Case Report
Hemolytic anemia as first presentation of Wilson’s disease with uncommon ATP7B mutation

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Abstract: Wilson’s disease (WD) is a rare inherited disorder of copper metabolism and the main manifestations are liver and brain disorders. Hemolytic anemia is an unusual complication of WD. We describe a 15-year-old girl who developed hemolytic anemia as the first manifestation of Wilson’s disease. An Arg952Lys mutation was found in exon 12 of the ATP7B gene, which is uncommon among Chinese Han individuals. From this case and reviews, we can achieve a better understanding of WD. Besides, we may conclude that the probable diagnosis of WD should be considered in young patients with unexplained hemolytic anemia, especially in patients with hepatic and/or neurologic disorder.

Keywords: Hemolytic anemia, Wilson’s disease, ATP7B

Introduction

Wilson’s disease (WD, hepatolenticular degeneration, HLD) is an autosomal recessive disorder of copper transport and is caused by mutations in the ATP7B gene, which is located on the long arm of chromosome 13 (13q14.1) consisting of 21 exons and encodes copper-transporting P-type adenosine triphosphatase [1, 2]. WD is characterized by excessive amounts of copper in the liver, brain, eye and other body tissues, and the main clinical symptoms are usually due to hepatic (42%) or/and neurologic (34%) involvement [3]. Hemolytic anemia is a rare complication. Here we report a case of WD patient whose gene analysis revealed an uncommon mutation of ATP7B, and initial presentation of the disease was hemolytic anemia.

Case report

A 15-year-old girl presented with fatigue and red wine-like urine. A routine blood test showed a hemoglobin level of 89 g/L, and a bone marrow smear supported the diagnosis of hemolytic anemia, accompanied by increased reticulocytes and indirect bilirubin. Urobilinogen was positive. Blood biochemistry showed that liver function was normal with the exception of bilirubin. Blood examination of antinuclear antibodies, hepatitis virus and Coomb’s test were all negative. The blood and bone marrow expression of CD55 and CD59 on the surface of granulocytes and erythrocytes was normal. The patient was diagnosed with Coomb’s test negative autoimmune hemolytic anemia and received dexamethasone at a dose of 10 mg/day in a local hospital. Twelve days later, blood and urine examinations were normal. She was advised to take oral prednisone and the dose was reduced gradually.

One month later, she presented with fatigue and red wine-like urine again. At that time, the daily dose of prednisone was 25 mg. A routine blood test showed that the hemoglobin level was 88 g/L and decreased to 69 g/L within three days. The reticulocytes occupied 10% of erythrocytes, total bilirubin was 74 μmol/L and indirect bilirubin was 27 μmol/L, albumin level was 25.7 g/L, accompanied by coagulation dysfunction. The results of a repeat Coomb’s test, Ham’s test, and CD55 and CD59 tests were all normal. A physical examination revealed edema of the extremities without bleeding. Abdominal ultrasound showed splenomegaly and ascites. The blood red cell morphology examination
showed 5% ragged red fibers. She was retreated with dexamethasone at a dose of 10 mg/day. A diuretic and hepatinica were also administered. One week later, she had abnormal spirit, however, her hemoglobin was normal. She initially presented with deliriousness, and then subsequent haziness of spirit/mind, dysarthria, and loss of alertness/cognition. An MR scan of the skull was normal. The patient showed hepatic and neurologic dysfunction. WD was considered, and the patient underwent copper metabolism assessment. Serum ceruloplasmin was 4.69 mg/dL, urinary copper was 1236 μg/L, and physical eye examination revealed Kayser-Fleischer rings. According to the scoring system developed at the 8th International Meeting on Wilson’s Disease, Leipzig 2001, the Leipzig score was 9 [4]. She was diagnosed with WD and received penicillamine 1 g/day. One week later, her mental state became normal. Routine blood, liver function and coagulation examinations all returned to normal. During the diagnostic procedure, gene analysis was also performed and a mutation of ATP7B located at exon 12, Arg952Lys, was found (Figure 1). This is an uncommon mutation in Chinese Han individuals.

