



Case Report

Neurological Manifestation of Wilson Disease at an Early Age: A Case Report

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Abstract

Wilson's disease (hepatolenticular degeneration), an inborn error of copper metabolism, is an autosomal recessive disorder characterized by degenerative changes in brain, liver disease and Kayser Fleisher (KF) rings in the cornea. It is due to a defect of p-type ATPase which is probably required for normal excretion of copper through bile. Hepatic manifestation of the disease is common at early age and neurological manifestation is common at an older age. We are reporting Wilson disease with neurological manifestation in a 10 year old boy.

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Introduction

Wilson disease (WD; also known as hepatolenticular degeneration) was first described in 1912 by Kinnear Wilson as "progressive lenticular degeneration," a familial, lethal neurological disease accompanied by chronic liver disease leading to cirrhosis.¹ Over the next several decades, the role of copper in the pathogenesis of WD was established, and the pattern of inheritance was determined to be autosomal recessive.^{2, 3} About one in 40,000 people get Wilson disease. Increased frequency has been found in certain countries where rate of consanguinity is high.⁴ It equally affects men and women. Symptoms usually appear between ages 5 to 35, but new cases have been reported in people aged 2 to 72 years. The basic defect lies in the processes of incorporation of copper into ceruloplasmin and excretion of excess copper into bile.⁵ The transport of copper is impaired in Wilson disease secondary to one of several mutations in the *ATP7B* gene

which encodes the copper-transporting protein P-type ATPase. By genetic linkage studies, Bowcock and colleagues narrowed the assignment of the Wilson disease locus to 13q14-q21.⁶ The excess copper acts as a promoter of free radical formation and causes oxidation of lipids and proteins. In the earliest stages of hepatocellular injury, ultrastructural abnormalities involving the endoplasmic reticulum, mitochondria, peroxisomes, and nuclei have been identified. Initially, the excess copper is stored in the liver and causes damage to the hepatocytes. Eventually, as liver copper levels increase, it is released into the circulation and deposited in other organs like brain, cornea and other tissue. The clinical presentations can be extremely varied i.e. all forms of acute and chronic liver disease, minimal to severe neurological disease, psychiatric problems, bony deformities, hemolytic anemia and endocrine manifestations. Patients with Wilson disease usually present with liver disease during the first

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decade of life or with neuropsychiatric illness during the third decade. We are reporting a case of Wilson disease presenting with neurological manifestation at an earlier age.

Case report

A 10 year old boy 1st issue of non-consanguineous parents presented with slowly progressive involuntary movement of all limbs, abnormal limb posture, and difficulty in walking for 1 year; deterioration of school performance for the same duration and difficulty in speech for 6 months. There is no history of fever, headache, early morning vomiting, convulsion, unconsciousness, jaundice, head injury. He was born by normal vaginal delivery without any complication. He developed normally and immunized as per EPI schedule. There is no family history of similar illness.

On examination the boy was conscious, oriented; had abnormal posturing of upper and lower limbs. Pulse: 72/min, BP: 90/60 mm Hg, RR: 32/ minute, there was no pallor, icterus, lymphadenopathy or edema. Weight: 22 kg K-F ring and sunflower cataract were present in both eyes which were later confirmed by slit-lamp examination. He had Dystonia of all four limbs; power normal, reflexes normal except extensor planter response. No focal neurological deficit. Gait: unstable. Liver was palpable 2 cm below right costal margin in right mid clavicular line, firm, non-tender. Upper border of liver dullness was in right 5th intercostals space. Spleen was palpable 3 cm below left costal margin in left midclavicular line. Other system examination revealed no abnormality.



Fig 1: K-F ring and sunflower cataract in eye

Investigation showed ESR: 20 mm/h, Hb: 14 gm/dl, TC: 7600/cumm; DC: neutrophil: 49%, lymphocyte: 42%, eosinophil: 5%, basophil: 0%, monocyte: 4%; S. bilirubin total: 0.7 mg/dl, direct: 0.2 mg/dl; S. total protein: 7.1 gm/dl; S. albumin: 4.3 gm/dl; SGPT: 24 U/L; S. Alkaline phosphatase: 302 U/L; S. creatinine: 0.7 mg/dl; S. copper: 28 µg; S. ceruloplasmin: nil; 24 hour urinary copper: 231µg; S. calcium: 8.8 mg%; S. phosphorus: 3.9 mg%; MRI brain: hyperintensity involving the lentiform nuclei, dorsal midbrain, claustrum and lateral thalami. The case was diagnosed as Wilson disease. He was prescribed Cap. Penicillamine 250 mg once daily (one hour before meal), Tab. Pacitane 1 mg thrice daily, Tab. Clonazepam 0.125 mg twice daily and Tab. Pyridoxin 10 mg once daily. Dietary advice was given. Sibling screening for Wilson disease was advised and genetic counseling was done. Patient was asked to come for regular follow up.

