Case Report

Wilson's Disease Masked by Glucose-6-phosphate Dehydrogenase Deficiency – A Case Report

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ABSTRACT

Wilson's disease usually presents with hepatic or neurological manifestations. Hemolysis is an unusual presentation. We describe a case of a young man who had multiple attacks of hemolysis, diagnosed as glucose-6-phosphate dehydrogenase (G-6-P D) deficiency, and followed many years later by hepatic manifestations eventually diagnosed as Wilson's disease.

KEYWORDS: hemolytic anemia, hepatic dysfunction

INTRODUCTION

Clinical presentation of Wilson's disease can vary widely. Hepatic dysfunction tends to affect younger individuals while neuropsychiatric manifestations are more common among older patients. Unusually, hemolysis can be the only presenting symptom[1]. The diagnosis of Wilson's disease can be difficult in this situation. The exact mechanism of hemolysis in Wilson's disease is uncertain. It can be due to oxidative damage of the red cell membrane. Inhibition of antioxidant enzymes including Glucose-6-phosphate dehydrogenase and glutathione reductase may also be involved[2]. The presence of G-6-P D deficiency poses a special challenge for a clinician. Recurrent hemolysis, in this case, can be a part of the disease process. On the other hand, it can delay the diagnosis of the disease, if the physician is not alert to the possibility of this diagnosis in a case of Coombs-negative Hemolytic anemia.

CASE PRESENTATION

A 42-year-old Iranian gentleman, married with three children, presented to our hospital with a history of increasing tiredness, easy fatigue and deepening jaundice and deterioration of level of consciousness. He gave a history of previous recurrent attacks of jaundice with multiple hospital admissions in Iran diagnosed as G-6-P D deficiency. He had multiple blood transfusions and was advised to receive desferral injections to decrease iron overload. He was otherwise well with no history of diabetes or hypertension. He was a lifetime non-smoker and denied any history of alcohol intake or drug abuse. Family history was positive for G-6-P D deficiency.

On examination, he was drowsy but oriented to time and place. There was hyperpigmentation of the skin and mild flapping tremors. Temperature was 37.5 ºC; blood pressure was 110/70 mm/Hg. There was no edema of lower limbs. Abdominal examination showed moderate hepatosplenomegaly and positive shifting dullness. Chest and cardiac examination was unremarkable and neurological examination showed no lateralization or signs of meningeal irritation.

Investigations

Laboratory data included hemoglobin of 89 g/L, white cell count of 6.6 x 10^9 /L, platelets of 80 x 10^9 /L, reticulocytic count of 3.28%, peripheral smear showed normocytic normochromic anemia with anisopoikilocytosis, pencil cells and target cells. Coomb's test was negative. INR was 1.8 and APTT was 43 seconds (ref up to 39).Glucose, urea and electrolytes were within reference range. Other investigations showed total bilirubin of 120 mcmol/L, direct bilirubin of 40 mcmol/L, aspartate aminotransaminase of 98 IU/L (ref up to 50), alanine aminotrasaminase of 210 IU/L (ref up to 60) alkaline phosphatase of 67 IU/L (ref, 30 - 110), and albumin of 30 g/L (ref, 35 - 50).

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Hepatitis panel testing and auto-immune liver antibodies were negative, and other miscellaneous measurements included iron of 51 mcmol/L (ref, 8 - 35), transferrin saturation 99.6% (ref, 10 - 50%), ferritin of 1035 ng/ml (ref 22 - 322), ceruloplasmin of 0.09 g/L (ref, 0.2 - 0.6), urinary copper of 3.2 mcmol/24 hours(ref up to 0.6). G-6-P D level was 26 (ref 118 - 999).

Ultrasound examination of abdomen showed mild hepatic enlargement with coarse echotexture, moderate splenomegaly and moderate ascites. Slit lamp examination of both corneas was normal. Based on clinical and biochemical findings, a diagnosis of Wilson's disease was made with a Leipzig score of 5.

During hospitalization, he was treated for hepatic encephalopathy. After his condition was stabilized and liver function tests and INR improved, transjugular liver biopsy was done and showed picture highly suggestive of Wilson's disease with moderate iron deposition in keeping with hemosiderosis (Fig. 1, 2). Hepatic concentration of copper could not be assessed because of lack of its unavailability in our hospital. He was treated with D-penicillamine, zinc and pyridoxine in addition to iron chelating therapy. Follow up of the liver function tests and coagulation profile after treatment revealed a steady improvement but remained elevated after discharge.

Given the young age of the patient, together with the fact that he presented with acute liver failure and the persistence of elevated liver enzymes after treatment, he was counseled regarding liver transplantation and he chose to go back to his country (Iran) where liver transplant was arranged for him. Prior to that, another liver biopsy was performed and at that time, hepatic copper concentration was high. After recovery, he came back to Kuwait. He was on immunosuppressive therapy. On follow up in medical outpatient clinic, six months after transplantation and three months later, he was asymptomatic and liver function tests and ceruplasmin level became normal. His anemia also improved and G-6-P D level was normal.

