Journal of Clinical and Nursing Research

Research Article

A Case Report and Literature Review of Wilson Disease

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Abstract: To investigate the clinical characteristics, auxiliary examination and treatment of Wilson's disease(WD). The clinical data of a child with WD were summarized and analyzed comprehensively in conjunction with the literature reference. WD is a hereditary disease with a large age span, diverse early symptoms, high misdiagnosis rate, abnormal liver function, decreased ceruloplasmin, increased urinary copper, K-F rings, ATP7B gene mutation, ATP7B gene mutations, and abnormalities in abdominal and cranial brain imaging, which can be clearly diagnosed and require lifelong treatment. WD can be diagnosed according to the clinical manifestations and auxiliary examination to reduce misdiagnosis. The timely diagnosis and treatment will improve the prognosis the quality of life.

Keywords: Wilson disease; Clinical features; Misdiagnosis; Treatment; Child

Publication date: May, 2020

Publication online: 31 March, 2020

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Hepatolenticular degeneration, also known as Wilson disease (WD), is an autosomal recessive genetic disease, which is a copper metabolic disorder caused by mutations in the ATP7B [1]. The clinical manifestations of the disease are diverse, which can involve multiple organs and be misdiagnosed easily. This disease is a treatable genetic disease. If it can be diagnosed early and treated reasonably, it will significantly improve the quality of life and prognosis of patients[2]. The following is a retrospective analysis of one case of WD combined with literature review.

1 Clinical data

Child's medical history: Admission number: 006*****, girl, 11 years old. The patient was admitted to the Pediatrics of Binzhou People's Hospital on May 5, 2019 with symptoms of "repeated facial swelling for more than 2 months, a fundus examination revealed a Kayser-Fleischer(K-F)rings for 1 day". The patient has repeatedly experienced facial swelling and discomfort after eating seafood, shellfish, kelp, chocolate, etc. for more than 2 months. It showed non-sagging and obvious eyelids, and may be accompanied by numbness of fingers, fatigue, weakness, no tremor, indistinct speech and slow movement. A local fundus examination revealed a K-F rings.

Patient G1P1, cesarean section at full term; no history of asphyxia after birth; normal growth and development, and intellectual development consistent with children of the same age.

The parents were married to non-close relatives, who denied that they had a history of liver disease in the family and a family history of genetic diseases, and lived near the sea.

Physical examination: Normal development, facial swelling without sagging, eyelid edema, no abnormalities in the heart and lungs. Soft abdomen without fluid tremor, 3 cm below the costal margin of the liver, hard, smooth, no tenderness, and the spleen was not touched. Meningeal irritation and pathological signs were negative.

2 Auxiliary examination

Liver function: ALT 60.5U/L, AST 70.4U/L, total bile acid 31.68μmol/L, total bilirubin 28.7μmol/L, direct bilirubin 11.52 μmol/L; no obvious abnormalities with

renal function, electrolytes, and myocardial enzyme spectrum; Hepatitis B, Hepatitis A and Hepatitis E antibodies were negative; Hepatitis C antibody was 0.11S/CO, human immunodeficiency virus antibody was 0.31S/CO, and treponema pallidum specific antibody was 0.15 S/CO; Urine routine: occult blood +, protein +, urobilinogen 3+, others are normal; 24-hour urine protein: 37.38mg; ceruloplasmin determination: 2.0mg/dl; fundus examination: K-F rings (+); abdominal ultrasound: diffuse liver symptoms, splenomegaly, increased renal parenchymal echo, seroperitoneum; Color ultrasound of the inferior vena cava and hepatic vein: no abnormalities; CT of the upper abdomen: consistent with cirrhosis and MRI of the spleen; DWI showed a small patchy high signal in the lower posterior segment of the right lobe of the liver, considering artifacts. Brain CT: no obvious abnormalities. Genetic testing showed that the child carried a pathogenic homozygous mutation in the ATP7B gene, located at Exon8, c.2333G> T, which was a missense mutation.

Treatment and follow-up: After diagnosis, treatment of penicillamine, calcium zinc gluconate oral solution, vitamin B6, and compound glycyrrhizinic acid capsules were given orally. After 3 months of oral administration, liver function would be normal, and abdominal ultrasound showed no obvious abnormalities.

