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Wilson's Disease: A Brief Review with Neuroimaging Features

Review Article

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Abstract

Wilson disease is a metabolic disease resulting from defective copper metabolism leading to deposition of copper in liver, brain and eyes. Gene involved is ATP7B on chromosome 13. Systemic involvement presents in form of hepatitis, fulminant hepatic failure, cirrhosis, dysarthria, dystonia, spasticity, seizures, behavioral changes, psychosis, hemolytic anemia, thrombocytopenia, renal tubular defect, congestive cardiac failure, arrhythmias, gynecomastia, parathyroid insufficiency etc. Diagnosis is made on the basis of laboratory findings of elevated serum bilirubin, deranged coagulation profile, low serum ceruloplasmin levels, increased 24 h urinary copper levels, increased hepatic copper levels. The brain lesions on MR imaging are frequently seen in the Putamen, Caudate nuclei, Globus Pallidus, Thalamus, Midbrain, Pons, Substantia Nigra, subcortical white matter, Centrum Semiovale, Periaqueductal gray matter, Dentate nucleus, Red nucleus and Vermis. Chelating agents are helpful in excretion of copper from the body. Chelating agents include D-Pencillamine, Trientene, Ammonium tetrathiomolybdate and zinc. Liver transplantation is the treatment of choice in fulminant hepatic failure.

Introduction

Wilson disease is a metabolic disorder with autosomal recessive inheritance involving a defect in excretion of copper from the body that results in accumulation of copper in liver, brain and eyes resulting in their damage, thus called as hepatolenticular degeneration. [1] Gene involved is ATP7B on chromosome 13, which is a copper transporting gene expressed mainly on hepatocytes and is responsible for biliary copper excretion. Mutations in ATP7B can occur anywhere along the entire 21 exons, which makes the identification of gene defects difficult. Identification of carriers and presymptomatic family members of affected individuals is achieved by polymerase-chain-reaction-based marker analysis [2]. Genetic defect in the form of either absence or malfunctioning of ATP7B gene results in decreased excretion of copper in bile leading to its accumulation in hepatocytes and when hepatocytes are overloaded there is redistribution to other organs (brain, eyes and kidneys). [3] Copper is taken into hepatocyte via CTR1 (copper transporter 1) on the sinusoidal aspect of hepatocyte. Copper bound to CTR1 binds ATOX1 which is copper chaperone and then it is delivered to Wilson disease protein ATP7B (which is bound to ceruloplasmin) which brings about transport into trans-golgi and loading into vesicles for transport of copper into bile and excretion from the body. The most common mutation is histidine to glutamine substitution at amino acid 1069Q (H1069Q). [3] ATP7B is mislocalised to the endoplasmic reticulum consistent with a failure of the mutant protein to undergo normal transport to trans-golgi apparatus thus leading to copper deposition.

Hepatic changes include microsteatosis, macrosteatosis, increased glycogen in the nucleus and areas of necrosis. In more

advanced disease, the changes observed are quite similar to those seen in autoimmune hepatitis, such as infiltration by inflammatory cells, piecemeal necrosis and fibrosis. In the brain, most copper is deposited in the basal ganglia, particularly in the putamen and Globus Pallidus (together called the *Lenticular Nucleus*). Hemolysis occurs in Wilson disease as copper has a direct effect on oxidation of hemoglobin, inhibition of energy-supplying enzymes in the red blood cell and direct damage to the cell membrane [4].

Clinical features

Hepatic involvement: Patient can present with fulminant hepatic failure in form of coagulopathy, encephalopathy and Coomb's negative hemolytic anemia. Cirrhosis associated with splenomegaly and portal hypertension. Hepatocellular carcinoma is rarely associated with Wilson disease [4].

CNS involvement: There is widespread involvement of brain with pathologic changes of degeneration and necrosis of the neurons and supporting cells in thalamus, mid brain, globus pallidus, caudate, putamen, cerebrum and cerebellum leading to dysarthria, tremor, lack of motor coordination, drooling, dysarthria, dystonia, and spasticity. Migraine headaches and insomnia have also been reported, although seizures could be more common. Along with behavioral changes, other psychiatric manifestations include depression, anxiety and frank psychosis [4].

