Case Report

Coincidental finding of Fabry’s disease in a patient with IgA nephropathy

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Abstract

We present the case of a woman with IgA nephropathy and concomitant Fabry’s disease. She was referred to our hospital with proteinuria and haematuria. A renal biopsy showed findings indicating IgA nephropathy under light and immunofluorescence microscopy. Electron microscopy, however, showed laminated inclusion bodies characteristic of Fabry’s disease. The α-galactosidase activity in her serum was low, and the diagnosis of Fabry’s disease was confirmed by genetic analysis. Fabry’s disease in a patient with IgA nephropathy is a very rare occurrence, and Fabry’s disease diagnosed only by electron microscopy has not been previously reported.

Keywords: Fabry’s disease; heterozygous female; IgA nephropathy

Introduction

IgA nephropathy, first described by Berger and Hinglais in 1968 [1], is now one of the most common forms of primary glomerulonephritis. In most cases, it presents as the primary disease, but occasionally, it develops associated with another disease. Although Schönlein–Henoch purpura is the most frequently associated disease, there are a lot of other cases associated with liver disease, inflammatory bowel disease, carcinoma or psoriasis. Fabry’s disease (also known as Anderson–Fabry disease) is an X-linked recessive inborn error of glycosphingolipid metabolism caused by deficient activity of the lysosomal enzyme α-galactosidase A (α-Gal-A) [2]. The enzymatic defect in this disease results in a progressive systemic accumulation of glycosphingolipids. It leads to many clinical manifestations such as angioedema, acroparesthesia, hypohydrosis, renal failure and cardiovascular disease. Heterozygous females have variable levels of α-Gal-A activity, and clinical manifestations may range from asymptomatic to severe.

Here, we report an unusual case of IgA nephropathy with concomitant Fabry’s disease that was incidentally diagnosed by electron microscopy.

Case report

The patient had been healthy until she was 49 years old, when hypertension and proteinuria were detected. Her father died of lung cancer at the age of 82, and he had no renal or cardiovascular disease. Her mother has hypertension. The patient has one sister with a past history of paroxysmal atrial fibrillation and two healthy brothers. The patient was prescribed an angiotensin-converting enzyme inhibitor and a Ca blocker at another hospital when she was 52 years old; good control of blood pressure was then attained, but proteinuria and haematuria persisted. She was therefore referred to our hospital a year later. On admission, her blood pressure was 126/70 mmHg, pulse was 63 beats/min and body temperature was 35.8°C. Physical examination of the head, face, breast, abdomen and extremities showed no abnormalities. There were no abnormal neurological or dermatologic findings. Full blood count was normal. The values of blood biochemical parameters were urea nitrogen 5.36 mmol/L (15 mg/dL), creatinine 47.7 μmol/L (0.54 mg/dL), uric acid 291 μmol/L (4.9 mg/dL), total protein 74 g/L, albumin 43 g/L and IgA 4.26 g/L. Electrolytes and the result of liver function tests were normal. Urinalysis showed a pH 6.0, 2+ of protein, 3+ of occult blood and no glucose. Urine sediment was significant for microhaematuria (50–99/high power field), and hyaline, epithelial and red blood cell casts. The 24-h protein excretion was 0.2 g, and the level of urine N-acetyl-β-D-glucosaminidase was 6.0 U/g creatinine. Her creatinine clearance was 1.79 mL/s (107 mL/min). The electrocardiogram revealed no abnormality. Renal biopsy was performed 2 days after admission. On light microscopy, 30 glomeruli were examined, two of which showed global sclerosis and three showed fibrous crescent formation (Figure 1A and B). The remaining glomeruli revealed segmental to global proliferation of mesangial cells and mesangial matrix expansion. Thickening of the glomerular basement membrane was not prominent. Infiltration of inflammatory cells and fibrosis were observed in the interstitium. Mild-to-moderate arteriosclerosis was observed. Immunofluorescence microscopy revealed intense
granular deposition of IgA, IgM and C3 in the mesangial area (Figure 1C). These light and immunofluorescence microscopic findings were indicative of IgA nephropathy. The results of electron microscopy (Figure 2A and B) obtained later revealed electron-dense deposits thought to be immune deposits of IgA in the paramesangial area. Moreover, lamellar inclusions, structures characteristic of Fabry’s disease, were partially observed in epithelial cells. Light micrographs were examined in detail, and only one epithelial lesion and/or endothelial vacuolation compatible with the diagnosis of Fabry’s disease was detected in one glomerulus (Figure 2C). Extensive tests for Fabry’s disease were subsequently undertaken. The level of leucocyte α-Gal-A activity was 15.5 Agal U (normal range: cut-off >20.0 Agal U). To further confirm the diagnosis of Fabry’s disease, a genetic study of the GLA gene was performed. In exon 7, codon 359, there was a cytosine instead of thymine. This mutation, which has not been previously reported as far as we investigated, produces an amino acid change from isoleucine to threonine at this position (I359T). The diagnosis of Fabry’s disease was thus established based on the results of this gene analysis. Nevertheless, the typical symptoms of Fabry’s disease—neuropathic pain, exercise intolerance, gastrointestinal symptoms, hypohydrosis and angioedemas—were not observed in this patient. Echocardiography showed that there was no left ventricular hypertrophy, and she did not present any ocular finding such as corneal changes. There was no apparent family history of Fabry’s disease, either. After obtaining the informed consent, mutation analysis of the GLA gene was performed in the mother, sister and son of the proband, using the standard restriction fragment length polymorphism method (Figure 3). Although the proband has two brothers who seemed to be healthy, gene analysis was not done because they did not provide informed consent. The mutation was not detected in the mother nor in the son, but it was detected in the proband’s sister. We speculated that the deceased father of the proband had carried the GLA gene mutation, but none of his siblings had a medical history suggesting Fabry’s disease. Incidentally, further examination of the proband’s sister was performed because she had had a history of paroxysmal atrial fibrillation. The 12-lead and 24-h Holter electrocardiogram revealed no pathological findings, and echocardiography showed no left ventricular hypertrophy. She did not appear for the follow-up examination 12 months later, and the clinical course thereafter is unknown. This patient has been treated with 10 mg of enalapril for IgA nephropathy. As for the treatment of Fabry’s disease, agalsidase alpha was adopted. To date, no progression of the disease has been noted.

