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Case Report

Wilson Disease: A Case Series

Jolly Rabha[1*], Rahul Sharma[2], Emjaj Rahman[2]

[1]Associate Professor, Department of Pediatrics, Assam Medical College and Hospital, Dibrugarh, Assam, India

[2]Post Graduate Trainee, Department of Pediatrics, Assam Medical College and Hospital, Dibrugarh, Assam, India

***Corresponding author:** Jolly Rabha, Associate Professor, Department of Pediatrics, Assam Medical College and Hospital, Dibrugarh, Assam, India; Email: jollyrabha@gmail.com

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Abstract

Wilson's disease is a rare autosomal recessive disorder that results in defective copper metabolism. It has a varied presentation and may be challenging to diagnose. Between 2022 and 2024, four female children at Assam Medical College presented with a range of hepatic, neurological and neuropsychiatric manifestations. Investigations in all cases revealed similar defects in copper metabolism, consistent with Wilson's disease. As for management, the earlier the intervention is initiated, the better the prognosis for recovery. Several treatment options are available and should be tailored to each patient with neurological Wilson disease. Neurological Wilson Disease is considered a form of copper toxicity and immediate diagnostic evaluation and early treatment initiation are crucial, as the disease is potentially curable.

Keywords: ATP7B Gene; Neurological; Copper Toxicity; Acute Liver Failure

Introduction

Wilson's Disease (WD) originates from mutations in the ATP7B gene, exhibiting an autosomal recessive pattern, with a prevalence ranging from 1:30,000 to 1:50,000 [1]. It was first described in 1912 by Kinnier Wilson as progressive lenticular degeneration lethal familial neurological disease with hepatic manifestation [2]. ATP7B encodes a crucial enzyme, transmembrane copper-transporting ATPase, pivotal for copper assimilation into ceruloplasmin and its elimination via bile. Insufficient or faulty enzyme function leads to progressive copper buildup in various organs, predominantly the liver, nervous system, corneas, kidneys and heart [3]. Children usually present hepatic forms of Wilson Disease and as the year advances the neuropsychiatric symptoms starts to develop. Around 20%-30% of WD cases present with Acute Liver Failure (ALF), while untreated patients typically progress to chronic hepatitis or cirrhosis. Although genetic testing aids diagnosis, clinical features and laboratory findings remain essential diagnostic criteria, the use of scoring system like lepzig score has been helpful [4].

Treatment objectives include lowering copper levels and averting its accumulation, especially in the central nervous system. Liver transplantation emerges as a life-saving measure for WD patients facing liver failure and encephalopathy. Adherence to chelating agent therapy is pivotal for long-term management success in WD patients.

Case Report

Case 1

A four-year-old Hindu girl, born of a non-consanguineous marriage, presented with decreased appetite, abdominal pain and distention for 15 days. There was no history of bleeding, trauma or bowel disturbances. Upon examination, the child appeared apprehensive, with mild jaundice, bipedal pitting edema, a distended abdomen and shifting dullness. No organomegaly or pallor was noted and other systems were normal.

Routine investigations were conducted on the first day of hospitalization. The child was found to have a hemoglobin level of 8.3 g/dL and total bilirubin of 18.9 mg/dL, with direct bilirubin at 6.8 mg/dL and indirect bilirubin at 12.1 mg/dL. The peripheral blood film revealed normocytic normochromic red blood cells. Liver function tests indicated elevated levels of alanine Aminotransferase (ALT) at 181 U/L, Aspartate Aminotransferase (AST) at 503 U/L, Alkaline Phosphatase (ALP) at 175 U/L and gamma-glutamyl transferase (GGT) at 130 U/L. Additionally, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR) were elevated (PT: 31.4 sec, APTT: 44.6 sec, INR: 3.1).

Given the clinical presentation and laboratory findings, a strong suspicion of Wilson's disease was considered and further special investigations were done. An ophthalmic examination using a slit lamp suggested the absence of Kayser-Fleischer (KF) rings. The 24-hour urinary copper test revealed 1286 micrograms/day (normal: <50 micrograms/day) and serum ceruloplasmin levels were low, confirming the diagnosis of Wilson's disease.

The child was subsequently started on D-penicillamine chelation therapy and zinc acetate, along with supportive treatment. She was then referred to a higher center for further management (Table 1,2).

