Fabry Disease in an Oligosymptomatic Male

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In Fabry disease, a common lysosomal storage disease, deficiency of the lysosomal enzyme α-galactosidase A results in progressive deposition of glycosphingolipids, predominantly globotriaosylceramide, in renal glomerular and tubular epithelial cells, myocardial cells, heart valve fibrocytes, neurons of dorsal root ganglia, and in endothelial smooth cells of blood vessels [1]. Fabry disease has multisystemic involvement with considerable phenotypic variability because of molecular heterogeneity and many private mutations. Since the gene is encoded on the X-chromosome there is often differential severity according to gender.

PATIENT DESCRIPTION

On routine testing, microalbuminuria was found in a 26 year old man of Iraqi/Yemenite descent; 24-hour urine collection showed 750 mg protein/24 hours. Anamnesis revealed that during childhood he occasionally had acroparesthesia; there were no other medical complaints. He served for 3 years (compulsory conscription) in a commando combat unit. There was no family history of neuronopathic pain, renal disease, cardiac disease or stroke.

Physical examination was normal: his weight was 72 kg and his height 173 cm; there were no angiokeratomas. Laboratory results included hemoglobin 14.3 g/dl, mean corpuscular volume 88 fl (normal 82–100 fl), ferritin 120 ng/ml (normal 20–220 ng/ml); liver function tests were normal, total protein 6.9 g/dl (normal 6–8 g/dl), albumin 4.8 g/dl (normal 4.5–5.5 g/dl), creatinine 0.9 (normal < 1.2), creatinine clearance 120 ml/min/24 hours (normal > 90 ml/min/24 hours), total urinary protein 750 mg/24 hours (normal < 500 mg/24 hours) on repeat testing. Antinuclear factor, rheumatoid factor, antineutrophil cytoplasmic antibodies, and sedimentation rate were within normal limits. Cardiac echocardiography, brain computed tomography and audiogram were normal.

Renal ultrasound was normal and proteinuria due to orthostatic hypotension was ruled out. Because of unexplained proteinuria, a kidney biopsy was eventually performed revealing diffuse intracytoplasmic glycosphingolipid accumulation in podocytes and epithelial cells of distal tubules, which were enlarged and vacuolated. Electron microscopy showed osmiophilic inclusion bodies in the cytoplasm of all renal cells ('onion skin' or 'zebra' appearance) suggestive of Fabry disease. Plasma and leukocytes assay for α-galactosidase A confirmed low enzyme activity (< 1% control); DNA sequencing identified the mutation R310X [2] in exon 6, which was not found in either parent.

Intravenous enzyme replacement therapy was initiated with agalsidase alfa [3] (0.2 mg/kg every other week) with no adverse effects or allergic reactions. Repeat urinary protein/24 hours after 8 months of the treatment was 400 mg/24 hours.

COMMENT

Fabry disease is difficult to diagnose in young patients with no family history, and a significant lag in diagnosis is common. In young children with Fabry disease, acroparesthesia and mild albuminuria, glomerular endothelial cell deposits and arteriopathy are associated with progressive renal disease [4].

It has been our position [5] that although one classically thinks of cardiac or renal 'variants' to describe the onset and trajectory of Fabry disease, it is possible that cardiac pathology is a harbinger of progression of visceral Fabry disease (since it is seen in boys and girls as they grow into adolescence) well before the devastating effects of renal pathology and early-onset stroke. It is our hypothesis that left ventricular cardiac hypertrophy [1] is the actual index of disease onset. In the patient presented here, and as distinct from many boys, presentation did not include a cardiac component and the renal presentation was circumscribed to mild proteinuria without other classic signs and symptoms of Fabry disease.

We believe that the index of suspicion for Fabry disease should be raised among general medical practitioners in Israel. The 'diagnostic odyssey' of patients with Fabry disease is infamous even in countries where more patients have been identified. In Israel we have identified only a few score of patients when theoretically ten times as many are expected based on disease estimates of 1:5000 to 1:30,000 [1].

The de novo mutation may be due to maternal germline mosaicism or spontaneous mutation, but knowing the mutation is helpful in predicting the untreated disease course or the response to enzyme replacement therapy.

Screening for Fabry disease based on family history and/or advanced cardiac and/or renal disease is available in some countries. Especially in cases of

unexplained left ventricular hypertrophy, early-onset cerebrovascular events, acroparesthesia, angiokeratoma, and/or proteinuria, absence of a family history of Fabry disease should not discourage further investigation since early initiation of enzyme replacement therapy may halt or slow disease progression and possibly delay involvement of other organ systems.

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