

Case Report

Coexistent of Fabry Disease and IgA Glomerulonephritis in a 39 Year Old Male

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ABSTRACT

Anderson-Fabry disease is a rare inherited X-linked lysosomal storage disease caused by deficiency of the enzyme alpha-galactosidase A. Hereby we report a 39 year old male that presented with proteinuria and edema. Histopathologic, immunofluorescence and ultrastructural examination of renal tissue were in favor of Fabry disease in associate with IgA nephropathy. Fabry's disease associated with IgA nephropathy apparently is extremely rare, and the present case is among few reported cases in literature.

Keywords: Fabry disease, IgA Glomerulonephritis, Iran

Introduction

Anderson-Fabry disease is a rare inherited X-linked lysosomal storage disease caused by deficiency of the enzyme alpha-galactosidase A. The deficiency of alpha-galactosidase activity leads to progressive, abnormal accumulation of neutral glycosphingolipids in the lysosome. With increasing age globotriaosylceramide (Gb3) progressively accumulates in different cells, tissues and organs throughout the body. Typically, the clinical onset of Anderson-Fabry disease occurs during childhood or adolescence, with early symptoms of neuropathic pain (recurrent episodes of severe pain in the extremities), angiokeratomas (characteristic cutaneous lesions), oedematous upper eyelids, peripheral vasospasm

and ophthalmological abnormalities. The disease progresses through adulthood and by the age of 30-40 years several major organ systems may be affected; cardiac disease, renal insufficiency, cerebrovascular attacks and neurologic findings are common (1).

The coexistence of Fabry disease and immune disorders such as systemic lupus erythematosus, rheumatoid arthritis and IgA nephropathy has been described in the literature (2). Fabry's disease associated with IgA nephropathy apparently is extremely rare (3). In Anderson-Fabry disease (AFd), the kidney is affected in all hemizygous males and in some heterozygous females (4).

Characteristic findings are noted on Electron Microscope (EM). The major findings are large numbers of "myelin figures" or "zebra bodies" within

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the cytoplasm of the podocytes, and to a variable extent, other renal cell types. These intracytoplasmic vacuoles consist of single membrane-bound dense bodies with a concentric onionskin appearance, or with a parallel arrangement of layers (5). Measurement of leukocyte enzyme levels is not sensitive and is not measurable in our country. The measurement of urinary ceramide digalactoside and trihexoside levels is used to identify the carrier state. Prenatal diagnosis can be made in amniotic fluid by measuring amniocyte enzyme levels (5). Fabry disease has not medically treatment but if it would be associated with IgA nephropathy and RPGN occurs; symptoms and signs of IgA nephropathy progression, creatinin raising and renal dysfunction require treatment with prednisolone. So importance of this report is stopping the process with IgA nephropathy treatment and proteinuria decrease that can result in glomerulosclerosis. The overall prevalence of Anderson-Fabry disease is 1/11700 or 1/40000 in (male) population (1).

Case Report

Reported case was a 39 y/o man who was a teacher came from Mazandaran Province, northern Iran and living in Noshahr. He was referred because of lower limb edema 3 years ago. In physical examination pitting edema of lower limb was detected but other examinations were normal and vital sings were stable. He had proteinuria about 3.5 gr in 24 hour urine in primary assessment so kidney biopsy was done. The result of light microscope was “ Focal Glomerulosclerosis in associate with extensive vacuolization of visceral epithelial cell cytoplasm; suggestive for Fabry’s disease “(Fig. 1).

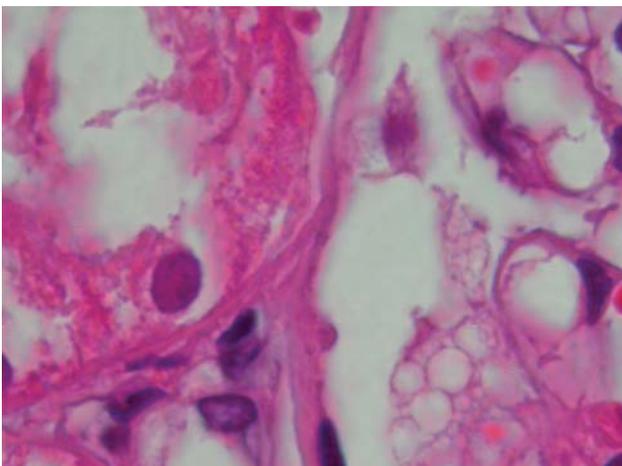


Fig. 1: Extensive vacuolization of visceral epithelial cell cytoplasm; suggestive for Fabry’s disease (H&E x400)

Immunofluorescence studies showed intense granular deposition of IgA limited to mesangial and paramesangial areas. Finally diagnosis of Fabry disease and IgA nephropathy was confirmed by electron microscopic study of renal tissue that showed numerous Zebra structures, mainly located in cytoplasm of podocytes in associate with mesangial and paramesangial electron dense deposits (Fig. 2). Patient was treated with enalapril, losartan and food diet that resulted in continuous increased proteinuria but renal function was normal. Sonographic assessment of kidneys bladder and prostate didn’t show any problem. FBS, BUN, Cr and complement level, ANA, Anti ds DNA and serum electrophoresis were normal too.

