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Case Report

Biochemistry Section

Wilson's Disease with Late Hepatic Involvement

MAHAVIR RAGHUNATH MUNDRA[1], MANJU CHAND ANKHEDE[2], PRADIP JAIN[3], ASHISH ANJANKAR[4]

ABSTRACT

Wilson's Disease (WD) is an autosomal recessive condition that affects copper metabolism and manifests itself clinically in different ways. The diagnosis is indicated by low serum copper and ceruloplasmin concentrations, increased urine copper excretion and/or increased hepatic copper concentrations. The present case report is about a 55-year-old male with chief complaints of loss of appetite, abdominal swelling, tremors in hand and head, slurring of speech for 10 days. Ultrasound (USG) findings were suggestive of liver cirrhosis with portal hypertension and liver function tests were also deranged. He was prescribed diuretics and asked to review after 10 days. Kayser-Fleischer ring was observed through slit lamp examination in both the eyes, which is a hallmark of WD. The Magnetic Resonance Imaging (MRI) of brain also revealed positive findings-hyperintensity throughout the mesencephalon for WD. Thereafter, the patient was treated with penicillamine and his symptoms improved after few days.

Keywords: Liver cirrhosis, Penicillamine, Tremor

CASE REPORT

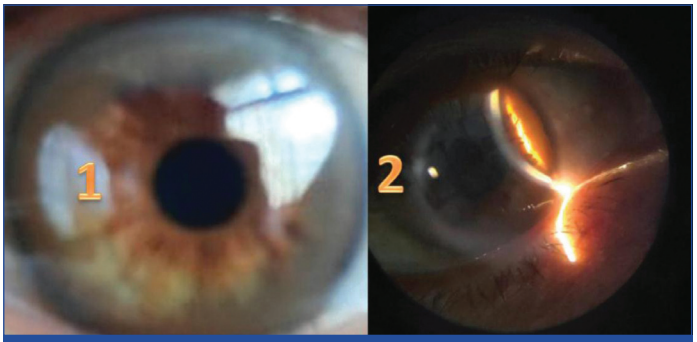
A 55-year-old male patient visited Outpatient Department with the complaints of loss of appetite, swelling and fullness in the abdomen, tremors in hand and head, slurring of speech since 10 days.

He was advised Ultrasound (USG) abdomen along with routine investigations. On USG, the liver appears to have a rough texture with echo, dilated portal vein, development of collaterals, and there is significant ascites. The patient was non alcoholic and tested seronegative for hepatitis B and hepatitis A. The patient was prescribed diuretics and called for review after seven days.

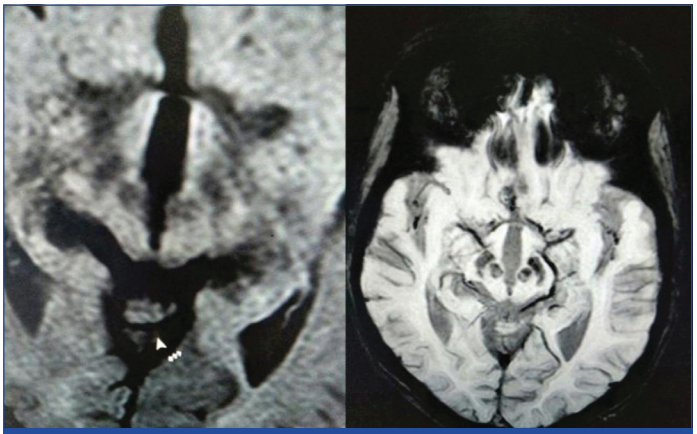
The patient visited for review after one week and he was feeling better but this time he revealed that he was diagnosed with Wilson's Disease (WD) 10 years prior, when he was 45 years old (previously reported to hospital with complaints of joint pains). For three years, the patient was on penicillamine with remission of symptoms. But it relapsed when he stopped the medication for five years (as penicillamine was not available in the area where he relocated). Few months ago he started the treatment again. Since the last few days, he had lost his appetite and weight, as well as acquired abdominal enlargement due to fluid accumulation in abdominal cavity. He had tremors in his head and hands with slurred speech.