Eye changes: Eye changes: Kayser Fleischer (K-F) rings are most apparent at the periphery of the cornea (Figure 1). They are caused by the granular deposition of copper on the inner surface of the cornea in Descemet's membrane. The upper pole is affected first. The rings have a golden brown appearance. KF ring starts from Schwalbe line and extends till 5mm on corneal surface. It starts from 10 to the 2 o' clock position. KF ring also starts in the inferior pole. Slit lamp examination is necessary to confirm the presence or absence of K-F rings [4].

Sunflower cataract is the another ocular finding in Wilson disease patients. Sunflower cataract consists of central disc with radiating folds. Sunflower cataract is also seen in intraocular copper bodies (chalcosis), primary biliary cirrhosis and Hereditary hyperferritinemia cataract syndrome [5].

Other eye changes are infrequent or absent blinking, jerky oscillatory movements of the eye, involuntary upward gaze, night blindness and pallor of discs and xerophthalmia in isolated cases [6].

Hemolytic changes: Hemolytic anemia due to copper induced oxidative damage to erythrocytes may be the initial manifestation of Wilson's disease. Thrombocytopenia has also been seen in Wilson disease. [4] Acute hemolytic syndrome can present as initial presentation of Wilson disease [7].

Renal involvement: Renal tubular dysfunction, with consequent hypercalciuria and hyperphosphaturia, may induce nephrocalcinosis. Hypokalemia with muscle weakness and even respiratory failure has also been seen in Wilson's disease, presumably secondary to renal tubular dysfunction [4].

Skin changes with hyperpigmentation of the anterior lower legs has been seen in Wilson disease [4].

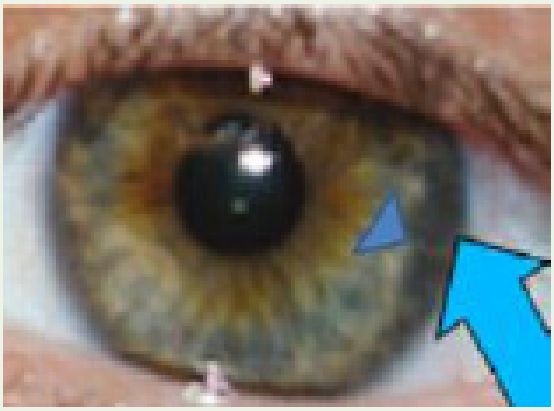

Figure 1: Ophthalmologic examination showing the presence of Kayser–Fleischer ring (between arrow and arrow-head).

Gynecological abnormalities (menstrual irregularity, delayed puberty, gynecomastia), **cardiovascular dysfunction** (congestive heart failure, cardiac arrhythmia), and other impairments (glucose intolerance, parathyroid insufficiency) have also been described [4].

Diagnosis

Laboratory findings: Elevated serum bilirubin, reduced serum albumin and coagulation factors [2].

Slit lamp examination: Kayser Fleischer ring may be seen in the periphery of cornea. The upper pole is affected first. The rings have a golden brown appearance. Sunflower cataracts are brilliantly multicoloured and are visible only by slit-lamp examination. They do not impair vision. Other less common findings include night blindness, exotropic strabismus, optic neuritis, and optic disc pallor [7].

Serum Ceruloplasmin levels: Low S. Ceruloplasmin levels <20mg/dl are consistent with Wilson disease when associated with KF ring. Extremely low S. Ceruloplasmin level < 5 mg/dl is strong evidence of Wilson disease [2].

24 h urinary copper excretion: In Wilson's disease, the 24 h urinary copper excretion is increased and the concentration taken as suggestive of disease is greater than 100 μg/24 h. Normal level of 24 h urinary copper excretion is < 40 μg/24 h [2].