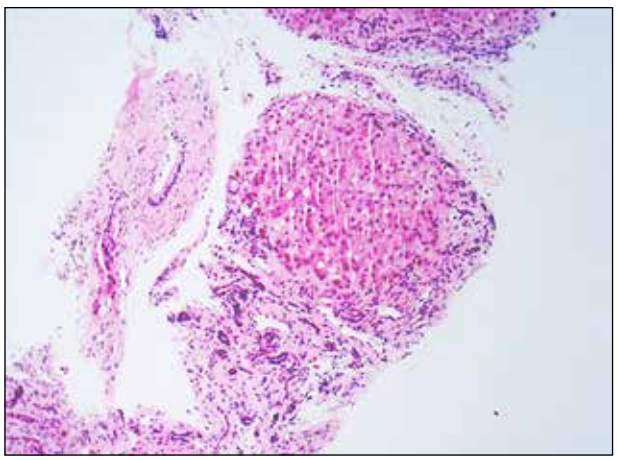

Fig. 1: Low power view of liver tissue shows fibrosis with micro-regenerative nodules, mild steatosis, and bile ductular proliferation. Some brown pigment also noted within hepatocytes.

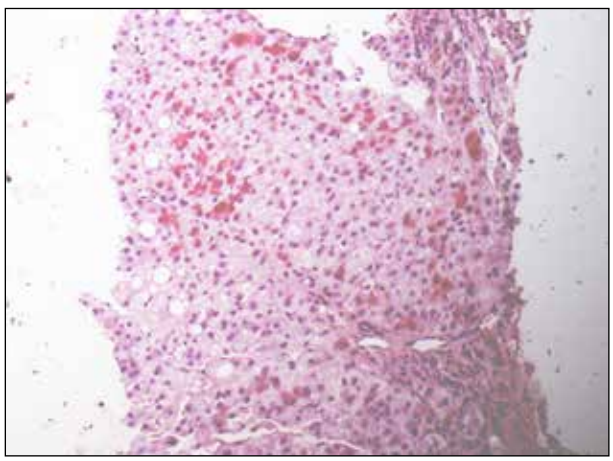

Fig. 2: Orcein stains some hepatocytes in keeping with copper-related proteien deposits

DISCUSSION

Wilson's disease is an inherited disorder in which defective biliary excretion of copper leads to its accumulation particularly in liver and brain[3]. Wilson's disease is due to mutation of ATP7B gene on chromosome 13[4]. Clinical presentation can vary widely, but the most common presentations are liver disease and neuropsychiatric disorders. Kayser-Fleischer ring is present in 95% of patients with neurological symptoms and over half of those without neurological symptoms.

Coombs-negative hemolytic anemia is an uncommon complication of this disease (5 - 20%). Marked hemolysis is commonly associated with severe liver disease. However, hemolysis can be the only initial symptom of the disease. In one series, hemolysis was a presenting feature in 12% of cases, either as a single acute episode, or recurrently[1]. Some patients presenting with neurologic symptoms report previous transient episodes of jaundice, probably due to hemolysis[5].

Self-limiting episodes of hemolytic anemia have been diagnosed, often retrospectively, as being the first manifestation of Wilson's disease, antedating symptoms of liver or neurologic disease by months to years[6]. The exact mechanism of hemolysis in Wilson's disease is uncertain. Excessive inorganic copper in circulation may cause oxidative damage of the red cell membrane. The action of antioxidant enzymes including Glucose-6-phosphate dehydrogenase and glutathione reductase may also be inhibited[2]. The erythrocyte enzyme activity was studied in some cases at times of hemolytic episodes, in which decrease in G-6-PD was reported[7, 8].

Table 1: Scoring system developed at the 8th International Meeting on Wilson's disease, Leipzig 2001[10].

Typical clinical symptoms and sign	Score	Other tests	Score
KF rings		Liver copper (in the absence of cholestasis)	
Present	2	>5 x ULN (>4 μmol/g)	2
Absent	0	0.8 - 4 μmol/g	1
Neurologic symptoms**		Normal (<0.8 μmol/g)	-1
Severe	2	Rhodanine-positive granules*	1
Mild	1	Urinary copper (in the absence of acute hepatitis)	
Absent	0	Normal	0
Serum ceruloplasmin		1 - 2 x ULN	1
Normal (>0.2 g/L)	0	>2 x ULN	2
0.1 - 0.2 g/L	1	Normal, but >5x ULN after D-penicillamine	2
<0.1 g/L	2	Mutation analysis	
Coombs-negative hemolytic anemia		On both chromosomes detected	4
Present	1	On 1 chromosome detected	1
Absent	0	No mutations detected	0

Total Score Evaluation: 4 or more = Diagnosis established; 3 = Diagnosis possible, more tests needed; 2 or less = Diagnosis very unlikely
*If no quantitative liver copper available. **or typical abnormalities at brain magnetic resonance imaging. KF, Kayser–Fleischer; ULN, upper limit of normal

The diagnosis can be established by the presence of Kayser-Fleischer ring with low serum ceruplasmin. When Kayser-Fleischer ring is not present (this is common with hepatic manifestation of the disease), a combination of tests may be needed[9]. A diagnostic score based on available tests was proposed by the Working Party at the 8th International Meeting on Wilson's disease, Leipzig 2001[10] (table 1). The Wilson's disease scoring system provides a good diagnostic accuracy[11]. A diagnostic algorithm is shown in Fig. 3.

