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Review

# Might be Fabry Disease?

Ayşegül ORUÇ

Division of Nephrology, Department of Internal Medicine, Uludag University Faculty of Medicine, Bursa, Turkey

## Abstract

Fabry disease, also known as Anderson-Fabry disease, is a X-linked lysosomal storage disease. Alpha-galactosidase A (alpha-Gal A) enzyme deficiency leads globotriaosylceramide (Gb3) accumulation in several cells which causes clinical manifestations of the disease. The clinical heterogeneity and non-specific symptoms cause under-diagnosis and diagnosis delay. There are several clinical variants of FD which are associated with genetic and residual enzyme activity and listed as the classical, atypical (later-onset), renal and cardiac variants. Renal, cardiovascular and neurovascular involvement are the main causes of morbidity and mortality. Patients with acroparesthesias, episodic pain crises, proteinuria, chronic kidney disease, ventricular hypertrophy and cerebrovascular evets of unknown etiology should be screened for Fabry disease. Early initiation of enzyme replacement treatment improves the quality of life and prognosis. Therefore, it is essential to have awareness and knowledge about Fabry disease. Herein we aimed to summarize Fabry disease and point out that a Fabry patient might have visited you at your outpatient clinic.

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## Introduction

Fabry disease (FD), also known as Anderson-Fabry disease, is a X-linked lysosomal storage disease. Alpha-galactosidase A (alpha-Gal A) enzyme deficiency leads globotriaosylceramide (Gb3) accumulation in several cells which causes clinical manifestations of the disease. Symptoms are linked to enzyme activity therefore clinical presentation is heterogeneous among sufferers. Furthermore, female heterozygotes have clinical differences due to X chromosome inactivation.

The consequence of clinical heterogeneity and non-specific symptoms are under-diagnosis and diagnosis delay. Renal, cardiovascular and neurovascular involvement are the main causes for morbidity and mortality. Early initiation of enzyme replacement treatment improves quality of life and prognosis. Therefore, it is essential to have awareness and knowledge about Fabry disease. Herein we aimed to summarize Fabry disease and point out that a Fabry patient might have visited you at your outpatient clinic.

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***Address for Correspondence:***
*Aysegül Oruç*
*Department of Internal Medicine, Division of ENephrology & Transplantation, Uludag University Medical School, 16059 Gorukle, Bursa, TURKEY*
*E-mail: aysegul13072@yahoo.com*

## Definition

FD is a glycosphingolipid metabolism disorder due to the deficiency of lysosomal alpha-galactosidase A (alpha-Gal A) enzyme. Alpha-Gal A is a hydrolase in globoside metabolism which catalyzes the cleavage of the terminal galactose from globotriaosylceramide (Gb3).[1] Thereby, in the FD, Gb3 accumulates in several cells because of the low activity of the alpha-Gal A. Gb3 and derivatives have cytotoxic, pro-fibrotic and pro-inflammatory effects.[2] Exposure of vascular endothelium and smooth muscle cells are associated with vascular occlusion, ischemia and infarction which lead organ dysfunction and failure.

## Epidemiology

FD is a X-linked genetic disorder which can be seen in all ethnicity. The prevalence is reported in a wide range as 1:1368 to 1:8882 in newborn studies.[3-6] The gene of the alpha- Gal A is encoded in the long arm of the X chromosome (Xq22.1 region).[7] Almost a 1000 mutations of alpha- Gal A gene have been identified. The effect of mutation on enzyme activity determines the phenotype. The hemizygous males are affected more seriously with undetectable enzyme levels. Besides, clinic manifestation differs among heterozygous females and is milder compared with hemizygous males. This diversity is a consequence of X chromosome inactivation. If the X chromosome with mutated gene is inactivated, the alpha- Gal A levels will be sufficient and she will be asymptomatic. Furthermore, in the same family phenotype can also be heterogenic among female members. This is explained by mosaicism pattern of X-inactivation. In this case Gb3 accumulation appears only in the tissues or organs in which defective X chromosome is inactivated.[8]

## Clinic

The clinic manifestations (Table 1) are closely related with alpha- Gal A activity. A 30-35% activity of the enzyme is sufficient for adequate ceramide metabolism. An enzyme activity below 1-3% means no residual enzyme activity and is presented as classical FD. Between these ranges there is residual enzyme activity and is seen in female heterozygotes and other variants.[9]

Involvement of small nerve fibers of the peripheral somatic and autonomic nerve systems leads neuropathic pain and acroparesthesias, episodic pain crises, chronic pain and are early manifestations. Gastrointestinal symptoms, abdominal pain, diarrhea, nausea, and vomiting which may be related to the deposition of Gb3 in the autonomic ganglia of the bowel and mesenteric blood vessels manifest early too. The other early symptoms are anhidrosis, hypohidrosis, heat and exercise intolerance, chronic fatigue, tinnitus, hearing loss. Eye and skin involvement are quite specific findings compared with others. Corneal opacities- cornea verticillata, retinal vessel tortuosity, and cataracts can be seen in childhood. The most visible early clinical feature of FD is angiokeratoma which are mostly located on the buttocks, groin, umbilicus and upper thighs, also sometimes on mucosal areas.[1]

The Fabry patients have typical facial characteristics with periorbital fullness, prominent lobules of the ears, thickening of the lips, and bulbous nose. Besides, the dysmorphic facial features are not expected in cases with residual enzyme activity.

