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Fabry Disease

Fabry Hastalığı

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ABSTRACT

Fabry disease is a X linked Lysosomal storage disorder caused by a defect in α-galactosidase enzyme. This defect causes accumulation of lipids progressively in the vasculature and internal organs resulting in multiple complications and life threatening situations. It is characterized by pain, neurological, gastrointestinal, renal, cardiovascular, dermatological, rheumatological and oral manifestations. This review renders the pathophysiology, clinical features, diagnostic criterias, differential diagnosis and management of Fabry disease. This review also portrays the recent advancements that have been proposed for the management for this disorder.
Key words: Fabry disease, lysosomal storage, enzyme replacement therapy

ÖZET

Fabry hastalığı α-galactosidaz enzimindeki bir eksiklikten kaynaklanan X'e bağlı bir lizozomal depo hastalığıdır. Bu enzim eksikliği damar sistemi ve iç organlarda lipid birikiminde yol açarak hastayı çoğul komplikasyonlar ve yaşamı tehdit edici bir duruma sürükler. Hastalık ağrı, nörolojik, gastrointestinal, romatolojik ve ağızla ilgili belirtilerle karakterizedir. Bu yazıda Fabry hastalığının patofizyolojisi, klinik özellikleri, ayırıcı tanısı ve yönetimi gözden geçirilmiştir. Bunların yanısıra hastalığı tedavisindeki son gelişmelere de vurgu yapılmıştır.
Key words: Fabry hastalığı, lizozomal depo hastalığı, enzim değiştirme terapisi

Introduction

Fabry disease is a rare inherited disorder first described by Drs. Johann Fabry and William Anderson in 1898. It is one of a large family of diseases known as lipid storage disorders. The enzyme that causes the disease was identified in the 1960s and since then much progress has been made in its treatment. Symptoms may appear in early childhood, and the disease can progress to kidney and heart failure[1]. This review describes the clinical, pathophysiology, genetics, cinical features, management with recent advancements in the patients with Fabry disease.

Pathophysiology

The disease, also known as Anderson-Fabry disease (AFD), Morbus Fabry, and angiokeratoma corporis diffusum universale, is caused by a defect in the gene for the lysosomal enzyme α-galactosidase (α-GAL, also known as α-galactosidase A and ceramide trihexosidase). This results in an inability to catabolize lipids with terminal α-galactosyl residues. These lipids, particularly globotriaosylceramide (GL-3; also known as Gb3, ceramide trihexoside, or CTH), accumulate progressively in the vascular endothelium and visceral tissues throughout the body. By the third to fifth decade, life-threatening renal, cardiac, or cerebrovascular complications typically occur. Before the advent of renal dialysis and transplantation, the average age at death for male patients was 41 years[2].

The α-GAL gene is localized to the long arm of the X chromosome (locus Xq22.1). The gene, which encodes a 429 amino acid polypeptide, including a 31 amino acid signal peptide, is 12 kilobases long and contains 7 exons. The defect that causes Fabry disease is very heterogeneous – to date, over 400 mutations of the α-GAL gene have been recorded in the Human Mutation Database. The majority of mutations are missense or nonsense nucleotide substitutions; however, splicing, small and gross deletions and insertions, contiguous insertions/deletions, gross duplications, and complex rearrangements have also been found. The wide range of mutations may explain variations in the clinical presentation of Fabry disease. Most families have "private" mutations (special to that family)[2].

The disease is pan ethnic, with estimates of incidence ranging from about one in 40,000 to 60,000 males. A founder effect exists in Nova Scotia in which an extended kindred has been

described. In this region, the frequency of disease is estimated to be as high as 1/15,000.13 Fabry disease predominantly affects males, although carrier females are also often affected[3].

Clinical Features

Symptoms are typically first experienced in early childhood. Symptoms can be very difficult to understand. The rarity of Fabry disease and unawareness of many clinicians sometimes leads to misdiagnoses. Manifestations of the disease usually increase in number and severity as individual ages[4].

