Case Report

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IgA nephropathy suspected to be combined with Fabry disease or Alport syndrome: a case report

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Abstract

Immunoglobulin A (IgA) nephropathy is the most common glomerular disease, and it often manifests as persistent microscopic hematuria or gross hematuria. Fabry disease and Alport syndrome are hereditary diseases caused by mutation of genes, and these diseases are rare in China. At present, patients can be diagnosed with IgA nephropathy by clinical manifestations and laboratory examinations, but there is still controversy about the simultaneous diagnosis of Alport syndrome and Fabry disease in patients with IgA nephropathy. The present case was a 17-year-old girl with hematuria and proteinuria who underwent a renal biopsy. Light microscopy and immunofluorescence showed that IgA was deposited in the mesangium. Under electron microscopy, zebra bodies with a lamellated structure were detected. A gene test showed a COL4A3 gene mutation. The patient was administered prednisone 40 mg once a day and dispersible tablets of mycophenolate mofetil 0.75 g two times a day. The patient's condition showed a trend of remission. The findings in our case emphasize the importance of renal biopsy and gene detection in hereditary kidney disease, especially for Fabry disease and its rare coexistence with Alport syndrome.

Keywords

IgA nephropathy, Fabry disease, Alport syndrome, genetic test, hematuria, kidney, renal biopsy

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Introduction

Immunoglobulin A (IgA) nephropathy with Fabry disease or Alport syndrome has been reported in various countries,[1]

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but coexistence of these three diseases has only been reported once in China.[2] Therefore, because Fabry disease and Alport syndrome are rare, there are high rates of missed diagnosis and misdiagnosis. There is no overall and macroscopic understanding of occurrence of this disease.

IgA nephropathy is the most common glomerulonephritis. IgA-based immunoglobulins and C3 deposited in the mesangium or glomerular capillary wall are the main diagnostic criteria of IgA nephropathy, and hematuria is the main clinical manifestation.[3] Fabry disease is a rare, X-linked, recessive, hereditary, multisystem, lysosomal storage disease. This disease is a disorder of glycosphingolipid metabolism caused by a lack of alpha-galactosidase A. Manifestations of various systems are diverse in Fabry disease.[4] Alport syndrome is a progressive hereditary glomerular disease caused by type IV collagen abnormalities, and it is often accompanied by sensorineural deafness and eye abnormalities.

We report a case of IgA nephropathy with suspected Fabry disease or Alport syndrome in a patient in China.

Case presentation

This study complied with the Declaration of Helsinki and was approved by The Second People's Hospital of Yibin, Sichuan, China. Written informed consent was obtained from the patient for publication of this case report.

A 17-year-old girl was admitted to the hospital on 6 May 2018 because of gross hematuria for longer than 1 year and repeated colds for longer than 3 days. She had no special medical history or personal history. Her parents are carriers of chronic hepatitis B virus. A physical examination showed that her body temperature was 36.5°C, blood pressure was 102/78 mmHg, and heart rate was 82 beats/minute. There was no skin rash on the body and no abnormalities in eye and ear examinations. Laboratory tests showed the following: erythrocyte sedimentation rate, 71.0 mm/hour; routine urine test, nephrotic proteinuria (24-hour proteinuria: 5.31 g), microhematuria (red blood cell count: 47.9 cells/high-power field), and microscopic white blood cells (7.7 cells/high-power field). Biochemistry analysis showed that the plasma albumin level was 32.4 g/L. The results of hepatitis virus, human immunodeficiency virus, and Treponema pallidum hemagglutination tests were negative. Immunological tests (complement, antinuclear antibody, double-stranded DNA, SSA, SSB, and antineutrophil cytoplasmic antibody) were normal. From 18 June 2018, the patient took prednisone 40 mg once a day and dispersible tablets of mycophenolate mofetil 0.75 g twice a day. During this period, the dosage was gradually adjusted, and then the level of hematuria and proteinuria gradually decreased. On 24 October 2018, laboratory tests showed the following: routine urine test, nephrotic proteinuria (24-hour proteinuria: 1.70 g), microhematuria (red blood cell count: 16.5 cells/high-power field), and microscopic white blood cells (1.2 cells/high power field). The plasma albumin level was 39.6 g/L.

