Analysis of renal impairment in children with Wilson's disease

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Original article

Background: **Since the diverse manifestations of renal impairment appear in different periods of Wilson's disease, misdiagnosis or missed diagnosis is not rare. This study was undertaken to find the clinical features of renal impairment in children with Wilson's disease or hepatolenticular degeneration (HLD).**

Methods: **Eighty-five children with HLD who had been treated at our department between January 1991 and June 2006 were retrospectively studied. The clinical data of 25 patients with renal impairment were analyzed.**

Results: **In the 85 HLD patients, 34 had renal impairment. Nine of the 34 patients with D-penicillamine treatment were excluded. In the remaining 25 patients, 7 had initiated symptoms of renal impairment, 5 of them with edema, 1 with gross hematuria, and 1 with acute hemolysis and acute renal failure. Twelve of the 25 patients had proteinuria, 14 had hematuria, and 5 had both proteinuria and hematuria. Urine glucose was positive in 4 patients, urine N-acetyl-β-D-glucosaminidase (NAG) increased in 5, and urine β2-microglobulin increased in 6. Urine red blood cell (RBC) phase was detected in 7 patients, including glomerular hematuria in 5 patients and non-glomerular hematuria in 2. Blood urea nitrogen and creatinine increased in 1 patient. B-ultrasound revealed bilaterally enlarged kidneys in 3 patients. Kidney biopsy showed diffuse mesangial proliferation and IgA deposit in mesangial region in 1 patient. All of the 25 patients had cornea K-F ring and the level of ceruloplasmin decreased. Six patients had a family history of HLD.**

Conclusions: **The manifestations of renal impairment with HLD are varied. HLD should be excluded from patients with unexplained renal impairment, while those with HLD should take examinations of the kidney to identify renal impairment. We propose that renal function and urinalysis should be checked regularly in patients receiving treatment of D-penicillamine.**

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Key words: **hepatolenticular degeneration; renal impairment; Wilson's disease**

Introduction

Wilson's disease or hepatolenticular degeneration (HLD) is an inherited, autosomal recessive, copper accumulation and toxicity disorder that affects about 30 individuals per million. It is caused by mutations in the gene encoding a copper-transporting P-type ATPase, which is important for copper excretion into bile, leading to copper accumulation.[1] The deposition of copper in tissues such as the liver, brain, kidney and cornea can cause multisystem damage. It is widely acknowledged that the disease is not as rare as once believed. Diagnostic errors are well recognized, and delays in diagnosis and initiation of treatment are common even in patients with a positive family history.[2] Few patients present with renal impairment as the initial symptom, which might lead to a misdiagnosis. In this study, we analyzed the clinical data of 25 HLD children with renal impairment in order to find the clinical features of renal impairment in children with Wilson's Disease and provide some clue to the early diagnosis of the disease.

Methods

From January 1991 to June 2006, 85 patients with HLD younger than 14 years old were treated at our hospital. All of them met the diagnosis critieria of HLD.[3] Renal involvement in HLD must fulfill one of the following parameters: (1) abnormal urinalysis results (proteinuria or hematuria); (2) tubular dysfunction (glucosuria, hypercalcinuria, increase of urine N-acetyl-β-D-glucosaminidase (NAG), etc); (3) abnormal renal

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function (BUN ≥7.14 mmol/L, Scr ≥176.8 μmol/L); (4) abnormal renal ultrasound or kidney biopsy; (5) excluding renal involvement caused by other factors.

The 85 HLD patients were subjected to urinalysis and biochemical examination including BUN and serum creatinine as a screening test for renal function. Fourteen patients took renal ultrasound and one had renal biopsy. Other laboratory examinations including urine red blood cell (RBC) phase, urine NAG, and urine β2-MG were done in some of the patients. The clinical data of 25 HLD children with renal impairment were recorded and analyzed.

