Immunoglobulin A Nephropathy as the First Clinical Presentation of Wilson Disease: A Case Report and Literature Review

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Case Report

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Abstract

Background: Wilson disease (WD) is a rare genetic disorder of copper metabolism. The difference in copper tissue accumulation lead to various clinical manifestations, including some atypical presentations. The complex clinical picture makes it easy to miss and misdiagnose, even delay the best chance for treatment.

Case presentation: A 26-year-old male patient who had nephritis-range proteinuria and elevated serum creatinine. The renal pathology indicated Immunoglobulin A (IgA) nephropathy and tubular injury which was inconsistent with glomerular lesions. Cirrhosis was also detected by imaging examination. Considering both kidney injury and liver damage, WD was suspected. According to further detected results of abnormal copper metabolism, corneal Kayser-Fleischer rings(K-F rings), and genetic disorder of ATP7B gene, he was finally diagnosed as a case of WD. The patient was given oral penicillamine and zinc sulfate daily and he was also prescribed losartan to control proteinuria on the premise of monitoring renal function and blood pressure. During the 2 years follow-up, the patient's 24h uric copper dropped to normal. The sign of tremor hands disappeared. The Urine protein and renal function keep stable. The patient had normal liver function and maintained good quality of daily life.

Conclusions: In some cases, IgA nephropathy patients with suspicious and unexplained neurological and liver symptoms cannot be ignored. They may eventually be diagnosed with WD.

1. Introduction

WD, also known as hepatolenticular degeneration, is an autosomal recessive hereditary copper metabolic disorder disease. The widely cited prevalence of WD is 1 in 30,000, and its onset age is mostly between 5 and 35[1]. The pathogenic gene of WD is localized to ATP7B on chromosome 13q14.3, which causes a weakened or loss of P-type copper transport ATPase function, resulting in decreased serum ceruloplasmin synthesis and gallbladder copper-discharging dysfunction. The most common clinical manifestations of WD include liver disease and cirrhosis, neurological disorder, and K-F rings at the corneal limbus. Its diagnosis is usually established by typical clinical symptoms, signs and examinations, especially serum ceruloplasmin and uric copper level, and also by the mutation analysis in the ATP7B gene. Some patients may have a positive family history. As one of the few treatable genetic diseases, if patients of WD can be timely and accurately diagnosed and treated in the early stage of disease, most of them can achieve a life quality and life expectancy similar to normal people. However, if the patient starts treatment in the late stage of disease, the treatment is basically invalid, and its lethality and disability rate are relatively high. Therefore, the identification of this disease correctly and timely is extremely critical. What bothers the doctors is that the face of WD is sometimes hidden behind some atypical symptoms, which may be manifested in different tissues, organs or systems. These patients with complex and varied clinical manifestations of WD are easily misdiagnosed or neglected, leading to poor prognosis. As a less common initial presentation of WD, renal injury has been described in some case series with small

samples [2]. This article reports a case of foam urine as the only clinical symptom and finally diagnosed as WD.

2. Case Presentation

A 26-year-old male patient complained that he had foam urine for three years, but the reason why patients are admitted to the clinic was that proteinuria was found in his routine physical examination one month ago. Laboratory data was as follows: urine analysis showed proteinuria (dipstick 2+) and hematuria (3+), 24h uric protein quantification was 0.75g/d (normal range, 0-0.15 g/d), serum creatinine (Scr) was 151umol/L (normal range, 88–104 umol/L). In view of the abnormalities in examination indicators, the patient was admitted to the nephrology with the initial diagnosis of glomerulonephritis and renal insufficiency.

Further detailed consultation and examination were carried out. The patient felt no other discomfort. His routine physical examinations showed no obvious abnormalities. He had no edema, no hypertension and his urine output was normal. During neurological examination, the patient was found to have imperceptible tremor hands. As to the past history, the patient had allergic purpura 22 years ago and pneumothorax 7 years ago. He denied alcohol consumption and history of any drug abuse. He also denied the history of hepatitis and family history of chronic diseases and genetic disease. His parents were not consanguineous marriage. Laboratory examinations indicated normal white blood cell and hemoglobin level. Urinalysis showed 2 + proteinuria with microhematuria (about 100 erythrocytes per high-power field). His 24h uric protein quantitative fluctuated in 0.75-1.1g / d. Abnormal renal function with Scr of 150-170umol/L was founded. While the liver function was normal, and others such as serum electrolytes, thyroid function, C-reactive protein, ASO, serum complement (C3 and C4) were also within the normal range. The immunoglobulin levels were normal of IgG and IgM, except for mild elevation of IgA (3.73g/L, normal range 0.97-3.2g/L). Serologic tests were negative for antinuclear antibody, antineutrophil cytoplasmic antibody, anti-GBM antibody, anti-hepatitis B virus, and anti-hepatitis C virus antibodies.

