²⁸

Histopathology

Light microscopic findings in Fabry's are well defined in literature. Fabry's deposits are best demonstrated using the tissue that has been fixed in glutaraldehyde stained with toluidine blue or methylene blue/Azure which yields dark blue cytoplasmic inclusions. Electron microscopy shows enlarged secondary lysosomes packed with lamellated membrane structure called myeloid or Zebra bodies.

Renal histology on light microscopy shows swelling and foamy vacuoles within cytoplasm and sometimes characteristic myelin like structures. Largest amount of lipid deposits are seen in visceral epithelial cells, than parietal epithelial, mesangial and glomerular endothelial cell, distal tubular epithelial cells pericytes and smooth muscle cell. With progressive disease there is interstitial fibrosis, tubular atrophy and glomerular obsolescence.²⁹

In heart histopathology of a Fabry's patient with myocardial involvement has shown extensive myocyte vacuolation, no extra cellular lipid deposits were found but extensive collagenous fibrosis was seen on autopsy.³⁰

In Eye, oil red o positive deposits were accumulated in sub epithelial layers of cornea³¹ demonstrated on autopsy.

Skin biopsy shows dilated lymph and blood vessels in upper dermis with ortho keratotic thickened horny layers in well developed angiokeratomas. Vesicular clear vacuolation seen in cytoplasm of secretory portion of eccrine sweat glands.³²

Diagnosis

Diagnosis of Fabry's disease is difficult. Many patients with

Fabry's have a long history of consultation with several different medical specialist and are often given a wrong diagnosis. Medical specialists who most often establish the diagnosis of Fabry's are nephrologists followed by geneticists. A positive family history contributed 46% of diagnosis in Fabry's patients.²⁶ The usual age for diagnosis of Fabry's is 28-29 years.²

Diagnosis of Fabry's requires a high index of suspicion, based on clinical presentation with involvement of the skin,^{18,19} eye,²⁰ CNS,^{27,28} kidneys,^{23,24} heart,^{21,22} as defined already. Causes of mortality in these patients include renal failure, cardiomyopathy, and cerebrovascular accidents.

For Enzyme Assay fluorometric method is used universally and this could be done on plasma, leukocyte, blood spot or cultured skin fibroblast. Majority of screening studies that looked for Fabry's disease used plasma α -galactosidase assay as the first line test. Assay on leukocyte is more reliable than plasma as with plasma more false negative results are seen however doing a leukocyte assay is more laborious.³³ There is insufficient information to determine whether dried blood spots would be more reliable than plasma in screening adult Fabry's patients.

Genetic analysis is more important in diagnosing female carriers who have normal to very low enzyme activity therefore their specific family gene mutation has to be demonstrated.

Prenatal Diagnosis

Hemi zygous can be identified prenatally by assaying for an XY Karyotype and deficient α -galactosidase activity in chorionic villi between 9-10 week or in cultured amniotic cells by amniocentesis done at 15 weeks.

Carrier Detection

Carriers can be identified reliably if plasma enzymatic assays are found low, however enzyme levels may be normal in carrier females. If genetic mutation is known, identification of gene mutation in one α -galactosidase gene allele through molecular genetic testing can be diagnostic of the carrier state. In cases where mutation is not identified ophthalmological examination for characteristic corneal opacity is helpful which is seen in 80-90% of carriers.

Recommendations for Screening

If an affected male is the patient, disease is to be screened in all daughters and mother who would be obligate carriers and female sibs who may or may not be a carrier.

In a female carrier, if the father is affected, female sibs are

also carriers, and male sibs are not affected.

If disease in a carrier female is inherited from a carrier mother, female sibs have a 50% chance of being carriers and male sibs have a 50% chance of being affected. Off spring of a carrier female if male, have 50% chances of being affected and female offspring's have 50% chance of being a carrier.

Aunts offsprings should also be screened for carrier state.

Management

Enzyme Replacement Therapy

First specific therapy for Fabry's disease is enzyme replacement with recombinant human α -galactosidase A, introduced in year 2000 that provides an exogenous source of deficient enzyme in patients with this progressive disorder.³⁴

There is multicentre, double blind placebo controlled study which shows clearance of micro vascular endothelial deposit from kidney and heart and skin by treatment with recombinant human α -galactosidase therapy.³⁴

Dose of recombinant human α -galactosidase A of 1mg/Kg of enzyme every 2 weeks as infusion is generally given however exact dose and duration of therapy for different indications are not fully known.

