

Hemizygous Fabry disease associated with IgA nephropathy: A case report

Fabry disease and IgA nephropathy

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Abstract

We report on a 22-year-old male patient who shows both classical Fabry disease and IgA nephropathy. He had proteinuria (1.5g/day), hypohidrosis, and neuralgia with fever. Serum creatinine and blood urea nitrogen were 0.9 mg/dl and 11.4 mg/dl, respectively. Renal biopsy showed strikingly vacuolated podocytes and tubular epithelium cells. Myelin-like bodies were detected in podocytes, mesangial cells, endothelial cells, and tubular epithelium cells by electron microscopy. On immunofluorescence microscopy, IgA and C3 deposits were detected in mesangial areas. From these results and a markedly low level of α -galactosidase A activity, we diagnosed this patient with classical Fabry disease and IgA nephropathy.

Keywords: Fabry disease, IgA nephropathy

Introduction

Fabry disease is a rare lysosomal storage disorder caused by a deficiency of α -galactosidase A. The progressive accumulation of glycosphingolipids results in multiple organ insufficiency. One of the major clinical features is a renal manifestation, especially proteinuria and decreasing glomerular filtration rate. Because this disease is an X-linked disorder, heterozygous females show mild symptoms after lyonization of the abnormal X chromosome. On the other hand, IgA nephropathy is the most prevalent form of glomerulonephritis worldwide (1). Thus, the occurrence of Fabry heterozygous females with IgA nephropathy may be more frequent than predicted. But to our knowledge, there is no report of a hemizygous male with classical Fabry disease having IgA nephropathy. Here we report on a classical Fabry disease case in a hemizygous male patient that is coincident with IgA nephropathy.

Case report

A 22-year-old male was referred to our hospital because of chance proteinuria. He showed proteinuria (1.5g/day), slight hematuria, and had experienced hypohidrosis and neuralgia with fever since he was 12 years old. The blood pressure was 118/72 mmHg. There was no edema. Serum creatinine and blood urea nitrogen were 0.9 mg/dl and 11.4 mg/dl, respectively. Hemoglobin was 13.1 g/dl. Average creatinine clearance in three days was 121 ml/min. Immunoglobulin and complement levels were normal. His mother also showed proteinuria and neuralgia with fever, but she had received no previous assessment regarding her proteinuria.

A renal biopsy was performed to examine the reason for the proteinuria. Three needle biopsy cores, including six glomeruli were submitted. One glomerular collapse with hyalinosis was observed, and other glomeruli contained strikingly enlarged and vacuolated podocytes (Fig. 1a, b). Vacuolated changes were also observed in some tubular epithelium cells (Fig. 1a, b). Paramesangial deposits are shown stained with periodic acid methenamine silver (PAM) (Fig. 1b). On

immunofluorescence microscopy, IgA and C3 deposits were detected in mesangial areas (Fig. 1c, d). Myelin-like bodies were detected in podocytes, mesangial cells, endothelial cells, and tubular epithelium cells by electron microscopy (Fig. 1e). Moreover, paramesangial electron-dense deposits were also observed (Fig. 1e). From the above renal biopsy results and a markedly low level of α -galactosidase A activity (0.12 nmol/hr/ml <6.0~10.8 nmol/hr/ml>), we diagnosed this patient with Fabry disease and IgA nephropathy. After diagnosis, genetic study was performed (now in progress) and enzyme replacement therapy with recombinant α -galactosidase A (Fabrazyme 55mg by drip infusion once every 2 weeks), Temocapril 1 mg by oral administration and Dipyridamole 300 mg by oral administration were initiated. Recently, some reports show the importance of additional therapies with ACE inhibitors or angiotensin receptor blocker (2,3). In our case, we used ACE inhibitor. Since our patient's blood pressure was low, we could not use high dose ACE inhibitor. He now attends our hospital for therapy. Three months after enzyme replacement therapy, blood GL-3 levels were decreased from 16.2mg/ml to

6.5mg/ml that was within normal limits, but the amount of proteinuria and renal function showed no change.

Discussion

Fabry disease was described by Fabry and Anderson in 1898 (4). The frequency of this disease is about 1/40,000 to 1/60,000 in men (4), and the hemizygous males show more severe phenotype than heterozygous females. In this case report, we have demonstrated a classical hemizygous male case of Fabry disease with IgA nephropathy. The combination of classical Fabry disease and IgA nephropathy are very rare. But Recently, the involvements of immunopathologies in different sphingolipidoses have shown (5). Previously, three cases of the combination of Fabry disease and IgA nephropathy have been reported (6-8). Two of the three cases were heterozygous females. Kawamura *et al* reported on a 28-year-old male patient with both IgA nephropathy and Fabry disease (6). But this case was unusual, because the patient did not show any clinical manifestations apart from an abnormal urinalysis. To our knowledge, our case is the first report on IgA nephropathy in a hemizygous male with classical Fabry disease. Recently, Whybra *et al* reported on two adolescent sisters heterozygous for Fabry disease with

mesangioproliferative IgA nephropathy (9). In their report, the authors suggest that the combination of Fabry disease and IgA nephropathy is not merely coincidental. Furthermore, they described a correlation between aberrant glycosylation in the hinge region of IgA1 molecules and the production of circulating immune complexes (10). In our case, we could not observe the severe proliferation of mesangial cells in light microscopy, but dominant depositions of IgA in mesangial areas was seen in immunofluorescence microscopy. Aberrant glycosylation in the hinge region of IgA1 molecules is one of the pathogenesis of IgA nephropathy, but there is no definitive cause of aberrant glycosylation in the hinge region of IgA1. In our case, if we can observe the disappearance of IgA deposition in mesangial areas after enzyme replacement therapy, the glycosphingolipidosis occurred by Fabry disease seem to be one of the reason of aberrant glycosylation in the hinge region of IgA1 molecules.

Conflict of interest statement. none declared.

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Figure (a): Light microscopy of kidney biopsy sample. Vacuolated podocytes and tubular epithelium cells are observed (hematoxylin-eosin stain x400) (b): Paramesangial deposits are shown (periodic acid methenamine silver stain x400) (c), (d): Immunofluorescence of kidney biopsy sample. Deposits of IgA and C3 are shown in mesangial area. (e): Electron microscopy of kidney biopsy sample. Myelin-like bodies are present in podocytes [P], mesangial cells, endothelial cells [E], and tubular epithelium cells. Paramesangial electron-dense deposit are also observed in the mesangial area (arrow).