We performed a renal biopsy to identify kidney disease. Renal biopsy through light microscope showed mesangial cells and matrix proliferation with glomeruli focal segmental hyperplasia and sclerosis (1/10 glomerulus) (Fig. 1A). The epithelial cells were vacuolated and granular degeneration, and brushing margins disappeared, lumen dilated, focal atrophy (atrophy area was about 15%) in part renal tubule. Interstitial focal inflammatory cells infiltrated accompanied by fibrosis, and the walls of arterioles had no obvious pathological changes (Fig. 1B). Immunofluorescence staining shows granular depositon of IgA+++ in mesangium (Fig. 1C). No glmeruli was found by electron microscopy. Silver staining showed tubule bristles shed and interstitial edema (Fig. 1D). The pathologic diagnosis was focal hyperplastic IgA nephropathy accompanied with acute tubular interstitial injury (Lee grade III, Oxford grade M1E0S0T1).

According to the hematuria, proteinuria and renal biopsy, it is easy to diagnose the patients as IgA nephropathy. But there are some doubts about renal pathological. Firstly, the pathological changes of IgA

nephropathy could not explain renal dysfunction. Secondly, the degree of tubular injury was not consistent with glomerular lesions. It was valid to consider that other reason, but not IgA nephropathy might attribute to tubular injury. More important, the young patient presented with liver atrophy and splenomegaly identified by liver MRI without a clear etiology. And combine that with the non-specific neurological abnormality of his tremor hands, WD was considered a possible diagnosis.

Renal biopsy was reexamined and found some neglected subtle changes. There seemed to be granular deposition in the cytoplasm of renal tubules epithelial cells by light microscope (Fig. 2A). While under electron microscopy, some renal tubular epithelial cells showed degeneration of mitochondria in the cytoplasm. The size of mitochondria varied, the inner and outer membranes were separated, and the cristae became shorter and disappeared (Fig. 2B). The lysosomes increased, and some round granules were deposited in the lysosome (Fig. 2C). Special copper staining, TIMM'S copper staining, suggested brown to black deposits in some renal tubular epithelial cells (Fig. 2D). Measurements of copper metabolism further confirmed the diagnosis of WD: lower levels of serum ceruloplasmin (0.02g/L, normal range 0.27–0.47g/L), and increased urinary excretion of copper (260.4μg/d, normal range 10–60g/d) although accompanied by normal copper serum levels (12.52 μmol/L, normal range 7.12–21.29 μmol/L). The existence of K-F rings in the patient's eyes by slit lamp examination also supported WD. To confirm the diagnosis of WD, we performed DNA sequence analysis and identified two mutations on the ATP7B gene, which one was known pathogenic mutations, the other was suspicious pathogenic mutations (Table.1). Finally, the patients was diagnosed as WD. The kidney damage was identified as WD associated renal injury, including renal tubulointerstitial injury and focal proliferative IgA nephropathy.

The patient then accepted targeted treatment, including penicillamine 250mg twice daily and oral zinc sulfate. Meanwhile, he was prescribed with losartan to control proteinuria on the premise of monitoring renal function and blood pressure. During the 2 years follow-up, the sign of tremor hands disappears. His 24h uric protein quantification fluctuated in 0.3-0.5g/d. Renal function was reversed and Scr was maintained about 110-130umol/L. 24h uric cooper dropped from 260.4 ug to 69 ug. The patient still had normal liver function and maintained good quality of daily life.

