A Neglected Case of Wilson Disease

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ABSTRACT

Introduction: Wilson’s disease is an autosomal recessive disorder, characterized by a disturbance in copper metabolism that leads to copper overload in different tissues of the body. Because of various manifestations of Wilson’s disease, physicians should have high index suspicion when patients manifest any type of liver disease, neurologic and psychiatric signs and symptoms.

Case Presentation: A 7.5-year-old boy was referred, presenting with generalized pruritus and stammer since the age of 4. Initial evaluation showed abnormal liver enzymes. Abdominal sonography revealed multiple echogenic lesions without acoustic shadow in the gallbladder, which was suggestive for gallstone. After about two years, he suffered from weakness, drowsiness, fever, nausea, epistaxis and abnormal liver function tests. With through clinical and laboratory work up, Wilson’s disease was finally diagnosed and appropriate treatment was started. Acceptable response to treatment was achieved.

Discussion: Wilson’s disease has a wide range of manifestation so physicians should have high index suspicion when patients present any type of liver disease, neurologic and psychiatric signs and symptoms. Any delay in diagnosis or management can result in catastrophic outcomes.

Keywords: Hepatolenticular Degeneration; Pruritus; Gallstone

1. Introduction

Wilson’s disease (WD), as a progressive hepatolenticular degeneration, is a rare autosomal recessive disease, which affects approximately 1 in 30,000 live births (1, 2). Although this disease has been known for almost a century, an exact pathogenesis of the disorder remains unclear (2). A mutation in ATP7B gene that encodes an essential protein for transportation of the cooper is suggested to play a role in WD (1). It is characterized by a disturbance in copper metabolism that leads to copper overload in different tissues of the body (1, 3). The overall clinical picture varies from asymptomatic to acute liver failure (1). Systemic accumulation of copper causes typical phenotypes that include progressive liver damage, neurological deficits, psychiatric illnesses, presence of Kayser-Fleischer (KF) rings, renal tubular disorders, arthropathy, cardiomyopathy, and hypoparathyroidism (2). Other manifestations of WD like hemolysis may occur with the formation of gallstones from the bilirubi-
nate calculations (1). Any unexplained acute or chronic liver disease in children and teenagers should raise the suspicion about Wilson’s disease. The clinical suspicion is confirmed by studying indices of copper metabolism. Serum ceruloplasmin level is one of these indices that usually decreases in Wilson’s disease (< 20 mg/dL). A 24-hour urinary excretion of copper should be investigated in all patients whom the diagnosis of WD is being considered. In symptomatic patients, this is typically > 100 mcg/day, but finding > 40 mcg/day is abnormal and needs further work up. The serum copper level may be elevated in early Wilson’s disease. Demonstration of KF rings by an experienced ophthalmologist is a variable finding in liver diseases. They might be found in patients with chronic cholestatic diseases and in children with neonatal cholestasis. Therefore, it is not specific for Wilson’s disease and its absence does not exclude the diagnosis (4, 5). Here we report on a neglected case of Wilson’s disease initially presenting with pruritus and asymptomatic gallstones.

