Clinical Case Report

Fabry disease: A treatable lysosomal storage disorder

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ABSTRACT

Fabry disease is a lysosomal storage disease with an X-linked inheritance pattern, which presents in childhood as acroparaesthesias. Its non-specific symptoms often lead to delays in the diagnosis. We report the case of a 13-year-old boy who presented with typical acroparaesthesia of Fabry disease, his younger brother had gastrointestinal manifestations of the disease and their mother's symptoms suggested that she is a carrier. Enzyme replacement therapy helped in ameliorating the patient's symptoms and preventing complications such as renal failure, stroke and cardiovascular disorders.

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INTRODUCTION

Fabry disease is an under-recognized, X-linked lysosomal storage disease. The disease is pan-ethnic, and the incidence is around 1 in 50 000 males.[1] It results from deficient activity of the enzyme a-galactosidase (a-Gal A) and progressive lysosomal deposition of globotriaosylceramide (GL-3) in cells throughout the body. The various synonyms used for this disorder are a-galactosidase A deficiency, ceramide trihexosidase deficiency, GLA deficiency, Anderson–Fabry disease, angiokeratoma corporis diffusum, angiokeratoma diffuse and hereditary dystopic lipidosis.

The classical form occurs in males with minimal (<1%) or undetectable a-Gal A activity. It has its onset in childhood with periodic crises of severe pain in the extremities (acroparaesthesias). The other features include vascular cutaneous lesions (angiokeratomas), hypohidrosis, characteristic corneal and lenticular opacities and proteinuria. Untreated the disease causes gradual deterioration of renal function to end-stage renal disease, which usually occurs in the third to fifth decade of life. Cardiovascular and cerebrovascular diseases are other major causes of morbidity and mortality.

Males with >1% a-Gal A activity have a cardiac or renal variant phenotype. They generally present later in life. GLA is the only gene currently known to be associated with Fabry disease. Enzyme replacement therapy (ERT) using recombinant human a-Gal A has a favourable safety profile and is effective in continuously decreasing plasma GL-3 levels, sustaining endothelial GL-3 clearance and preventing organ damage. We present the case of a boy with Fabry disease whose mother and younger sibling also had some manifestations of the disease.

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THE CASE

A 13-year-old boy was referred to our department with complaints of long standing severe pain of unknown cause involving the lower extremities. He was asymptomatic till about 6 years of age, when he started complaining of burning sensation in the soles of both feet. Gradually, over the next 1–2 years it was accompanied by pain in the great toes. The symptoms were intermittent and not associated with any swelling or increased local temperature. At about 10 years of age the symptoms increased in frequency and intensity, especially during the summer months. He also started having fever, without any identifiable cause. During this period he received several courses of non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics. Over the next 2 years, the pain became unbearable, and NSAIDs were ineffective in controlling pain. He had some relief of pain with the use of carbamazepine. He could not attend school on most days due to unbearable pain and uncontrolled fever. These painful episodes increased during the summer months. Investigations for infective causes of fever and all known inflammatory causes of pain were inconclusive. The thyroid profile, serum uric acid and serum creatinine were normal. Tests for anti-nuclear antibody and rheumatoid factor were negative. The patient had been referred to the clinical immunology department but results of his clinical and laboratory examinations did not fulfil the criteria for juvenile rheumatoid arthritis.

On examination, he was a normal-looking child with a troubled look on his face and minimal coarsening of facial features. He was born to non-consanguineous parents with no family history of a similar disorder in either parent's family. He was the second of four siblings. The older sister and two younger brothers were apparently normal. His growth parameters and blood pressure were within normal limits. The physical examination was unremarkable. He did not have angiokeratomas and the electrocardiogram was normal. Urine examination showed albuminuria on two occasions. Slit-lamp examination revealed corneal deposits. On enzyme assay, his a-galactosidase activity was very low: 0.1 μ/L/hour (normal 2.0–14.6 μ/L/hour).

The mutation analysis done from the patient's genomic DNA detected the mutation in the a-Gal A gene. The nonsense mutation, W236X confirmed Fabry disease in this boy.

On the basis of the clinical symptoms and enzyme assay, ERT with agalsidase beta was started before the report of mutation analysis was available. A dose of 1 mg/kg i.v. was given once in 2 weeks. The boy reported a decrease in pain after 4–6 months. He has been receiving ERT for about 2 years and is on regular follow up. He attends school regularly and has a sense of well-being. He takes fewer carbamazepine tablets, feels comfortable and is free of pain. A review of the family history showed that his mother (45 years of age) had corneal deposits and proteinuria. Recently, his 12-year-old younger sibling presented to our outpatient department with a history of frequent diarrhoea and failure to gain weight for the past 5–6 years. The a-galactosidase activity in the leucocytes of the mother was 8.6 nmoles/hour/mg

(normal 13–67 nmoles/hour/mg) and that of his younger sibling was 0.02 nmoles/hour/mg. The proband in this family presented with typical acroparaesthesia of Fabry disease, whereas the mother seems to be a manifesting carrier and the younger brother has the gastrointestinal form of Fabry disease.