There were no abnormalities in a chest X-ray, electrocardiogram, and craniocerebral magnetic resonance imaging. Abdominal ultrasound showed that the echo of bilateral kidney parenchyma was slightly enhanced and bilateral kidney calculi were observed (0.2–0.4 cm). A kidney biopsy was performed. We found mesangial proliferative IgA nephropathy with partial glomerular crescent formation (M1E0S0T0C2) and Fabry disease was suspected. (Figure 1) Light microscopy (26 glomeruli were observed) showed glomerular mesangial light to moderate hyperplasia, spheroidal sclerosis (0/26), cellular crescents (3/26), small cell crescents (8/26), small cell fibrotic crescents (6/26), and acute tubulointerstitial

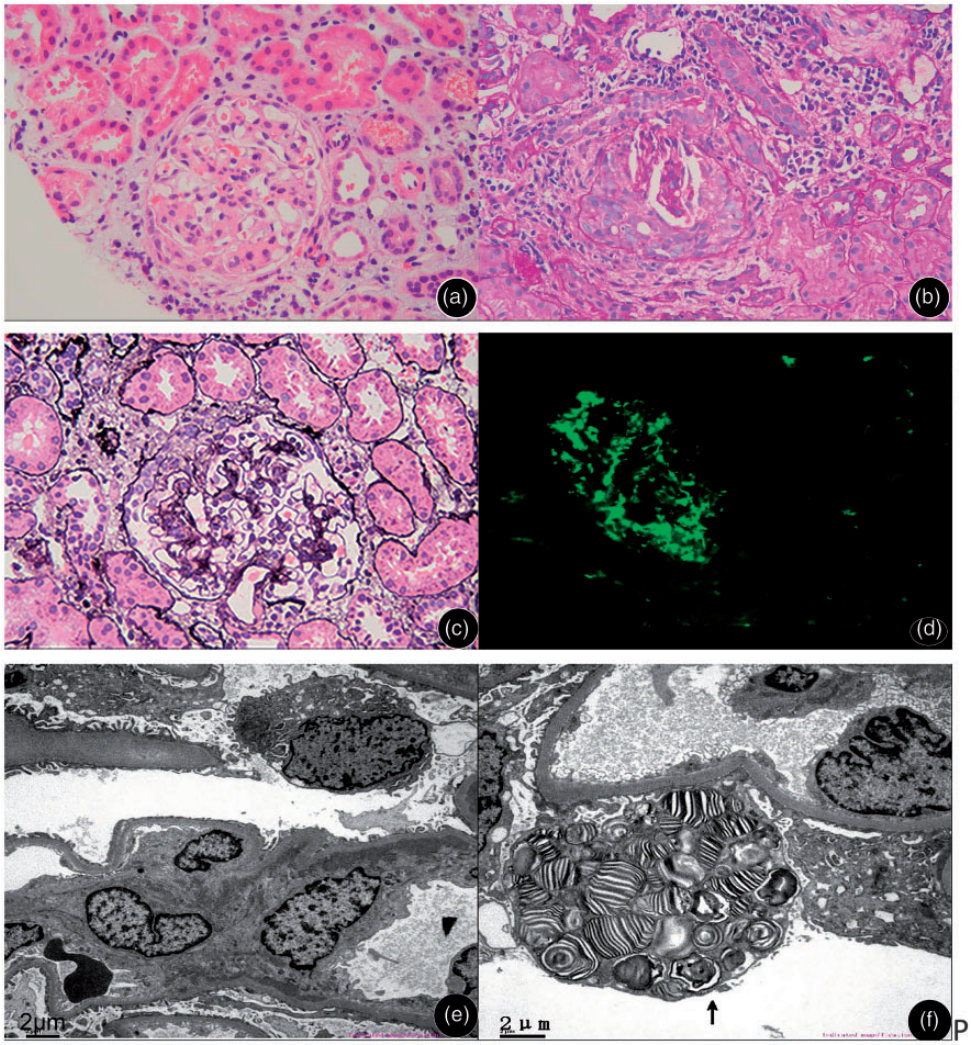

Figure 1. (a) Light microscopy shows an increase in the number of cells in the glomerulus (hematoxylin and eosin, ×400). (b) Periodic acid-Schiff stain shows formation of a cellular crescent (×400). (c) Periodic acid-silver methenamine stain shows formation of a cellular fibrous crescent (×400). (d) Immunofluorescence shows deposition of immunoglobulin A (×400). (e) Electron microscopy shows ultrastructure. (f) Electron microscopy shows a zebra-like corpuscle (↑).

lesions with mild chronic disease (Figure 1a–c). Immunofluorescence was strongly positive for IgA, positive for IgM, and negative for IgG, C3, and C1q-. Immunofluorescence of alpha-5 (IV) chain in renal tissue was negative in the glomerular mesangial area (Figure 1d).