3. Discussion

It is widely accepted that WD is not as rare as once believed, especially after the identification of ATP7B[3]. Since abnormal biliary excretion of copper due to ATP7B gene mutation is the etiology, liver abnormalities are the most common initial manifestation and 40–70% patients diagnosed as WD are on the basis of the presence of liver lesions[4]. In this case, coexistence of asymptomatic and unexplained cirrhosis become the key of diagnosis of this patients. Neuropsychiatric symptoms are another common findings which are at a rate of 50%[5],and the tremor hands is another clue in our case. Till to now, many atypical organs with copper deposition are reported and this leads to different and complex corresponding clinical symptoms and also leads to difficulty of diagnosis (Table.2). Given the difficulties of diagnosing WD, a weighted diagnostic scoring system, also known as Leipzig criteria, are established to help clinicians to evaluate patients for WD better. The system encompasses many key investigations

involving clinical, biochemical, and even molecular genetic testing for making the diagnosis[6]. Although WD can be diagnosed with increased accuracy given better understanding of the disorder and also the addition of molecular diagnostic testing, one thing has not changed with time that WD is still a disease which can be delayed or missed the diagnosis easily. Therefore, the report of special cases will make clinicians better aware of the disease.

In this case, the patient's earliest symptoms appeared in adulthood and kidney abnormalities including hematuria, proteinuria and renal dysfunction are his initially manifested. Renal involvement is a relatively rare manifestation, especially as initial presentation of WD. Some case reports have demonstrated that renal involvement has different manifestation, such as glomerulonephritis, nephrotic syndrome, IgA nephropathy, IgM nephropathy, even renal function impairment. However, renal tubular function disorder, which can manifest renal tubular acidosis, aminoaciduria, and Fanconi syndrome, is relatively common compare to glomerular injury. A retrospective study analyzed 25 children with WD involving with renal injury and proved that renal tubular injury is relatively common injury. This is mainly attributed to the more deposition of copper in the epithelium of proximal and distal convoluted tubules, which cause basement membrane thicken and further interfere with the reabsorption function of renal tubules. In our case, a relatively serious tubular injury inconsistent with glomerular lesions was found. It further proved the deposition of copper in tubular epithelial cells. IgA nephropathy is another pathologic change in the case. At present, the precise pathogenesis of IgA nephropathy associated with WD remains uncertain. While IgA nephropathy is more likely to be associated with WD-induced liver damage than with the direct copper deposition, since no copper depositions were found in glomeruli, such as in our case or another cases[7]. But different from our case, in that case, the kidney showed only IgA nephropathy without tubular damage, and no copper deposition in tubular epithelial cells. In some studies, it had been mentioned that the decreased ability of the liver to clear immunoglobulin and immune complexes may lead to their increase in serum and deposition in the glomerulus, thereby causing nephropathy and membranoproliferative glomerulonephritis (MPGN). Gunduz reported a case of a boy diagnosed with WD, whose liver injury had manifested as cirrhosis, the renal biopsy histopathology showed MPGN with deposition of IgA[8]. Similarly, a report described a case in Pakistan of WD complicated with IgM nephropathy[9].

Although the clinical manifestations, kidney pathology and abnormal copper metabolism of this patient nearly confirm the diagnosis of WD, investigation of gene mutation is necessary. There are several disorders appear to qualify as mimics of WD, also known as disease-mimic of WD[10]. For example MEDNIK syndrome with mutations in AP1S1 have manifestations including liver damage consistent with WD, neurological involvement, even with low serum ceruloplasmin, elevated basal 24h urinary copper excretion and some degree of hepatocellular copper overload[11]. In this case, there are two mutations in ATP7B identified to support the diagnosis. Till to now, there are more than 500 known disease-associated mutations, but no single mutation is regarded as dominant mutation. Most patients are compound heterozygotes with a different mutation on each allele of the gene[12]. May be the different mutation in one patient contribute to the individually manifestation.

Once a diagnosis of WD is established, treatment must be initiated. D-penicillamine and zinc salts are still standard first-line treatment. After treatment, symptoms of the patient are relieved. In recent years, efforts have been made to find new drugs to treat WD, including oral medicines (such as trientine) that increase life-long adherence [13], and methanobactins, a new drug that promotes copper excretion[14]. New therapeutic strategies are still in need [15, 16].