The patient was referred for ophthalmological examination, Magnetic Resonance Imaging (MRI) brain and liver was advised, and blood investigations for serum copper, serum ceruloplasmin and urinary copper excretion were suggested. Kayser-Fleischer (KF) rings were observed in both eyes during a slit lamp examination [Table/Fig-1]. T2 and Fluid Attenuated Inversion Recovery (FLAIR) hyperintensity was found in tegmentum of midbrain on MRI. The red nucleus and thalamus were spared [Table/Fig-2]. The ventricular system and the basal cisterns were somewhat dilated. In the subcortical and periventricular white matter of both cerebral hemispheres, T2 and FLAIR hyperintensities were seen. On MRI scans of the abdomen, the liver showed macronodular cirrhosis.

Thus, WD was confirmed based on the biochemical tests that included serum ceruloplasmin, serum copper, and 24-hour urine copper. Penicillamine therapy at a dose of 1 gm per day was restarted. Tablet Zinc 50 mg twice daily, Tablet pyridoxine 25 mg twice daily, Tablet pacitane 2 mg twice daily, Tab. Torsemide 10 mg Once a day, Tab. Propanolol 20 mg three times a day were among the other drugs. Within 2-3 days, the patient's condition had improved. He regained his appetite as well as his general sense of well-being. The ascites and tremors lessened significantly.



[Table/Fig-1]: Slit lamp Examination showing Kayser- Fleischer ring.



[Table/Fig-2]: MRI Brain-Midbrain showing hyperintensity throughout the mesencephalon with sparing of red nucleus, substantia-nigra and superior colliculus.

DISCUSSION

Wilson's disease is very uncommon genetic cause of abnormal copper metabolism characterised by copper buildup in the liver, brain, and other tissues. It affects one in every 30,000 people [1]. The metal is first deposited in the liver, then released in the circulation, and then chronically accumulated in the Central Nervous System (CNS) and other tissues. Cirrhosis of the liver

develops at an early age. Midbrain and basal ganglia are most adversely affected areas in the brain. A study done in Germany concluded that individuals who come before 10 years of age have mostly liver related symptoms, whereas those who present in the third decade have mostly neurological symptoms [2]. Wilson's disease is a progressive condition that can be fatal if left untreated. The condition is frequently misdiagnosed, and early detection is difficult. Wilson's disease typically begins with hepatic involvement and progresses to the central nervous system later on. But in this case the neurological involvement was observed before the hepatic involvement. Tremors of head and hands were the initial symptom. There are also other case reports where the first presentation was related to the neurological system without involving the liver and the patient was over 40 years old [3,4]. Penicillamine can make things worse. This is due to the mobilisation of copper from the liver, which causes an increase in unbound copper, causing neurological symptoms to worsen. Following penicillamine medication, 30-75 percent of patients experienced initial neurological impairment, according to several studies [5,6]. Several additional reports contradicted this [7]. In the present case, medication with penicillamine and anticholinergics improved the tremor. The medication, on the other hand, was responsible for the hepatic symptoms.

According to the World Health Organisation, the prevalence of WD is 1:10,000-30,000 people worldwide [8]. By using current genetic testing, it has now progressively risen to around 142 per million. The highest prevalence (370-885 per million) has been reported in some regions of Europe, including Romania and Sardinia, where six mutations account for 85% of the cohort [9]. The frequency of a person possessing two mutant ATP7B alleles was calculated to be one in 7026 by sequencing ATP7B in 1000 control persons in the United Kingdom [10]. The prevalence in Chinese han population in Anhui province is approximately 5.87 per 100,000 people [11].

