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Topical Review

Fabry Disease: A Disorder of Childhood Onset

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ABSTRACT

BACKGROUND: Fabry disease, an X-linked disorder of glycosphingolipids, markedly increases the risk of systemic vasculopathy, ischemic stroke, small-fiber peripheral neuropathy, cardiac dysfunction, and chronic kidney disease. **METHODS:** We performed an extensive PubMed search on the topic of Fabry disease and drew from our cumulative 43 years of experience. **RESULTS:** Most of these complications are nonspecific in nature and clinically indistinguishable from similar abnormalities that occur in the context of more common disorders in the general population. This disease is caused by variants of the *GLA* gene, and its incidence may have been underestimated. However, one must also guard against overdiagnosis of Fabry disease and unjustified enzyme replacement therapy, because some of the gene variants are benign. Specific therapy for Fabry disease has been developed in the last few years, but its clinical effect has been modest. Novel therapeutic agents are being developed. Standard "nonspecific" medical and surgical therapy is necessary and effective in slowing deterioration or compensating for organ failure in patients with Fabry disease. **CONCLUSIONS:** Fabry disease is a treatable and modifiable genetic risk factor for a myriad of clinical organ complications. Fabry disease may be frequently overlooked but on occasion overdiagnosed.

Keywords: angiokeratoma, stroke, heart disease, genetic disease, sphingolipids, X-linked

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History and etiology

Dermatologists Johannes Fabry and William Anderson first described "angiokeratoma corporis diffusum" in 1898.[1,2] It was recognized early as a systemic vascular disease and later as a storage disorder[3] of lipids.[4] The accumulation of the glycolipids ceramide trihexoside (now called globotriaosylceramide [Gb_3 or GL-3]) and galabiosylceramide in a variety of different cell types was identified in 1963.[5] In addition, blood group antigens B, B1, and P1 also increase in certain individuals. The defect was established several years later as insufficient activity of the enzyme ceramidetrihexosidase which catalyzes the hydrolytic cleavage of the terminal molecule of galactose from Gb_3.[6] The anomeric specificity of ceramidetrihexosidase (α-galactosidase A) was determined in 1970.[7] The X-linked nature of the disease was first recognized in 1965.[8] The gene was cloned and sequenced in the mid-1980s.[9]

The disease incidence is about 1 in 117,000 live births for males,[10] although recent newborn screening surveys suggest that the incidence may be much higher, up to 1 in 3100.[11,12] In Taiwan, the incidence of the relatively mild IVS4+919G>A mutation is 1 in 875 male live births and 1 in 399 female live births.[13] Because of this recently discovered high incidence at birth, the nonspecific nature of the complications of Fabry disease, and the common occurrence of single complications, it is likely that many undiagnosed patients exist. Various at-risk populations exhibit a higher incidence of Fabry disease than the general population. Among those are young patients with stroke,[14] hypertrophic cardiomyopathy of unknown cause,[15] patients with chronic kidney disease,[16] and possibly even patients with common heart disease[17] or pediatric patients with pain.[18] Furthermore, the presence of equal numbers of females and males in large series suggests that up to 50% of the

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females with Fabry disease may be asymptomatic or are not identified.[19] *GLA* polymorphisms can modulate the expression of α-galactosidase A and play a role when other abnormalities are present in the same gene.[20] However, in some individuals with Fabry, related clinical manifestations have been wrongly attributed to benign *GLA* variants.[21,22]

Molecular basis or pathophysiology

The α-galactosidase A gene (*GLA*; MIM No. 300644) is located on Xq22.1.[23] It is 12-kb long with seven exons. *GLA* encodes for 429 amino acid precursor proteins that is processed to 370 amino acid glycoproteins functioning as a homodimer.[24] Based on The Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff (http://www.hgmd.cf.ac.uk/ac/index.php), there are currently 649 variants described. These include missense and/or nonsense type mutations, small and large deletions, splice defects, small insertions, complex rearrangements, and one large insertion. The cause of this large number of different mutations in the *GLA* gene is not known. One might speculate that having the Fabry trait presents a selective advantage such as resistance to certain types of bacterial infections, in particular those that express the Escherichia coli Shiga-like toxin verotoxin.[25] Patients with the classic, most severe form of Fabry disease almost always have a mutation that causes a total absence of α-galactosidase A activity, whereas patients with missense mutations often have some residual enzyme activity ranging from 2% to 25%.[26]

Clinical manifestations

Fabry disease may present at any age, in children and in adults (Table 1).[27,28] It is a progressive disease with a decreased life expectancy. Median survival is 50 to 55 years for men and 70 years for women.[29]

TABLE 1.
Key Symptoms and Findings of Fabry Disease Stratified by Age

Finding	Childhood	Adolescence	Adulthood
Neuropathic pain	+	+	+
Cornea verticillata	+	+	+
Abdominal pain, recurrent diarrhea, 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.

Patients with the classic form of the disease (males with no residual α-galactosidase A activity) have typical mild dysmorphic abnormalities, particularly in the face. These dysmorphisms have been described quantitatively and in detail[30] and include periorbital fullness, prominent lobules of the ears, bushy eyebrows, recessed forehead, pronounced nasal angle, generous nose or bulbous nasal tip, prominent supraorbital ridges, shallow midface, full lips, prominent nasal bridge, broad alar base, coarse features, posteriorly rotated ears, and prognathism. Other abnormalities including those of the extremities have been identified.[30] Fabry disease may be considered a congenital disorder with evidence of glycosphingolipid accumulation at birth or very early in life.[31] The disease manifestations may start in children as young as four years of age and include episodes of extremity pain, fever of unknown origin, and hypohidrosis that often lead to decreased exercise tolerance.[27] Episodic diarrhea and abdominal pain are common, often associated with fatty foods.[32] These symptoms often reduce quality of life and school attendance in children but because of their relatively nonspecific nature usually do not lead to correct diagnosis in the absence of family history.[27] More specific disease manifestations that are usually present in late adolescence are typical vascular skin lesions termed angiokeratoma (Fig 1) and asymptomatic corneal opacities, cornea verticillata (Fig 2).[33,34] These symptoms may lead to diagnosis by alert dermatologists or ophthalmologists. However, the significance of Fabry disease lies in the increased risk of developing a progressive renal insufficiency, a variety of cardiac abnormalities, and 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.[35-37]

Small fiber neuropathy

The neuropathic pain (often referred to as acroparesthesia) is thought to be due to a length-dependent small fiber neuropathy.[38] It often begins in childhood and is present in the vast majority of patients.[39] It reaches its highest severity in the third and fourth decades of life and

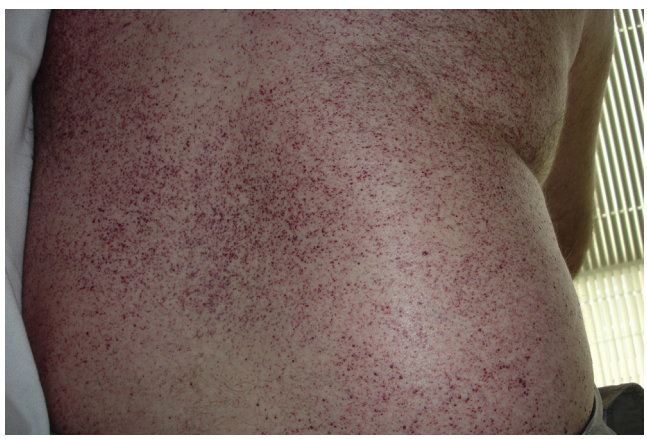

FIGURE 1.
Angiokeratoma on the back of a male patient. (The color version of this figure is available in the online edition.)