Electron microscopy was performed. Three glomeruli were detected under microscopy. Capillary endothelial cells were markedly vacuolated. Red blood cells were aggregated in individual lumens, with no obvious endothelial cell proliferation, and glomerular capillary loops did not

show stenosis. There was no obvious thickening of the renal capsule wall. There was vacuolar degeneration of parietal cells and no obvious proliferation. The basement membrane showed no obvious thickening, with a thickness of approximately 250 to 430 nm, and segmental shrinkage. Visceral epithelial cells showed swelling and vacuolar degeneration. The foot processes were partially fused, and zebra-like bodies were formed in the podocytes of one region. The tubulointerstitium showed vacuolar degeneration of tubular epithelial cells and atrophy of a few tubules. A small amount of inflammatory cells infiltrated the renal interstitium. Renal interstitial vessels showed aggregation of erythrocytes in the lumen of individual capillaries. The walls of arterioles were thick (Figure 1e,f).

Whole-exon sequencing showed a c.3209C>T:p.Thr1070Met mutation of the patient's COL4A3 gene. The mother and the sister also carried the c.3209C>T:p.Thr1070Met mutation of the COL4A3 gene, all of which were heterozygous mutations. The father did not show this gene mutation. The mutation position of this gene in the chromosome was chr2:228155601. The proband and her mother and sister showed heterozygous mutations, and the father had no mutations (Table 1).

Ig A nephropathy and nephrotic syndrome (mesenchymal proliferative IgA nephropathy with partial glomerular crescent formation [M1E0S0T0C2]) was diagnosed. Whether this condition was associated with Fabry disease or Alport syndrome needs to be further determined with long-term, regular follow-up.

Discussion

There have been reports of IgA nephropathy with mitochondrial disease, nail-patella syndrome, and other hereditary diseases.[5] IgA nephropathy with Fabry disease has been reported[6] and IgA nephropathy with Alport syndrome has also been reported.[7] In our case, the evidence for diagnosis of IgA nephropathy was sufficient, but there is controversy about whether Alport syndrome or Fabry disease was present. Zebra-like corpuscles were a prominent manifestation of renal pathology in this patient, which is a clue for diagnosis of Fabry disease. In Fabry disease, the kidney is characterized by proteinuria or even nephrotic syndrome and renal failure. The incidence of dialysis patients is 0.12%.[8] The clinical manifestations are often different because of random inactivation of X chromosomes.[9] Men with typical symptoms (e.g., hypertension, hematuria, proteinuria) in the early stage of Fabry disease have a worse prognosis than women with atypical symptoms or women with either phenotype.

Fabry disease is a disorder of glycosphingolipid metabolism that occurs in cells of different organs in the body. This disease easily affects the kidneys and skin in the early stages. Fabry disease is often difficult to diagnose because of the lack of early

Table 1. Genetic testing information.

Sample	Verification site	Mutation site sequence	Validation results
Proband	NM-000091:exon37: c:3209C>T:p.Thr1070Met	CCGGGACCAA[C/T]GGTATATAGG	Het
Mother		CCGGGACCAA[C/T]GGTATATAGG	Het
Father		CCGGGACCAA[C/C]GGTATATAGG	N
Younger sister		CCGGGACCAA[C/T]GGTATATAGG	Het

Het: heterozygous mutation; N: did not show this mutation.

sensitive and non-invasive biomarkers. The diagnostic basis of Fabry disease is as follows. 1) Alpha-galactosidase A enzyme activity is detected in Fabry disease, with a general enzyme activity of $< 25\%$. Men show significantly lower alpha-galactosidase A enzyme activity and approximately 30% of women show a normal range of this enzyme. This enzyme needs to be combined with a pathological diagnosis for Fabry disease. 2) Determination of Gb3 in blood and urine and globular Gb (lyso-Gb3) are useful for auxiliary diagnosis.[10] 3) "Myelin-like" or "zebra-like" bodies are helpful for diagnosis of Fabry disease by electron microscopy.[11] Taking chloroquine, amiodarone, and diuretics may also cause similar changes, which need to be identified.[12] 4) Gene detection is the gold indicator for diagnosis of Fabry disease. Several cases of Fabry disease with IgA nephropathy have been reported.[13] However, whether there is a common pathogenic mechanism between these two diseases is unclear. The mechanism may be that accumulation of sugar and lipids stimulates the immune system and Gb3 to induce glomerulonephritis.[11]