Discussion

Diagnosis of WD is based on presence of KF ring, low serum ceruloplasmin, high 24 hour urinary copper and hepatic copper estimation. Among them 24 hour urinary copper is the most sensitive test for diagnosis of WD particularly when liver biopsy can't be performed due to coagulation abnormality.⁷ But hepatic copper estimation is the most reliable test.⁸ The reported case has KF ring, nil serum ceruloplasmin and high 24 hour urinary copper excretion. Though hepatic copper estimation could not be done due to lack of facility, the other laboratory features strongly suggest the diagnosis of Wilson disease. Kayser-Fleischer rings are almost invariably present in patients with a neurological presentation.^{9, 10} So presence of KF rings strongly suggest involvement of brain in Wilson disease as is in our case. The uncommon features of Wilson's disease in our patient include a sunflower cataract. Sunflower cataracts, found by slit-lamp examination, represent deposits of copper in the lens.¹¹ Both Kayser-Fleischer rings and sunflower cataracts will gradually disappear with effective medical treatment or following liver transplant, though the rate of disappearance does not correlate with resolution of clinical symptoms.^{12, 13} The

reappearance of either of these ophthalmologic findings in a medically treated patient in whom these had previously disappeared suggests noncompliance with therapy. Treatment of Wilson disease includes a low copper containing diet, copper chelating agents, medications that block copper absorption from the GI tract and liver transplant. Patients should generally avoid eating foods with a high copper content, such as liver, chocolate, nuts, mushrooms, legumes, and shellfish (especially lobster). Drinking water from atypical sources (e.g., well water) should be analyzed for copper content and replaced with purified water. D-Penicillamine was introduced as the first oral agent for treating WD in 1956.¹⁴ The major effect of D-penicillamine in WD is to promote the urinary excretion of copper. D-Penicillamine may also act by inducing metallothionein in individuals with WD.¹⁵ Adequacy of treatment is monitored by measuring 24-hour urinary copper excretion while on treatment. This is highest immediately after starting treatment and may exceed 1000 µg (16 µmol) per day at that time. With chronic (maintenance) treatment, urinary copper excretion should run in the vicinity of 200-500 µg (3-8 µmol) per day on treatment.¹⁶ Trientine (triethylene tetramine dihydrochloride or 2,2,2-tetramine) is another copper chelating agent. Like penicillamine, trientine promotes copper excretion by the kidneys. Trientine and penicillamine may mobilize different pools of body copper.¹⁷ Ammonium Tetrathiomolybdate is a very strong decoppering agent. At low doses, it removes copper from metallothionein, but at higher doses it forms an insoluble copper complex, which is deposited in the liver.¹⁸ Zinc was first used to treat WD by Schouwink in Holland in the early 1960s.^{19,20} Zinc induces enterocyte metallothionein, a cysteine-rich protein that is an endogenous chelator of metals. Metallothionein has greater affinity for copper than for zinc and thus preferentially binds copper present in the enterocyte and inhibits its entry into the portal circulation. Once bound, the copper is not absorbed but is lost into the fecal contents as enterocytes are shed in normal turnover.²¹ Zinc

may also act by inducing levels of hepatocellular metallothionein.^{22,23} Liver transplantation corrects the hepatic metabolic defects of WD and may serve to initiate normalization of extrahepatic copper metabolism.²⁴ It is reserved for severe or resistant cases.¹⁶

Conclusion

Though uncommon but Wilson disease with only neurological manifestation can occur at an early age. So children presenting with unexplained neurological disorder should be investigated for Wilson disease even in absence of any hepatic manifestation. Early diagnosis and treatment is crucial for the prognosis.

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