

NEUROLOGICAL INVOLVEMENT WITHOUT HEPATIC DERANGEMENT IN WILSON DISEASEShailendra Kumar Tiwari¹, Nutan Singh²¹3rd Year Junior Resident, Department of Paediatrics, Government Medical College, Haldwani.²Associate Professor, Department of Paediatrics, Government Medical College, Haldwani.**ABSTRACT**

Wilson's Disease (hepatolenticular degeneration) is a rare, autosomal recessive disorder that can be associated with degenerative changes in the brain, liver disease, and Kayser-Fleischer rings in the cornea. The incidence is 1 in 50000 birth worldwide. It is caused by a mutation in the copper-transporting gene, ATP7B. The diagnosis depends primarily on the clinical features, the biochemical parameters and the presence of the Kayser – Fleischer ring. It is progressive and potentially fatal if untreated; specific effective treatment is available. Here, we are reporting two cases which were affected by Wilson's disease, with only neurological manifestations, without any hepatic involvement or derangement. We also present here a review of literature on Wilson's disease.

KEYWORDS

Wilson's disease, Neurological involvement, Hepatic derangement, Kayser Fleischer ring.

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INTRODUCTION: Wilson's Disease (WD), also known as hepatolenticular degeneration, was first defined by Dr Samuel Alexander Kinnier Wilson in 1912.⁽¹⁾ WD is a rare, autosomal recessive inborn error of the copper metabolism, which is caused by a mutation in the copper-transporting gene, ATP7B. The WD gene, ATP7B, is located on chromosome 13q14, which encodes a metal-transporting P-type adenosine triphosphatase (ATPase), which is expressed mainly in hepatocytes. The incidence of WD is estimated to be 1 in 30,000 individuals and the carrier frequency is approximately 1 in 90.⁽²⁾ An absent or a reduced function of the ATP7B protein leads to a decreased hepatocellular excretion of copper into bile. This results in hepatic copper accumulation and injury. Eventually, copper is released into the bloodstream and it is deposited in other organs, notably in the brain, kidneys, and the cornea. The hepatic production and the secretion of the ceruloplasmin protein without copper and apoceruloplasmin, result in the decreased blood level of ceruloplasmin which is found in most of the patients with WD, due to the reduced half-life of apoceruloplasmin.⁽³⁾ The manifestations are more likely to be hepatic in early childhood and to be neurological in adolescents.⁽⁴⁾ The neurological manifestations of Wilson's disease can vary extremely and they are often diagnosed after long delays. Here, we are reporting Wilson's disease with only neurological presentations and no hepatic involvement or derangement, in two patients.

CASE REPORT:

CASE 1: A 12-year-old female, a product of a non – consanguineous marriage, presented with pain in both legs for 6 months which was treated by many physicians with

minimal symptomatic improvement. After one month of the onset of the pain, she developed abnormal uncoordinated body movements and posturing of both upper and lower limbs in the form of involuntary, non-repetitive, brief, irregular movements, which were progressive. Over the next month, she became non – ambulatory. Her parents consulted many physicians for these problems but the diagnosis was missed. There was no improvement, and she was then brought to our institute. These abnormal movements subsided during sleep. The patient also had progressive dysarthria. Her elder brother also had a history of very slowly progressive abnormal movements and dysarthria and died at 12 year of age. Her developmental milestones were normal. On examination, her vital signs were found to be normal. There was no pallor, icterus or significant lymphadenopathy. Her nervous system examination revealed dystonia and exaggerated deep tendon reflexes. Her muscle power was >4/5 in all the limbs. The Kayser – Fleischer ring (K – F ring) was visible in both corneas by the naked eye (Fig-1), which was confirmed by slit lamp examination. Her other systemic examinations did not reveal any abnormality. Her complete blood counts were within normal limits and serum electrolytes and the renal functions were normal. Ultrasonography of the abdomen was normal. The total serum bilirubin was 0.4 mg/dl (direct bilirubin 0.2 mg/dl), the total serum protein was 6.8 gm/dl (Albumin 4.4 gm/dl) and the serum transaminases (AST, ALT) and Alkaline Phosphatase (ALP) were 45, 40, and 355 IU/L respectively. Her Prothrombin Time (PT) and her activated Partial Thromboplastin Time (aPTT) were within normal limits. Her serum ceruloplasmin was 90 mg/L (normal 180–350 mg/L) and her 24 hours' urine copper excretion (with D- penicillamine challenge) was increased to 2337.6 µg (normal <1600 µg). Magnetic resonance imaging (MRI) of the brain, T2 & T1-weighted image revealed hyperintensity & hypointensity in bilateral basal ganglia & putamen region (Figure 2).