Renal, cardiac and cerebrovascular involvements are major ones that are associated with mortality and morbidity. Podocytes are the first affected part of the kidney and proteinuria is the initial presentation of the renal involvement. Renal manifestation begins at 2$^{nd}$ decade and progress to chronic kidney disease with glomerular, interstitial and tubular findings. Cases commonly reach end stage at 4$^{th}$-5$^{th}$ decade and require renal replacement treatment.[1]

Cardiac involvement includes ventricular hypertrophy, myocardial fibrosis, heart failure, coronary artery disease, aortic and mitral valve abnormalities, and conduction abnormalities. Although severe cardiac symptoms are generally present at 4$^{th}$ decade, arrhythmias can manifest trough childhood.[1] Right ventricular hypertrophy is an important finding of Fabry disease.

Cerebrovascular manifestations are consequences of ischemia due to vascular involvement and Gb3 accumulation in nerve fibers. Neuropathic pain, ischemic cerebral events, headache, vertigo/dizziness, transient ischemic attacks, ischemic strokes and vascular dementia

**Table 1.** Clinical features of Fabry disease

| | Early signs and symptoms (1st and 2nd decade) | Late signs and symptoms (3rd to 5th decade) |
|---|---|---|
| **Skin** | Angiokeratoma, hypohidrosis | |
| **Eye** | Corneal and lenticular opacities, vasculopathy (retina, conjunctiva) | |
| **Nervous system** | Acroparesthesias, Neuropathic pain, nerve deafness, heat and/or cold intolerance, tinnitus | TIA; ischemic stroke and (less frequently) hemorrhagic stroke; cerebral venous thrombosis; cervical carotid dissection |
| **Gastrointestinal system** | Nausea, vomiting, diarrhea, abdominal pain and bloating, early satiety, difficulty gaining weight | |
| **Psychological** | | Common: depression; anxiety; panic attacks; social adaptive function difficulties. Rarely: cognitive decline and dementia |
| **Renal** | Albuminuria, proteinuria, impaired concentrating ability, increased urinary Gb3 excretion | Decreased glomerular filtration rate progressing to kidney failure |
| **Cardiovascular** | Impaired heart-rate variability, arrhythmias, ECG abnormalities (shortened PR interval), mild valvular insufficiency | Hypertrophic Cardiomyopathy, reduced exercise tolerance; syncope; cardiac fibrosis; heart failure (mostly with preserved ejection fraction). Bradycardia – chronotropic incompetence; atrial fibrillation, ventricular tachycardia; sudden cardiac death |
| **Lung** | Dyspnea, wheezing; dry cough; sleep-disordered breathing | |
| **Other** | | Lymphedema in all or part of a limb (also below eyes), pitting edema; Osteopenia, osteoporosis |

are common neurologic symptoms.[1]

Other clinical manifestations are lung involvement such as chronic bronchitis, wheezing, or dyspnea; lymphatic involvement, such as lymphedema, subconjunctival lymphangiectasia, varicosities, hemorrhoids, or priapism; subclinical hypothyroidism; azoospermia; and osteopenia or osteoporosis and aseptic osteonecrosis. Psychological manifestations, such as depression, anxiety, and chronic fatigue, are also common.[10]

## Clinical variants

There are several clinical variants of FD which are associated with genetic and residual enzyme activity and listed as the classical, atypical (later-onset), renal and cardiac variants.

### *Classical variant*

The patients who have the mutations causing no residual enzyme activity manifested and defined as the classical variant/ classical FD. These are almost hemizygous males with no enzyme activity. But also some heterozygous females present as classical variant. Clinical findings begin in childhood and spectrum of involvement progressively increases. Acroparastesia, gastrointestinal symptoms, skin abnormalities, heat intolerance were presented in childhood and adolescence. In adulthood, untreated patients were exposed to progressive renal, cardiac and cerebrovascular involvements which are associated with mortality usually after 5th decade.

### *Heterozygous females*

Heterozygous females have phenotypic variability due to aforementioned reasons. They can be asymptomatic or present whole spectrum of involvement. In general compared with hemizygous males symptoms are milder and occurs on later ages.

***Atypical (later onset) variant***

They present later in life than those with the classical variant and have residual alpha-Gal A activity (between 3-30% of the normal mean). The clinic is typically dominated by a particular organ system, most commonly the heart.

***Renal variant***

Some patients may present with clinic limited to the kidney. At later ages other organ involvements like cardiac may occur.