Table.1. General features

Specialty	Presenting Feature(s)
Pediatrics	Fabry pain crises, acroparesthesia, exercise intolerance, telangiectases, angiokeratomas, fever with elevated erythrocyte sedimentation rate, hypohidrosis/anhidrosis, heat and cold intolerance
Primary care	Acute and chronic pain, fatigue, weakness, heat and cold intolerance, hypohidrosis/anhidrosis, fever,angiokeratomas, depression
Genetics	Family history of certain symptoms, especially renal problems among maternal male relatives
Nephrology	Proteinuria, tubular dysfunction (polyuria, polydipsia), symptoms suggesting Fanconi's syndrome, elevated serum creatinine, progressive renal insufficiency of unknown etiology
Cardiology	Left ventricular hypertrophy, mitral valve prolapse and/or regurgitation, premature coronary artery disease, angina, myocardial infarction, arrhythmia
Gastroenterology	Episodic diarrhea, post-prandial pain, nausea, vomiting, constipation
Eye care	Cataracts, whorled corneal and lenticular opacities, retinal and lenticular abnormalities
Dermatology	The hallmark of the disease, angiokeratoma, is a lightly verrucous, deep-red to blue-black papule varying in size from punctate to 0.5 cm.[5] Varicose veins, stasis-related edema, lymphedema of the arms and legs, and edematous upper eyelids.[5] Early, small lesions may not be hyperkeratotic.[5] Great variation in lesion size is evident, making patients appear as if they are "peppered with buckshot.[5]
Rheumatology	Joint pain, angiokeratomas, fever, elevated erythrocyte sedimentation

	rate. Osteopenia and osteoporosis have been linked to Fabry disease.[5] Bilateral femoral head and distal tibial osteonecrosis have also been linked to Fabry disease. Osteopenia is common in Fabry disease patients[5]
Urology	Abnormal urinalysis – proteinuria, hematuria, lipiduria
Neurology	Acroparesthesia, transient ischemic attacks, early stroke, muscle weakness, hemiparesis, vertigo/dizziness, tinnitus, hearing loss, nystagmus, head pain, hemiataxia, ataxia of gait, personality changes
Oral manifestations[6]	Most patients have symmetric, pinpoint, macular, purplish spots (angiokeratomas) on the lips, particularly on the lower lip near the skin-mucosal junction, on either side of the midline. The lesions are smaller than those on the skin. The buccal mucosa appears to be involved to a lesser degree. The gingiva, soft palate and uvula are only rarely involved. The tongue is not affected. Involvement of the nasal mucosa with resultant epistaxis has been reported. Hearing loss has been noted. Glycosphingolipid accumulation has been demonstrated in dental pulp from hemizygous males

Psychosocial Impact

Fabry disease generally has a serious impact on quality of life which could be exacerbated by the shame and embarrassment anecdotally reported by families. Patients also comment on poor on-going medical care even after diagnosis, suggesting that professionals' lack of understanding and sympathy may affect quality of life. AFD has a significant impact on school attendance, employment and social life in males and females[6].

Differential Diagnosis

The condition can be diagnosed in hemizygous males by determining a history of acroparesthesias, the presence of characteristic skin lesions, and corneal and/or lenticular changes. Heterozygotes usually are asymptomatic; however, about 80% of patients have corneal lesions that can be observed by slit-lamp microscopy. The skin lesions are so characteristic in distribution that need for differential diagnosis is extremely limited. The lesions of hereditary hemorrhagic telangiectasia are larger, do not involve the lower trunk and thighs, and are less numerous and more irregular. The Fordyce type of angiokeratoma is usually limited to the scrotum, and the Mibelli type forms warty lesions on the extremities or

ears. Angiokeratomas are also found in aspartylglycosaminuria, β- mannosidosis, fucosidosis, and galactosialidosis[7].

Diagnosis

Table.2. Diagnostic Criteria of Fabry Disease

Major Criteria	**Details**
Family history of Fabry disease	
Angiokeratoma	
Renal disease	Renal insufficiency or isolated proteinuria
Corneal whorls	
Acroparesthesias	Hands and feet
Hypertrophic cardiomyopathy	LV wall thickness (either posterior wall or septum) greater than 13mm. Measurement to be obtained by either MRI, or 2D echocardiography. LVH by ECG using Estes- Rohmhilt criteria. ECG score must be 5 or greater. LV mass index, either by 2D echo or MRI, must be above normal limit for gender by at least 20%.
Other cardiac criteria (major)	Diastolic filling abnormalities: Must be measured using 2D echocardiography. The E/A ratio must be greater than 2, and the deceleration time (DT) should be 140 msec or less.
Premature TIA and single or multiple small cerebral infarcts documented by a neurologist	Not diabetic, not hypertensive
Minor Criteria	
Chronic gastrointestinal disturbance	Diarrhea, abdominal pain/cramps[not vomiting, nausea]
Hypohidrosis	
Heat intolerance	
Lymphedema	
Hearing impairment, tinnitus	
Postural hypotension	
Cardiac criteria (minor)	Increased left atrial size on 2D echocardiography. In the parasternal long axis view (PLAX) the LA size should be

	>33mm, and in the four chamber view it should be > 42mm Conduction abnormalities: AV block, short PR interval (in the absence of known Wolf- Parkinson-White Syndrome), ventricular or atrial tachyarrhythmias, left bundle branch block. Moderate mitral or aortic insufficiency in the absence of other known valvular abnormalities.
Unexplained MRI white matter changes	
Vertigo	
Monocular blindness (ischemic optic neuropathy)	
Joint pain (arthralgias/arthritis)	Often indistinguishable from arthritis

Treatment

There is currently no cure for Fabry disease and until recently treatment was entirely symptomatic. The successful use of ERT in Gaucher disease, where it is now the current standard of care has led to recognition of its potential role in treating other lysosomal disorders such as Fabry disease[6].