Hepatic copper levels: Hepatic parenchymal copper content >250 g/g dry weight provides critical diagnostic information. In untreated patients, normal hepatic copper content (<40-50 g/g dry weight) excludes a diagnosis of Wilson disease. Further diagnostic testing is indicated for patients with intermediate copper concentrations (70-250 g/g dry weight of liver) especially if there is active liver disease or other symptoms of WD [2].

Neuroimaging

Copper is accumulated in the liver, and once hepatic binding sites are saturated, it is released. Following which, there is development of systemic disease which is accompanied by abnormal deposition

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of copper in the brain, particularly in the Putamen and Globus Pallidus . [8,9] The neurologic signs and symptoms associated with this disease are secondary to increase in cerebral copper at levels sufficient to destroy nerve cells. Histopathological changes that are observed in Wilson's disease involving the brain includes edema, necrosis, and spongiform degeneration. [10] MR imaging not only makes available biochemical information on heavy metal distribution in brain parenchyma but also furnishes an insight into the pathologic and anatomic correlates of clinical signs and symptoms in Wilson's disease. [11] Interval changes seen on follow-up MR imaging have an excellent parallel with clinical symptoms, and can be helpful in assessing the clinical response to treatment of children with Wilson disease [12].

MR imaging findings of the brain in children with Wilson disease can be divided into three diverse groups. [12] In first group, MR imaging findings are normal.

In second group, the basal ganglia are hyperintense on T1-weighted images, which implies hepatic involvement—that is, chronic liver parenchymal disease. In third group, hyperintense lesions are seen on T2-weighted images, which suggests cerebral involvement and show a fine correlation with neurologic symptoms.

The brain lesions are commonly seen in the Putamen, Caudate nuclei, Globus Pallidus, Thalamus, Midbrain, Pons, Substantia Nigra, subcortical white matter, Centrum Semiovale, Periaqueductal gray matter, Dentate nucleus, Red nucleus and Vermis. These lesions are usually bilateral and symmetrical [Figure 2]. The basal ganglia are show most common involvement followed by the thalami, brainstem, cerebral and cerebellar atrophy.[9] In chronic cases, atrophic changes may be seen. Hypointense signal intensity on T2- weighted images in corpus striatum and superior colliculus can be appreciated sometimes, due to paramagnetic effects of the copper or iron deposition. [13-15] Sometimes, foci of restricted diffusion can be visualised early in the disease process due to inflammatory cell swelling due to excessive copper deposition [16].

The midbrain "face of the giant panda" sign [14] comprises hyperintense signal in the tegmentum, unchanged signal intensity of the lateral portion of the pars reticulata (substantia nigra) and red nucleus (arrowhead), and hypointense signal of the superior colliculus [Figure 3]. Also, a "face of panda cub" [Figure 4] may be visualized in the dorsal pons. "Eyes of the cub" are created from the relative hypointensity of the central tegmental tracts (CTT) (arrowhead) compared to the hyperintensity of the aqueduct opening into the fourth ventricle ("nose and mouth of the panda") and bounded inferiorly by the superior medullary velum. The cub's "cheeks" are formed from the superior cerebellar peduncles [8]. Face of the giant panda and her cub comprise the "double panda sign" [8] which is typical for this disease.

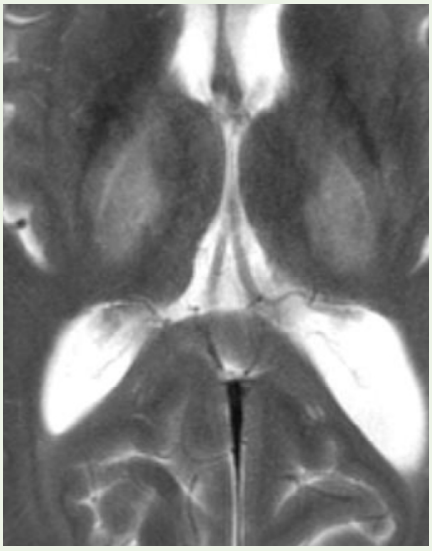

Figure 2: T2-weighted MRI image shows hyperintense signal in the bilateral thalami and subtle hyperintense signal in putamen.

