Wilson Disease among Filipino Children: The Spectrum of Hepatic Illness

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ABSTRACT

Wilson disease is an autosomal recessive disorder of copper metabolism that is rarely reported among Filipinos. Four children with Wilson disease presenting with various hepatic manifestations, namely, an asymptomatic elevation of transaminase levels, prolonged jaundice and acute liver failure are presented. The diagnosis was based on a combination of clinical and biochemical findings. Early recognition and management is important as effective treatment could reverse the damage caused by copper toxicity.

Introduction

Wilson disease (WD) is a rare autosomal recessive disorder of copper metabolism, which commonly presents either as a liver disease, progressive neurological disorder or psychiatric illness.[1] The disease is present in 1 in 30,000 to 100,000 individuals but is rarely reported in the Philippines. A review of local literature revealed only four cases afflicted with WD, three with hepatic illness[2,3] and a 16-year old with neurological symptoms.[3] Since WD disease is a genetic disorder, this may suggest that mutations to the copper-transporting gene *ATP7B*[4] is either rare among Filipinos or the disease is under-recognized. In children, the most common presentation of WD is that of a liver pathology and the spectrum of hepatic illness encountered can range from one who is asymptomatic with only biochemical abnormalities to those in acute liver failure requiring liver transplantation.[5] It is important to recognize WD at any stage as treatment that is effective and can prevent or reverse the condition is available.

In the last three years, we have encountered four children diagnosed with WD with varied hepatic manifestations. We present these cases to increase our awareness of the disorder and to discuss the clinical findings and biochemical investigations that may help in the diagnosis. A summary of these cases is presented in Table 1.

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Case series

Case 1. A 5½-year old male consulted for elevated transaminase levels ranging from 140 to 535 IU/L (nv: 0-38). A liver function test was performed as the patient's 8-year old sister died of sudden onset of jaundice that subsequently led to liver failure. The sister's diagnosis was not disclosed. Past medical history was unremarkable. Physical examination was essentially normal including a normal slit lamp examination of the eyes. Further investigations showed normal serum albumin (>3.5 g/L), prothrombin time and liver ultrasound and a non reactive HBs antigen. Antinuclear antibody was positive at a titre of 1/320. Histology was described as mild chronic portal inflammation mostly lymphocytes with fibroblastic proliferation in the portal areas and presence of fatty changes, interpreted as chronic hepatitis with mild steatosis. The patient was diagnosed and treated as a case of an autoimmune hepatitis. He was given high-dose prednisolone with additional azathioprine later in the course. After four months, no improvement was seen in the transaminase levels, thus Wilson disease was considered. Investigations showed low serum ceruloplasmin <0.02 g/L (nv 0.2-0.6) and increased 24-hour baseline urine copper of 438 μg/day (nv 15-60). The patient was initially started on elemental zinc at 25 mg twice per day. After three months, 24-hour urine copper excretion was still increased at 334 μg/day. Zinc was further increased to 25 mg 3x per day and his liver transaminase normalized after 6 months of initiating zinc treatment. For the last three years, the 24-hour urine copper has been in the normal levels from 17 to 66 μg/day. He is presently a well grown 9-year old with normal BMI (BMI: 17.8; z=+1) and no signs of chronic liver disease. Screening of his 11-year old brother showed normal levels of serum transaminase and ceruloplasmin.

Case 2. A 10-year old male initially consulted for a three week history of jaundice and facial edema later followed by 3 to 7 episodes of yellowish watery stools. Past and family histories were unremarkable and he is the only son of non-consanguinous parents. Physical examination showed a well-nourished boy (BMI: 14.7, z= -1) with generalized jaundice, the liver edge was firm and palpable up to 8 cm below the right costal margin. The spleen was not palpable. There were no signs of edema, cyanosis nor clubbing. Neurological examination was essentially normal. The initial diagnosis was acute hepatitis, probably infectious

Table 1. Summary of work ups, treatment and outcome of patients with Wilson disease