Parameters	Case 1	Case 2	Case 3	CASE 4
Haemoglobin (gm/decilitre)	8.3	5.4	9.9	6.8
TLC	9500	13900	28100	18000
Neutrophils	56%	70	63	41
Lymphocyte	35	19	32	54
eosinophil	2	02	1	1
MONOCYTE	1	9	4	4
Platelet count (LAKH/CUBIC MM)	1.8	3.6	1	4
PCV	26	9.3	30.7	22

Table 1: Lab investigations: Hematological parameters.

Parameters	Case 1	Case 2	Case 3	Case 4
Total Bilirubin (mg/dL)	18.9	9.8 (DAY 1) 25.84 (DAY 4)	1.3(Day 5) 5.64(Day 13)	6.8
Direct bilirubin (mg/dL)	6.8	4.98 (Day 1) 22.48 (Day 4)	0.4(Day 5) 1.5 (Day 13)	3.21
Indirect bilirubin (mg/dL)	12.1	4.82 (Day 1) 3.3 (Day 4)	0.92(Day 5) 4.11(Day 13)	3.65
SGPT (U/L)	181	335 (Day 1) 24 (Day 4)	88(Day 5) 42(Day 13)	137
SGOT (U/L)	503	130 (Day 1) 284 (Day 4)	95(Day 5) 95(Day 13)	457
ALP (U/L)	175	188	170	389
LDH	-	>1000	-	-
Total protein (gm/dL)	6.7		4.99	
Albumin (gm/dL)	2.46	2.7	2.3	2.48
PT	31.4	51	27.1	26.8
APTT	44.6	33.5	41.2	46
INR	130	4.1	1.4	2.8
Other Special Parameters				
KF Ring	Absent	Present	Present	Absent
Neuropsychiatric	Absent	Present	Absent	None

Manifestation				
Urinary Copper (3 -50 Microgram/Day)	1286 Microgram/ Day	-	160.65 microgram/day	646
Serum Ceruloplasmin	Low	8.3	3.02	3.2

Table 2: Biochemical and other parameters.

Case 2

A 9-year-old girl, born of a second-degree consanguineous marriage, presented to the Outpatient Department (OPD) with complaints of vomiting, decreased appetite, generalized weakness and yellowish discoloration of her eyes and skin for four days. She had no past history of jaundice, hematemesis or abdominal distension. The child was a single child and her scholastic performance was satisfactory. There were no signs of malnutrition.

On admission, she was alert, conscious, afebrile and cooperative. She exhibited severe pallor and icterus, with no edema, cyanosis or clubbing. Her abdomen was tender, with hepatomegaly measuring 2 cm and splenomegaly measuring 1 cm. No ascites was noted and the rest of the systems were within normal limits.

On day 2 of hospitalization, all routine investigations were sent. However, by day 3, the child began to develop neuropsychiatric symptoms, including behavioral changes and an inability to remember her parents. But other neurological examinations were normal. The initial investigations revealed severe anemia (hemoglobin = 5.4 g/dL) with a deranged coagulation profile. Viral markers were negative and both direct and indirect Coombs tests were negative. Total serum bilirubin was 9.8 mg/dL, with direct bilirubin at 4.98 mg/dL and indirect bilirubin at 4.82 mg/dL. Liver enzyme levels showed SGOT at 130 U/L and SGPT at 336 U/L, with an albumin level of 2.7 g/dL and LDH greater than 1000 U/L.

Ultrasonography of the abdomen showed chronic hepatic parenchymal disease with features of portal hypertension, ascites, right-sided pleural effusion and gallbladder sludge. Some special investigations were planned. On day 4, a hepatic Fibroscan was performed, which suggested liver cirrhosis. An ophthalmic examination using a slit lamp revealed the presence of Kayser-Fleischer (KF) rings. A repeat liver function test showed a further increase in total bilirubin and deranged enzyme levels: total serum bilirubin was 25.84 mg/dL, with direct bilirubin at 22.48 mg/dL and indirect bilirubin at 3.3 mg/dL. SGOT was 284 U/L, SGPT was 24 U/L, albumin was 2.1 g/dL, GGT was 214 IU/L and LDH remained greater than 1000 U/L. Serum ceruloplasmin levels were found to be 8.8 mg/dL (normal range is >20 mg/dL) and a 24-hour urinary copper test was planned.

The child was started on D-penicillamine chelation therapy along with zinc acetate and supportive treatment. She received 2 units of Fresh Frozen Plasma (FFP) and 2 units of Packed Red Blood Cells (PRBC). The child showed marginal improvement, but the parents decided to take her to a higher center, where she underwent liver transplant surgery. She is currently healthy and enjoying good health.

