

# Fabry's Disease in a Female, Still an Under-Recognised Disease

## Abstract:

Sir

A nine-year-old girl presented with an asymptomatic eruption on her right leg which had been present for 2 years. She complained of severe acral pain and paraesthesiae for several years, despite treatment with numerous analgesics, amitriptyline, gabapentin and carbamazepine. On occasion she had been confined to a wheelchair and required home schooling. On examination she had a unilateral eruption affecting her right thigh and lower leg (Figure 1). On closer view, there were erythematous, hyperkeratotic and haemorrhagic papules. Histopathological examination of a skin biopsy showed hyperkeratosis and dilated blood vessels in the dermis consistent with angiokeratomas. Electron microscopy demonstrated intralysosomal glycolipid deposits, arranged in a lamellar fashion, within the endothelial cells lining dermal blood vessels (Figure 2).

Further investigations showed a normal lysosomal enzyme screen. Her  $\alpha$ -galactosidase A enzyme level was at the lower limit of normal at 3.1 U (reference range 3.0  $\pm$  12 U). Globotriaosylceramide to sphingomyelin urinary sediment ratio was raised at 0.08 (normal < 0.03). DNA mutation analysis showed a point mutation at position 514 of thymine for cytosine. This mutation is heterozygous for Fabry's disease. Ophthalmology examination revealed corneal verticillata and tortuous retinal vessels  $\hat{a}$  features highly suggestive of Fabry's disease. A whorled corneal opacity was also seen, which is an associated finding. Our patient was commenced on enzyme replacement therapy with marked reduction in her pain and significant improvement in her quality of life.

Figure 1: There was an eruption on the posterior aspect of the right thigh extending distally in a serpiginous pattern. Topical anaesthetic under occlusion is visible on the right thigh at the biopsy site.

Figure 2: This electron microscopy picture reveals the intralysosomal glycolipid deposits.

Fabry's disease is a rare, x-linked lysosomal storage disorder caused by deficiency or absence of  $\alpha$ -galactosidase A. This results in the accumulation of globotriaosylceramide in the lysosomes of pericytes, smooth muscle cells and endothelial cells resulting in multi-organ involvement. Recent data demonstrates a high incidence of affected females. Presentation varies widely due to x-linked mosaicism. Females usually present at a later stage than males, however, also often develop symptoms in childhood. <sup>2</sup> Neurological, gastrointestinal, ophthalmological and dermatological manifestations are common. Angiokeratomas are the characteristic cutaneous manifestation. Angiokeratoma corporis diffusum is the typical association. Cherry angiomas and telangiectasia also occur. Sweating abnormalities are common.

Females with Fabry's disease may develop serious manifestations including cerebrovascular events, renal failure and valvular heart disease. Without enzyme replacement therapy, there is an average reduced life expectancy of 15 years in females and 20 years in males. As females can have normal levels of  $\alpha$ -galactosidase A, the diagnosis depends on using molecular studies to demonstrate a specific family mutation on Xq221 encoding  $\alpha$ -galactosidase A gene. More than 300 mutations have been identified; most are missense or nonsense mutations. Enzyme replacement therapy is of benefit in stabilising renal function, reducing heart size, reducing pain and improving quality of life. <sup>4</sup> It is expected to reduce mortality but this data is not available yet. Agalsidase alpha and beta are both licensed for use. In conclusion, our patient was a young female with typical features of Fabry's disease, yet despite this her diagnosis was delayed. She required chromosomal analysis to confirm the diagnosis. Treatment with enzyme replacement therapy can significantly reduce symptoms as in our patient, and may reduce long-term sequelae and improve life expectancy.

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