The Interesting Case

Isolated glomerular proteinuria as the only clinical manifestation of Fabry’s disease in an adult male

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Introduction

The clinical manifestations of Fabry’s disease are the consequence of the multiorgan alterations produced by progressive deposition of neutral glycosphingolipids in different tissues [1]. Fabry’s disease is an X-linked recessive inherited disorder of glycosphingolipid metabolism caused by deficient tissue activity of the enzyme alpha-galactosidase A [2].

Hemizygous males are severely affected whereas heterozygous females may be asymptomatic, or have a slight clinical form. Rarely, heterozygous females may be affected similarly to hemizygous males [2].

The defect in the lysosomal hydrolase alpha-galactosidase A leads to the progressive accumulation, within the lysosomes of cells in most visceral tissues, of specific neutral glycosphingolipids characterized by terminal alpha-galactose moieties, i.e. cerebrosidetrihexoside and cerebroside trihexoside.

The onset of clinical manifestations of Fabry disease in hemizygous males usually occurs as early as childhood or adolescence. Vascular cutaneous lesions, crises of severe pain in the extremities, acral paraesthesia, testicular involvement, jejunal diverticulosis, juvenile coronary disease, corneal dystrophy, hypohidrosis, fever, leg oedema without hypoalbuminaemia, and renal impairment have been reported [3–10].

Affected males usually show three clinical phases. The first occurs in childhood and adolescence and is distinguished by myalgia, acroparaesthesia, arthralgia, cutaneous angiokeratomas, corneal opacities, and fever. The second phase is characterized by renal involvement, and the third phase involves vascular, cardiac, and cerebral disease and renal functional deterioration.

Death occurs around the fifth decade from renal, cardiac, and cerebral complications. Nevertheless, clinical evidence supports phenotypic heterogeneity of Fabry’s disease, and genetic heterogeneity has been demonstrated as well [11]. The frequency of the clinically atypical cases has not been determined.

Ultrastructural demonstration of typical osmophilic cytoplasmic inclusions on biopsied tissue samples confirms diagnosis of Fabry’s disease [12], and deficiency of alpha-galactosidase A can be easily identified in peripheral leukocytes in the serum and in biopsy specimens of affected persons [13].

We report herein the unusual clinical case of a 23-year-old man with well-documented Fabry’s disease whose clinical manifestation of the disease only included isolated glomerular proteinuria.

Case report

The proband, 20-years-old, was admitted to the hospital because of isolated glomerular proteinuria, which was detected by chance. The patient’s father and four sisters were healthy, his mother was reported to have cysts in normal-sized kidneys; a maternal uncle died with renal failure and the maternal grandmother was ‘nephropathic’. Renal biopsy was performed, revealing the typical light-microscopic and ultrastructural features of Fabry’s disease; immunofluorescence was negative.

At 23 years of age the patient was re-evaluated. There was no history of acroparaesthesia, hypohidrosis and no angiokeratoma was observed on careful examination. The arterial blood pressure was normal. A careful search was performed to determine extra-renal involvement. An ophthalmological examination detected only slight right corneal opacities, and audiometry revealed a slight hypacusia in the left ear. Echocardiography revealed mild left ventricular hyper-
trophy and mild aortic, tricuspid, and pulmonary regurgitation.

Normal values were obtained for the laboratory studies except for urinalysis, which confirmed isolated glomerular proteinuria (150–230 mg/dl), with normal GFR and negative immunological tests. The ultrastructural study of the urinary sediment revealed lamellar electron-dense osmiophilic bodies inside the epithelial cells. The enzymatic activity of alpha-galactosidase A in the serum and in leukocytes was markedly reduced (leukocytes, 3.0 nmol/h/mg, NV 24–58; plasma, 0.18 nmol/h/mg, NV 2.1–10.9); urinary glycosphingolipids were significantly increased (5.5 mg/mg creat., NV 0.2–0.62); especially ceramide trihexoside (73%, NV 4.6–8.8).