Programs for newborn screening have unsatisfactory outcomes. Serum ceruloplasmin screening reveals a prevalence of 124 per million in Japanese children aged six months to nine years [12]. The optimum time to diagnose the disease in children is after they turn three years old [12,13]. Community-based incidence and prevalence studies of WD don't exist in India. In tertiary hepatobiliary centres, WD makes upto 7.6-19.7% of juvenile liver disorders. The number of new cases of WD reported in referral neurology facilities each year ranges from 15-20 [13].

Clinical features of WD: This includes-

A) Hepatic manifestations [14]

- Childhood and adolescence have a higher rate of isolated hepatic involvement than adults, indicating an age-related phenotypic nature of the disease.
- Cirrhosis and portal hypertension are frequently seen in hepatic WD patients.
- Acute Liver Failure (ALF), acute hepatitis, asymptomatic hypertransaminasemia, fatty liver, cholelithiasis, and in extremely rare circumstances, hepatobiliary malignancies are among the additional hepatic WD symptoms.
- Patients with WD who present with ALF almost always have concurrent haemolysis.

B) Neuropsychiatric manifestations [15]

- The only presenting clinical symptom of WD may be neurological or neuropsychiatric symptoms.
- Hepatic form of WD typically manifests earlier than the neuropsychiatric type.
- Clinical findings may vary from mild tremors to dystonia, seizures, Parkinsonism, ataxia, cognitive abnormalities, and overt behavioural problems.
- If a child or young adult exhibits neuropsychiatric symptoms, WD screening should be taken into consideration.

C) Ocular manifestations [14,16]

- KF rings are frequently bilateral and occur in more than 50% of neurological cases and nearly all cases of hepatic WD. A slit lamp examination is required for diagnosis.
- Although it may take years, the disappearance of KF rings frequently indicates that chelation therapy is effective.

D) Renal manifestations [14,17]

- In WD, nephrocalcinosis (microscopic haematuria) and renal tubular failure are common.
- Proteinuria in children on Penicillamine therapy should be routinely assessed in order to detect drug-induced glomerular impairment.

E) Haematological manifestations [14,15]

- In asymptomatic WD, mild Coombs-negative haemolytic anaemia can develop.
- The early sign of ALF linked to WD can be acute severe haemolysis.
- WD should be suspected in children and young adults with Coombs-negative haemolytic anaemia.

F) Other manifestations [14,17]- The initial symptoms of WD may be development of arthritis. One should suspect WD if they get early-onset osteoarthritis or chondrocalcinosis in the second or third decade.

Diagnosis of WD: The most popular method for diagnosing WD is the combination of 24-hour urine copper, KF rings, and serum ceruloplasmin. The measurement of dry copper and liver biopsy have always been considered useful in ambiguous circumstances. The KF ring and extrapyramidal symptoms confirm the diagnosis of WD.

A) Serum Ceruloplasmin [18]

- A value below 10 mg/dL for ceruloplasmin significantly supports the diagnosis of WD.
- Borderline or normal results do not rule out the condition; more testing is necessary to confirm the diagnosis.
- In WD, values above the normal are rare.

B) 24 hour urinary copper [18]: A baseline 24 hour level >100 mcg is a very useful diagnostic test in symptomatic patients.

C) KF rings [19]

- The KF ring is quite specific for WD, although the diagnosis is still valid in the absence of the ring.
- Patients with liver disease have a 50-60% chance of having a KF ring, whereas patients with neuropsychiatric diseases almost always have one.
- To confirm or rule out a KF ring, a skilled ophthalmologist must do a slit lamp examination.

D) Serum copper [18]: Serum total copper levels are not used to make the diagnosis of WD.

E) Haemolytic anaemia [19]

- Any degree of haemolysis in the presence of Coombs-negative liver illness raises the possibility of WD.
- In a person with ALF, substantial haemolysis is usually invariably caused by WD.

F) Biopsy of Liver and concentration of copper in liver tissue [12]: There are no pathognomonic histological characteristics for WD. Liver copper estimation is only marginally effective because the test is unavailable globally at many places and there are logistical and quality issues.

