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CASE REPORT

Wilson's Disease Diagnosed Postnatally Due to Neurological Manifestation

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Introduction

Wilson's disease (WD) is an autosomal recessive disorder due to the mutation in the ATP 7B gene. This gene is on chromosome 13 and codes for P-type ATPase which is responsible for transport of copper from intracellular chaperone proteins in hepatocytes into the secretory pathway. There is defective incorporation of copper into apo-ceruloplasmin for synthesis of functional ceruloplasmin as well as improper biliary excretion of copper, which leads to its accumulation in liver, brain and cornea [1]. The clinical presentation of WD varies widely. In an Indian cohort studied over three decades by Taly et al., 69.1% presented with neurological manifestations followed by hepatic, pre-symptomatic, hepato-neurological, psychiatric and Osseo-muscular in that order. Majority present between the age of 5 and 35 years [1]. The commonest association in women of reproductive age group is with infertility and recurrent abortions [2]. We present a case of a 30-year-old woman with rare presentation of neurological symptom in the postnatal period. The workup which led to the diagnosis of Wilson's disease is detailed.

Case Report

A 30-year-old woman, G_3A_2, was admitted at 39 weeks of gestation in active labor. She was booked at a private hospital outside and had an uncomplicated antenatal period. She delivered a live, male baby of 3.4 kg by outlet forceps. After 24 hours of delivery, fine tremors of both hands were noted during rest and exaggerated during posture. On general physical examination, the pulse rate was 86 beats per minute and blood pressure was 110/70 mm of Hg. There was no icterus or eye signs of hyperthyroidism. Abdominal examination revealed marked splenomegaly. Liver was not palpable. On examination for higher mental status, the patient was conscious, alert, oriented and no memory loss was noted. Cranial nerve examination was done, and all reflexes were found to be intact. On motor system examination, the patient had normal gait, power of 5/5 in all four limbs, normal muscle tone; fine tremors of both hands were noted during rest and exaggerated during posture, and there were no other abnormal movements such as chorea, athetosis, dystonia or dysarthria. Superficial, deep and cortical sensations were normal. Cerebellar function tests were normal. Parkinsonian features such as rigidity, bradykinesia, parkinsonian gait, postural instability and micrographia were absent.

Investigations

Her blood investigations showed normocytic normochromic anemia [Hb-9 g/dL] and thrombocytopenia [platelet count

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45,000/µL]. Her thyroid function tests, liver function tests and renal function tests were within normal limits. Ultrasound abdomen showed altered echotexture of liver, suggestive of parenchymal liver disease, and splenomegaly with dilated portal and splenic veins (Fig. 1), suggestive of portal hypertension.

Diagnosis

Based on the symptoms, clinical examination, blood investigations and ultrasound findings, Wilson's disease was suspected in our patient. A slit lamp examination was done which showed the presence of Kayser–Fleischer ring (Fig. 2) in both eyes. Biochemical tests revealed low serum ceruloplasmin [0.03 g/L], normal serum copper [95.40 µg/dL or 14.98 µmol/L] and normal 24-h urine copper [34.8 µg/24 h or 0.55 µmol/24 h]. Diagnosis of WD was confirmed as the patient presented with neurological symptom along with KF ring and low serum ceruloplasmin. Upper gastrointestinal (GI) endoscopy did not show any evidence of esophageal varices. MRI of brain showed mild atrophy of midbrain and pons.

Treatment

The patient was started on d-penicillamine tablet 500 mg twice daily. On follow-up, there was no worsening of tremors. Penicillamine can be given safely in lactating mothers as few studies suggest penicillamine was not detectable in breast milk but it reduced the copper and zinc secretion in breast milk, the effects of which are not known.

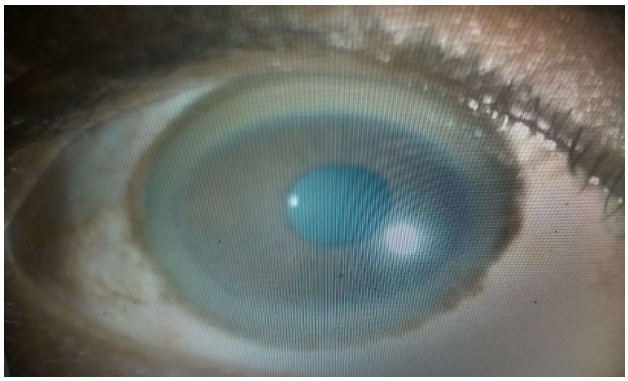

Fig. 2 Kayser–Fleischer ring

Discussion

Wilson's disease is an autosomal recessive disorder with a similar prevalence worldwide of about 1 in 30,000 [1, 3]. There is no single diagnostic test for Wilson's disease. A scoring system for diagnosis based on clinical and laboratory parameters was proposed at the eighth international conference on Wilson's disease, which might be of some help in making a diagnosis [Table 1].Patients presenting with liver disease with a decreased serum ceruloplasmin and detectable Kayser–Fleischer rings have been generally regarded as having classic WD.

Our patient had a score of 5 based on the scoring system and was diagnosed to have Wilson's disease. Liver biopsy for liver copper measurement was not considered necessary as she already was diagnosed based on the above parameters.