The patient’s relatives were subsequently investigated and the sisters proved to be healthy, whereas the mother was found to have chronic renal failure and cardiac involvement. The determination of lysosomal alpha-galactosidase A and urinary glycolipids revealed values consistent with a carrier condition. An echocardiogram was indicative of infiltrative cardiomyopathy.

Discussion

The frequency of Fabry’s disease is estimated to be 1:40,000 individuals [2] and is transmitted by a gene encoding for alpha-galactosidase A localized on the long arm of the X chromosome in the region q21–q22 [14]. The renal involvement of hemizygous males is characterized by proteinuria in their 20s with gradual deterioration of renal function in the third and fourth decades of life, evolving to end-stage renal disease [15].

In our asymptomatic male patient, proteinuria was detected by chance. At 20 years of age he underwent kidney biopsy, showing the characteristic glomerular and tubular lesions of Fabry’s disease with light, immunofluorescence and electron-microscopic studies [12].

The diagnosis was confirmed by demonstrating alpha-galactosidase A deficiency in plasma and leukocytes and by the detection of increased urinary excretion of ceramide trihexoside in both proband and his mother.

The electron-microscopic evaluation of the urinary sediment of the patient showed typical lamellar electron-dense bodies within tubular epithelial cells (Figure 1).

It is well known that the clinical manifestations of Fabry’s disease are protean, but the clinical feature of our male patient does deserve some comments because he presents only isolated glomerular proteinuria with normal GFR; a slight form of ophthalmological involvement could be detected only by careful examination. There is evidence that phenotypic Fabry’s disease may be caused by several types of enzymatic defects. In fact, the precursor protein is synthesized and glycosylated within the rough endoplasmic reticulum of the cells and another glycosylation subsequently takes place in the Golgi apparatus and finally, after transport to lysosomes, the glycosylated peptide acts as a mature enzyme [2]. In pathological circumstances an unstable precursor is formed or there is no synthesis of the enzyme precursor at all. Another scenario includes the synthesis of a mutant precursor, followed by abnormal glycosylation, or a normal precursor is synthesized with the formation of a mutant enzyme protein [16–17].

The presence of several gene mutations in Fabry’s disease, including complete and partial deletions or duplications, point mutations, small insertions, which can variably affect the synthesis, stability and catalytic activity of the alpha-galactosidase A enzyme, supports the existence of different phenotypes of the disease.

The clinical findings of Fabry’s disease are the pathological and pathophysiological consequences of the progressive deposition of neutral glycosphingolipids in body tissues. Their accumulation occurs as a result of intracellular production, as well as LDL receptor-mediated endocytosis [18] and, obviously this deposition precedes symptoms and clinical signs.

We think that the young age of the patient herein described (23 years) may partially explain the oligosymptomatic form of Fabry’s disease. In fact the literature reports that the mean age at the time of
diagnosis is 29 years, and delays in diagnosis are frequent because of superficial evaluation of symptoms which tend to develop with age [19]. Nevertheless, we cannot exclude that the well-known variety of mutations in Fabry’s disease might result in the expression of different phenotypes. In our patient, an enzymatic activity could be detected in the serum, although at a very reduced level.

The diagnosis of Fabry’s disease could be overlooked and the disease may be more common than we believe. Moreover, the proteinuria is often non-nephrotic, which favours misinterpretation, and therefore careful evaluation is required. Molecular analysis of affected families should be performed to improve genetic knowledge, and to identify female carriers and prenatally at-risk males. Renal biopsy should be pursued in any patient with the combination of moderate proteinuria and familial history of renal disease, or ophthalmological, dermatological, cardiac or neurological alterations.

We agree with Desnick [20] that patients with renal failure of unknown aetiology should have plasma alpha-galactosidase A determinations for appropriate genetic diagnosis and counselling. In fact, a correct diagnosis in these cases has important socioeconomic implications (familial advice, genetic counselling), and possibly also therapeutic consequences (outcome after renal transplantation).

References