In conclusion, our case is a rare case of WD with kidney disease as the first symptom. We reported the first case that IgA nephropathy and renal tubular injury caused by copper deposition coexist in WD patients, which is also a very important clue for us to analyze the condition and ultimately diagnose WD. From the case, we should know the possibility of WD in patients of renal disease, especially with suspicious neurological or hepatic abnormalities. Although with the improvement of copper metabolism monitoring methods and the popularization of gene monitoring, the diagnosis of WD has become more and more convenient and accurate, the disease is still an easily missed and misdiagnosed disease, so case report is helpful for clinicians to know more about special WD disease and improve the diagnostic rate.

Abbreviations

WD: Wilson disease; IgA: Immunoglobulin A; K-F rings: Kayser-Fleischer rings; Scr: serum creatinine; MPGN: membranoproliferative glomerulonephritis;

Declarations

Consent to participate:

Informed consent was obtained from the patient.

Consent for publication

Not applicable.

Availability of data and materials

The relevant data and materials pertaining to this study are available upon request.

Competing interests

The authors declare that no conflict of interests exists.

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Authors' contributions

Research idea and study design: BZ; data acquisition: YZ and JG; data analysis/interpretation: YZ, PH, RY, MT, and YW; statistical analysis: YZ; supervision or mentorship: JG.

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Patient has provided informed consent for publication of the case.

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Tables

Table.1

Genetic analysis of the patient's ATP7B gene mutations

Exon score	Location	Nucleotide mutation	Amino acid alteration	Allele	known pathogenic
8	2333	G>T	p.Arg778Lcu	heterozygote	mutations
11	2621	C>T	p.Ala874Val	heterozygote	suspicious pathogenic mutations

Table.2

Possible clinical manifestations of WD

Target organ	Clinical features
liver	Abnormal liver enzymes, asymptomatic hepatomegaly, acute or chronic hepatitis, cirrhosis, hepatic encephalopathy, and fulminant hepatitis[4]
nervous system	Motor dysfunctions: dystonias, prkinsonism, choreoathetosis, tremor, and ataxias, Dysarthria, Oropharyngeal disfuctions. Seizures[17]; Nonmotor symptoms: school failure, personality disorders, mood changes, psychosis, cognitive abnormalities, sleep disorders, and autonomic disturbances, impulsiveness, sexual exhibitionism, inappropriate behavior[17]
Ophthalmologic manifestations	Kayser–Fleischer ring; sunflower cataract[18]; slowing of saccades, impaired upgaze, and strabismus
blood	Hemolytic anemia—coombs-negative hemolytic anemia[19]; thrombocytopenia—HELLP syndrome; leukopenia
kidney	Glomerulonephritis; nephrotic syndrome; renal tubular function disorder—renal tubular acidosis, aminoaciduria[20]; IgA nephropathy[7]; IgM nephropathy[9]; Fanconi syndrome[21]; nephrolithiasis[22]
Musculoskeletal and joint diseases	Osteoporosis; osseomuscular; arthritis or arthralgias[23]; muscle weakness[24]
Endocrine system	Male feminization; paramenia[25]; habitual abortion[26]; infertility, sexual retardation[27]; hyperprolactinemia; hypoparathyroidism; insulinoma[28]; hypokalemia
Cardiovascular system	Electrocardiographic abnormalities; cardiac interstitial fibrosis[29], myocarditis[29]
others	Pancreatitis[30]; cholangitis[31]; hyperpigmentation[32]; acanthosis nigricans[33]

Figures

Figure 1

A Light microscopy of the kidney showed mesangial cells and matrix proliferation of glomeruli (H&E stain, ×400). B Light microscopy showed brushing margins disappeared and lumen dilated of partial renal tubules , renal interstitial edema and inflammatory cell infiltration (H&E ×400). C Immunofluorescence staining of the kidney showed bright granular depositon of IgA (×400). D Silver staining of the kidney showed tubule bristles shed and interstitial edema(×400).

Figure 2

A Light microscopy of the kidney showed granular deposition in the cytoplasm of renal tubules epithelial cells (H&E stain, $\times 400$). B Some renal tubular epithelial cells showed degeneration of mitochondria in the cytoplasm. The size of mitochondria varied, the inner and outer membranes were separated, and the cristae became shorter and disappeared by electron microscopy ($\times 7500$). C Electron microscopy of some round granules deposition in the lysosome ($\times 7500$). D Brown to black deposits in renal tubular epithelial cells by TIMM'S copper staining ($\times 400$)

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