Int J Clin Exp Med 2021;14(6):2016-2021
www.ijcem.com /ISSN:1940-5901/IJCEM0121516

Case Report

Hematuria as the initial symptom of Wilson disease in identical twins: a case report

Jiajia Wang[1,2], Minxia Hu[1], Qiang Zhu[1], Lanting Sun[3]

[1]Department of Diagnostic Ultrasound, Beijing Tongren Hospital, Capital Medical University, Beijing, China; Departments of [2]Ultrasound, [3]Encephalopathy, The First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei, China

Received September 1, 2020; Accepted December 30, 2020; Epub June 15, 2021; Published June 30, 2021

Abstract: Wilson disease (WD) is a rare autosomal recessive disorder of copper transport with copper accumulation in various organs. The clinical presentations of WD are variable. The diagnosis of WD can be challenged when patients show clinically rare symptoms. This report described a case of identical twin brothers diagnosed with WD who initially presented with mild-moderate microscopic hematuria and had a consequent delay in the diagnosis and treatment. The 6-year-old younger brother initially presented with hematuria before he was admitted to our hospital at his age of 11. He was found with mild gait disturbance in physical examination upon admission. Further evaluation revealed abnormalities including laboratory investigations of cooper metabolism, brain MRI, liver ultrasound, and Kayser-Fleischer (K-F) rings. The older twin brother presented with hematuria and proteinuria without hepatic and neurological symptoms at age 11. K-F rings were also confirmed. Genetic testing was performed on the twins and revealed mutations of R778L and A874V on both alleles of ATP7B gene. The diagnosis of WD was made on the twins according to the Leipzig scoring system. The twins regularly received sodium dimercaptopropane sulphonate (DMPS) treatment, supplemented with a Chinese traditional medicine, called Gandou decoction. The symptoms of the twin brothers were improved after treatment. The two patients had been reported no renal, hepatic, or neurological abnormalities during a 5.5-year follow-up period. The study demonstrates that WD should be considered as one of differential diagnoses when long-term renal abnormalities with unknown etiology occur in pediatric population. An early diagnosis and treatment are essential for the WD patients to avoid irreversible multi-organ injury.

Keywords: Wilson disease, hematuria, ultrasound, case report

Introduction

Wilson Disease (WD), first described in 1912, is a rare autosomal recessive genetic disease, resulting from accumulation and deposition of copper in tissues such as the liver, brain, kidney, cornea, etc. [1]. Gene mutation of copper-transporting P-type ATPase (ATP7B) on chromosome 13q14.3 has been shown to be related to WD [2]. The incidence of WD in China is estimated to be six individuals per million [1, 3]. The typical symptoms of WD are mainly hepatic (40-60%) and neurological (18-68%) damage [4, 5]. Patients with typical initial symptoms are rarely misdiagnosed [6, 7]. However, delay in diagnosis and treatment can occur in patients with rare presentations, such as damages to the kidney, bone, and heart, resulting in irreversible damage and severe complications [8, 9]. Hematuria as the initial sign of WD is rarely reported with an incidence of 1.3% in the literature [10]. In this case report, we first described identical twin brothers with WD who presented with hematuria as the first symptom of WD.

Case presentation

A 6-year-old younger twin brother with mild to moderate microscopic hematuria was referred to our hospital in 2009. The patient did not complain about abdominal pain and backache. Physical examination was unremarkable. The urine analysis and liver function test were normal except for the presence of hematuria. Given that the etiology of hematuria has not been elucidated, the patient was followed up without intervention. The patient routinely had

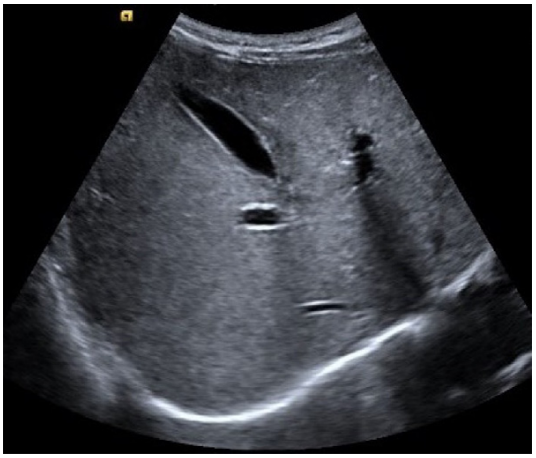

Figure 1. Liver ultrasound of the younger twin brother shows the liver with a normal size, regular contour, and homogenous hyperechogenic parenchyma.

