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Case Report

Hidden Intricacies of Chronic Liver Disease in a Young Adult: A Case Report on Wilson's Disease

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Abstract:

Wilson's disease, a rare autosomal recessive disorder of copper metabolism, often manifests with hepatic, neurological, or psychiatric symptoms due to toxic copper accumulation. This case report describes a 20-year-old male from a remote tea garden in Sylhet, Bangladesh, diagnosed with Wilson's disease during an evaluation for chronic liver disease. The patient presented with anemia, jaundice, ascites, and splenomegaly. Investigations revealed elevated liver enzymes, suggestive ultrasonographic findings, a raised hepatic Fibro-Scan score, and esophageal varices. Notably, the patient had a family history of Wilson's disease, with two older siblings previously diagnosed. Despite the absence of consanguinity between the parents, this prompted further biochemical workup. The patient's serum ceruloplasmin level was low, although 24-hour urinary copper excretion was within the normal range. Slit-lamp microscopy confirmed the presence of a Kayser-Fleischer ring in both the patient and the affected siblings. He was started on chelation therapy with penicillamine, alongside supportive management for chronic liver disease. This case highlights the extraordinary misfortune of three siblings from a non-consanguineous family being affected by a rare autosomal recessive disorder.

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Introduction:

Wilson's disease (WD) is a rare genetic disorder characterized by excessive copper accumulation in the body, leading to damage in the liver, brain, kidneys, and corneas.[1]

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It is caused by mutations in the ATP7B gene that impair copper transport, preventing copper from being excreted into bile or incorporated into ceruloplasmin, the copper-carrying protein in the blood.[2] Though consanguinity between parents is an expected condition in WD, its autosomal recessive inheritance pattern can affect individuals in any population, even from non-sanguineous parentage.[3]WD has a global prevalence of 1 in 30,000 to 1 in 40,000 live births.[4]The clinical presentation of WD pertaining to three main categories of symptoms i.e., hepatic, neurological, and neuropsychiatric manifestations, can be present independently or together, depending on factors like age, genetic variability, and the extent of copper accumulation.[5]Around half of WD patients present with liver-related symptoms, as is the reported case.[6]A high index of clinical suspicion is the key to prompt diagnosis of WD.[7] Slit lamp

ophthalmoscopic evaluation can be a pathognomonic, thus an important tool for diagnosis.[8] The non-invasive biomarkers, serum ceruloplasmin levels and urinary copper excretion, are crucial in monitoring disease progression.[5,6] Enhanced imaging techniques like quantitative MRI have also improved the accuracy of liver and brain assessments.[9] Genetic testing for diagnosis has evolved with the modern era but is seldom applied as a common practice.[10,11]WD is one of the treatable causes of chronic liver disease. So, early diagnosis and treatment have an enormous impact on outcome.[7,12] Moreover, its primary treatment is very simple with one of a few recommended oral medications. Zinc supplementation prevents copper absorption; penicillamine and trientine act by copper chelation in the treatment of WD.[5,6] This case report, a young man presenting with chronic liver disease with a background of positive family history, highlights the necessity of screening of siblings in relevant families so that the disease can be detected and treated at an early stage.

Case summary:

A 20-year-old male presented to the medicine inpatient department of Sylhet Women's Medical College with generalized body swelling for one week, which started in the abdomen. He mentioned generalized weakness and loss of appetite for the same period. Over the past nine months, he noticed yellowing of his skin and eyes. The abdominal swelling was not associated with pain, itching, dark urine, or pale stools. There was no history of hematemesis, melena, behavioral changes, or loss of consciousness. Additionally, there was no recent use of hepatotoxic drugs or blood transfusions. He experienced occasional difficulty in breathing onlying down, though this was not accompanied by fever, cough, palpitations, or chest pain. He was the youngest of four siblings, born to non-consanguineous parents, and two of his elder sisters had been diagnosed with Wilson's disease several years ago. On physical examination, he had anemia, jaundice, mild edema, huge ascites, and splenomegaly suggestive of chronic liver disease **(Figure 1)**. However, other stigmata of chronic liver disease (CLD) were absent. His jugular venous pressure was normal, and bedside urine examination did not show evidence of proteinuria or glycosuria. Examination of the respiratory system revealed a few coarse crepitations at the left lung base. However, the cardiovascular, locomotor, renal and neurological systems revealed unremarkable features.