Discussion

WD is a rare inherited disorder of copper metabolism. The incidence of WD is approximately 1 in 35,000-100,000 live births, and the age at onset is usually between 5 and 35 years of age [5]. Hepatic manifestations of WD are more likely to occur in early childhood, while neurological symptoms are more commonly observed in adolescents [6]. Hemolytic anemia is an uncommon complication, especially as the first manifestation of WD. The initial clinical manifestations are hepatic in origin in 42% of cases, neurological in 34%, psychiatric in 10%, hematological and endocrinological in 12%, and renal in 1%. Approximately 25% of patients have evidence of the involvement of more than one organ at presentation [7].

Herein, we report an adolescent patient presenting with hemolytic anemia as the initial manifestation of WD. The patient improved with glucocorticoid therapy. However, this effect was not sustained. Hemolytic anemia recurred and further investigations revealed features of WD, including Kayser-Fleischer rings, low serum ceruloplasmin and high 24 h urinary copper. Based on the diagnostic criteria of AASLD [8], WD was diagnosed.

It is known that hemolysis in WD is due to a deficiency in ceruloplasmin, the copper transport protein which results in excessive inorganic copper in the blood circulation, much of which accumulates in red blood cells (RBCs). Although the exact mechanism is not known, increased copper accumulation in the RBCs may damage the cell membrane, accelerate oxidation of hemoglobin and inactivate enzymes of the pentose phosphate and glycolytic pathways. Coomb’s negative hemolytic anemia associated with WD is mainly due to acute liver failure. Low-grade hemolysis may be present when liver disease is not clinically evident, and may be the initial manifestation of the disease in 1%-11% of cases [8]. High-dose glucocorticoids can be used to protect against acute hemolysis.

WD is known to be caused by abnormalities in the copper-transporting protein encoding gene.
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ATP7B. Over 500 mutations have now been reported in the ATP7B gene in all 21 exons according to the Wilson’s disease mutation database [9]. The most common mutation in European populations is an amino acid substitution in exon 14, p.His1069Gln, and another frequent mutation is located in exon 8 [2, 10]. Analysis of eight exons (exons 2, 5, 8, 13, 14, 18, 19 and 20) detected 82% of the mutations found, and mutations in exon 12 were uncommon in the UK population [10]. In Chinese Han individuals, mutations were most frequently found in exon 8 in addition to exons 2, 12, 13, 16 and 18, and the most common mutation was Arg778Leu located in exon 8 [11-13]. In the present case, the patient’s family also underwent gene analysis and found an Arg952Lys mutation in exon 12 of ATP7B, which is an uncommon mutation in Chinese Han individuals. No definite genotype-phenotype correlations have been established so far. However, a few reports have suggested a possible relationship between age at onset or clinical course with a specific genotype. One of the most common mutations, p.H1069Q, may be associated with a later age (around 18 years) at presentation and milder disease phenotype [14, 15]. Mutation T1288R may be related to the onset of hemolytic anemia [16]. Our patient with WD showed the genetic mutation, Arg952Lys of ATP7B, first presenting with Coomb’s-negative hemolytic anemia, and later with liver and brain involvement, accompanied by Kaiser-Fleischer rings, and a high response to penicillamine. Thus, there may be a relationship between Coomb’s-negative hemolytic anemia and the Arg952Lys mutation.

In conclusion, WD is a disorder of copper metabolism due to mutation of the ATP7B gene. Many mutations have been identified, and Arg952Lys is an uncommon mutation located in exon 12. Hemolytic anemia may be the presenting feature in some patients with WD, especially in young patients, accompanied by hepatic disorders. The differentiation between Coomb’s negative hemolytic anemia and WD is mainly by the persistent therapeutic effect of glucocorticoids. The treatment is aimed at WD, and glucocorticoids can help patients to get through the hemolytic crisis. More research on the relationship between WD and hematological disorders is needed, especially gene studies. The probable diagnosis of WD should be considered in young patients with unexplained hemolytic anemia, especially in patients with hepatic and/or neurologic disorder. For these patients, treatment with glucocorticoids is inappropriate, while chelation therapy with penicillamine or zinc is effective.

Disclosure of conflict of interest

None.

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