Infusion reaction includes tachycardia, hypertension, throat tightness, chest pain or tightness, dyspnoea, fever, chills, rigors, abdominal pains, pruritis, urticaria, nausea, vomiting, lip or ear oedema, rash, hypotension, myalgia, and headaches. Other serious reported events are stroke, pain, ataxia, bradycardia, cardiac arrhythmias, cardiac arrest, decreased cardiac output, vertigo, hypoacusia, and nephritic syndrome. Pretreatment with antipyretics are recommended. Allergic reactions can be avoided by slowing rate of infusion. If allergic reactions occur then antihistamines or steroids can be used.

Symptomatic Management²⁰

Life style modification includes avoiding all stimuli that precipitate pain, cessation of smoking thus controlling impact on vascular disease and low salt diet to help controlling blood pressure.

Control of neuropathic pain- Medicines recommended are diphenyl hydantoin, Carbamazepine, Gabapentin and opioids. Non steroidal analgesia is to be avoided as it gives poor control of pain and with them risk of renal toxicity is significant.

Protenuria control with angiotensin converting enzyme

inhibitors.

Antiplatelet agents like aspirin, ticlopidine, and dipyridamole for recurrent thrombotic events.

Management of cardiac involvement in Fabry's

In cardiac involvement in a Fabry's patient, enzyme replacement therapy should be started before myocardial fibrosis has developed to achieve long term improvement in myocardial morphology, function and exercise capacity. No benefit on left ventricular hypertrophy is demonstrated with enzyme replacement therapy.³⁵

Management of renal involvement in Fabry's

Renal involvement in Fabry's patients is evaluated on diagnosis of Fabry's by proteinuria measurement, renal function evaluation through measurement of glomerular filtration rate and performing renal biopsy to confirm diagnosis and to see extent of renal damage.³⁶

Control of hypertension should preferably be treated with angiotensin antagonist therapy.

Early diagnosis of individuals affected with Fabry's is important as ERT has a definite role in improving glomerular structure by reduced glycolipid deposits in kidney and improvement in renal functions, attempting to halt further renal deterioration.³⁶

Renal transplant can be performed without any high risk in Fabry's patients when end stage renal failure occurs²⁵ or these patients can be on maintenance haemodialysis.

Management of CNS Disease

Symptomatic management is given for neuropathic pain and antiplatelet agents are used for recurrent thrombotic strokes.

Role of ERT is yet not proven to be beneficial in Fabry's with CNS involvement. Jardin et al while comparing pretreatment and post treatment structural changes on imaging in eight Fabry's patients with CNS involvement found no change in few, whereas few improved and few worsened.²⁸

Recommended Investigations and Follow UPS²⁰

Annual checkup by a Fabry's expert.²⁰

Once diagnosis of Fabry's is confirmed other tests include Complete blood picture, Biochemistry, Urinalysis, Spot urine albumin creatinine ratio, blood grouping as blood group B is associated with more severe prognosis.²⁰

Creatinine clearance every 2 years, Echocardiography and electrocardiogram every 2 years and follow up MRI brain are recommended.

Female carriers should also have baseline investigations and follow ups at 3-5 years.

Genetic Counseling

Genetic counseling of patients with Fabry's is a valuable adjunct as it provides individual and families with information on nature, inheritance and implications of the genetic disorder and helps them to make informed medical and personal decisions.³⁷

Also genetic counseling helps affected young adults and carrier to plan their family and to discuss availability of prenatal testing before pregnancy.

Conclusion

Fabry's is a progressive, destructive and life threatening disease which reduces life expectancy significantly, so all attempts should be made for an early diagnosis of Fabry's as early start of therapy is the only hope to arrest progression of disease.

Once thought simply a carrier, but heterozygous females can have variable manifestations from mild to severe disease.

Enzyme replacement therapy has a promising role in renal and cardiac disease however beneficial role is not yet defined in CNS involvement.

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