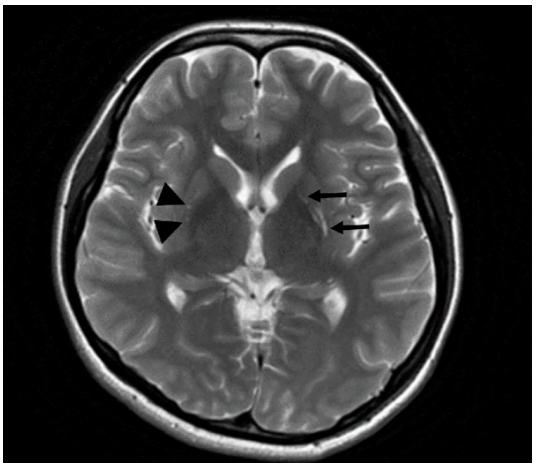

Figure 2. T2WI-weighted image of the brain magnetic resonance imaging (MRI) of younger twin brother shows cord-like hyperintense foci in the left basal nucleus (arrows) and small hyper-intense foci in the right basal nucleus (triangular arrows).

urine and liver function tests every three months thereafter. During 5-year follow-up period, the laboratory tests were negative except for mild to moderate microscopic hematuria existed. The patient developed proteinuria at age 11. At the same time, his identical twin older brother was initially found with hematuria and proteinuria. With the consideration of the similar renal abnormalities developed on the twin brothers, hereditary disease was suggested. The twin brothers were then admitted to our hospital for further evaluation.

For the younger twin brother, laboratory test revealed red blood cell count of 206.2/μl (normal range, 0-25/μl), mild proteinuria, and 24 h proteinuria of 0.32 g/24 h (normal value, <0.15 g/24 h). Abdominal ultrasound examination showed homogenous hyperechogenic parenchyma of the liver (**Figure 1**), which implied that liver disorder existed though liver function test was normal for this patient. Mild gait disturbance was noted in physical examination and neurological disorder was suspected. Brain MRI clarified hyperintensity signals in the bilateral basal ganglia (**Figure 2**). Taken together, WD was suspected because WD is a hereditary disorder that is typically characterized with hepatic and neurological damage. A series of specific tests for the definite diagnosis of WD were performed. K-F rings were detected on slit-lamp fundoscopy (**Figure 3**). Laboratory investigations revealed serum ceruloplasmin concentration of 0.071 g/L (normal range, 0.02-0.60 g/L), serum copper concentration of 4.25 μmol/L (normal range, 11-24.4 μmol/L), and 24-h urine copper excretion of 1,583.06 μg/24 h (normal value, <100 μg/24 h). Furthermore, DNA analysis revealed ATP7B-R778L (inherited from father) and ATP7B-A874V (inherited from mother) mutations (**Figure 4**). The patient had 11 points on the Leipzig scoring system, and the diagnosis of WD was eventually established (four or more points are needed for the WD diagnosis) [11] (**Table 1**).

The older twin brother was previously healthy until he developed hematuria and proteinuria at age 11. The urine test showed moderate occult blood, red blood cell count of 196.2/μl, mild proteinuria, and 24 h proteinuria of 0.28 g/24 h. Physical examination revealed no neurological abnormalities. Liver ultrasound and MRI examinations were unremarkable. The possibility of WD diagnosis was considered due to the similar initial symptoms occurred on the twin brothers. Further work-up for the diagnosis of WD were arranged. Slit-lamp fundoscopy confirmed K-F rings (**Figure 3**). The investigation of copper metabolism revealed serum ceruloplasmin concentration of 0.070 g/L, serum copper concentration of 3.3 μmol/L, and 24-h urine copper excretion of 1,121.41 μg/24 h. The genetic analysis confirmed the ATP7B mutations on both alleles (**Figure 4**). The diagnosis of WD was made for the patient because he had 10 points on the Leipzig scoring system [10] (**Table 1**).

