Wilson's disease: A case report with review of literature

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ABSTRACT

Wilson's disease is a rare inborn error of metabolism characterized by abnormal deposition of copper in various tissues caused by the inability to excrete copper into the bile. Wilson's disease is also known as hepatolenticular degeneration because liver and lentiform nuclei in the brain are the most commonly involved areas. Cerebral involvement in Wilson's disease results in typical characteristic radiological signs on magnetic resonance imaging (MRI). Here, we report the case of a 27-year-old female who presented with neurologic manifestations and diagnosed as Wilson's disease with typical MRI findings.

Key words: *Copper metabolism, Face of giant panda sign, Magnetic resonance imaging, Wilson's disease*

Wilson's disease is an autosomal recessive inborn error of copper metabolism caused due to mutation of ATP7B gene located on the chromosomal region 13q21, which codes for the synthesis of an ATP7B protein [1]. ATP7B protein resides in the hepatocytes and its function is to incorporate six copper molecules into apoceruloplasmin and thus form ceruloplasmin. Mutation in the ATP7B gene leads to defective ATP7B protein and consequent progressive accumulation of copper in hepatocytes [2]. In Wilson's disease, serum ceruloplasmin level will be low and excessive copper is seen in plasma and urine, leading to deposition of copper in various tissues such as liver, brain, and eyes.

The age of presentation in Wilson's disease is from early childhood to 50 years [3]. Wilson's disease has a slight male predominance (52%) [4]. Hepatic manifestations such as chronic liver disease or hemolytic anemia are more common in young children, whereas neurological manifestations are more common in young adults. Bilateral symmetrical basal ganglia and brainstem abnormalities are the most common findings on magnetic resonance imaging (MRI) in Wilson's disease, followed by cerebral atrophy and asymmetric central white matter abnormalities. We report a case of a young adult who presented with neurologic manifestations and diagnosed as Wilson's disease with typical MRI findings.

CASE REPORT

A 27-year-old female patient presented to the department with a history of slurring of speech, postural instability for 1 month, and tremors of the right upper limb for 10 days. No history of similar complaints in the family members was found. On general examination, the patient had no pallor, icterus, clubbing/cyanosis, and lymphadenopathy. The patient had stable vitals with a blood pressure of 130/80 mmHg, pulse rate=74/min, respiratory rate=14/min, and temperature=98°F. Neurological examination showed dysarthria, ataxic gait, and tremors of the right upper limb. The ophthalmological examination revealed Kayser–Fleischer rings in both eyes (Fig 1).

The laboratory investigations included hemoglobin=13.4 g/dl (normal=12–15 g/dl); white blood cells=5.8 × 10^3/mm^3 (normal=4.0–10.9 × 10^3/mm^3), red blood cells=4.14 × 10^6/mm^3 (normal=4.0–5.4 × 10^6/mm^3), platelet count=202 × 10^3/mm^3 (normal=150–400 × 10^3/mm^3), serum ceruloplasmin=3.27 mg/dl (normal=18–35 mg/dl), and 24 h urine copper=230 µg/day (normal=2–80 µg/day).

Based on the clinical examination and above-mentioned investigations, a provisional diagnosis of Wilson's disease was considered. The ultrasound of the abdomen showed coarse echotexture of the liver (Fig 2). However, liver function tests including total bilirubin, alkaline phosphatase, serum glutamic-oxaloacetic transaminase, and serum glutamic pyruvic transaminase were normal.

MRI of the brain revealed bilateral symmetrical T2-weighted (T2W) and FLAIR hyperintensities involving caudate, putamen, thalami, midbrain, pons, cerebellar dentate nuclei, and inferior cerebellar peduncle (Fig 3) with hypointense red nuclei and substantia nigra forming "face of giant panda" sign (Fig 4). The atrophy of bilateral putamen was noted. Mild hyperintensity on diffusion-weighted imaging noted in midbrain with minimal reduction of apparent diffusion coefficient values (Fig 5), and T1-weighted (T1W) hyperintensity noted in bilateral basal ganglia and subthalamic nuclei suggestive of hepatic encephalopathy (Fig 6).

Hence, a final diagnosis of Wilson's disease was made, and treatment with penicillamine 750 mg/day and zinc acetate 150 mg/day along with clonazepam 0.5 mg/day was initiated.