Case 3

A 10-year-old girl, previously healthy, was referred to our institution for nephrotic syndrome. She presented to the pediatric emergency department with a two-week history of facial and leg swelling, decreased urine output and fever. Notably, she had a past history of a skin infection two weeks prior and had been placed on oral prednisolone by a local practitioner.

On examination, there was bilateral pedal edema and abdominal distension. Engorged superficial veins were observed over the abdomen and shifting dullness was present. Other systems were within normal limits. She continued taking prednisolone as prescribed, but her condition did not improve. On day 4, she started developing abdominal distension. By day 7 of hospitalization, the abdominal distension increased and the patient developed icterus. A review of her history did not reveal any familial history of similar illness.

Initial investigations showed hemoglobin of 8.9 g/dL and a total white blood cell count of 28,100/mm^3, with normal serum renal function tests, serum electrolytes and serum cholesterol levels. Proteinuria was graded at 1+ and the spot urine-to-creatinine ratio was 0.4. Both direct and indirect Coombs tests were negative. A liver function test was done on day 5. Total serum bilirubin was

1.30 mg/dL, with direct bilirubin at 0.5 mg/dL and indirect bilirubin at 1 mg/dL. Liver function tests indicated SGOT at 95 U/L, SGPT at 88 U/L, albumin at 2.6 g/dL, GGT at 90 IU/L and LDH greater than 1000 U/L. Tuberculosis workup performed was negative.

On day 7, an ultrasound of the abdomen revealed chronic hepatic parenchymal disease with gross ascites and splenomegaly. Viral markers and Antinuclear Antibodies (ANA) were negative. A CT scan of the abdomen on day 8 suggested hepatic parenchymal disease with features of portal hypertension, splenomegaly, varicosities and ascites. On day 9, with suspicion of a metabolic liver disease, some special investigations were planned. An ophthalmic examination via slit lamp showed the presence of bilateral Kayser-Fleischer (KF) rings. Serum ceruloplasmin levels were low at 3.02 mg/dL (normal: >20 mg/dL) and a 24-hour urinary copper test showed 160 micrograms/day (normal: 3-50 micrograms/day).

Subsequent liver function tests on day 13 indicated further deranged enzyme levels. Total serum bilirubin remained at 1.30 mg/dL, with direct bilirubin at 0.5 mg/dL and indirect bilirubin at 1 mg/dL. SGOT was 95 U/L, SGPT was 88 U/L, albumin was 2.6 g/dL, GGT was 90 IU/L and LDH was greater than 1000 U/L. ANA immunoflorosence was negative. The child was started on D-penicillamine and zinc supplementation and a high-calorie diet with low protein and copper content was advised. Unfortunately, within a month, she developed hepatic encephalopathy and succumbed to her illness.

Case 4

A 6-year-old female child, born out of a non-consanguineous marriage, with a normal birth and development history and no significant family history, presented with yellowish discoloration of the eyes and body for the past 4 days. She also experienced intermittent abdominal pain for 4 days and two episodes of hematemesis over the last day. On examination, the child had pallor and icterus. Anthropometric measurements were between the 50th and 25th percentiles. The abdomen was slightly distended, with the presence of shifting dullness and hepatomegaly of 3.5 cm below the subcostal margin. The liver was non-tender, soft to firm in consistency, with an irregular surface and margin and a liver span of 8.5 cm. No splenomegaly was noted.

Preliminary laboratory investigations revealed anemia with a hemoglobin level of 6.8 gm/dl, microcytic hypochromic cells and the presence of target cells, with a reticulocyte count of 1.2%. The Total Leukocyte Count (TLC) was 18,000/cumm, with 54% lymphocytes, 4% monocytes and 41% neutrophils. The platelet count was 4 lakhs/cumm. Liver function tests showed hyperbilirubinemia (total bilirubin: 3.21 mg/dl, indirect bilirubin: 3.21 mg/dl, direct bilirubin: 3.65 mg/dl), elevated AST (457 U/L), ALT (137 U/L) and ALP (389 U/L), with hypoalbuminemia (serum albumin: 2.48 gm/dl, globulin: 6.18 gm/dl). Coagulation profile was deranged, with PT of 26.8 sec, INR of 2.8 and APTT of 46 sec.

On day 3, an ultrasound of the abdomen, including a portal venous study, showed coarse hepatic parenchymal disease with hepatomegaly and minimal ascites. Doppler imaging of the portal venous system was normal. Serological tests for hepatitis A, B, C and E were negative. Evaluation for anemia, including HPLC, was suggestive of beta-thalassemia (HbE disease) with high fetal hemoglobin and both Direct and Indirect Coombs Tests (DCT and ICT) were negative.