2. Case Presentation

A seven and half-year-old boy referred presenting with generalized pruritus for 4 years. The itching had become progressively worse during the last couple of weeks before his attendance and had not responded to the treatments (topical calamine lotion and hydroxyzine syrup). He had no abdominal pain or any other gastrointestinal complaints and history of fever and icterus was negative. Parents revealed that in his past medical history his physical development had been delayed and he had had stammer. He had neither had history of drug ingestion, nor known allergies. Clinical examination had not revealed any rash or other abnormalities, although slight excoriation of the skin had been present. No abnormality had been observed in head and neck. Abdomen had been firm without tenderness or distention. Liver span had been 9 cm in physical examination. The Morphy sign had been negative. In liver function test SGOT of 148 U/L, SGPT of 243 U/L and alkaline phosphatase of 1157 U/L had been detected. However, total bilirubin had been 0.8 mg/dL and direct bilirubin had been 0.2 mg/dL. Hepatophilic viral markers had all been negative. His cholesterol and triglyceride had been 291 and 231 respectively. HDL of 68 and LDL of 178 had been detected. Lipid profiles of the parents had been totally normal. Abdominal sonography had revealed multiple echogenic lesions without acoustic shadow in the gallbladder which had been suggestive for gallstone. No specific evaluation for stone analysis had been done at this period. Hepatic and splenic spans had been reported 12 and 10 cm respectively in sonologist report. Thyroid function test had been normal. In ophthalmologic examination, allergic changes in both eyes had been seen. A pediatric gastroenterologist had visited him in course of hospital stay and due to abnormality in liver enzymes and pruritus, had prescribed ursodeoxycholic acid. At that time, no specific investigation for Wilson’s disease had been recommended. The patient had been discharged with the diagnosis of allergic disease with topical calamine lotion and hydroxyzine syrup. No lipid-lowering medication had been prescribed to him. Two years later the patient referred, presenting with weakness, drowsiness, fever, nausea and epistaxis. This time, SGOT of 810 U/L, SGPT of 405 U/L, total bilirubin of 4.7 mg/dL and direct bilirubin of 2.3 mg/dL were detected. Prothrombin time (PT) was 18 seconds (INR = 1.9). Albumin level was about 2.2 gr/dL. In the abdominal sonography, liver was 14 cm and several stones were seen in the neck of the gallbladder. Thickness of gallbladder was 4 mm with the hypo-echoic rim around the inflammation, which was suggestive of acute cholecystitis. Initial measurements were done for stabilizing his condition. Due to concomitant neurologic and hepatic manifestations, we conducted through para-clinical investigations, which revealed low ceruloplasmin level (11 mg/dL). Twenty-four-hour urine collection for copper excretion was 483 mcg/dL that is highly in favour of Wilson’s disease. Presence of Kayser-Fleischer (KF) rings was approved via Slit-lamp examination by an ophthalmologist. His parents did not allow the clinician to carry out liver biopsy. Then after the appropriate medical and supportive treatment (d-Penicillamine and zinc appropriate to body weight) was started, finally, parents discharged him by informed consent to continue his treatment in a pediatric liver transplant center.

3. Discussion

Wilson’s disease is an autosomal recessive disorder with the prevalence of approximately 1/30,000 newborns worldwide (6). This disorder is caused by over 480 different kinds of mutations in the ATP7B gene which encodes a membrane-bound copper transporting ATPase (7). Disorder of hepatic copper metabolism causes the accumulation of copper in many organs and tissues, initially liver and then other tissues (7, 8). The hallmarks of the WD include hepatic, neurological and psychiatric symptoms. Kayser-Fleischer rings which show copper accumulation in brain, are common in neurological WD (9) and are present in 5% of patients with neurological symptoms, 50-60% of patients without neurological symptoms and only 10% of asymptomatic siblings. (8) Although Kayser-Fleischer rings and neurological abnormalities may not be present in most patients, it is believed that all patients have some degrees of hepatic dysfunction, which varies from acute and chronic hepatitis to cirrhosis and fulminating hepatic failure (6, 8, 10). Acute Wilsonian hepatitis is identical to other acute liver diseases caused by toxins or viruses. (8) Episodes of hepatitis with spontaneous regression can happen and liver cirrhosis would occur without adequate therapy. (7) Severe hemolytic anemia, which happens when stored copper is released from the liver, can complicate acute liver disease, although it is not pathognomonic (8, 9). Increased intravascular hemo-
A Case of Wilson Disease

Halimiasl A et al.

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There is no single diagnostic test for WD and diagnosis is usually made by lab tests following clinical suspicions (1). Diagnosis is based on low serum copper and ceruloplasmin levels (< 20 mg/dL; immunoassay), high copper concentrations in the liver (>250 mcg/g dry weight), high copper excretion in the 24-hour urine (>100 mcg/day), and conducting a penicillamine challenge test (urinary copper excretion >1,600 or 1,057 mcg/day) (6) if doubt remains, tests should be repeated at a later stage (2). In most of the cases, diagnosis can be made with the tests described above, however a group of patients cannot be diagnosed by them (6). Serum ceruloplasmin may be in the low to normal range in up to 45% of patients with hepatic Wilson’s disease. Also in severely malnourished patients or in heterozygous carriers of the Wilson’s disease gene or patient with autoimmune hepatitis, ceruloplasmin can be low. Mutation analysis for diagnosis is not valued, as there are many mutations, which are all rare, and most of the patients carry two different mutations (8). Finally, it should be mentioned again that because of various manifestations of WD, physicians should have high index suspicion when patients present any type of liver disease, neurologic and psychiatric signs and symptoms. WD has different faces and not even in two patients, is ever quite alike. Screening tests including slit lamp examination for KF ring by an experienced ophthalmologist, abdominal ultrasound for studying changes in liver, serum copper and ceruloplasmin, and 24-hour urinary copper should be done for all suspected patients (5, 12).

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