3 Discussion

WD is a single-gene hereditary disease that exists in all ages and occurs mostly at 5-12 years of age. In recent years, younger children with WD have been diagnosed[3-4]. ATP7B mutations lead to WD, and its mutation types are complex and complicated, resulting in different occurrence ages of disease and clinical manifestations of patients, and some patients with WD are atypical, which is easily ignored in clinical practice and leads to misdiagnosis.

WD is divided into liver type, brain type, other types and mixed type, of which liver type includes: persistent elevated serum transaminase, acute or chronic hepatitis, cirrhosis, and fulminant liver failure (with or without Hemolytic anemia), *etc*[5]. Brain type includes: Parkinson syndrome, dyskinesia, oro-mandibular dystonia, mental symptoms, *etc*.; other types: mainly kidney, bone, joint and muscle damage or hemolytic anemia; mixed type: a combination of the above types. Patients may be asymptomatic at an early stage, and with the continuous accumulation of copper in the body, organ damage gradually occurs. Children often have liver damage as the early clinical manifestation[6-7]. In this case, the child with WD is of mixed type, with liver damage as the main cause.

The clinical manifestations of children with WD have a certain correlation with age. Generally, liver disease symptom appears after age of 2; K-F rings appears after age of 10; hemolysis occurs after age of 7; neurological and psychiatric symptoms appear after age of 15, but it has been reported that they can appear at the age of 7-9; other systemic manifestations are currently uncertain at age [5].

It is reported by Chinese literature[3,8-13] that about 62.12% of Children have liver damage as the early symptom. 19.19% of children have mental and nervous system problem as the early symptom, and about 3.54% of the children have blood system problem (mainly anemia) as the early symptom. About 4.04% have the early symptoms of the urinary system. About 1.52% come to the hospital for screening because of relatives with the disease, and about 9.60% have other symptoms. In Table 1, the liver function, ceruloplasmin, serum copper, urinary copper, K-F rings, abdominal ultrasound, brain CT / MRI, and ATP7B tests were summarized and analyzed in these children with WD. The positive rates were: 83.12%, 95.91%, 67.31%, 74.47%, 57.58%, 60.0%, 49.12%, and 94.74%. A review of the Chinese literature on children with WD [3, 8-13] found that the youngest age was 3 months and the oldest was 16 years old, which has a large span; The initial clinical symptoms are diverse. The clinical manifestations are more atypical with the younger age of children; there is no 100% positive rate in all auxiliary examinations, which increases the difficulty of clinical diagnosis and the misdiagnosis rate. The facial swelling and K-F rings were the first symptoms in this case. The symptoms of impaired liver function, cirrhosis, splenomegaly, ascites occurred, but portal hypertension and upper gastrointestinal bleeding did not occur. In Table 2, the misdiagnosis rate of WD in Chinese children is 39.9%. Some patients had symptoms occurred in childhood, but the diagnosis is confirmed after childhood, so the misdiagnosis rate of children with WD should be higher. Among them, 32.5% were misdiagnosed as hepatitis and cirrhosis, 24.7% were misdiagnosed as nephritis, 13.0% were hemolytic anemia, 5.2% were nephrotic syndrome, and 2.6% were systemic lupus erythematosus. About 22.0% were misdiagnosed as other diseases[3,10,11,14].

In order to improve the early diagnosis rate of WD and reduce misdiagnosis, it need to be paid highly attention when children appear the symptoms of: unexplained liver abnormalities, neuromotor disorders, unexplained renal tubular or bone lesions, recurrent hemolytic anemia, unstable gait and (or) uncoordinated movements, psychiatric symptoms accompanied by liver disorder. Further checks of liver function tests, ceruloplasmin determination, 24-hour urinary copper, abdominal color ultrasound, craniocerebral MRI, and ATP7B tests can be performed to confirm the diagnosis; Once diagnosed, the parents, siblings of the child should check liver function, copper metabolism index and genetic tests[15-18]. A small number of children were diagnosed with abnormal liver function during physical examination at kindergarten. After the diagnosis of this case, the liver function tests of his sister, brother, and parents showed no abnormalities, but genetic testing showed that they carried the disease-causing genes. And it is recommended that those with the above conditions in the family should be further examined to determine the cause of disease.