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CASE 2: A 12 years old boy, a product of a non-consanguineous marriage, presented with a history of progressive dysarthria and abnormal body posturing for the past 6 months. He had been treated by many physicians without any improvement. On examination, his vital signs were found to be normal. His nervous system examination revealed dysarthria, dystonia, exaggerated deep tendon reflexes. His muscle power was normal. On ophthalmological examination, the Kayser – Fleischer ring (K – F ring) was found to be present on both the sides. His other systemic examinations were normal. His haemogram, liver function test and renal function test and ultrasonography of the abdomen were normal. His serum ceruloplasmin was 90 mg/L (normal 180 - 350 mg/L) and his 24 hours' urine copper excretion (with D- penicillamine challenge) was increased to 2260 µg (normal <1600 µg). The diagnosis of Wilson's disease with a neurological manifestation was made on the basis of the dystonia, the K-F ring in the both eyes, the low serum ceruloplasmin, and the 24 hours' urinary copper excretion.

Parents of both the patients were explained regarding the prognosis of the disease and the available treatment in our country. Both the patients were started on D-penicillamine 20 mg/kg/day before meal in two divided dose and oral zinc (as zinc acetate) at a dose of 25 mg TDS. Oral pyridoxine was also started as D- penicillamine is pyridoxine antagonist. They were advised to avoid food with a high copper content, such as chocolates, nuts, legumes, mushrooms, shellfish and liver. Their parents were also advised to avoid the use of copper utensils in the household for the storage of water and for cooking food. The patients are on regular follow up and their dystonia has reduced.

DISCUSSION: Wilson's Disease (WD) is a rare, autosomal recessive, inborn error of the copper metabolism, which is caused by a mutation in the copper-transporting gene, ATP7B. Copper first accumulates in the liver; after the liver storage capacity for copper gets saturated, copper gets redistributed, with accumulation in the nervous system, the cornea, the kidneys and other organs.⁽⁵⁾ Most of the patients present in the second decade of life with a primary hepatic presentation, with the remainder of the patients presenting during the third and fourth decades, with a primarily neurologic or a psychiatric presentation.⁽⁶⁾ However, in our study, both the cases presented with neurological manifestations in the 2nd decade of life (adolescent), which was similar to the findings of Kalra et al., as was seen in their study which was done at the All India Institute of Medical Sciences.⁽⁴⁾ Study done by More et al also had similar findings.⁽⁷⁾ In most of the Indian studies, the disease was found to manifest at a younger age in Indian children. This could be most likely due to higher average intake of copper in India, which ranges from 5.7 – 7.1 mg/day and it is higher than the reported 0.34 – 1.1 mg/day in the western countries. The practice of cooking food and storing drinking water in copper/copper alloy pots might be contributory.^(5,8) In Wilson's disease with neurological presentations, the symptomatology is predominantly extra pyramidal, like

dystonia, tremors, dysphasia, dysarthria, and ataxia. The neurological symptoms are usually secondary to the cerebral copper deposition, which is sufficient to destroy the nerve cells. Both our cases had neurological manifestations, predominantly dystonia, dysarthria and some cognitive impairment. None of our patients had either clinical nor a biochemical evidence of a hepatic involvement.

The serum ceruloplasmin levels should not be considered for making a definitive diagnosis, because they are normal in up to 10% of the affected patients and are reduced in 20% of the carriers. The Kayser – Fleischer rings can only be diagnosed definitively by an ophthalmologist using a slit lamp.

Urine copper is an important diagnostic tool but it must be collected carefully to avoid contamination. An estimation of the 24-hour urinary copper excretion is another reliable test which can be done for the confirmation of WD. The normal excretion of copper is between 20 and 50 µg per day; in the cases of WD, the excretion is increased in excess of 100 µg per day. In cases with unequivocal urinary copper values, a diagnostic urinary copper excretion with D – Penicillamine challenge is preferred. Two doses of D – Penicillamine (500 mg/dose, 12 hours apart) are given during the collection period of 24 hours. A urinary copper excretion of > 1600 µg in 24 hours is considered positive for WD. The "Gold standard" for the diagnosis remains a liver biopsy with quantitative copper assays. The affected patients have values of > 200 µg/gm dry weight of the liver.⁽⁹⁾

In both the cases, we had made the diagnoses on the basis of the clinical presentations, the serum ceruloplasmin levels, the 24 hours' urinary copper excretion (with D – Penicillamine challenge) and neuroimaging (MRI). Although a liver biopsy with quantitative copper assays is the "Gold standard", due to the parents' refusal, liver biopsies were not done in our patients.