His blood counts revealed hemoglobin 3.9 g/dl, ESR 02 mm, total count of WBC 1,720 /cu-mm with neutrophil 63% lymphocyte 27%, eosinophil 05%, monocyte 05%, platelet 50,000/cu-mm and, red cell 2,68,000 /cu-mm. Pancytopenia was the impression on peripheral blood film examination. His serum creatinine (0.76 mg/dl) and, electrolytes (sodium 135, potassium 3.6, chloride 110 and, bicarbonate 24 mmol/L) were normal. His iron profile revealed a low serum iron (12 mcg/dL) and, ferritin (8ng/mL). The liver function tests revealed some derangements, notably a raised serum bilirubin (3.8 mg/dl), reduced albumin (1.8 gm/dl), mildly raised alanine transaminase (59 U/L), alkaline phosphatase (223U/L) and, prolonged prothrombin time (25 sec) with INR 50. His viral markers, HBsAg and, anti HCV were negative. Urine for routine and microscopic examination revealed normal findings. USG of the whole abdomen showed coarse hepatic parenchyma, splenomegaly, huge ascites and, a thickened wall of gall bladder **(Figure 2a)**. Endoscopy of the upper gastrointestinal tract revealed medium to large varices at the lower end of the esophagus (Figure 2b). A hepatic elastogram revealed a hepatic stiffness index of 24.5 kPa indicating stage 4 (16-75 kPa) fibrosis **(Figure 3)**. His serum ceruloplasmin is low at 0.010 g/L (0.15-0.30), and 24-hour urinary copper excretion is 12.62 mcg/24 hours. On slit lamp examination of the eyes by an expert ophthalmologist showed bilateral Kayser Fleischerrings in the corneas **(Figure 4)**. His ECG was normal and chest X-ray showed a few opacities at the left lower zone **(Figure 5)**.

Figure 1: Ascites, pale complexion, jaundice

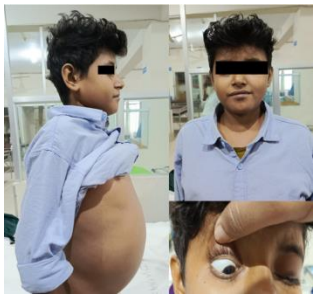


Figure 2: a. Ultrasonography of abdomen showing coarse liver, enlarged spleen and ascites b. Endoscopy showing esophageal varices. Please note arrows.

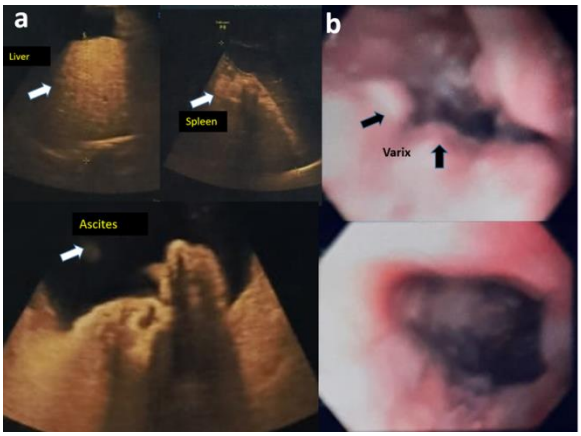


Figure 3: Hepatic elastogram revealing stiffness index of the liver

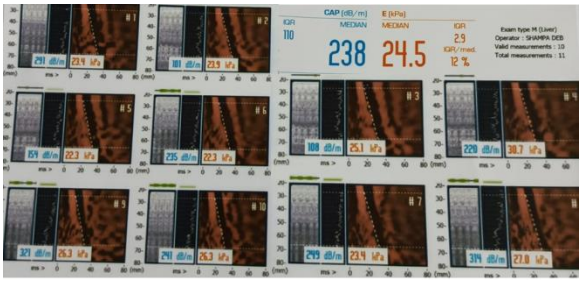


Figure 4: Slit-lamp microscopy showing brownish deposition of copper at the sclera-corneal junction- the KF ring (arrows)

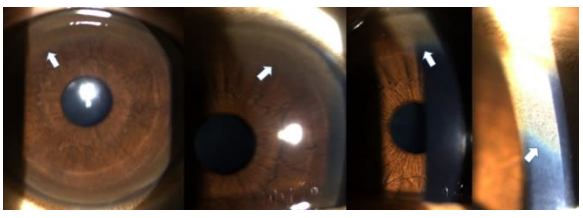
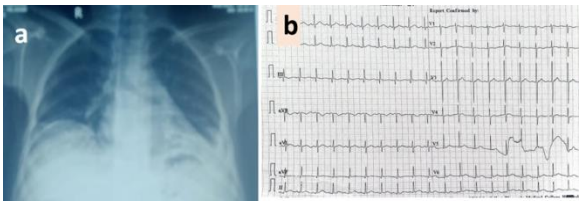


Figure 5: a. Chest X-ray showing a few opacities in left lower zone b. Normal ECG



Discussion:

Wilson's disease (WD) is an autosomal recessive disorder requiring the inheritance of two defective copies of the *ATP7B* gene, one from each parent, to manifest.[13]WD is more prevalent in populations with consanguineous marriages due to the increased likelihood of both parents carrying the same genetic variant. However, it can also occur in individuals born to non-consanguineous parents,[14] as was the case in this report. Unfortunately, this rare genetic transmission affected multiple siblings in this family. The index case has two elder sisters with WD who are living normal lives with medication. Both sisters were diagnosed at the same medical facility seven years ago, with the eldest sister's case reported at that time.[15]The second sister was screened and diagnosed concurrently, but the youngest brother missed screening due to the family's remote living conditions and failure to follow up.