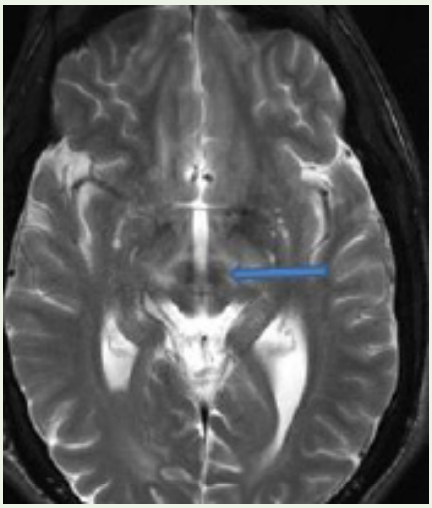

Figure 3: T2-weighted MRI image shows the "face of the giant panda" in the midbrain with hyperintense signal in Tegmentum and normal red nuclei (arrow).

Treatment [17,18]: Anti copper therapy has to be life-long

Chelating agents: Pencillamine is cysteine, doubly substituted with methyl groups. A free sulphydryl group acts as the copper-chelator. The initial dose of Penicillamine is 1000-1500 mg per day in two to four divided doses. The treatment is best taken 1 h before or 2 h after food. Early side-effects in the first 1-3 weeks include sensitivity reactions with fever, rash, lymphadenopathy, neutropenia, thrombocytopenia, and proteinuria. If these adverse effects are noticed, then Penicillamine should be stopped and an alternative treatment used. Later side-effects include nephrotoxicity (a lupus-like syndrome) and bone marrow suppression (thrombocytopenia and aplasia). Skin complications have arisen with long-term use of penicillamine including progeriatric changes (with long-term doses greater than 1000 mg per day), elastosis perforans serpiginosa and aphthous stomatitis.

Triethylene tetramine dihydrochloride (Trien, TETA, trientine) at a dose of 0.5-2.0 g/day for adults and 20 mg/kg/day for children.

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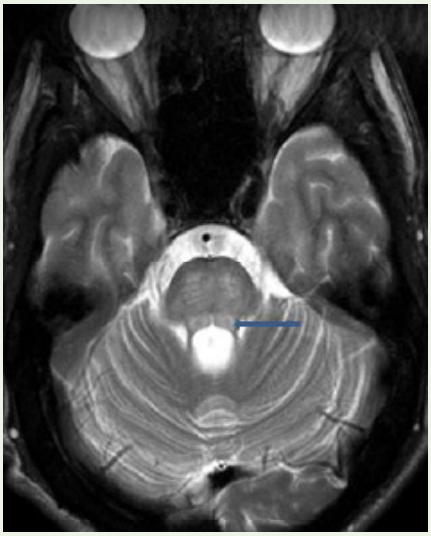

Figure 4: T2-weighted MRI shows the "face of the miniature panda" in dorsal Pons with hypointensity of central tegmental tracts (arrow).

Ammonium tetrathiomolybdate: It is emerging as the drug of choice because of its rapid control of free copper, preservation of neurologic function and low toxicity. The initial dose is 120 mg/day (20 mg between meals TID and 20 mg with meals TID). If a nighttime snack is eaten, another 20 mg is given with the snack. Side effects include anemia, leukopenia, thrombocytopenia and mild elevations of transaminases.

Zinc impairs the gastrointestinal absorption of copper. Zinc acetate is given in adults at a dose of 25–50 mg of elemental zinc three times a day and 25 mg three times a day in children >5 yr of age.

Liver transplantation is the only effective treatment for patients with Wilson disease who have acute liver failure and patients who present with decompensated liver disease.

Special conditions

Pregnancy: Chelating agents should be reduced to minimum. Zinc can be continued throughout pregnancy. Breast feeding is not recommended in cases of women taking D-Pencillamine as it may harm the baby.

Conclusion

MRI not only gives biochemical information on heavy metal distribution in brain parenchyma but also present an insight into the pathologic and anatomic correlates of clinical signs and symptoms in Wilson's disease.

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