	Case 1	Case 2	Case 3	Case 4
Age (yrs)	5 ½	10	16	9
Sex	Male	Male	Female	Male
Kayser-Fleischer ring	Negative	Positive	Negative	Positive
Serum ceruloplasmin (nv: 0. 2-0.6 g/L)	<0.02	0.09	0.68	0.043
Baseline 24 hour urine copper (nv: 15-60 μg/day)	438	2755	123	77
Histology	Chronic hepatitis with mild portal inflammation and fibrosis and mild steatosis		Chronic hepatitis mild portal inflammation and fibrosis and presence of intracellular cholestasis	Chronic hepatitis with moderate portal inflammation and fibrosis and steatosis.
Treatment for Wilson disease	Zinc	Trientine and Zinc	Zinc	Zinc
Duration of follow-up (months)	41	7	3	6
Present status	No signs of liver disease with normal levels of AST, ALT and 24 hour urine copper	Still with increased 24 hour urine copper level but with almost normal liver function tests	Died of pneumonia after three months of treatment for Wilson disease	No signs of liver disease with normal levels of AST, ALT and prothrombin time; improving albumin level

in etiology. However, HBsAg, anti-HBcIgM and anti-HAV IgM were non-reactive. Laboratory investigations showed a slightly low hemoglobin of 110 g/L (nv: 120-170) with a normal reticulocyte count and deranged liver function tests: total bilirubin 37.2 mg% (nv: 0.5-1.5); direct bilirubin 33.5 (0.1-0.4); AST 182 IU/ (0-38); ALT 134 (0-41); total protein 6.8 g/L (6-7.8); and albumin 2.5 (4.5-5). Prothrombin time was prolonged with 18 secs difference from control and an INR between 2.5 and 3.0 even with Vitamin K supplementation. An ultrasound of the liver showed hepatomegaly with diffuse parenchymal changes and cholelithiasis. With the negative hepatitis markers and the patient in liver failure, further work-ups were done which showed presence of Kayser Fleischer ring on slit lamp examination of the eyes. Serum ceruloplasmin was low at 0.09 g/L (nv 0.2-0.6) and 24-hr urine copper was markedly increased at 2755 μg/day (nv 15-60). The patient was started on trientine at 20 mg/kg/day and immediately referred to a liver transplant team. A computerized tomography scan of the brain showed no neuropathology. After seven months of treatment, he is no longer jaundiced, with almost normal liver function tests: total bilirubin 0.98 mg% (nv: 0.5-1.5); direct bilirubin 0.44 (0.1-0.4); AST 50 (0-38); ALT 45 (0-41); total protein 7 g/L (6-7.8); albumin 36 (4.5-5). Prothrombin time is within two seconds of the control. His 24-hr urine copper remains increased at 186 μg/day (15-60), thus, zinc was added at 75 mg per day in three divided doses. At the time of this writing, we plan on performing a liver biopsy on the patient.

Case 3. A 16-year old female presented with a 6-month history of jaundice and weight loss despite a good appetite. She also had amenorrhea and cold intolerance. Past and family histories were unremarkable. She is the 3rd of 9 siblings but lives with the paternal aunt. Physical examination revealed a poorly nourished patient (BMI=14; z=-3) with a vacuous smile (Figure 1) who is awake with generalized jaundice, a firm liver palpable 12 cm below the right costal margin, spleen 4 cm below the left costal margin and presence of bipedal edema. No facial telangiectasia, spider nevi and clubbing were observed. A diagnosis of chronic liver disease probably Wilson disease was considered. Slit lamp examination showed absence of Kayser Fleischer ring. Further work-ups revealed deranged liver function tests: total bilirubin 5.3 mg% (nv: 0.5-1.5); direct bilirubin 3.6 (0.1-0.4); AST 367 (0-38); ALT 150 (0-41); albumin 2.9 (4.5-5). Prothrombin time was within 3 seconds of the control value. HBsAg and anti-HCV were both non-reactive. An ultrasound was performed which revealed moderate hepatosplenomegaly with diffuse parenchymal changes. Both 24-hr urine copper and serum ceruloplasmin were increased at 123 μg/day (15-60) and 0.68 g/L (nv 0.2-0.6), respectively. Histology showed chronic hepatitis with mild portal inflammation and portal fibrosis, presence of intracellular cholestasis and fatty change. The patient was started on zinc treatment at 50 mg three times per day with good compliance. Unfortunately, after three months of treatment, she developed a three day history of fever and cough and went into respiratory distress. She died of respiratory failure secondary to a community-acquired pneumonia.