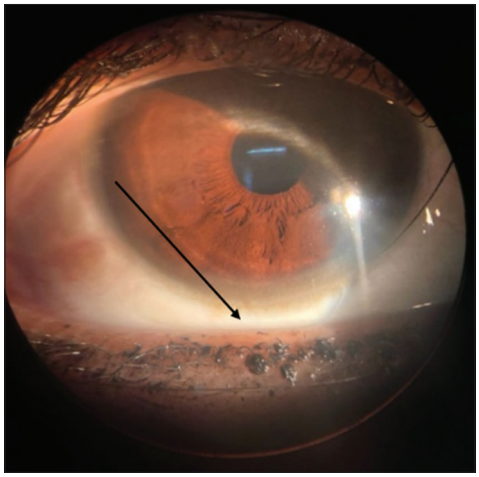

Figure 1: Kayser–Fleischer ring noted at the periphery of the cornea inferiorly

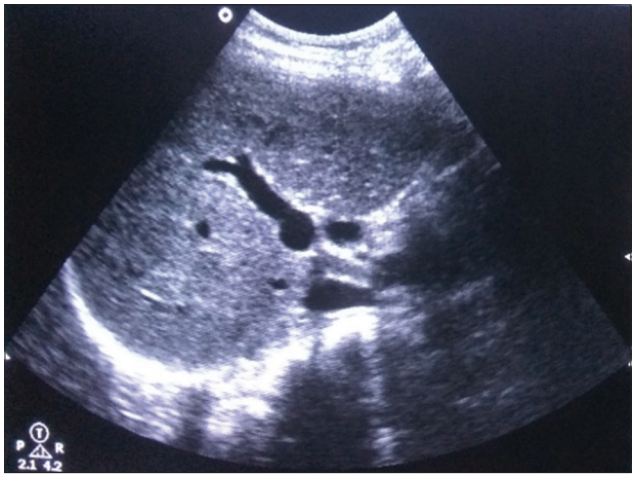

Figure 2: Ultrasound image showing coarse echotexture of liver

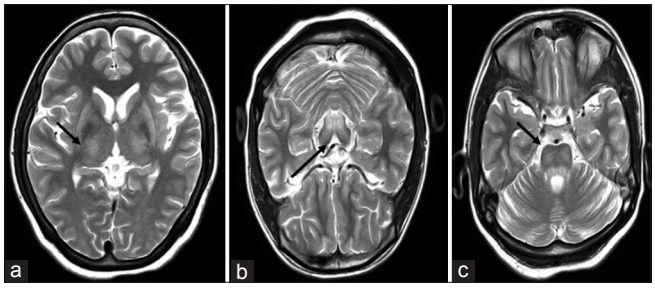

Figure 3: T2-weighted magnetic resonance image showing bilateral, symmetric hyperintensities (a) involving caudate, putamen (arrow), thalami with atrophy of bilateral putamen; (b) involving midbrain (arrow) and (c) pons (arrow)

On subsequent follow-up after 1 week, the patient showed symptomatic improvement.

DISCUSSION

Wilson's disease is a rare autosomal recessive disorder of copper metabolism. The deposition of copper occurs in various tissues, leading to toxicity. An estimated worldwide prevalence of Wilson's disease is one case per 30,000 live births in most populations [5]. Coffey *et al*. conducted a genetic study of Wilson's disease using

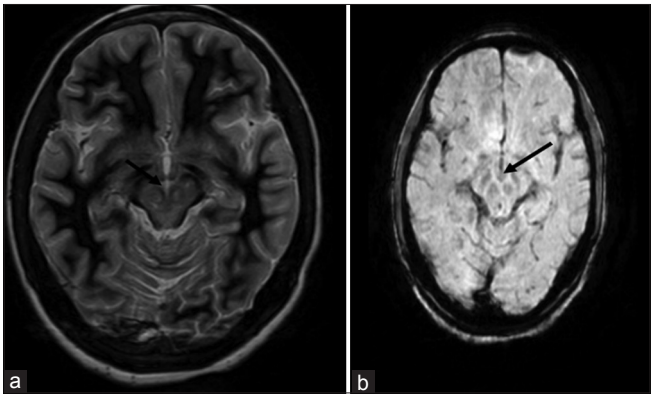

Figure 4: (a) T2-weighted and (b) VenBOLD magnetic resonance images showing "face of giant panda" sign in midbrain (arrow)

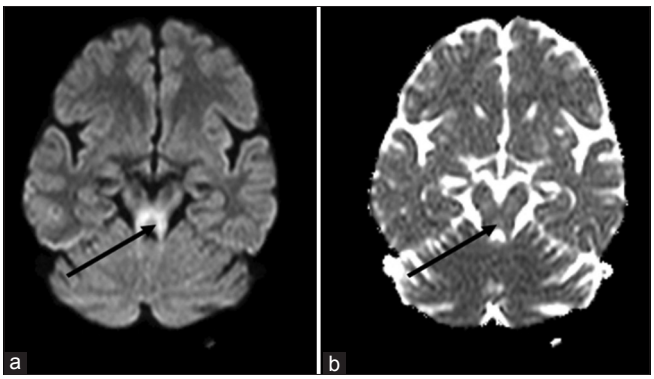

Figure 5: (a) Diffusion-weighted imaging magnetic resonance image showing hyperintensity in midbrain (arrow) and (b) apparent diffusion coefficient (ADC) map showing hypointensity in midbrain (arrow) due to minimal reduction of ADC values

