Review Article

FABRY DISEASE: A DISORDER OF CHILDHOOD ONSET[1]

Schiffmann R, Ries M. *Pediatric Neurology* 2016;64:10-20.

Fabry disease is a congenital disorder with evidence of glycosphingolipid accumulation at birth or very early in life.[1] The X-linked disorder results in insufficient activity of the enzyme α-galactosidase, which catalyses the hydrolytic cleavage of the terminal molecule of galactose from globotriaosylceramide (GL-3).[1] It is a progressive disease with a decreased life expectancy.[1]

Incidence is about 1 in 117 000 live births for males, although recent newborn screening surveys suggest that the incidence may be much higher, up to 1 in 3100.[1]

Various at-risk populations exhibit a higher incidence of Fabry disease than the general population:[1]

- Young patients with stroke
- Patients with hypertrophic cardiomyopathy of unknown cause
- Patients with chronic kidney disease
- Patients with common heart disease
- Paediatric patients with pain

The disease manifestations may start in children as young as 4 years of age and include episodes of extremity pain, fever of unknown origin, and hypohidrosis that often lead to decreased exercise tolerance.[1] Table 1 describes the key symptoms and findings of Fabry disease stratified by age.[1]

TABLE 1.

Key Symptoms and Findings of Fabry Disease Stratified by Age

Finding	Childhood	Adolescence	Adulthood
Neuropathic pain	+	+	+
Cornea verticillata	+	+	+
Abdominal pain, recurrent diarrhoea, and constipation	+	+	+
Angiokeratoma	(+)	+	+
Electrocardiogram abnormalities	-	+	+
Sensorineural hearing loss	-	(+)	+
Proteinuria	-	(+)	+
End-stage renal disease	-	-	+
Cardiomyopathy	-	-	+
Cerebral white matter lesions	-	-	+
Strokes	-	(+)	+

Please note that females can develop any of the complications that are seen in males.
In general, the clinical abnormalities are more variable, less severe, and of later onset compared to males with similar *GLA* mutations.
+ Present, - Absent, (+) occasionally present or absent.

The significance of Fabry disease lies in the increased risk of developing complications, such as:[1]

- A progressive renal insufficiency
- A variety of cardiac abnormalities
- A propensity for cerebrovascular stroke

These complications may initially present in the second decade of life, but more commonly in the third to fifth decade, resulting in decreased life expectancy.[1] Median survival is 50 to 55 years for men and 70 years for women.[1]

Clinical manifestations

Pain	Neuropathic pain (often referred to as acroparaesthesia) often begins in childhood and is present in the vast majority of patients. It reaches its highest severity in the 3rd and 4th decades of life.[1]
Kidney dysfunction	Often associated with progressive proteinuria (may be observed early in 2nd decade of life) and with a decline in glomerular filtration rate.[1]
Heart disease	Electrocardiogram is abnormal in most adults with Fabry disease, and echography combined with a Doppler heart study is helpful in characterising cardiac abnormalities of Fabry disease.[1] Progressive bradycardia and decreased exercise capacity are very common.[1]
Cerebrovascular stroke	It is estimated that, depending on the age-range cohort, patients with Fabry have a 5.5- to 12.2-fold increased risk of stroke compared to the general population.[1] Stroke may occur at any age, including children.[1]

Fabry disease variants

- Besides the classic form of the disease, patients with significant residual α-galactosidase A activity (up to 25 % to 30 % of normal values) often have a later onset, less severe form of the disease.[1]
- Often only one organ, most often the heart, is affected, which makes the diagnosis of Fabry disease particularly difficult.[1]

The expression of the disease in female patients depends on the particular α-galactosidase A gene (*GLA*) mutation and especially on the pattern of X chromosome inactivation in each organ.[1]

A presumed diagnosis of Fabry disease must be confirmed by the finding of low α-galactosidase A activity.[1]

Fabry disease is a genetic risk factor for a myriad of clinical organ complications.[1]

Enzyme Replacement Therapy (ERT) is the first specific therapy for Fabry disease.[1]

Disease management

Two forms of recombinant α-galactosidase A for ERT are currently available.[1]

Both forms of the enzyme usually are administered every two weeks.[1] Accumulating evidence suggests that:

- **ERT slows the decline of renal glomerular function.[1]** It may be particularly effective if initiated before kidney reserve is exhausted and glomerular filtration rate becomes significantly decreased.[1]
- **Neuropathic pain seems to decrease** over time, but is often not completely eliminated and patients commonly need to continue with their pain medication, albeit at a lower dose.[1]
- **ERT showed reduction in left ventricular mass** in some open-label studies, but not in others.[1]
- **ERT does not reduce the risk of stroke.[1]**

Reference: 1. Schiffmann R, Ries M. Fabry Disease: A disorder of childhood onset. *Pediatric Neurology* 2016;64:10-20.

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