WILSON'S DISEASE PATIENTS WITH NORMAL CERULOPLASMIN LEVELS*

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Wilson's disease, an inborn defect of copper metabolism, is a fatal disease unless specific treatment is given. Hepatic presentation mimics almost all kinds of liver disease and the diagnosis is sometimes problematic. The diagnosis is based on clinical findings, family history, presence of Kayser-Fleischer rings, and results of key laboratory tests such as low serum ceruloplasmin level, increased urinary copper excretion and hepatic copper content.

We report four patients with Wilson's disease with hepatic manifestations with unknown there were difficulties in making the diagnosis because of normal serum ceruloplasmin levels. Inspite of normal ceruloplasmin levels and absence of Kayser-Fleischer rings, strong family history suggested Wilson's disease and the diagnosis was confirmed by increased urinary and hepatic copper amounts. *Key words: Wilson's disease, ceruloplasmin.*

Wilson's disease (WD) is an inborn defect of copper (Cu) metabolism and is inherited in an autosomal recessive pattern. Therapeutic success with oral chelating agents have made this disease one of the treatable metabolic liver diseases[1]. The patients usually present with either hepatic involvement or neurological manifestations; some exhibit findings in both organ systems[1]. Progressive accumulation of Cu in the liver due to impaired Cu excretion and its subsequent deposition in other organs cause the varied clinicopathologic features of WD[1]. Although a low ceruloplasmin level had been considered as a pathogenic factor in WD, normal ceruloplasmin levels have been reported in up to 18 percent of patients with WD[2].

Because of the high rate of consanguineous marriages in Turkey, WD is not rare. We followed 152 patients with WD and here in report four of them with whom there were diffuculties in making the diagnosis because of normal ceruloplasmin levels.

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Case Reports

Case 1

An eight-year-old girl presented with a one-month history of abdominal distension and jaundice. She had two siblings with WD, one of whom had died; the other had a low serum ceruloplasmin level (4 mg/dl). On admission she had icterus and hepatomegaly. Kayser-Fleischer ring (KF) was absent. Laboratory evaluation showed anemia with a hemoglobin of 7.4 g/dl, alanine aminotransferase (ALT) 429 IU/L, aspartate aminotransferase (AST) 182 IU/L, total bilirubin 2.2 mg/dl, conjugated bilirubin 1.3 mg/dl, total protein 8.4 g/dl, albumin 3.2 g/dl, and serum ceruloplasmin 38 mg/dl (normal range 20-40 mg/dl). Copper excretion in 24-hour urine was increased (320 μg/day, normal < 100 μg/day). Liver biopsy was consistent with cirrhosis, and copper content of the liver was 1200 μg/g dry weight (normal < 50)[1]. She was treated with a low-Cu diet, D-penicillamine and zinc sulphate and has been followed for one year without any complication.

Case 2

A 14-year-old girl of consanguineous parents was referred with abdominal distension. Her brother had died of cirrhosis. Physical examination revealed hepatosplenomegaly and icterus. Kayser-Fleischer ring was absent. On laboratory evaluation the hemoglobin level was 8.1 g/dl, ALT 104 IU/L, AST 34 IU/L, total bilirubin 19.3 mg/dl, conjugated bilirubin 12.9 mg/dl, serum ceruloplasmin concentration 40 mg/dl, and urinary copper 520 μg/day. Liver histology showed cirrhosis and liver Cu concentration was 300 μg/dry weight. Splenoportography indicated portal hyertension and spontaneous splenorenal shunts. She has been followed with the treatment of a low-Cu diet, D-penicillamine and zinc sulphate for six months.

Case 3

An eight-year-old girl was admitted with abdominal distension and jaundice. Her parents were first-degree relatives and two brothers had died of cirrhosis at six and eight years of age. She had hepatosplenomegaly and icterus; KF ring was absent. Laboratory tests showed anemia (hemoglobin 8.9 g/dl), and elevated ALT (252 IU/L), AST (409 IU/L), and total and conjugated bilirubin (4.2 and 2.2 mg/dl, respectively). Serum ceruloplasmin level was normal (50 mg/dl); urinary Cu was increased (480 μg/day). Liver biopsy was compatible with cirrhosis, and liver Cu content was raised at 450 μg/g dry weight. A low-Cu diet, D-penicillamine and zinc sulphate treatment was given. She has been followed for three months without any complaints.

Case 4

A six-year-old girl, sister of Case 3, presented with abdominal distension. She had hepatosplenomegaly; KF ring was absent. Laboratory evaluation revealed a normal complete blood count and bilirubin levels, and elevated ALT (185 IU/L) and AST (151 IU/L), serum ceruloplasmin 55 mg/dl, urinary Cu excretion 144 µg/g day, and liver Cu content 680 µg/g dry weight. She has been followed for three months with the treatment of a low-Cu diet, D-penicillamine and zinc sulphate.

Discussion

In patients with WD, hepatic dysfunction is the leading symptom during childhood and adolescence and it mimics various forms of liver disease ranging from asymptomatic transaminasemia to cirrhosis[1,3,4]. Therefore, there is often a serious delay before the correct diagnosis. Most patients have cirrhosis at presentation similar to our patients. It is important to start the treatment before irreversible damage occurs.

No single test can be used for the diagnosis of WD; clinical findings, family history, and key laboratory tests establish the diagnosis. Criteria for the dignosis are low serum ceruloplasmin levels, presence of KF rings, increased 24-hour urinary Cu excretion, and hepatic Cu content. Among them, the last two are valuable diagnostic tests[1,3]. Kayser-Fleischer (KF) rings are almost always present in patients with neurological involvement, but may be absent in patients with hepatic disease[5]; therefore, the absence of KF ring does not exclude WD in a patient with liver disease. It means that extrahepatic accumulation of Cu has not become extensive. Although the majority of patients with WD have low ceruloplasmin levels, some have normal levels due to hepatic inflammation[2,3,5]. If WD is not considered in the differential diagnosis in a patient with liver disease and a normal ceruloplasmin level, further evaluation is generally not done. There was a strong family history in our patients who had exclusively hepatic manifestations. Although their ceruloplasmin levels were normal and KF rings were absent, tests to determine urinary Cu excretion and liver Cu content were performed and diagnosis of WD was confirmed.

In fact it is difficult to make a differential diagnosis among causes of hepatic Cu overload, other than WD, such as Indian childhood cirrhosis and Cu-associated childhood cirrhosis. Presentation age is younger in patients with Indian childhood cirrhosis and there are specific histological manifestations[6]. D-penicillamine is also used for the treatment of both diseases[1,6].

Medical management in WD patients is reduction of accumulated Cu by therapy with several Cu chelating agents, zinc sulphate and a low-Cu diet[1,3]. Penicillamine therapy early in the course of the disease has resulted in reduction in mortality and improvement in hepatic histology[1,7]. Wilson's disease (WD) needs to be

considered in almost all patients with liver disease and a family history, like in our patients. Normal ceruloplasmin levels do not exclude WD even if the siblings had low serum ceruloplasmin levels. Without treatment, WD is uniformly fatal, therefore, urinary excretion of Cu and liver Cu assays should be done for the diagnosis, and treatment should be started as early as possible in the course of the disease. Early diagnosis is also important for screening of other family members to detect asymptomatic patients[8].

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