MRI is a very sensitive method for revealing the abnormalities in WD. On the T1 – weighted sequence, hypointensities in the basal ganglia are seen in two-thirds of the cases while in the T2 – weighted images, hyperintensities in the basal ganglia, the white matter, the thalamus or the brainstem are seen. These abnormalities are caused by a neuronal loss, gliosis, degeneration of the fibres, and vacuolisation, which are associated with the increased water content in the brain. The typical 'face of the giant panda' can be seen in the midbrain on the T2 – weighted axial MRI sequence of the brain and the 'face of the miniature panda', can be seen in the tegmentum region of the pons in the T2 – weighted sequence.^(10,11)

D - Penicillamine was previously the primary anti-copper treatment, but now, it plays only a minor role because of its toxicity and because it often worsens the existing neurologic disease if it is used as the initial therapy. If penicillamine is given, it should always be accompanied by 25 mg/d of pyridoxine. Trientine is a less toxic chelator and it supplants penicillamine when a chelator is indicated. The drug of choice for Wilson's disease with neurologic/ neuropsychiatric symptoms is Ammonium tetrathiomolybdate, but in most of

the countries, it is not available commercially and it is still an experimental medicine. For the patients with hepatitis or cirrhosis, without an evidence of a hepatic decompensation or neurologic/psychiatric symptoms, zinc is the therapy of choice, although some advocate the therapy with trientine. Zinc has proven its efficacy in Wilson's disease and it is essentially nontoxic. It produces a negative copper balance by blocking the intestinal absorption of copper, and it induces hepatic metallothionein synthesis, which sequesters the additional toxic copper. All the presymptomatic patients should be treated prophylactically, since the disease is close to 100% penetrant.^(9,12) Both of our cases were treated with D- penicillamine 20 mg/kg/day 12 hourly, oral zinc (as zinc acetate) 25 mg/ dose 8 hourly, and pyridoxine 25 mg/day. After 2 weeks of treatment, an improvement in the symptomatology was seen in the both of our cases.

Genetic therapy and hepatocyte transplantation represent the future curative treatments for WD, along with the currently available liver transplantation.⁽¹³⁾

CONCLUSION: The present cases gave us valuable information that Wilson's disease, an uncommon, autosomal recessive, metabolic disorder, is often missed early when the patients present with only neurological manifestations without any hepatic derangement. A high index of suspicion is required while dealing with adolescents and young adults with abnormal movements and neurobehavioural abnormalities even when there is no hepatic involvement. A non-invasive investigation like screening for KF ring in such patients may be helpful. An early detection of WD is critical, because an early initiation of the treatment can prevent a catastrophic outcome.

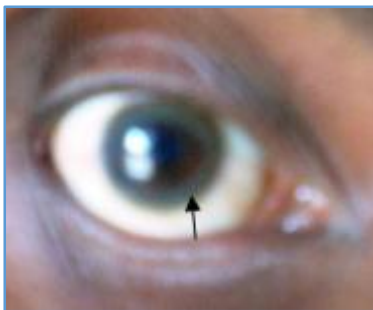


Fig. 1: Kayser – Fleischer ring (arrow) due to copper deposition on Descemet's membrane visible by naked eye examination in case 1

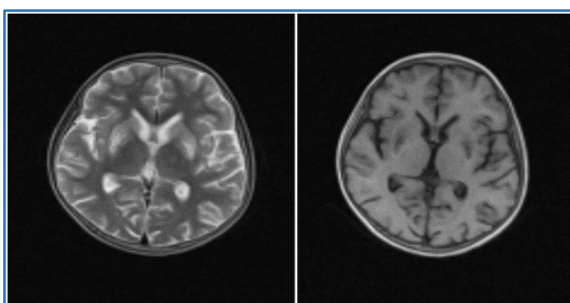


Fig. 2: MRI T2 & T1-Weighted image revealing hyperintensity & hypointensity in bilateral basal ganglia & putamen region in case 1

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