Case 4. A 9-year old male consulted with a 3-month history of jaundice and fever followed by bipedal edema. There was also a history of gait disturbance and knee and ankle pains. The past and family histories were both unremarkable. On physical examination, his nutritional status was within normal (BMI: 15.7; z= -2). He was not jaundiced, liver and spleen were not palpable and there was no ascites. The patient also had no facial telangiectasia, spider nevi or clubbing. Neurologic examination was normal. Slit lamp examination showed presence of Kayser Fleischer ring and sunflower cataract (Figure 2). Subsequent

work-ups showed hemoglobin 110 g/L (nv: 120-170); albumin 1.5 g/L (4.5-5); prolonged prothrombin time which was 12 secs from control value (INR 2.3); AST 86 IU/L (0-38); ALT 56 IU/L (0-41). Her 24-hr urine copper was slightly increased at 77 μg/day (15-60) but the serum ceruloplasmin was low at 0.043 g/L (nv 0.2-0.6). An ultrasound was done which showed normal liver size and echopattern and presence of minimal ascites. Magnetic resonance imaging of the brain was unremarkable. Two months after treatment with zinc at 25 mg 3x per day, the prothrombin time has improved to 3 secs of the control value, thus, a liver biopsy was done which showed chronic hepatitis with moderate portal inflammation and fibrosis and presence of steatosis (Figure 3). The patient has been on zinc treatment at 50 mg three times per day for the last 6 months with good compliance. His AST and ALT levels are within normal and his albumin has increased to 2.4 g/L.

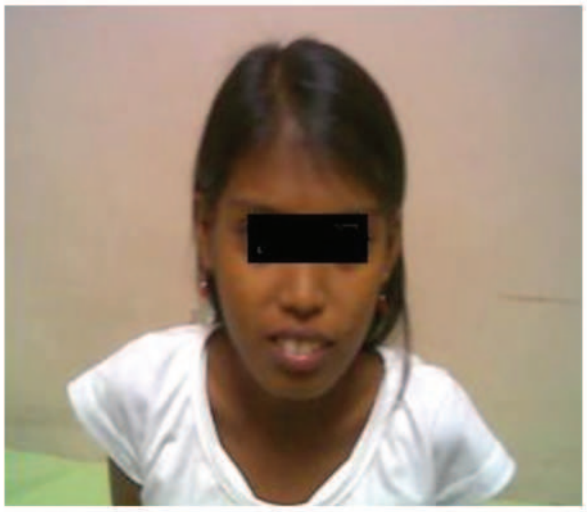

Figure 1. Vacuous smile which is a mask facie with an open mouth caused by dystonia of facial and mandibular muscles.

Discussion

We have presented four children with Wilson disease (WD) with varied hepatic manifestations in the form of: (1) an asymptomatic child with only an elevation of transaminase levels (case 1), (2) an acute hepatitis in acute liver failure (case 2); and (3) a prolonged jaundice of 3 and 6 months duration (cases 3 and 4). The varied clinical manifestations of WD make it difficult and challenging to diagnose and a high index of suspicion is required. In the first case, the diagnosis of autoimmune hepatitis was reconsidered as the patient did not readily respond to standard immunosuppressive therapy. Although the patient had detectable autoantibodies of the anti-nuclear type and a chronic hepatitis on histology, these features may also be present in WD.[6, 7]

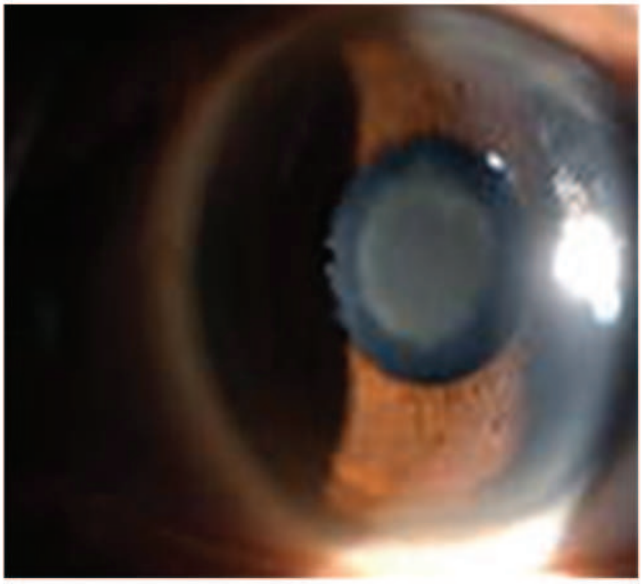

Figure 2. Copper deposition at the outer membrane of the cornea **(**Kayser Fleischer ring) and at the lens (sunflower cataract).