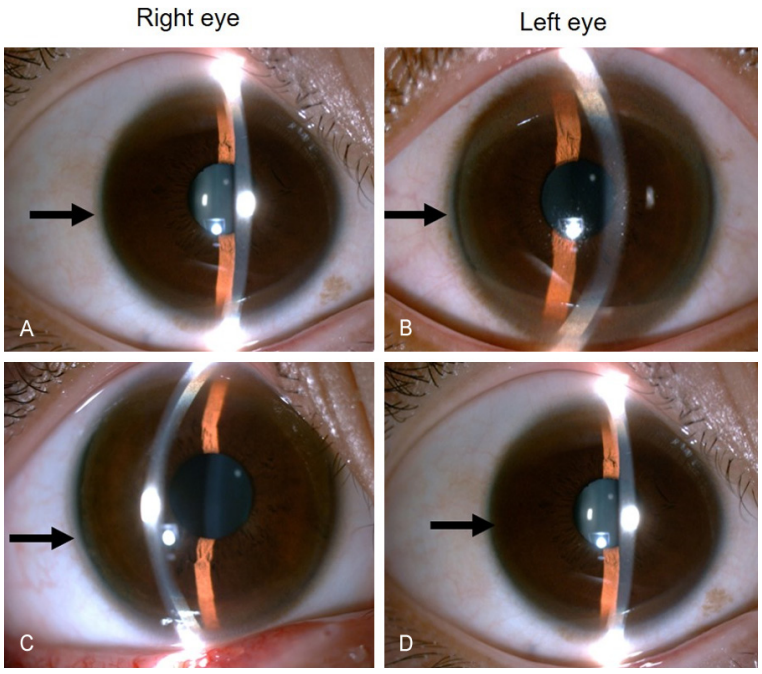

Figure 3. Slit-lamp fundoscopy shows Kayser-Fleischer (K-F) ring (arrow) in the corneal periphery of both eyes of the younger twin brother (A, B) and the older twin brother (C, D).

The twin brothers were started on sodium dimercaptopropane sulphonate (DMPS) treatment 20 mg/kg daily. Two weeks later, the urine test for both of them were normal. And the symptom of gait disturbance in the younger brother disappeared. After the two brothers were discharged from our hospital, they received dimercaptosuccinate (DMSA) 1 g daily and Gandou decoction (a Chinese traditional medicine) therapy, and a low copper diet was also advised. The patients had been reported no renal, hepatic, or neurological symptoms during a 5.5-year follow-up period.

This study was approved by the Ethics Committee of the First Affiliated Hospital, Anhui University of Chinese Medicine (2018AH-08). Patients of this study have provided informed consent for publication of the case.

Discussion

WD is a relatively rare autosomal recessive disorder with a clinically high variability in phenotype. This report described the case of 6-year-old identical twin brothers with initial symptom of renal abnormalities who were misdiagnosed due to a lack of typical signs of WD.

Though WD patients have copper metabolism disorder from birth, they generally have typical presentations only when the accumulation or deposition of copper reach the saturated state. In our report, the younger twin brother had initial symptom of mild-moderate hematuria at the age of 5, otherwise he was healthy. We speculated that the copper concentration did not reach the saturation point until he presented with typical WD manifestations at the age of 11. The diagnosis of WD can be challenging when non-typical abnormalities present prior to typical symptoms such as hepatic and neurological damages, which may result in delay in diagnosis and treatment. The case report indicates that WD should be considered as one of differentials when long-term renal abnormalities with unknow etiology occur in pediatric population.

Renal symptoms as initial signs of WD have been reported as uncommon. Lai investigated the initial symptoms of WD in pediatric patients, 42% had liver injury, 34% showed neurological symptoms, and only 1% developed renal abnormalities [11]. Renal damage can occur in any stage of WD. Though the mechanism is unknown, copper observed to be deposited in the epithelial cell on the renal tubule may result in renal tubular dysfunction [12]. Renal damage of WD is characterized by the presence of hematuria, proteinuria, glycosuria, and high phosphate and uric acid levels. The younger twin brother was found to have the first symptom of renal injury at the age of 5. It was consistent with the study by Wang et al. [13], in which the authors found that the average age of the first symptom of renal injury was 6.5 years old.

Gait disturbance is a clinical presentation that indicates the possibility of neurological damage [14]. Mild gait disturbance can be less apparent in early stage of WD [15]. However, gait abnormalities show a tendency towards progression with the progression of WD. The