Considering a provisional diagnosis of Wilson's disease, serum ceruloplasmin and 24-hour urinary copper levels were tested on day 4. The results showed a very low serum ceruloplasmin level (3.2 mg/dl) and a high urinary copper level (646 micrograms/day), which are suggestive of Wilson's disease. However, ophthalmological examination was normal and negative for Kayser-Fleischer (KF) rings.

The child started on D-penicillamine and zinc, along with vitamin B6 supplementation, along with other supportive measures. But later, the parents decided to take the child to a higher center for further treatment.

Discussion

Wilson’s disease is a rare autosomal recessive inherited disorder which leads copper overload. It leads to toxic accumulation of copper in liver and subsequently to other sites such as brain. Phenotypically, Wilson Disease is highly variable clinically characterised by hepatic disease and neurological symptoms [5]. Children with Wilson Disease are usually normal at birth [6]. The majority of the patient are diagnosed between the age of 5-35 years of age (nair). Various hepatic manifestation of Wilson Disease include acute liver failure along with coombs negative hemolytic anemia, acute hepatitis, chronic hepatitis, steatosis and

cirrhosis with other effect of hepatic dysfunction (delayed puberty, ammenorrhoes, coagulation defect) while neurological symptoms may present as behavioural or psychiatric problems, depression, personality changes, irritability, dysarthria and/or movement disorder [7] . One of our patient had presented with proteinuria and generalized edema but the pattern of progression of edema did not support renal etiopathogenesis. Indeed, it is known that patients with Wilson Disease could have some degree of proximal tubulopathy which may be partial or generalized [8]. Other clinical manifestation of Wilson's disease includes presence of KF ring. However, they are absent young patients with hepatic Wilson upto 50% of the time but are present in 95% patient with neurologic symptoms. In patients with suspicion of Wilson's disease, a complete blood count, liver function test, serum ceruloplasmin and copper level, a slit lamb examination and a 24 hour urinary cooper should be obtained. Depending on the results of these tests, a liver biopsy can help to determine the extend and severity of liver disease and for measuring the hepatic copper content. Hepatic copper accumulation is the hallmark of Wilson Disease and measurement of hepatic parenchymal copper content is the method of choice of diagnosis. The copper deposition in the liver leads to cirrhosis and later eventually neurological symptoms may progress untill the patient becomes severely dystonic, akinectic and mute. If left untreated, Wilson's disease is universally fatal. However, the prognosis of the patient who are diagnosed on time and are compliant to treatment have excellent prognosis [9,10].

None of the laboratory investigations available are perfect and may not be specific for Wilsons disease. Therefore, a diagnostic score based on available tests were proposed by the working party at 8th international meeting on Wilsons disease called Lepzig score and was adopted in the European association for the study of liver clinical practice guidelines for Wilsons disease. Lepzig scoring system provides a good diagnostic accuracy [11]. Once the diagnosis is made, lifelong treatment should be started and it should be focused on limiting the copper uptake and promoting copper excretion through dietary and pharmacological methods. First degree relatives of parents should be screened for Wilsons disease [12].

In asymptomatic patients diagnosed by screening tests, chelating agents should be started which include D - penicillamine or trientine. Zinc may be also be used. The dietary intake of copper should be restricted to <1 mg/ day and high copper containing food such as liver, shellfish, nuts and chocolate should be avoided.

The first line for treatment of symptomatic patient is to start copper chelating agents at a higher dose until the vitals are stable. Trientine may be preferred if a patient is intolerant to D - penicillamine. Later on, maintenance dose can be achieved with a lower dose of chelators or by zinc. However, those patients presenting with acute liver failure need liver transplant [12]. It is therefore very important to have a vigilant lookout for Wilson's disease as early detection and prompt treatment would decrease the morbidity and mortality.

Conclusion

Wilson Disease is a rare but treatable metabolic liver disease which if identified on time is treatable. It may present at any age with various manifestation. Clinical presentation may be hepatic, neurological or psychiatric or more than one manifestation may be present. Genetic evaluation for ATP7B gene is a effective for screening in first degree relatives of known cases. Medical treatment remains highly effective even for those with cirrhosis. Liver transplantation is the only treatment for failed treatment or acute liver failure. A multidisciplinary approach will help to decrease the morbidity and mortality.

Conflict of Interests

The authors have no conflict of interest to declare.

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