DISCUSSION

The diagnosis of Fabry disease among children is difficult in the absence of a family history. The average age at diagnosis is 29 years[2,3] and the average duration of onset of symptoms and diagnosis is around 10.8 years in adult males. In our patient, the age at diagnosis was 13 years; the total duration of disease from appearance of symptoms to diagnosis was about 7 years.

Non-specific symptoms and a lack of physical findings often lead to delays in the diagnosis of Fabry disease. The neuralgic pain is misdiagnosed as gout or other rheumatological disorder and at times as malingering. Many patients, such as ours, do not have classical angiokeratomas (Fig. 1); and isolated renal, cardiac or cerebrovascular symptoms manifest in some patients. Limited awareness of the disease and lack of easy availability of enzyme assay also contribute to the delay in diagnosis.

Though no Indian data are available, a large neonatal survey suggested that the late onset phenotype is more frequent (1 in 4000).[4] Fabry disease accounts for about 1% of end-stage renal disease,[5] 6.3% of late onset hypertrophic cardiomyopathy[6] and 4.9% in males and 2.4% in females of cryptogenic stroke.[7] The life expectancy is decreased due to the involvement of the heart, kidneys and cerebral vasculature, and most patients die in the fourth or fifth decade of life; the average lifespan in untreated cases is about 40 years.

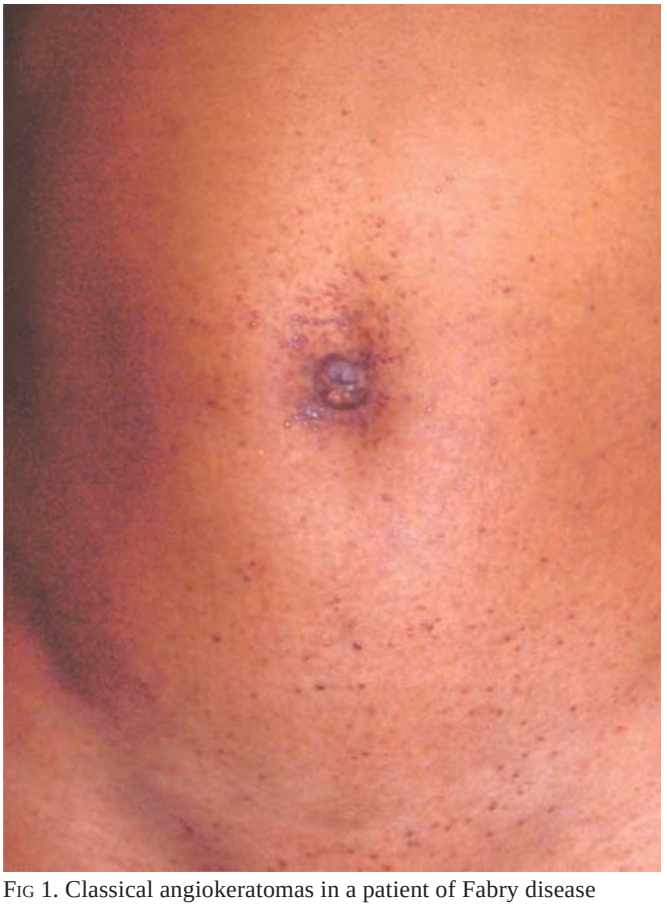

FIG 1. Classical angiokeratomas in a patient of Fabry disease

Enzyme replacement therapy has been available in Europe since 2001 and in the USA since 2003. ERT removes the enzyme GL-3 from the vascular endothelium and other cells, thus reducing the progression of organ involvement.[8] Moreover, ERT for 1 year has been shown to improve pain and quality-of-life scores.[9] The 2001 report of the 'Fabry Registry' estimates that globally there are more than 1200 patients on ERT.

Two enzyme preparations using recombinant human a-Gal A have been subjected to clinical trials: Fabrazyme (agalsidase beta; Genzyme Corp) and replagal (agalsidase alpha; Transkaryotic Therapies, Inc). The clinical trials of the two drugs were carried out at different doses. Comparative studies have shown that the two drugs are equally effective.[10,11]

As ERT is now available, it is important to suspect the disease in appropriate clinical situations such as when patients have limb paraesthesias, episodic limb pain, angiokeratomas, a corneal opacity not affecting vision, hypohidrosis, unexplained fever, mild proteinuria and gastrointestinal symptoms. It is also important to investigate for Fabry disease in patients with unexplained renal problems, cardiac problems (idiopathic left ventricular hypertrophy and late onset hypertrophic cardio-myopathy) and stroke as well as asymptomatic relatives of a diagnosed case. Though Fabry disease is considered to be a male disease, women also need to be investigated; the prevalence of symptoms is high among women,[12,13] and 30% of carrier women have debilitating compli-cations of the disease.[14] Prenatal diagnosis can be offered by mutation analysis or enzyme assay on chorionic villous sample.[15] We hope that our experience of finding multiple affected family members with different forms of Fabry disease will help in increasing awareness about the disease and its manifestations.

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