Discussion

Fabry’s disease is an X-linked disease that is fully expressed in hemizygous males. Heterozygous females, however, have variable levels of α-Gal-A activity. In heterozygous females, clinical manifestations may range from asymptomatic to severe, similar to hemizygous males. In this case, there were no apparent clinical symptoms or family history of Fabry’s disease, and it was virtually impossible to detect it at an earlier stage. Three reports of IgA nephropathy and concomitant Fabry’s disease have already been published in the English literature. The first report described the case of a 36-year-old Japanese woman with proteinuria and haematuria who had no clinical manifestations of Fabry’s disease [3]. The
second report described a 28-year-old Japanese man whose α-Gal-A activity was very low, and his mother’s α-Gal-A activity was low [4]. The third report referred to two adolescent sisters whose father had Fabry’s disease, and they had the typical manifestations of Fabry’s disease [5]. Typical histological features of Fabry’s disease were observed in light photomicrographs in all these cases. Including our case, three reports (75%) were from Japan, and four patients (80%) were females. The incidence of IgA nephropathy in East Asian countries is thought to be relatively high, but Fabry’s disease is rare in Japan, although its precise incidence has not been determined. The specific relationship between IgA nephropathy and Fabry’s disease has not been unveiled, but it is reported that the incidence of autoantibody-positive patients was high in Fabry’s disease [6]. There might be some immunogenic mechanisms linking IgA nephropathy with Fabry’s disease.

In our patient, renal involvement of Fabry’s disease was so mild that it was almost impossible to detect the complication of this disease from light microscopic findings.

Fig. 2. (A), (B) Lamellar inclusions (arrow) partially observed in the epithelial cells [(A) ×1000 and (B) ×5000]. (C) Epithelial and endothelial vacuolation (arrowhead) compatible with Fabry’s disease in a glomerulus (PAS ×400).
However, arteriosclerosis had developed to some extent, and it was not only due to hypertension considering her hypertension history but also to arteriopathy caused by Fabry’s disease. No other cardiac manifestation was observed in this patient, which was considered quite uncommon since only one case of renal-limited Fabry’s disease without cardiac involvement has been previously reported [7]. The cause of this organ-specific manifestation has not been elucidated. Another peculiar point of this case is that the deceased father of the proband whose GLA gene was assumed mutated lived out his 82-year life without any manifestation of Fabry’s disease. However, it is not so exceptional in Fabry’s disease that patients of the family with the same mutation can have markedly variable phenotypes due to the influence of modifier genes and/or other genetic and environmental factors [2]. Therefore, we assumed the disease remained subclinical during his lifetime.

As far as we investigated, there has been no report of electron microscopic findings as the first findings indicative of Fabry’s disease. The reason for female dominance in this overlapping morbidity is not understood at present. In male patients with Fabry’s disease, symptoms generally appear in childhood, and the clinical course is rapid. Therefore, progression of Fabry’s disease to end-stage renal disease may precede the onset of IgA nephropathy in patients not subjected to renal biopsy.

The cause of proteinuria and haematuria in our patient seemed to be IgA nephropathy more than Fabry’s disease.

Enalapril was administered for IgA nephropathy aiming at reducing proteinuria, and no other renal protective therapies nor corticosteroids were introduced because the disease activity was not high. As for the treatment of Fabry’s disease, this may be controversial. This patient was thought to be heterozygous, and there was no clinical manifestation except for a minor renal lesion possibly due to a relatively preserved enzyme level. She might need no treatment considering her age. Several reports, however, indicate the importance of enzyme replacement therapy from an early stage, from renal and cardiac viewpoints [8, 9]. Enzyme replacement therapy was therefore adopted after considering the pros and cons. Setting-up a screening target of Fabry’s disease is an issue that remains to be solved because it was completely impossible to suspect Fabry’s disease in this patient before tissue examination by electromicroscopy. In the future, it may be desirable to screen every newborn infant for Fabry’s disease.

Conflict of interest statement. None declared.

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