***Cardiac variant***

It is the most common late-onset variant. They are generally asymptomatic for most of their lives and present at the 5th to 8th decade of life with ventricular hypertrophy, hypertrophic cardiomyopathy, conduction abnormalities, and arrhythmias. In the studies the rate of the cardiac variant of FD is up to 4% among patients with unexplained hypertrophic cardiomyopathy.[11-14]

## Diagnosis

There are some specific points about diagnostic approach both for screening population and instruments. Because the clinic presentation of FD is usually with non-specific symptoms as aforementioned, there is a delay for almost 10 to 15 years from the earliest symptom until correct diagnosis.[15] If the clinician has knowledge about the disease and can keep in mind FD as a possible diagnosis, adequate diagnostic approach provides the diagnosis of approximately 5 more Fabry patients with the index case.[16]

An evaluation for FD should be performed in males or females with at least one of the clinical features of acroparesthesias, angiokeratomas, hypo- or anhidrosis, corneal and lenticular opacities; abdominal pain, nausea, and/or diarrhea of unknown etiology in young adulthood; left ventricular hypertrophy or hypertrophic cardiomyopathy, arrhythmias of unknown etiology; stroke of unknown etiology at any age; chronic kidney disease and/or proteinuria of unknown etiology, multiple renal sinus cysts discovered incidentally (Table 2). Family history of the features mentioned above is strong suggestive indicators.[1, 10, 17, 18]

The instruments for diagnosis differ among genders. The enzyme, alpha Gal-A, activity measurement is the initial method for males. The activity below 1-3% of the normal mean confirms the diagnosis for the males. Subsequently, genetic testing should be performed and genetic counseling in the patient's family is essential. If the enzyme activity is resulted between 3-35% of the normal mean, genetic testing should be done to define a disease-causing mutation.[1, 10, 18]

Genetic testing should be performed initially for the females, because there might be residual enzyme activity due to X inactivation.

All patients for both genders require mutation analysis to confirm the genetic variant. There are almost 1000 genetic mutations defined for GLA gene. However the phenotypic significance of the mutation is important. In these huge genetic findings there are reported mutations with unknown significance and the genetic disorder is significant to the extent that it affects the enzyme activity.[18]

**Table 2.** Recommendations for Screening Fabry disease

| |
|---|
| Acroparesthesia or neuropathic pain in hands or feet, anhidrosis, hypohidrosis, heat and exercise intolerance beginning in childhood or young adult |
| Corneal and lenticular opacities, vasculopathy of retina and conjunctiva |
| Persistent proteinuria of unknown etiology |
| Chronic kidney disease of unknown etiology |
| Hypertrophic cardiomyopathy, especially with prominent diastolic dysfunction |
| Stroke or transient ischemic attack of unknown etiology |
| Family history of ESRD, stroke, or hypertrophic cardiomyopathy |
| Persistent, or recurrent abdominal pain associated with nausea, diarrhea, and tenesmus of unknown etiology |

## Treatment

Management of FD is composed of Enzyme replacement treatment (ERT) and concomitant therapy for symptoms and organ involvements. ERT is the mainstay of FD management. It is essential to start the ERT as early as possible to prevent organ failure. There are 2 forms of ERTs, agalsidase alpha and agalsidase beta, which are both available in Turkey. Studies confirm that initiation of ERT at early ages has better outcomes. The patients in whom ERT was administered after 40 age and/or with moderate to severe organ damage do not have expected amelioration. Besides the oral small-molecule pharmacological chaperone migalastat, is available in Europe and Canada for the treatment of a subset of Fabry patients with particular mutations.[18]

Anticonvulsants for neuropathic pain, renin angiotensin aldosterone system blockers for proteinuria, stroke prophylaxis with anti-thrombotics and anti-coagulants, metoclopramide and H-2 blockers for gastrointestinal symptoms, bronchodilators for airway obstructions, renin angiotensin aldosterone system blockers and beta blockers for ventricular hypertrophy and arrhythmias, cardiac pacing if needed are adjunctive therapies for FD.

Hemodialysis, peritoneal dialysis and kidney transplantation can be performed when the patient requires renal replacement therapy. Fabry nephropathy does not recur in kidney graft. And transplanted Fabry patients have better outcomes compared with ones on dialysis.

## Conclusions

In conclusion, FD is a genetic, multisystemic, progressive disease with generally non-specific symptoms. Furthermore, ERT is available which ameliorates symptoms and prevents organ failure in early cases. Although it has low prevalence, FD should be considered as an initial diagnosis in patients with acroparesthesias, angiokeratomas, hypo- or anhidrosis, ocular findings, ventricular hypertrophy, proteinuria, chronic kidney disease, stroke of unknown etiology. When the diagnosis is confirmed it is appropriate to transfer the patients for multidisciplinary management composed of geneticist, cardiologist, neurologist, nephrologist, and ophthalmologist experienced for FD.

*Conflict of interest*

The author declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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