A number of drugs are available for the treatment of Wilson's disease. Chelating agents have been the cornerstones in treatment for decades. D-penicillamine promotes the urinary excretion of copper. It may also act by inducing metallothionein[12]. In patients with symptomatic liver disease, recovery of synthetic liver function and recovery in clinical signs occur typically during the first 2-6 months [10]. Trientine is an alternative chelating agent. Its potency in comparison to D- penicillamine is controversial[13].

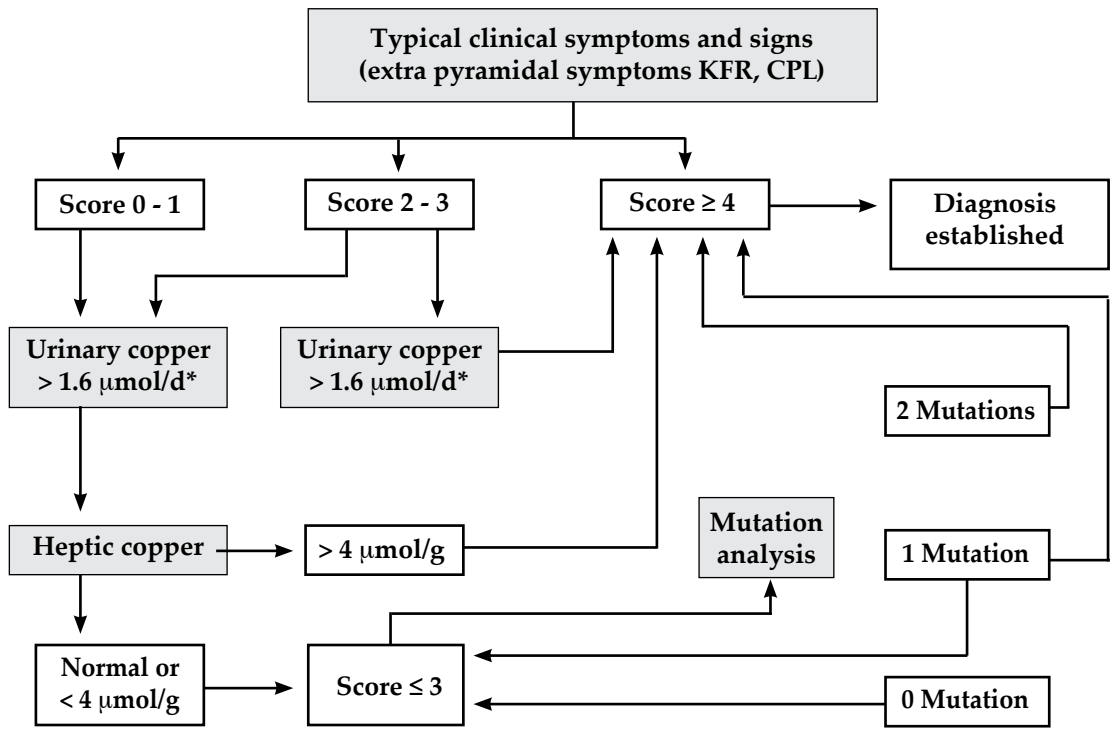

Fig. 3: Diagnostic algorithms for Wilson's disease based on Leipzig score[10].

* In children, the cut off can be lowered to 0.64 μml/d

Adverse effects due to D-penicillamine resolve when it is substituted for trientine. Zinc was first used to treat Wilson's disease in the early 1960s. It interferes with the uptake of copper from the gastrointestinal tract. Zinc induces enterocyte metallothionein, an endogenous chelator of metals. Zinc appears to be equally effective as D- penicillamine but better tolerated[14].

Liver transplantation is frequently necessary for patients presenting with acute liver failure and is indicated for all patients with decompensated cirrhosis due to Wilson's disease not responsive to treatment. The median survival after orthotopic liver transplantation in one study was 2.5 years. Survival at one year was 79%[15]. Living related donor transplantation (where the donor is an obligate heterozygote) gives excellent results[16].

CONCLUSION

The association between hemolytic anemia and Wilson's disease can easily be missed by clinicians. We emphasize the importance of checking liver functions tests in young patient with coomb's negative hemolytic anemia. Recurrent hemolysis, as in G-6-P D deficiency, may mask the picture of Wilson's disease. A high index of suspicion is needed in such cases.

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