WD requires life-long treatment and regular follow-up. The current treatments include: restriction of the intake of copper-containing food, drug treatment, liver transplantation and new treatment methods such as gene therapy, cell transplantation and antioxidant treatment. Penicillamine is the first clinical choice. When children are intolerant or have serious side effects, trientine, dimercaptosulphonic acid, dimercaptosuccinic acid and other drugs can be used. As a copper chelator, penicillamine is widely used in China, but it has been reported that [2,19] 11% -50% of patients with cerebral WD have an irreversible nervous system response after treating with penicillamine, so it is not recommended as the initial treatment of cerebral WD. Studies have shown that zinc can be used as first-line medication for WD [2], especially for initial treatment of the WD patients with cerebral type and asymptomatic, children, and WD patients in gestation. It can also be used as preoperative treatment of WD patients and maintenance treatment of various types of WD patients. In this case, the child was treated with penicillamine, zinc, and compound glycyrrhizin. After 3 months, liver function improved, liver cirrhosis reversed, ascites absorbed, and spleen size were normal. No side effects of penicillamine were found.

In summary, the diagnostic criteria and classification of WD are clear, but the clinical manifestations are diverse, and it is easy to cause misdiagnosis. When the child has an unexplained abnormal liver function, psycho-nervous system symptoms, etc.; the possibility of WD should be considered, and the clinical symptoms, auxiliary examinations, and family history of disease should be used to make comprehensive judgment and early diagnosis, so as to take reasonable treatment, improve prognosis and the life quality of children.

Table 1. Literature review of clinical features of WD and auxiliary examination

items	Ji Yu, et al[8] (2008)	Yan Yu, et al[9] (2011)	Wei Ke, et al[10] (2011)	Qiaohui Zeng,et al[3] (2013)	Yuan Chen, et al[11] (2015)	Ying Huang, et al[12] (2016)	Kaihua Yang, et al[13] (2017)	total
age	3months -16 years old	7months -16 years old	3years old -12 years old	9months -14 years old	4years old -15 years old	2months -14 years old	3months -16 years old	-
male: female	18:16	14:5	17:10	12:9	14:7	21:17	23:15	119:79
family disease history	2/34	1/19	-	-	2/21	4/38	1/38	10/150
initial clinical symptom								
abnormal liver function	23/34	14/19	15/27	14/21	12/21	18/38	27/38	
psycho-nervous system	7/34	2/19	8/27	4/21	3/21	11/38	3/38	28/198
blood system	2/34	0/19	0/27	1/21	1/21	2/38	1/38	7/198
urinary system	2/34	0/19	1/27	1/21	2/21	1/38	1/38	8/198
screening	0/34	0/19	0/27	0/21	2/21	0/38	1/38	3/198
other	0/34	3/19	3/27	1/21	1/21	6/38	5/38	19/198
auxiliary examination								
abnormal liver function	34/34	-	22/27	20/21	16/21	22/34	-	
decreased ceruloplasmin	32/34	17/17	27/27	21/21	-	31/34	36/38	
decreased serum copper	14/30	-	-	-	7/21	14/17	-	35/52

Continued table 1

items	Ji Yu, et al[8] (2008)	Yan Yu, et al[9] (2011)	Wei Ke, et al[10] (2011)	Qiaohui Zeng,et al[3] (2013)	Yuan Chen, et al[11] (2015)	Ying Huang, et al[12] (2016)	Kaihua Yang, et al[13] (2017)	total
increased urinary copper	14/24	8/19	-	-	-	16/18	32/33	70/90
K-F rings	27/31	16/19	22/27	-	8/21	12/29	10/38	95/165
abdominal ultrasound abnormity	-	9/14	-	-	12/21	-	-	21/35
brain CT/MRI abnormity	29/30	5/5	5/5	-	4/21	8/15	5/38	56/114
ATP7B mutation	-	-	-	-	-	-	18/19	18/19

Table 2. Literature review of rates and types of WD misdiagnosis

items	Wei Ke, et al[10] (2011)	Qiaohui Zeng,et al[3] (2013)	Yuan Chen, et al[11] (2015)	Anzhen Chu, et al[14] (2015)	total
case of misdiagnosis	10/21	15/27	8/21	44/124	77/193
misdiagnosed disease					
hepatitis, hepatic cirrhosis	3/20	8/15	1/8	13/44	25/77
nephritis	1/10	1/15	0/8	17/44	19/77
nephrotic syndrome	0/10	0/15	3/8	1/44	4/77
blood disease	2/10	0/15	1/8	7/44	10/77
systemic lupus erythematosus	1/10	0/15	0/15	1/44	2/77
others	3/10	6/15	3/8	5/44	17/77

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