Liver-related clinical presentation is more common than neurological or neuropsychiatric presentation, particularly in younger individuals with the genetic defect. These patients may present with hepatitis, fatty liver, cirrhosis, or acute liver failure.[1,2,16] Around 40% of cases, especially in older adolescents or young adults, exhibit neuropsychiatric features such as movement disorders, tremors, dystonia, and dysarthria, caused by copper accumulation in the brain. Parkinsonism-like symptoms may arise when deposition occurs in the basal ganglia. Neurological symptoms typically present later than hepatic symptoms and may dominate in those diagnosed later in life.[17]Additionally, 20–30% of patients present with mixed hepatic and neuropsychiatric symptoms, such as signs of chronic liver disease alongside cognitive decline, depression, mood swings, or personality

changes. Mixed presentations complicate management, as both hepatic and neurological symptoms require tailored treatment. Neuropsychiatric symptoms can be subtle and are often underreported, affecting an estimated 10-20% of patients, especially in the early stages. Symptoms include cognitive changes, depression, irritability, personality changes, and mood disorders, which can sometimes precede more overt neurological or hepatic symptoms.[9,10] In the index case, the patient and his siblings did not exhibit any neurological or psychiatric symptoms, although brain imaging was not conducted. Despite a low serum ceruloplasmin level, urinary copper excretion was within the normal range. It is worth noting that low ceruloplasmin levels can occur alongside hypoalbuminemia (1.8 g/dL), and urinary copper excretion levels, theoretically expected to exceed 100 mcg/dL, do not definitively rule out other chronic liver diseases.[6]However, urinary copper excretion can at times be false negative or false positive.[18]The diagnosis of WD in the reported case is primarily based on a strong family history and the presence of Kayser-Fleischer rings on slit-lamp examination, raising some concerns among investigators regarding the sufficiency of these criteria.[8,19] However, in the case of the patient's elder sister, the diagnosis was established through the fulfillment of the Leipzig scoring system having a score of 7.[15]

Markers for viral hepatitis, common causes of cirrhosis, were negative. Serum iron (12 mcg/dL) and ferritin (8 ng/mL) levels were low, but hypoalbuminemia likely influenced these values, complicating their interpretation.[20] However, iron deficiency anemia was considered a plausible cause of the patient's anemia, particularly given the presence of esophageal varices, which may have caused chronic blood loss. Treatment focused on copper chelation using oral penicillamine and, endoscopic band ligation was planned for the esophageal varices.

Advances in genetic screening enable earlier diagnosis, even in asymptomatic individuals, through family screening and newborn testing. Numerous mutations in the responsible gene have been identified that influence the severity of the condition.[3,7]However, genetic screening for WD is not routinely performed unless there is a family history or clinical suspicion. As a result, estimates of prevalence in non-consanguineous families rely on general carrier rates and probabilities associated with recessive inheritance.[6,9]Though genetic testing was beyond the means of the family of this case and the healthcare facility, counseling was provided regarding the hereditary nature of the disease, the importance of avoiding consanguineous marriages within the family, and the need for screening the next generation.

Zinc supplementation, which inhibits copper absorption, has gained popularity as an effective therapy, particularly in pre-symptomatic and mild cases. Chelating agents such as penicillamine and, trientine remain primary treatments, though newer formulations with fewer side effects are being explored. For instance, trientine has shown potential in reducing copper levels with lower toxicity.[7]A systematic review of 23 studies, involving over 2,000 patients, aimed to compare the therapeutic benefits and drawbacks of zinc, penicillamine, trientine, succimer, and no treatment. The findings indicated that zinc was safer than penicillamine while offering comparable therapeutic efficacy. However, the authors expressed concerns about the quality of the included trials.[21]The index case and his two siblings were treated with penicillamine due to its availability, and all three tolerated the therapy well.

Recent advancements in the management of Wilson's disease (WD) include experimental gene therapy targeting ATP7B gene mutations, which holds promise as a potential cure.[22,23] Progress has also been made in understanding the neurological effects of WD, including motor and cognitive symptoms. Innovative strategies, such as neuroprotective drugs and rehabilitative therapies, are being developed to address these issues and enhance patients' quality of life.[24] Liver transplantation remains a treatment option for patients who respond poorly to medical therapy or present with acute liver failure.[25]

Early diagnosis and targeted therapy are critical, as they can prevent severe organ damage and allow individuals with WD to ensure healthier lives of the patients. Ongoing research and clinical trials continue to improve understanding and management of this condition.

Conclusion:

In conclusion, WD exhibits a wide range of symptom patterns. Hepatic manifestations are more common in younger patients, while neurological symptoms are more prevalent in adults. Almost one third of the patients experience both hepatic and neurological or neuropsychiatric symptoms. These varied presentations highlight the critical need for early and accurate diagnosis, as timely treatment can profoundly influence the disease progression and thus improve quality of life. This case report emphasizes the importance of screening all family members, even in the absence of consanguinity.

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