Results

Patients

In the 85 HLD patients, 34 had renal impairment, 9 of whom were diagnosed as having HLD at admission and treated with D-penicillamine and/or zinc. The course of treatment ranged from 1 month to 3 years. They were excluded from this study. The other 25 patients had never received any treatment. Among them, 18 were boys and 7 girls, with age ranging from 6 to 14 years. The disease course ranged from 1 week to 6 years. Two patients had a history of nephritis. Six patients had a family history of HLD; the parents of one patient were both recessive carriers, and the parents of another patient had a consanguineous marriage.

Clinical presentations

The clinical features of the 25 HLD children varied (Table 1). Seven patients had renal impairment as the initial symptom, with a disease course ranging from 1 week to 5 years. On admission, acute nephritis was diagnosed in 1 patient, persisting glomerulonephritis in 1, nephrotic syndrome in 2, lupus nephritis in 2, and hemolytic uremic syndrome in 1. Five patients had eye swelling or dark brown urine with symptoms of other systems as the initial symptom. Thirteen patients had the initial symptoms of other systems and renal impairment was discovered by examination. Eleven also had symptoms of the nervous system (with the manifestation of speech disturbance, hypodynamia and tremor, dyscinesia, obtuse reaction, dysphagia, etc).

Laboratory examination

All the 25 patients had a low level of ceruloplasmin (20-150 mg/L). They showed an increased level of urine copper and positive cornea K-F ring. The abnormal results of examination are shown in Table 2. In patients with proteinuria, the volume of urine protein was 1.0-4.0 g/L. One patient had nephrotic syndrome with a urine protein volume of 2 g/24h (>50 mg/kg/24h). In 7 patients with urine RBC phase, 2 had non-glomerular hematuria and 5 had glomerular hematuria (abnormal RBC>37500/ml, germ 7%-16%). Five patients had an increased level of urine NAG, and 6 had an increased level of urine β2-microglobulin. In 1 patient, the level of urine calcium increased and that of urine phosphorus decreased. One patient had mild renal tubular acidosis accompanied with secondary hypocortisolism. B-ultrasound revealed bilaterally enlarged kidneys in 3 patients. The level of blood albumin decreased in 10 patients and that of glutamate-pyruvate transaminase increased in 5. Renal biopsy showed mild hyperplasia of intercapillary cells and interstitial, and deposition of IgA in the mesangial region.

The presentation of glucosuria, proteinuia and hematuria, increase of urine NAG and β2-MG, and renal tubular acidosis can be explained by renal tubule damage. While hematuria with abnormal RBC, mass proteinuria, the increase of BUN and Scr may be due to the involvement of renal glomerulus.

An illustrative case of initial symptom of renal failure

A 10-year-old girl developed acute hemolytic anemia and acute renal failure on admission to our department. Laboratory tests revealed a markedly increased level of serum bilirubin, but a normal level of aminotransferases. Coombs-negative hemolytic anemia was noted. BUN was up to 30.5 mmol/L and Scr 389 μmol/L. Wilson's disease was diagnosed because of urinary copper excretion (1950 μg/24h), lower level of ceruloplasmin than normal, and K-F ring in the cornea.

Table 1. Clinical features of 25 HLD patients with renal impairment

	Symptoms	*n*
Renal involvement as initial symptoms	Pitting edema (eyelid or both lower extremities)	5
	Pink urine	1
	Acute hemolysis and acute renal failure	1
	Jaundice	7
	Abdominal distention	6
Other accompanied symptoms	Osteoarthralgia	3
	Epistaxis	2
	Upper gastrointestinal bleeding	1
	Hepatomegaly	3
	Splenomegaly	1

Table 2. The abnormal results of examination

Abnormal renal manifestations	*n*	%
Proteinuria	12	14.1
Hematuria	14	16.5
Proteinuria and hematuria	5	5.8
Glucosuria	4	4.7
Renal failure	1	1.2