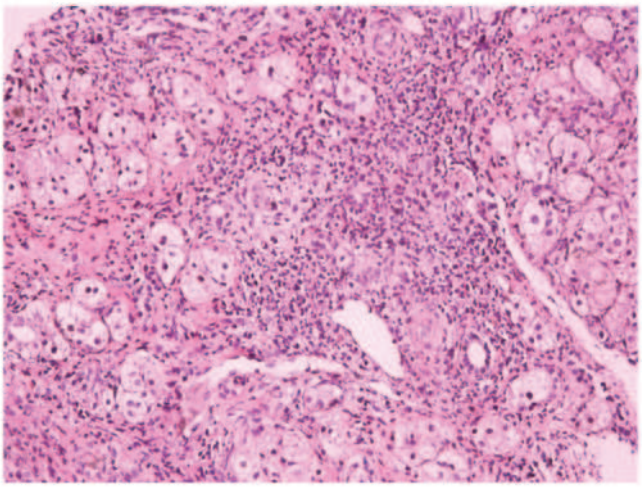

Figure 3. Liver biopsy showing portal tract inflammation and fibrosis with interface hepatitis and steatosis.

There are different biochemical investigations to detect copper abnormalities but there is no single test that is considered diagnostic of WD, thus, a combination of clinical and biochemical findings is needed to establish the diagnosis. The presence of Kayser-Fleischer rings on slit lamp examination of the eyes, as seen in 40-60% of cases[8,9] and noted in two of our patients, is suggestive of WD, although they may also be present in patients with chronic cholestasis. Biochemical parameters commonly used to diagnose WD include a low serum ceruloplasmin (<0.2 g/L), increased baseline 24-hour urine copper (>100 μg/day) and an elevated hepatic copper levels (>250 μg/g dry weight).[10] None of our cases underwent hepatic copper determination

as this requires sufficient liver tissue (at least 1 cm of a 1.6 mm diameter core) for adequate analysis which was not possible to obtain due to the risk of bleeding in children. Three of our patients had a low serum ceruloplasmin (<0.2 g/L) level but these findings may be secondary to the hypoproteinemic states, as seen in liver failure (case 2). Conversely, ceruloplasmin is an acute phase reactant and the concentrations may be increased with inflammation which may explain the elevated level (case 3). Our findings also showed that the baseline 24-hour urinary copper excretion was increased in our first three cases but it was surprisingly normal in case 4 despite the presence of a low ceruloplasmin level and KF rings with sunflower cataract, indicative of copper deposition in the lens. The normal value may suggest inadequate 24-hour urine sample collection which is important for proper quantification. There are also studies that have shown that basal 24-hour urinary copper excretion may be less than 100 μg at presentation in 16%-23% of WD.[11-13] In some centers, the sensitivity and specificity of 24-hour urinary excretion has been shown to increase after a total of 1 gm penicillamine administration, given 12 hours apart.[14] However, penicillamine is not readily available in the Philippines.

Using the King's College Hospital criteria,[5] a patient is diagnosed to have WD in the presence of hepatic manifestations if at least two of the following findings are present: (1) positive family history; (2) low serum ceruloplasmin (<0.2 g/L); (3) elevated liver copper (>250 μg/g dry weight); (4) presence of Kayser-Fleischer rings; (5) elevated baseline 24-hour urinary copper excretion (>1.6 μmol or 100 μg/24 hours); (6) elevated 24-hour urinary copper excretion following administration of 1 gm of penicillamine (>25 μmol or 1600 μg /24 hours); and (7) Coombs' negative hemolytic anemia. Using this observation, only our 3rd patient did not fulfil two criteria, with only an increased baseline 24-hour urine copper. However, we treated this patient as WD on the basis of her overall findings including the presence of a 'vacuous' smile, which is a mask facie with an open mouth caused by dystonia of facial and mandibular muscles. Genetic mutational analysis for WD could have been done on her but may still be inconclusive because of several mutations in the ATP7B gene.[15-17]

It is important that a diagnosis of WD is made as effective treatment is presently available including penicillamine and trientine, which are chelating agents and zinc, which blocks the intestinal absorption of copper. Compliance with lifelong treatment is important. If treatment is adequately given, the patient remains clinically well, the liver function test including the prothrombin time improves and the repeat 24-hour urinary copper is <75 μg/day, as we have demonstrated in the first case. Noteworthy is our second patient who initially consulted in acute liver failure with a prolonged INR unresponsive to Vitamin K administration but eventually responded with trientine and zinc therapy. There are reports that zinc alone is effective as first line treatment.[18]

In summary, WD is a rare genetic disorder that should always be considered in the differential diagnosis of any child presenting with jaundice, hepatomegaly or an isolated elevation of transaminase levels. Early recognition and management is important since effective treatment could reverse the damage caused by copper toxicity.

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