Our patient was the proband with a negative family history of inherited disease. She only had hematuria and proteinuria, and evidence from genetic testing was required. The c.3209C>T:p.Thr1070Met mutation of the COL4A3 gene was found in the patient. This is a missense mutation, which causes amino acid 1070 of the gene to be mutated from threonine to methionine. This mutation is a clinically ambiguous mutation, which may be related to the disease, and needs to be judged in combination with clinical findings. This mutation has not been reported in the literature. Additionally, this mutation is not recorded in the ESP6500 database and ExAC database. The patient's genetic test suggested Alport syndrome because of a mutation in the COL4A3 gene. Alport syndrome is caused by mutations in genes encoding alpha-3, alpha-4, and alpha-5 chains of type IV collagen. There are three genetic modes of X-linked, autosomal recessive, and autosomal dominant Alport syndrome. The prevalence of this disease is approximately one in every 50,000 live births.[14] A total of 0.3% to 2.3% of new cases of end-stage renal disease are Alport syndrome.[15] The clinical manifestations of Alport syndrome are eye abnormalities (anterior conical lens), sensorineural hearing loss, and kidney abnormalities. In addition to persistent hematuria or hematuria with proteinuria, the diagnosis of Alport syndrome includes one of the following three findings: abnormal staining of collagen type IV in the kidney and skin basement membrane is detected by immunofluorescence; layering of the glomerular basement membrane is shown by electron microscopy; and one pathogenic mutation of COL4A5 or two pathogenic mutations of COL4A3 or COL4A4 are found.[2,16,17] In some patients with Alport syndrome, the α-chain of collagen type IV may not be deleted, and there is no exact mechanism to explain it, presumably because some mutations have little effect on its results and functions. Moreover, not all patients with Alport syndrome show characteristic pathological changes. Some show normal or diffuse thinning of the glomerular basement membrane under electron microscopy in the early stage of the disease.

The patient denied a history of drug use that may have led to formation of zebra-like corpuscles, but the COL4A3 gene was mutated, which provided inconsistent diagnostic information. The genetic mutation found in our patient was not confirmed to be a disease-causing mutation. Therefore, long-term follow-up and observation are required.

At present, 25% to 50% of Alport syndrome mutations are glycine substitution mutations. Glycine is considered to be the smallest amino acid, and it can insert into

the tight triple helix of type IV collagen. Substitution mutation in Alport syndrome can destroy formation of the helix, and then affect the structure of the basement membrane and lead to disease. However, the results of patients with threonine mutation to methionine do not support Alport syndrome.[17–19]

Multidrug combination is mainly used to slow progress of disease. Target therapy is expected to change the prospects of IgAN treatment strategies.[20] However, there is no radical treatment for Alport syndrome. Enzyme replacement therapy is the main treatment for Fabry disease.[21] Our patient was treated with prednisone and mycophenolate mofetil. The level of hematuria and proteinuria then gradually decreased. Our patient showed a decline in urinary protein levels after using hormones and immunosuppressants.

Alport syndrome and Fabry disease are rare hereditary nephropathies. Their combination with IgA is rare. When a family history of these patients is negative and there are no typical manifestations, pathological and genetic tests point to different diseases, the rate of missed diagnosis is high, and the prognosis is poor. Therefore, close follow-up and systematic diagnosis and treatment ideas are required. There are some deficiencies in study of the pathogenesis of hereditary nephropathy in China, especially when IgA nephropathy is complicated by Alport syndrome or Fabry disease. If early extrarenal manifestations of Fabry disease and Alport syndrome are atypical, they are easily overlooked, leading to loss of genetic information.

Conclusion

According to clinical manifestations and renal biopsy, IgA nephropathy can be clearly diagnosed. At present, the diagnosis of IgA nephropathy combined with Alport syndrome or Fabry disease cannot be confirmed by relevant examinations. Long-term follow-up is required to observe the late manifestations of each disorder.

Statement

All data and clinical data mentioned in this article are known to patients and their families, and they signed informed consent and agreed to use this information for the case report.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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