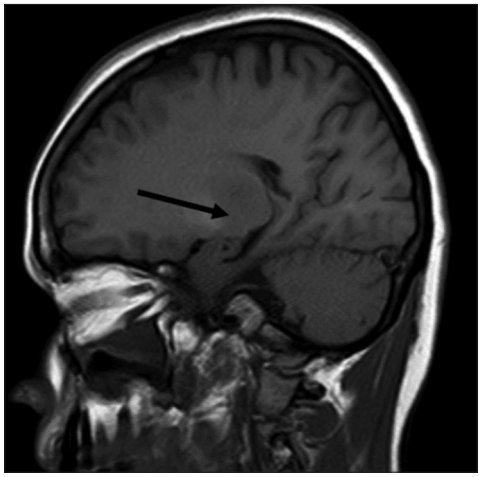

Figure 6: T2-weighted magnetic resonance image showing hyperintensity in basal ganglia (arrow)

molecular sequencing in the United Kingdom which suggested a higher prevalence of one case in 7021 [6].

The early manifestations of Wilson's disease include yellowish discoloration of the skin and mucous membranes and abnormal liver function tests due to hepatic dysfunction. Hepatic presentations may vary from acute liver failure, autoimmune hepatitis, cirrhosis, and hepatocellular carcinoma [7,8]. After the liver disease, neurological manifestations such as the flexion-extension tremor of a wrist, grimacing, difficulty in writing, slurred speech, and drooling

occur. Late manifestations of Wilson's disease include psychiatric manifestations ranging from depression to schizophrenia, Kayser–Fleischer rings, renal tubular damage, and osteoporosis. Deposition of copper in Descemet's membrane of cornea leads to the appearance of characteristic Kayser–Fleischer rings seen in Wilson's disease. Renal manifestations may include aminoaciduria, glycosuria, phosphaturia, uricosuria, and renal tubular acidosis.

Neuroimaging findings in Wilson's disease include bilateral symmetrical involvement of putamen, caudate nuclei, globus pallidi, ventrolateral thalami, midbrain, pons, cerebellum, and cortical and subcortical lesions (usually in the frontal lobe) may also occur. On computed tomography scan, gray matter abnormalities appear as hypodensities that do not enhance on contrast. On MRI, they appear hypointense on T1W images and hyperintense on T2W images [9].

Pathologically gliosis, edema, and variable necrosis with cavitation occur due to neurotoxicity of copper [10,11], and this accounts for the hyperintense signal on T2W images. The normal signal intensity of red nucleus and substantia nigra against the background of hyperintense signal in tegmentum gives rise to the characteristic "face of giant panda" sign [12]. The "face of the miniature panda" sign is seen in the pons, caused by hypointensity of central tegmental tracts in contrast to the hyperintensity of the aqueduct opening into the fourth ventricle. The "double panda" sign refers to a combination of the face of giant panda and face of miniature panda signs [13]. The asymmetric, confluent T2W hyperintensities may be seen in the cortical gray matter and subcortical white matter. In a study by Jha *et al*., an incidence of white matter lesions was reported to be 10% [14]. Cerebellar atrophy and cerebral atrophy with dilatation of frontal horns of lateral ventricles may be seen in Wilson's disease.

On T1W MRI, high-signal intensity is seen in the globus pallidus, putamen, and mesencephalon in association with hepatic dysfunction due to copper toxicosis. On diffusion-weighted MR, recent lesions show a restricted diffusion which is likely due to cytotoxic edema [15]. Kishibayashi *et al*. studied diffusion-weighted MRI in four patients with Wilson's disease and noted abnormally high-signal intensity in some areas of basal ganglia in each case [16].

On MR spectroscopy, there will be reduced N-acetyl aspartate/creatinine ratio in the involved areas and increase in myoinositol/creatinine ratio [17]. Differential diagnosis of Wilson's disease includes Leigh's disease and hypoxic-ischemic encephalopathy. However, characteristic biochemical and radiological findings can differentiate them. In some cases, liver biopsy for copper analysis may be essential for confirmation of Wilson's disease. The treatment for Wilson's disease includes penicillamine which chelates copper from the body and zinc acetate which prevents the absorption of dietary copper from the gut. Prognosis is good if the treatment is initiated early. In 6–12 months, liver function will return to normal if the treatment is initiated when there is only mild-to-moderate liver failure [18].

CONCLUSION

Early diagnosis of Wilson's disease with clinical, biochemical, and characteristic radiological findings is very essential to initiate the treatment early and to halt the progression of the disease.

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