

Wilson's Disease - A Rare Hereditary Cause of Chronic Liver Disease in Children, The First Ethiopian Case Report

Abebe Habtamu

Department of Pediatrics and Child Health, Addis Ababa University, Addis Ababa, Ethiopia

Abstract: *Wilson's disease is an autosomal-recessive disorder caused by mutation in the ATP7B gene, with resultant impairment of biliary excretion of copper. It is universally fatal without effective therapy. Individuals without Kayser-Fleischers ring who have subnormal ceruloplasmin and abnormal liver tests can undergo liver biopsy to confirm the diagnosis. If available, molecular testing for ATP7B mutations or haplotype studies should be obtained and may be used as primary screening.*

1. Introduction

Wilson's disease (WD) is an autosomal recessive disorder of the copper metabolism leading to the accumulation of this metal in different organs and tissues. Hepatic and neurological symptoms are the main clinical features of the disease (1). Copper is absorbed in the duodenum and proximal part of the small intestine. The liver utilizes some copper for metabolic needs, synthesizes and secretes the copper-containing protein **ceruloplasmin**, and excretes excess copper into bile. Secretion of **apoceruloplasmin**, results in the **decreased blood level of ceruloplasmin** found in most patients with Wilson's disease due to the reduced half-life of apoceruloplasmin.

Wilson's disease is a rare autosomal-recessive disorder. A prevalence rate of 30 cases per million (or one per 30,000) and a birth incidence rate of one per 30,000 to 40,000 are often quoted. (2-5) It has been estimated that there are 600 cases of Wilson's disease in the United States and that 1% of the population are carriers (4).

In some cases, physicians may misdiagnose, because they do not consider the hidden causes of chronic hepatitis. Wilson's disease (WD), a genetic disorder involving biliary copper excretion, can cause elevated liver enzyme levels, lasting for more than 6 months in asymptomatic patients (6,7). (4,5) While the prevalence of Wilson's disease (WD) is very low, it is a treatable liver disease and therefore needs to be properly identified (8). (6)

2. Case Report

This is a 9 years old male child who presented with yellowish discoloration of the eyes and anorexia of 3 years duration. Six months after the illness, he was seen by Adult gastroenterologist and with the impression of autoimmune hepatitis, he was given and was taking Azathioprine and prednisolone for one year.

Otherwise, there is no urine and stool color change, no fever, no behavioral change, no abdominal pain, and no contact history with such patients. He has no history of bleeding tendency and consanguinity.

He took prophylactic antibiotics and vitamins while he was visiting different private clinics. Finally, he was evaluated by pediatrics gastroenterologist/ hepatologist and decided to investigate for hereditary metabolic liver disease after ruling out AIH (autoimmune hepatitis). Hence, he was sent to abroad, Thailand, Bangkok on July, 2004, stayed for 20 days and returned after investigations were done.

Vital signs: PR = 92/m regular full, RR = 28, T = 37.5°C, BP = 90/60. Anthropometry measurement showed that Weight = 20kg (< -3 Z-score), height = 117cm (< -3 Z-score), Weight/height (-1 to -2 Z score), Body mass index (BMI) = 16cm.

Pink conjunctivae and icteric sclerae. Liver is 10cm BRCM with TVLS = 16cms, Spleen is 6cm along the line of growth. No sunflower cataract or other eye signs of WD.

Assessment = Underweight, stunting and Jaundice secondary to ?? Wilson's disease.

Investigations = WBC 5100 N = 61%, L = 39%, **Hgb** = 10.7 gm/dl, **HCT** = 32.2%, **Platelets** = 251,000. Total serum protein 7gm/dl, Albumin = 2.5mg/dl, Globulin 4.5gm/dl, direct bilirubin = 14.4mg/dl, total bilirubin 17.3mg/dl, ALP = 464u/l, AST = 123u/l, ALT = 81u/l, Gamma glutamyltransferase (GGT) = 463 u/l. RFT, BUN = 4 mg/dl, Creatinine = 0.2mg/dl, amylase = 12u/dl, serum electrolyte were in the normal range. Viral markers HBSAG, HBcIgM, Anti HCV antibody, Anti HAV(IgG) and Anti HAV(IgM) were Negative. TORCH infection (screening for CMV IgM, Rubella IgM, Toxoplasma IgM, HSV Ab(IgM) were Negative). HIV Ag/Ab = Negative. Serum Iron = 102 ug/dl (45 -182), TFT (T4 = 10.2, TSH = 4.4, all normal). PTT = 39sec, PT = 21 sec, INR = 1.77, EBV Ab(IgM) = negative.