Enzyme Replacement Therapy

The recent introduction of enzyme replacement therapy to address the underlying pathophysiology of Fabry disease has focused attention on the need for comprehensive, multidisciplinary evaluation and management of the multi-organ system involvement[8].

A number of randomised controlled trials have investigated the therapeutic effect of recombinant alpha galactosidase A on the clinical manifestations of Fabry Disease. No clinical or drug trial has yet addressed the appropriate starting time of treatment or the group of patients most likely to benefit from therapy. However this is a chronic, progressive disorder. The aim of treatment is to prevent progression and where disease is already manifest to try and reverse or stabilise the disease. It is anticipated that treatment will be most successful when started early in the course of the disease[9].

A study in which two enzyme preparations have been approved in the European Union by the European Agency for the Evaluation of Medicinal Products (EMEA): agalsidase beta (Fabrazyme, Genzyme Corporation), produced in Chinese hamster ovary cells; and agalsidase

alfa (Replagal, Shire Human Genetic Therapies, Inc.), produced in human cell lines. Agalsidase alfa was found to be effective in treating pain and in reducing heart size in patients with Fabry disease, to stabilize kidney function and to improve hearing, sweating and quality of life. It is able slow down progression of renal failure in patients with end-stage renal disease[10].

Table.3. Symptomatic Treatment of Fabry Disease [7]

Pain	Chronic pain: anticonvulsants (eg carbamazepine, gabapentin, phenytoin); AFD crises or when necessary: non-steroidal antiinflammatory drugs or opiates Minimisation of activities that trigger painful crises eg physical exertion, temperature changes, emotional stress
Angiokeratoma	Removal (if desired by the patient) with argon laser therapy
Renal disease	Early stages of impairment: ACE inhibitors (in patients without renal artery stenosis); Renal failure: dialysis or transplantation
Cardiovascular diseases	Chest pain: anti-anginals (A7-blockers, calcium antagonists, nitrates); Heart failure: Diuretics, ACE inhibitors, digoxin, A7-blockers; Atrial ventricular tachycarrhythmia: antiarrhythmics anticoagulants, ICDs Symptomatic bradycardia: pacemaker
Gastrointestinal symptoms	Low-fat diet, small and frequent meals, motility agents
Hypertension	Rigorous control eg ACE ingibitors. Avoid beta blockers where sinus bradycardia
Hyperlipidaemia	Statin
Neurovascular disease	Aspirin, clopidogrel

Initiation of effective ERT in patients with multi-system manifestations of Fabry disease is a straightforward decision on clinical grounds. Complication factors include the logistics of biweekly infusions, and the availability of comprehensive insurance coverage for the cost of the drug[11].

The following signs and symptoms are among the important evidence of serious implications of Fabry disease in females that warts initiation of enzyme treatment, the only available disease specific treatment[12].

- Uncontrolled pain at any age that requires alteration of lifestyle and interferes with quality of life

- Presence of and a progressive increase in proteinuria, exceeding 300 mgs/24 hours; or a renal biopsy result which shows significant renal involvement
- Patients on dialysis or transplanted
- Ischemic heart disease with or without cardiac dysfunction; Moderate to severe heart enlargement (LVH)
- Cardiac arrhythmias
- Significant brain involvement or MRI changes
- Frequent and severe vertigo episodes
- Severe fatigue

Gene Therapy

Gene therapy for Fabry disease is in the early stages of investigation. Research has identified two different approaches. The first one is direct delivery of the α-GAL gene using modified adenoviral and adeno-associated viral vectors[2]. The second one is genetic alteration of hematopoietic stem cells.

Substrate Reduction Therapy

Substrate reduction therapy (SRT) circumvents enzyme replacement/modification by inhibiting synthesis of globotriaosylceramide. This approach involves the use of a glucosylceramide synthase inhibitor, which would slow the rate of Gb3 synthesis, and thus decrease lysosomal storage[13].

Residual Enzyme Activation

Enzyme activators may increase the residual activity of mutant GLA in the lysosomes of patients with Fabry disease, thereby lessening lysosomal storage of the substrate and alleviating symptoms[13].