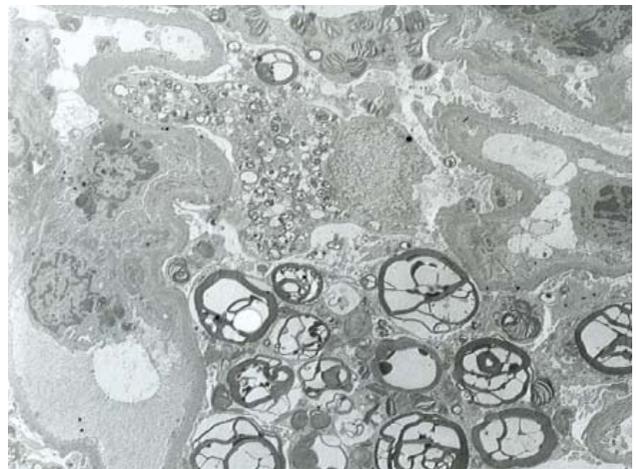


Fig. 2: Multiple zebra structures mainly located in visceral epithelial cell cytoplasm

After about 3 years later the patient showed a rising in creatinin and impairment in renal function including proteinuria (2000 mg), ↑Cr (800 mg) and ↑urea (1450 mg) in 24 hour urine. At this time he had normal FBS, TG, LDL, Alp and uric acid. The quantity of Cr and urea was 1.7 and 50, respectively. The patient was treated with pulse therapy of methylprednisolon and celecept with the suspicion of IgA nephropathy progression. Now he has Cr: 1.4 and urea: 40. In 24 hour urine examination, proteinuria is 650 mg and creatinin is 900 mg (urine volume: 1600 cc).

Discussion

Fabry disease (FD) is an X-linked disorder of glycosphingolipid catabolism that results from a deficiency of the lysosomal enzyme alpha-

galactosidase A. This defect leads to the accumulation of its substrates, mainly globotriaosylceramide, in lysosomes of cells of different tissues (2). Typically, the clinical onset of Anderson-Fabry disease occurs during childhood or adolescence, with early symptoms of neuropathic pain (recurrent episodes of severe pain in the extremities), angiokeratomas (characteristic cutaneous lesions), oedematous upper eyelids, peripheral vasospasm and ophthalmological abnormalities. The disease progresses through adulthood and by the age of 30-40 years several major organ systems may be affected; cardiac disease, renal insufficiency, cerebrovascular attacks and neurologic findings are common (1,5,6). The coexistence of Fabry disease and immune disorders such as systemic lupus erythematosus, rheumatoid arthritis and IgA nephropathy has been described in the literature (2). Fabry's disease associated with IgA nephropathy apparently is extremely rare (3). The patient's chief complaint was pitting edema in his lower limbs and there wasn't any associated disease in him. In this case kidney involvement in Fabry disease is more prevalent and heterogeneous than previously reported. Proteinuria is an early complication, but may not be overt in patients with advanced kidney disease (7).

The overall prevalence of Anderson-Fabry disease is 111700/ or 140000/ in (male) population (1). Different studies have shown the involvement of immunopathologies in different sphingolipidoses. The detection of a high level of autoantibodies must be correlated clinically to determine the existence of an underlying autoimmune disease (2). Immunofluorescence assessment of kidney biopsy in this patient showed IgA 3+. Characteristic findings are noted on EM. The major findings are large numbers of "myelin figures" or "zebra bodies" within the cytoplasm of the podocytes, and, to a variable extent, other renal cell types. These intracytoplasmic vacuoles consist of single membrane-bound dense bodies with a concentric onionskin appearance, or with a parallel arrangement of layers (5).

No safe and completely effective treatment is currently available. Enzyme replacement therapy is not practicable in our country at this time, but Fabry disease is an ideal candidate for the application of recombinant DNA technology (5,8,9). In the first stage, the patient was treated with enalapril,

losartan and food diet that resulted in continuous increased proteinuria. After creatinin rising, the patient treated with methylprednisolon pulse therapy and celecept with the suspicion of IgA nephropathy progression at the second stage that resulted in creatinin and proteinuria decrease. In one case report that was reported in 2007 In spite of very typical symptoms, delayed diagnosis was made: after the first investigation of alpha-galactosidase an activity in dry blood sample, diagnosis of Fabry's disease was rejected; only after lysosomal enzyme activity assay in heparinized blood leukocytes, this diagnosis was confirmed (10).

The disease prognosis is not good and by the age of 30-40 years several major organ systems may be affected (1,5). Death occurs usually secondary to renal, cardiac or cerebrovascular complications during the fourth or fifth decades of age (1). IgA nephropathy in FD is not merely coincidental (11). So the importance of performing the ultrastructural examination of the kidney biopsy is stressed, especially in heterozygous Fabry patients to evaluate the degree of renal involvement (4,12).

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