G) MRI brain [14]: Tectal plate hyperintensity on an MRI of the brain is a pathognomonic sign of WD.

H) Family history [18]: Favourable family history, and a history of sibling death in a patient with signs suggestive of WD makes its diagnosis likely.

I) Genetic studies [20]: To confirm the diagnosis of WD in a patient who is suspected of having the condition, the clinical diagnostic test of ATP7B mutation analysis is indicated. Genetic testing is suggested as a clinical diagnostic test for siblings of a proband with WD, especially if the proband has an ATP7B mutation. It is not advised to routinely diagnose WD during pregnancy.

Wilson Disease Treatment Regime

Pharmacological Therapy [21,22]

1. WD patients with hepatic symptoms need to be treated with a chelation therapy. Due to its simplicity of use, low cost, and effectiveness, D-Penicillamine (DP) is favoured.
2. Unless the patient has undergone a liver transplant, lifelong care is required.
3. DP has a number of adverse effects but is still a good chelator [23].
4. Initial monotherapy in Wilson disease shows that both D-penicillamine and zinc appear to effectively control the disease in the majority of patients. Presymptomatic patients achieve the best results with both types of therapy. Given the higher incidence of severe side effects seen in patients with hepatic and neurological presentations on D-penicillamine therapy versus zinc treatment (12.5% vs. 0.9% in our analysis), zinc appears to be preferred as the first-line treatment for presymptomatic patients [23].

Liver transplantation [24]

1. To consider a liver transplant if a patient has hepatic encephalopathy or haemolytic crises.
2. Heterozygous sibling living donor liver transplantation is effective and safe for both the donor and the recipient.
3. Transplanting the liver is not advised in cases of isolated severe neurological WD.

Monitoring on treatment [25]:

1. To ascertain the positive and negative effects of the medications, careful clinical monitoring is required. Complete blood counts, urine analyses, liver function tests, 24-hour urinary copper and protein, and serum free copper levels should be examined at the start of treatment and atleast once every 6-12 months after that. KF rings must be checked yearly.

Drug therapy for neurological symptoms [26]:

1. Baclofen and anticholinergics can be utilised to treat dystonia in patients who do not respond to chelation therapy. Botulinum toxin injections may be an option for people who have refractory focal dystonia or persistent dystonia.
2. Primidone, propranolol, levodopa for Parkinson's, and tetrabenazine for hyperkinesias may all be helpful for patients with residual postural tremors.
3. Patients with neurological WD benefit from both speech and physical therapy during their rehabilitation.
4. Percutaneous Endoscopic Gastrostomy (PEG) tubes are a temporary solution for patients with severe dysphagia until their condition improves with chelation therapy.

CONCLUSION(S)

Wilson's disease is a relatively uncommon genetic disease accompanied by hepatic, neurological, and ophthalmic problems. Usually, the patient presents with hepatic disease first latter there is development of neurological and other symptoms. But in the present case the patient have neurological manifestations first and after 10 years he developed hepatic disease. This case demonstrates the diagnosis of WD in the absence of congruent clinical signs. Early diagnosis and treatment can delay the onset of problems such as liver failure. Hence, WD should be kept as differential diagnosis in patients presenting with neurological symptoms so as to start the treatment early and prevent hepatic involvement.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Biochemistry, Datta Meghe Medical College, Nagpur, Maharashtra, India.
2. Associate Professor, Department of Biochemistry, Datta Meghe Medical College, Nagpur, Maharashtra, India.
3. Professor and Head, Department of Biochemistry, Datta Meghe Medical College, Nagpur, Maharashtra, India.
4. Professor, Department of Biochemistry, Jawaharlal Nehru Medical College, Sawangi, Wardha, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Mahavir Raghunath Mundra,
Associate Professor, Department of Biochemistry, Datta Meghe Medical College,
Nagpur, Maharashtra, India.
E-mail: drmahavir123@gmail.com

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