Discussion

Hepatolenticular degeneration is also called Wilson's disease. The genetic mutation of P-type ATPase which codes copper transportation leads to its functional incapacitation and makes it unable to combine the copper delivered by copper-companion with A2 globulin and leads to the abnormal synthesis of copper-protein. The decreased combining power of copper and copper-protein leads to less discharge of bile copper and more free copper that gradually deposits in tissues such as the liver, brain, kidney, muscle and eyes, thus causing cellular damage and corresponding clinical symptoms of the involved system.[4] Because of individual variation, the main organs that copper deposits are different and so symptoms vary. The early clinical manifestation is multiple, especially untypical in children. The initial symptoms in younger patients are usually seen in the liver and bone, and in elder patients or those with longer course of disease, the symptoms of the nervous system can be typical, whereas patients with renal involvement as the initial symptom are less, which is easy to be misdiagnosed.[5] In this study, 7 patients with renal impairment as the initial symptom were all diagnosed as having other renal diseases on admission, but they had not been definitely diagnosed by routine examination. With K-F ring in the cornea or a family history of HLD, ceruloplasmin and urine copper were checked, and a final diagnosis of HLD was made. The illustrated case also demonstrates that Wilson's disease may be difficult to diagnose at the appearance of initial acute manifestations.

In the 85 children with HLD, 34 suffered from renal impairment. Excluding 9 of the 34 patients with penicillamine treatment, 25 (29.4%) of the 85 patients were found with renal impairment. Obviously renal involvement of HLD is not rare. The main manifestations of renal involvement in the 25 patients included hematuria (mainly microscopic hematuria), proteinuria, glucosuria, increased NAG and β2-microglobulin, enlarged kidneys on B-ultrasound, acute renal failure, renal tubular acidosis, etc.

Renal involvement occurs in any period of HLD, but its mechanism is unknown. It is recognized that copper mainly deposits in the epithelium of proximal and distal convoluted tubules. The thickening of basement membrane interferes with the reabsorption function of renal tubule, resulting in renal glucosuria, aminoaciduria, hypercalcinuria, phosphaturia, and proteinuria.[6] Proteinuria is due to the low molecular weight protein.[7] Urinary excretion of NAG and urine β2-MG are sensitive markers of proximal tubular damage. Urinary NAG is considered to be a sensitive and reliable index of proximal tubular toxicity and a possible predictor of proteinuria.[8] The increase of urine NAG and β2-MG in our study supported the viewpoint of reabsorption dysfunction of renal tubules in Wilson's disease. Besides, the IgA and IgA complex scavenging capacity of the liver is decreased. Serum IgA increases and deposits in the glomerulus to cause secondary IgA nephropathy.[9] In our study, renal biopsy in one patient showed mild hyperplasia of intercapillary cells and interstitial deposition of IgA in mesangial region. Moreover, renal biopsy of patients with HLD complicated by renal impairment showed mesangial proliferative nephritis, which may be due to high deposits of copper in the glomerular mesangium, causing mesangial proliferation and glomerular damage, characterized by renal hematuria, proteinuria, and renal failure.[10,11] The cause of non-glomerular hematuria can be hypercalcinuria or abnormal blood coagulation.

Besides, the adverse effect of penicillamine treatment should be taken into consideration. The patients who are on the treatment with penicillamine may develop proteinuria, hematuria, or even renal insufficiency.[12] The most common histopathological finding is membranous glomerulonephritis.[13]

In summary, the manifestations of renal impairment in HLD are varied, but mostly hematuria or proteinuria. Therefore HLD should be excluded from patients with edema, hematuria, proteinuria and other abnormalities that cannot be explained by primary renal disease. Patients with HLD should take such examinations as urinalysis, renal function (including tubule function) and B-ultrasound of the kidney to find out renal impairment. For the side-effect of D-penicillamine that leads to renal injury, we propose that renal function and urinalysis should be checked regularly in patients who are receiving the treatment with D-penicillamine.

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