Ceruloplasmin = 15mg/dl (low) (normal > 20mg/dl), **Serum copper** = 254 (70-140 ug/dl), Uric acid = 4.5mg/dl (low for his age), **Urine copper** = 78 micg/24h (10-60), tumor marker AFP = 1.6ng/ml (normal). **Abdominal ultrasound;** Hepatosplenomegally with coarse echotexture.

Index = Chronic liver disease (CLD) 2° ??

Abdominal CT; Impression - there are multiple matted small LNs at the hepatic hilar region surrounding the CBD, portal vein and hepatic artery proper, common hepatic artery with largest one (inferior to main portal vein) measuring 22.7x17.7 mm. Screening for AIH and tuberculosis were all negative.

Liver Biopsy; Done abroad showed that **hepatic copper** was 345mg/g (significantly elevated.)

3. Discussion

The causes of jaundice in the neonate and older infants are not the same as the causes of jaundice in the older child or adolescent. The approach to the problem varies with age.

There is no single specific test for the diagnosis of Wilson's disease (WD). Diagnostic approach to the child or adolescent with hyperbilirubinemia includes ALT, alanine aminotransferase; ANA, antinuclear antibody; ASMA, antismooth muscle antibody; AST, aspartate transaminase; CBC, complete blood cell count; DIC, disseminated intravascular coagulation assay; EBV, Epstein-Barr virus antibody; ERCP, endoscopic retrograde cholangiopancreatography; GGT, γ -glutamyltransferase; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin M; LKMA, liver-kidney microsomal antibody; MRCP, magnetic resonance cholangiopancreatography; PT, prothrombin time; PTC, percutaneous transhepatic cholangiography; PTT, partial thromboplastin time (9).

Episodes of hepatitis can occur with elevated liver enzymes, and then, show spontaneous regression. WD leads to liver cirrhosis without adequate therapy and most of these patients eventually develop cirrhosis (10). In a study of 439 patients in Korea, 75% of the adult WD patients with hepatitis were diagnosed with liver cirrhosis because of delayed diagnosis. The neurological manifestations of WD typically occur in patients in their early twenties. Neurological symptoms such as dystonia, incoordination, and tremor have been observed along with psychiatric symptoms such as depression, hyperactivity, or loss of sexual inhibition (11)

In the present case, it was difficult to make an early diagnosis, because even with a history of increased liver enzyme levels, more precise examinations were not prescribed, and the patient was prescribed hepatotonics in the local clinic. This patient did not have any other complications except hepatitis.

The long-term treatment of symptomatic cases of WD entails the chronic use of copper chelators and zinc, while liver transplantation provides a cure [12]. The copper chelators commonly used for WD are penicillamine and trientine hydrochloride but these chelators are not available in our country. While we attempt to source trientine abroad, we based our decision to commence a zinc-based treatment on a case series which showed favourable improvement in symptomatic children treated with zinc only [13].

4. Conclusion

For patients with liver disease due to WD, histologic evaluation of the liver biopsy showing hepatic Copper accumulation, ceruloplasmin levels, urine copper excretion and clinical findings of Kayser Fleisher rings and sunflower cataract are important criteria for its diagnosis. Two or more of those criteria should be fulfilled to diagnosis WD. In this patient, liver biopsy revealed high copper accumulation, low ceruloplasmin, high urine copper excretion and evidences of chronic liver disease. Hence, this patient is a real case of WD fulfilling the diagnostic criteria.

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