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Case Report

A case report on neurological Wilson disease in an adolescent boy

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ABSTRACT

Wilson disease is an inherited metabolic multi-system disease that affects primarily the liver and brain. The cirrhotic liver combined with degenerative changes in lenticular nuclei of brain gives it the name of hepatolenticular degeneration. It is a rare disease involving the ATP7B gene and its protein. Here we discuss a case of a 15-year-old male who presented with predominantly neurological symptoms such as tremors, gait abnormality, dysphagia, and dysarthria which turned out to be a case of Wilson disease. Early identification is usually difficult since it has a long latent period and involves multiple systems with varied manifestations. It is a treatable with fair prognosis if diagnosed early.

Keywords: ATP7B, Wilson disease, Hepatolenticular, Kayser Fleischer, Neurology

INTRODUCTION

Wilson disease is a chronic disease of copper metabolism that occurs due to a mutation of the ATP7B gene on chromosome 13 and is characterized by copper deposition in various organs, especially in the liver, brain, eye, and other vital organs.[1,2] This deposition of copper leads to cirrhosis, liver failure, psychological issues, neurological manifestations such as involuntary movements, gait abnormalities, speech difficulties, and Kayser-Fleischer (KF) rings in the eyes, in addition to other symptoms.[3] The culprit gene encodes for P-type ATPase which is mainly responsible for incorporating copper into apo-ceruloplasmin for the synthesis of functional ceruloplasmin.[4] In Wilson disease failure of this incorporation leads to deposition of free copper in organs and can cause free radical injury. While the disease process is present from birth, patients often appear between the ages of five and 45 years.[5] It is of note that hepatic abnormalities are likely to predominate if Wilson disease occurs in childhood, whereas 50% of patients will develop neurological symptoms if disease onset is in the second or third decade. It is a treatable disease with a good outcome. Wilson disease is found worldwide with an incidence of 30 cases per million and a carrier frequency of one in 90.[6]

CASE REPORT

A 15-year-old boy was admitted in the medicine department with difficulty of speech and swallowing for the last nine months and a tremor in the left upper limb with intermittent dystonic movements for last six months, which gradually progressed over time to involve the right upper limb. There was also a decline in his scholastic performance over time. He had a normal birth and developmental history. Family history was non-contributory. Upon examination, he was a thin-built and average-nourished boy without pallor or icterus. Neurological examination revealed a slow and clumsy gait with choreiform movements in between. Slit lamp examination of the eyes revealed KF rings circumferentially in both eyes with early features of sunflower cataract. The rest of the examination revealed no gross abnormalities. His vitals were within normal limits. His routine blood workup, including complete blood count, liver function, and kidney function tests revealed no abnormalities. His serum ceruloplasmin levels were found to be 0.02 g/l (normal range 0.22-0.58 g/l). His 24-hour urine copper levels were 199.48 mcg/l (normal range 2.00-80.00 mcg/l) (Table 1).

Table 1: Laboratory values showing decreased serum ceruloplasmin and raised 24-hour urine copper.

Tests	Result	Reference range
Hemoglobin (g/dl)	13.2	12-15
MCV (fL)	86.06	76-96
TLC (cells/cu.mm)	8200	4000-10000
Platelet count (lacs/cu.mm)	1.70	1.5-5
Urea (mg/dl)	24	13-45
Creatinine (mg/dl)	0.8	0.7- 1.4
Total bilirubin (mg/dl)	0.7	0.1-1.2
ALT (IU/l)	30	5-34
AST (IU/l)	26	0-42
Alkaline phosphatase (IU/l)	200	<240
Ceruloplasmin (g/l)	0.02	0.22-0.58
24-hour urine copper (mcg/l)	199.48	2-80

A contrast-enhanced magnetic resonance imaging (MRI) of the brain revealed hyperintensity on T2-weighted and FLAIR imaging in the bilateral caudate nucleus, globus pallidus, and lateral thalamus (Figure 1). His abdominal sonography revealed an altered parenchymal echotexture of the liver.

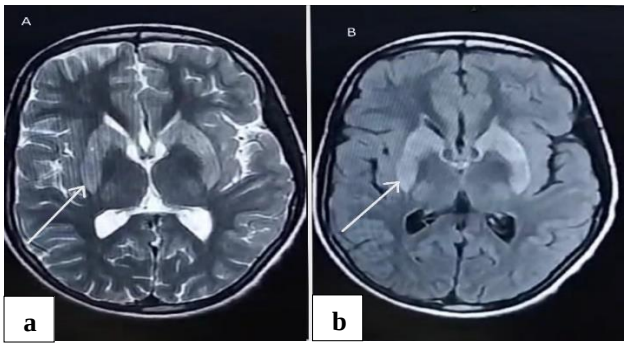

Figure 1: Contrast-enhanced MRI of brain showing hyperintensity (arrows) in the bilateral caudate nucleus, globus pallidus, and lateral thalamus, (a) T2 weighted MRI, and (b) fluid-attenuated inversion recovery (FLAIR).

