



# Fabry Disease ( $\alpha$ -galactosidase Deficiency)

## Background

Fabry Disease is defined by alpha-galactosidase deficiency. Alpha-galactosidase (GLA) is needed to metabolize globotriaosylceramide and galabiosylceramide, which are glycosphingolipids. This deficiency leads to a progressive accumulation of glycosphingolipids (mostly globotriaosylceramide, GL-3) in endothelial cells throughout the body. Glycosphingolipids accumulate over time which leads to progressive multi-system organ damage. Morbidity and mortality are the result of renal failure, cardiomyopathy or cerebrovascular events (strokes). Fabry Disease is an X-linked lysosomal storage disorder and is classified as a sphingolipid degradation disease. It is also known as Anderson-Fabry Disease and Angiokeratoma Corporis Diffusum. There is an overall incidence of 1 in 117,000 with an incidence of 1 in 40,000 males.

## Clinical

Males with Fabry Disease have minimal, if any, alpha-galactosidase activity and can therefore expect to exhibit the full spectrum of disease manifestations. Females with one mutation have a significant risk for exhibiting clinical symptoms. Since females have a wider range of alpha-galactosidase activity, they have a more variable disease presentation. For both males and females, if symptoms are treated individually, the clinical presentation of Fabry Disease may be overlooked. With young patients exhibiting unexplained strokes, renal insufficiency and cardiomyopathy, it is important to look at all symptoms collectively to help recognize Fabry Disease.

Fabry Disease begins to manifest in childhood with acroparesthesia, hypohidrosis, and angiokeratomas in both males and females. Acroparesthesia can be brought on by exposure to extreme temperatures, exercise, and fevers; episodes can last from hours to days. Renal function is greatly diminished by GL-3 accumulation in the endothelium with renal insufficiency being observed in adolescence. Frequent episodes of diarrhea and abdominal pain are common. Proteinuria is found in males and females and is often an indicator of Fabry Disease in older undiagnosed females. Cerebrovascular events, specifically cryptogenic strokes, occur in the 2nd and 3rd decade. The rate of strokes in patients with Fabry Disease is as high as 24%. Young patients, especially males, who present with a stroke should be evaluated for Fabry Disease. Cardiovascular symptoms result from changes in angioarchitecture due to abnormally functioning endothelial cells. Left ventricular hypertrophy is seen in older patients with undiagnosed Fabry Disease. Corneal clouding is seen, but vision is not affected. Intellect is also not affected by Fabry Disease. Secondary symptoms include vertigo, seizures, hearing loss, and asymmetrical lymphedema in the lower extremities.

Milder forms of Fabry Disease have a later-onset of symptoms. They are more cardiac-focused and have atypical presentations of clinical symptoms. Like-wise, patients with residual enzyme activity have a delayed onset of symptoms, and usually only 1-2 organs are involved, therefore it may be harder to recognize the disease.

## Testing

Fabry Disease is diagnosed through enzyme assay of plasma, serum or leukocytes. Urinalysis and skin biopsies are also useful in detecting excess lipids in cells. Classic Fabry Disease has an enzyme activity level of <1%. Enzyme analysis is the recommended method for diagnosing Fabry Disease in males, but it is not conclusive for diagnosing females as they can have residual enzyme activity that may inappropriately define them as unaffected carriers. Therefore, gene mutation analysis is crucial in reliably diagnosing asymptomatic females. Due to the significant morbidity and mortality in females as well as males, it is important to not overlook heterozygous females. Females who are asymptomatic should be evaluated regularly for early indication of disease manifestation.

Prenatal diagnosis is available through amniotic fluid and CVS enzyme analysis. It is important to determine the fetus's gender in order to accurately analyze enzyme activity results.

When a patient is diagnosed with Fabry Disease, it is important to test other family members, especially females. There is a concern that not all heterozygous females affected with Fabry disease will be detected through newborn screening due to residual alpha-galactosidase activity levels.

## Treatment

Enzyme replacement therapy (ERT) has proven to be beneficial in treating Fabry Disease. It improves renal, cardiac and cerebrovascular function and decreases the rate of disease progression in these organs. ERT is available in two forms: agalsidase-alpha (Replagal) and agalsidase-beta (Fabrazyme). It is important to administer ERT soon after diagnosis so as to prevent irreversible organ damage. When left untreated, patients succumb to renal or cardiac failure or a cerebrovascular event by the 4th or 5th decade. Kidney transplant and dialysis have been shown to extend the lifespan into the 5th- 6th decade, especially when the patient is also receiving ERT. The transplanted kidney is not adversely affected by Fabry Disease as it is able to produce its own alpha-galactosidase to metabolize GL-3. However, this transplant does not alter the overall course of Fabry Disease in other organ systems, thus the need for ERT. The long term prognosis in Fabry Disease is promising when treatment includes renal transplant/hemodialysis and ERT.

Due to multi-system involvement, a multidisciplinary medical team that includes a metabolic geneticist who specializes in lysosomal storage disorders is necessary for long term care and treatment of patients with Fabry Disease. The Fabry Board of Advisors has established an assessment and evaluation schedule for patients with Fabry Disease to help detect future manifestations. See guidelines in reference section below.

## Inheritance

There are over 370 different mutations associated with Fabry Disease (chromosome Xq22.1) which makes genotype/phenotype correlations difficult to determine. Interfamilial variation is seen. Fabry Disease was previously considered to be a recessive X-linked disorder; however, it has been found that many heterozygous females do experience significant, life-threatening manifestations of Fabry Disease at a rate much higher than expected when considering Lyonization. Therefore, an unaffected female carrier is the exception with this disease.

X-linked disorders are inherited on the X chromosome. This means that affected men cannot pass a Fabry gene on to their sons, but will pass a Fabry gene on to their daughters. Women who have one Fabry gene (heterozygous) have a 50% chance of passing that affected gene on to their children (male or female). Women who are homozygous for Fabry Disease pass an affected gene to all of their children; all sons will be affected and daughters will be at risk for disease manifestations.

Genetic counseling is vital in determining other family members who may be at risk for having Fabry Disease, especially asymptomatic females.

## References

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