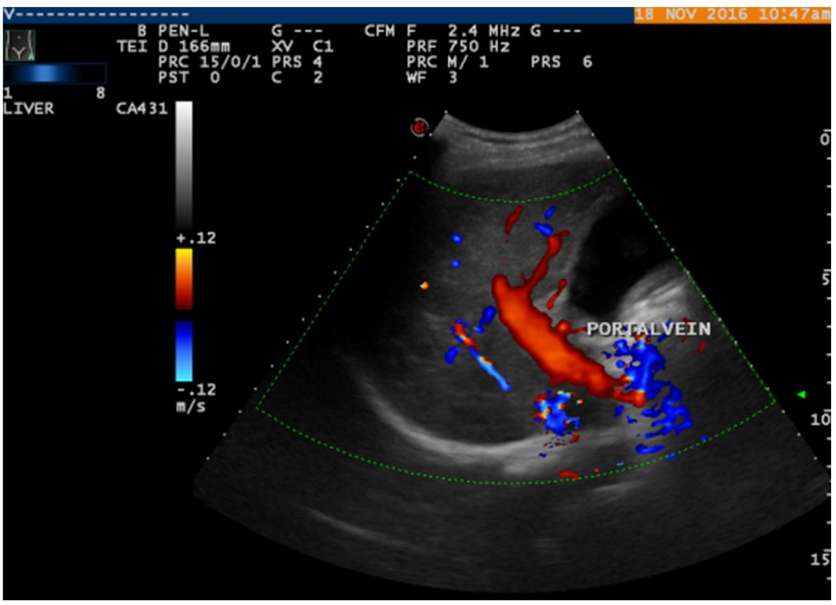

Fig. 1 Dilated portal vein

Table 1 Scoring system developed at eighth international meeting on Wilson's disease, 2001

Typical symptoms, signs and other tests	Score
Kayser–Fleischer rings	
Present	2
Absent	0
Neurological symptoms (or typical abnormalities on brain MRI)	
Severe	2
Mild	1
Absent	0
Serum ceruloplasmin	
Normal (0.2 g/L)	0
0.1–0.2 g/L	1
< 0.1 g/L	2
Coombs-negative hemolytic anemia	
Present	1
Absent	0
Liver copper (in the absence of cholestasis)	
> 5 × ULN (> 4 µmol/g)	2
0.8–4 µmol/g	1
Normal (< 0.8 µmol/g)	− 1
Rhodamine-positive granules on liver biopsy	1
Urinary copper (in the absence of acute hepatitis)	
Normal	0
1–2 × ULN (0.8–1.6 µmol/24 h)	1
> 2 × ULN (> 1.6 µmol/24 h)	2
> 5 × ULN after penicillamine (> 4 µmol/24 h)	2
Mutation analysis	
On both chromosomes detected	4
On 1 chromosome detected	1
No mutations detected	0
Total score	**Evaluation**
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

ULN Upper limit of normal

Mutation analysis by whole-gene sequencing is possible and should be performed on individuals in whom the diagnosis is difficult to establish by clinical and biochemical testing, and for screening family members; but mutation analysis could not be done for our patient or family members as she was not affording for the investigation.

In women, WD is known to cause menstrual irregularities, infertility and recurrent abortions due to deposition of excess copper in the uterus [4]. Reports on pregnancies in patients with prior diagnosis of WD suggest that, in treated women, pregnancy can have an uneventful course and a successful outcome [4, 5], whereas in untreated patients, recurrent abortions are common. Obstetric complications such as preeclampsia and abruption have been reported in patients with Wilson's disease. The presence of portal hypertension increases the risk of bleeding from esophageal varices, which can occur in 50% of pregnant women with varices and mortality rate in patients with esophageal bleed in 50% [5].

Although it is rare to have a successful outcome in pregnancies with undiagnosed and untreated WD, there are two case reports which have described WD detection in the postpartum period with a successful outcome of pregnancy. Aydagmus et al. reported a successful outcome in a pregnancy terminated due to suspected hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome due to preeclampsia with elevated liver enzymes, thrombocytopenia and hemolysis. These features could have been due to WD per se and were interpreted as HELLP syndrome; she was evaluated for WD when she had persistently elevated liver enzymes, bilirubin, INR, with bleeding manifestations [6]. Similarly, in another case report, two cases have been described who presented as HELLP syndrome and had successful pregnancy outcomes but on further workup diagnosed as WD. Our patient who also had a successful pregnancy outcome had manifested in the immediate postnatal period with neurological symptoms and was diagnosed by that which has not been reported yet. As there are over 500 mutations causing WD, variable penetrance of mutation is evident by the decreased number of cases who present with clinical manifestation [2].

It is possible that high estrogen of pregnancy may delay the hepatic failure as suggested by Kasai and colleagues through studies done on animal model and as was seen in the case by Shimono et al. where a previously diagnosed case of WD on d-penicillamine treatment for 12 years had discontinued treatment during her antenatal period and had an uneventful course, but she developed hemolytic crises during the immediate postnatal period from which she recovered with supportive treatment and restarting d-penicillamine but ultimately succumbed to a second hemolytic crises and fulminant liver failure on postnatal day 50.

It can be extrapolated that withdrawal of high estrogen and progesterone after pregnancy in puerperium may precipitate presentation of Wilson's disease symptoms in undiagnosed patients.

In women most of them present before pregnancy with classical symptoms of WD or with infertility and recurrent abortions, there are rare cases like ours which are diagnosed postnatally after an uneventful pregnancy. In young women presenting with new onset neurological symptom like tremors associated with splenomegaly, the workup for diagnosing Wilson's disease should also form priority as the progress

of disease and target organ affection can be controlled by appropriate treatment.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and Animal Rights This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed written consent has been obtained from the patient for the publication of the case report and images.

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