A Leipzig score of 8 was found and the diagnosis of Wilson disease was established. The patient was advised on a copper-free diet and zinc, d-penicillamine, and trihexyphenidyl tablets in appropriate doses and duration. Two months following therapy, the patient was followed on an outpatient basis which showed improvement in gait, swallow, and speech function.

DISCUSSION

Wilson disease, or hepatolenticular degeneration, is a rare autosomal recessive disorder which affects a vast array of organs due to the deposition of copper. Copper is an essential element in the body required for adequate growth, cardiovascular integrity, neovascularization, neuroendocrine function, and formation of neurotransmitter.[7] Dietary copper intake is usually between 1 to 2 mg per day and is mainly absorbed from the stomach and duodenum.[8,9] The transport of copper within hepatocytes is regulated by ATP7B which mediates the incorporation of six copper atoms into apoceruloplasmin to form ceruloplasmin. In Wilson disease, there is decreased incorporation of copper into apocerulosplasmin which causes decreased transport of copper from the liver into bile, leading to copper excess in the liver. Increased hepatic copper content causes cellular damage via oxidative injury due to enhanced free radical production. Once hepatocyte damage sets in there is release of copper in the blood where it binds to albumin or small peptides. This non-ceruloplasmin-bound serum copper is the main cause of copper deposition and subsequent toxicity in the brain and other tissue.[10] Copper accumulation in the brain invariably affects the brain stem, basal ganglia, and cerebellum. Many Wilson disease patients may not initially show signs of liver failure since the disease usually affects the brain after the liver. Rather, neurological and mental abnormalities are the first clinical indications to appear.[11]

The liver is the primary site of copper accumulation in Wilson disease. Clinical presentation ranges from asymptomatic transaminitis to acute hepatitis/liver failure or chronic hepatitis and cirrhosis. Tremor, dystonia, dysarthria, gait abnormality, and incoordination, in varied severity from moderate to severe, are commonly seen in Wilson disease. Less commonly seen are, chorea, athetosis, cognitive impairment, seizures, and dysautonomia.[12] Psychiatric manifestations including mood disorder, sleep disorder, and psychosis may occur alone or in combination with hepatic and neurological manifestations.[13] Kayser-Fleischer rings are golden-brown rings made of copper which can be seen in the periphery of the cornea. Neurological Wilson disease has almost 100 percent association with Kayser-Fleischer ring, whereas there is only an association of 50 percent with hepatic Wilson disease. Sunflower cataracts are another ocular manifestation of Wilson disease that occurs when copper accumulates on the lens. Renal, rheumatologic, cardiac, endocrine, and dermatologic manifestations have also been defined in relation to Wilson disease.[14]

The diagnosis of Wilson disease depends on multiple clinical, laboratorial, and imaging findings. The Leipzig score is currently used to assess the certainty of diagnosis. The scoring system includes biochemical testing (ceruloplasmin, urinary copper excretion), clinical manifestations (KF rings and neurological symptoms), and molecular testing for ATP7B. Liver biopsy remains the gold standard for diagnosis due to its ability to reveal high copper content.

The management of Wilson disease starts with dietary modification which includes avoiding foods with high copper content such as shellfish, nuts, chocolate, and

organic meats. Copper chelating agents such as D-penicillamine and trientine are usually the first-line of therapy.[15] D-penicillamine is associated with the initial worsening of disease due to the mobilization of copper from the liver.[16] Most patients report improvement in symptoms in two to six months after starting therapy. Oral zinc reduces the absorption of copper from the gut by inducing metallothionein which is an endogenous chelator of metal.[17]

CONCLUSION

This case report demonstrates a 15-year-old male having Wilson disease with predominantly neurological manifestation, a highly rare disease. Wilson disease is an inherited metabolic disease. The gene affected is ATP7B and its protein P-type ATPase leads to the deposition of non-ceruloplasmin copper in many organs, especially the liver. Clinically, it should be suspected in young individuals with unexplained hepatic and neurological manifestations. Diagnosing Wilson disease involves multiple facets including clinical acumen, lab studies, and imaging modalities. Early detection and treatment are pivotal in reducing the severity and complications related to Wilson disease. Once the diagnosis is established, treatment and diet modifications often result in a considerably good outcome with a decrease in mortality and morbidity. Lifelong adherence to therapy should be promoted and genetic testing in siblings should be advised.

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