GLA Promoter Activation

Specific small molecule promoter activators may increase the amount of GLA in lysosomes by stimulating expression of the target protein. In this one, a promoter activator binds the GLA promoter in the nuclei of cells and enhances GLA transcription, thereby increasing the

synthesis of mutant GLA protein. This results in an increased amount of GLA in the lysosomes, as the enhancement of mutant enzyme expression could proportionally increase protein trafficking to the lysosome[13].

Protein Homeostasis Regulation (Proteostasis)

Another treatment strategy involves altering the proteostasis network in cells, which consists of many highly regulated biological pathways that influence protein synthesis, folding, trafficking, disaggregation and degradation[13].

Chemical Chaperone Therapy

Chemical chaperones are small molecules that bind to mutant enzyme proteins and assist in their correct folding, maturation, and trafficking to their functional site, such as the lysosome[13].

Monitoring

Aerts and co-workers reported on the occurrence of lyso-Gb3 in plasma of patients with Fabry disease. Lyso-Gb3 is structurally similar to Gb3 which could not be identified in plasma from control individuals. In hemizygotes a strong correlation between plasma Gb3 and lyso-Gb3 was found, but there was no correlation observed between lyso-Gb3 and the Mainz-Severity-Score-Index as a clinical index for disease severity in male patients. The latter finding may not necessarily limit the impact of lyso-Gb3 but may be related to methodological concerns regarding the MSSI as a cross-sectionally used severity score[14].

Another approach for a biomarker was presented by Thomaidis and colleagues, who suggested membranous CD77, the membranous form of Gb3. The amount of membranous CD77 shall mirror the tissue load of Gb3, and it has been shown to decrease under ERT with Agalsidase alfa in a kidney cell model. Since CD77 may play an important role in apoptosis and necrosis, there may be a link to kidney failure in patients with Fabry disease and accumulation of Gb3[14].

Prognosis

The life expectancy of males with Fabry disease is estimated to be approximately 40 -60 years[4]. Transient ischaemic attack (TIA) or stroke affect 15-20% of Fabry disease patients. They frequently recur and have a poor prognosis[9].

Conclusion

Fabry disease is a multisystem disorder that requires multispecialty approach. As this disorder affects multiple organs; management of individual features are essential. Early diagnosis and follow up can prevent the life threatening complications. Newer treatment modalities, such as gene therapy and molecular approaches have shown promising results to the patients with Fabry disease.

References

1. Understanding Fabry disease. http:// www.aakp.org/ userfiles/ file /Fabry%20Disease%20Brochure.pdf. (Accessed: Aug 11, 2012).
2. Fabry disease. A Lysosomal Storage Disorder Characterized by α-Galactosidase A Deficiency. http://www.fabrycommunity.com/~/media/Files/Fabry/PDF/FabrUSP006_0608_Fabry_Disease _Monograph.pdf. (Accessed: Aug 11, 2012).
3. Fabry Disease: Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy in Canada. http://www.garrod.ca/data/attachments/CanadianFabryGuidelinesNov05.pdf. (Accessed: Aug 11, 2012).
4. Fabry disease. http://en.wikipedia.org/wiki/Fabry_disease. (Accessed: Aug 11, 2012).
5. Scheinfeld NS. Angiokeratoma corporis diffusum. http://emedicine.medscape.com/ article/1102964-clinical#a0217. (Accessed: Aug 11, 2012).
6. Mehta A. New developments in the management of Anderson-Fabry Disease. QJ Med. 2002; 95:647-53.
7. Gorlin RJ, Cohen MM, Hennekam. Syndromes of Head and Neck,4th Ed. New York, Oxford University Press, 2001.
8. Eng CM, Germain DP, Banikazemi M, Warnock DG, Wanner C, Hopkin RJ. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. Genet Med. 2006; 8:539-48.
9. Hughes DA, U. Ramaswam U, Deegan PEP, Lee P, Waldek S, Apperley G. Guidelines for the Diagnosis and Management of Anderson-Fabry Disease http://www.dh.gov.uk/ prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4118408.pdf . (Accessed: Aug 11, 2012)
10. Beck M. Agalsidase alfa for the treatment of Fabry disease: new data on clinical efficacy and safety. Expert Opin Biol Ther. 2009; 9:255-61.
11. Warnock DG. Fabry disease: diagnosis and management, with emphasis on the renal manifestations. Curr Opin Nephrol Hypertens. 2005;14:87-95.

12. Banikazemi M. Fabry disease and new advances in treatment. Genetics in the 3rd Millennium. 2006; 4:880-7.
13. Motabar O, Sidransky E, Goldin E, Zheng W. Fabry disease: current treatment and new drug development. Curr Chem Genomics. 2010; 4: 50-6.
14. Hoffmann B. Fabry disease: recent advances in pathology, diagnosis, treatment and monitoring. Orphanet J Rare Dis. 2009; 4:21.

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