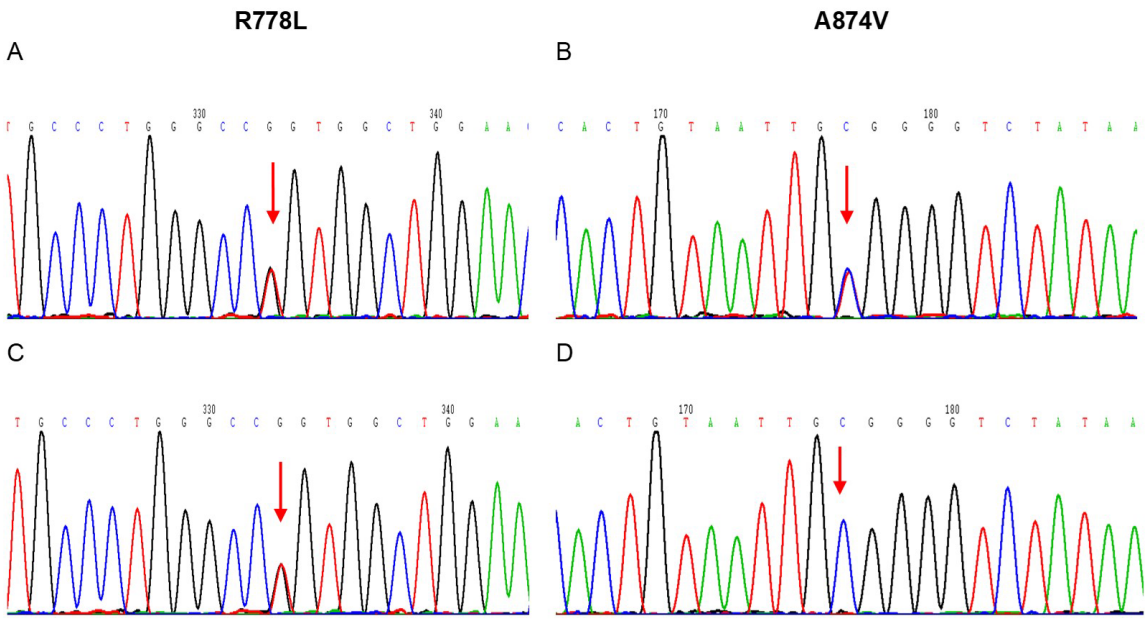

Figure 4. DNA sequencing shows compound mutations of R778L and A874V of ATP7B gene in the younger twin brother (A, B) and the older twin brother (C, D).

Table 1. Clinical symptoms, laboratory tests, genetic analysis of the twin brothers upon admission

	Younger twin brother	Older twin brother
Clinical symptoms		
Age at presence of hematuria	5-year-old	11-year-old
K-F ring	Presence	Absence
Neurological symptoms (gait disturbance)	Presence	Absence
Abnormalities on brain MRI	Presence	Absence
Abnormalities on liver ultrasound	Presence	Absence
Urine test		
Erythrocyte (μl)	206.2	196.2
24-h proteinuria (g/24 h)	0.32	0.28
Copper metabolism		
Serum copper (μmol/L)	4.25	3.3
Ceruloplasmin (g/L)	0.071	0.070
24-hour urine copper (μg/24 h)	1583.06	1121.41
Pathogenic gene analysis	c.2333G>T; p.R778L c.2621C>T; p.A874V	
Leipzig scoring system	11 points	10 points

younger twin brother was observed with mild gait disturbance in physical examination upon admission, which provided critical diagnostic basis of WD. The patient might have developed gait disturbance before admission, but it was not recognized due to the mild disorder until he was admitted to our hospital. Our case suggests that complete neurological examination is needed for early detection of WD.

The genetic analysis confirmed R778L and A874V missense mutations in the twin brothers. These mutations have been involved in a disorder of the copper-transporting ATPase, ATP7B [16-18]. R778L is the most common pathogenic gene of WD in the Chinese population, accounting for 30% of all WD patients. It was reported that 74% of WD patients with R778L mutation had liver damage [19, 20]. A874V is relatively rare in WD, only accounting for 3.6% of cases [21]. It's impractical to clearly identify the correlation between gene phenotype and clinical phenotype since more than 700 ATP7B mutations were found in WD [21]. Of note, so far, no WD patients with both A874V and R778L mutations have been reported. Genetic analysis plays an important role in the diagnosis of WD. The patient with mutations on both alleles of ATP7B had four points on the Leipzig scoring system, and the diagnosis

of WD should be made even with no clinical manifestations presented.

In a study by Albert et al. [22], the authors assessed the hepatic damages in 98 WD patients (26 children and 72 adults) using liver biopsy. The study confirmed that pediatric patients tended to develop hepatocyte steatosis (73% vs 46%) whereas the adults were more likely to develop fibrosis (54% vs 27%). The authors thus suggest that hepatocyte steatosis is associated with early stage of WD. In our report, the ultrasound examination of the younger brother showed homogenous hyperechogenic parenchyma of the liver. This finding implied the development of hepatocyte steatosis though liver biopsy was not performed on the patient. For the WD patients, liver ultrasound should be annually used to evaluate the liver damage, to adjust the treatment plan promptly in order to prevent the occurrence of liver fibrosis or cirrhosis [1].

In conclusion, WD is a rare hereditary disease. Misdiagnosis can often occur due to the lack of typical initial symptoms. The delay in diagnosis and treatment significantly affects the prognosis of the disease. WD should be included in the differential diagnoses in patients with long-term unknown hematuria. Furthermore, liver ultrasound and brain MRI should be performed to assess organ damages, and other family members should be genetically tested to early detect asymptomatic patients.

Acknowledgements

The authors thank the patients and their family for their invaluable contribution to this study.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Qiang Zhu, Department of Diagnostic Ultrasound, Beijing Tongren Hospital, Capital Medical University, No. 1, Dong Jiao Min Xiang Street, Dongcheng District, Beijing 100730, China. Tel: +86-10-58268134; Fax: +86-10-65131244; E-mail: qzhu_mail@126.com

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