Wilson disease in a 19-year-old female

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A 19-year-old, previously healthy female patient presented to the emergency department with 3 weeks of nausea, vomiting, progressive abdominal pain and distention. One week before her presentation, she was treated for a urinary tract infection with a 5-day course of nitrofurantoin. She was also treated for possible constipation with laxatives, which did not improve her symptoms. The patient was not on any regular prescription medications, herbal medications or dietary supplements, and reported infrequent use of alcohol. She had no family history of hereditary liver disease.

On examination, the patient was alert and oriented. Her vital signs were blood pressure 132/88 mm Hg, heart rate 99 beats/min, oxygen saturation 100% (room air) and temperature 36.9°C. She had scleral icterus and jaundice without asterixis. Her abdomen was distended and tender in the bilateral upper quadrants. Bedside ultrasonography showed a mild volume of free fluid in the abdomen. Her neurologic examination was normal.

Admission bloodwork is shown in Table 1. We considered a broad differential for acute liver injury (Table 2). Viral serologies for hepatitis A, B, C and E, cytomegalovirus and Epstein–Barr virus were negative, as were tests for autoantibodies, although immunoglobulin G levels were elevated at 19.17 (normal 6.00–16.00) g/L. Urine pregnancy test, urine drug screen and tests for acetaminophen and alcohol levels were negative. The patient had no symptoms of lung disease to suggest α-1 antitrypsin deficiency. Abdominal ultrasonography showed normal flow through the portal and hepatic veins. Computed tomography scans of the abdomen and pelvis showed hepatosplenomegaly with no morphologic features of cirrhosis.

We considered drug-induced liver injury, given the patient's recent use of nitrofurantoin, although chart review revealed elevated aminotransferase levels and thrombocytopenia before use of nitrofurantoin; therefore, we did not consider it a major contributor to her current presentation. We started intravenous

Key points

- Wilson disease is an uncommon genetic disorder with defective biliary excretion of copper causing its accumulation in tissues, particularly the brain and liver; patients can present with symptoms at any age.
- The clinical spectrum of liver disease can range from asymptomatic to acute liver failure or cirrhosis; adults may have additional psychiatric or neurologic manifestations.
- Wilson disease should be considered in patients with unexplained acute liver injury.
- Key investigations include slit lamp examination for Kayser–Fleischer rings, serum ceruloplasmin and 24-hour urinary excretion of copper.

Table 1: Investigations for a 19-year-old female with Wilson disease

Investigation	8 mo before admission	1 wk before admission	On admission	Days since admission				Normal range
				1	2	3	4	
Hemoglobin, g/L	127	121	108	98	106	97	103	115–155
Platelets, × 10^9/L	349	96	73	64	61	75	56	150–450
Total bilirubin, μmol/L			63	59	71	61	64	0–17
AST, U/L			305	245	257	228	266	8–40
ALT, U/L		180	143	116	123	114	132	8–40
ALP, U/L			158	114	97	92	100	48–110
Albumin, g/L			21			19	20	35–55
INR			2.3	2.3	2.2	2.3	2.2	0.9–1.2

Note: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = international normalized ratio.

Table 2: Differential diagnosis for a young adult patient with acute liver injury

Diagnosis	Key features and investigations
Viral hepatitis	• Aminotransferase levels can exceed 1000 U/L • Positive viral serologies (e.g., hepatitis A–E, herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein–Barr virus)
Ischemic hepatitis	• Aminotransferase levels can exceed 1000 U/L • Often associated with an episode of shock or hemodynamic instability
Drug-induced liver injury	• Thorough medication history, including prescribed and nonprescribed medications, mushroom ingestion, herbals, dietary supplements • Elevated acetaminophen and alcohol levels
Hepatic thrombosis	• Review prothrombotic risk factors • Abdominal ultrasonography with Doppler
Autoimmune hepatitis	• Occurs predominantly in females • Positive anti-nuclear antibodies, anti-smooth muscle antibodies, anti-liver–kidney antibodies • Elevated total immunoglobulin G
Wilson disease	• Can have psychiatric or neurologic manifestations • Slit lamp examination for Kayser–Fleischer rings, decreased serum ceruloplasmin and elevated 24-h urinary excretion of copper
α-1 antitrypsin deficiency	• May be associated with lung manifestations (e.g., early-onset emphysema) • Decreased serum α-1 antitrypsin level
Hypertensive disorders of pregnancy	• Features of hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome • Severe hypertension with less prominent liver dysfunction as in HELLP
Acute fatty liver of pregnancy	• Usually presents between 30 and 38 wk gestation • Rapid development of acute liver failure

N-acetylcysteine empirically for undifferentiated acute liver injury, which did not lead to improvement in the patient's synthetic function. Urgent liver biopsy showed acute-on-chronic hepatitis, with severe active lobular inflammation and background cirrhosis on initial pathology. She had no evidence of autoimmune or lymphoproliferative processes.

Given the patient's age, clinical presentation and lack of a clear cause for acute liver injury, we considered Wilson disease. We consulted an ophthalmologist, who observed bilateral peripheral corneal deposits in the Descemet membrane, highly suspicious for Kayser–Fleischer rings, on slit lamp examination. The following day, copper rhodanine stain was found to be strongly positive within the hepatocytes (Figure 1). Investigations showed a ceruloplasmin level of 0.13 (normal 0.15–0.55) g/L, quantitative hepatic copper concentration of 1907 (normal 10.0–35.0) µg/g and 24-hour urinary copper excretion of 32.80 (normal 0.06–0.28) µmol/d.

We diagnosed Wilson disease based on the presence of Kayser–Fleischer rings, rhodanine-positive hepatocytes, elevated 24-hour urine copper, elevated quantitative hepatic copper and decreased serum ceruloplasmin. Given evidence of cirrhosis and synthetic dysfunction, we contacted a transplant centre, who considered a transplant to be indicated. Four days after presentation, the patient was transferred to a transplant centre, and she received a deceased donor liver transplant the following week. Her postoperative course was complicated by intraoperative hypoxemia and postoperative blood loss requiring a short stay in intensive care, but she was discharged from hospital 1 month after transplantation.

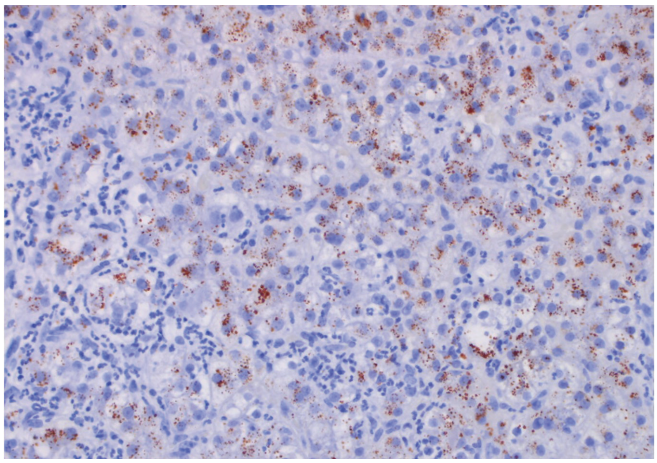

Figure 1: Liver biopsy of a 19-year-old female showing positive copper rhodanine stain (reddish brown stain) within the hepatocytes (magnification × 40).

Discussion

Acute liver injury can be caused by a broad list of differential diagnoses. Although the most common causes among adults are viral illnesses, drugs and ischemia, acute liver injury in a young adult patient also requires consideration of metabolic, genetic and pregnancy-related causes (Table 2).

Wilson disease affects 1 in 30 000 live births[1] and patients can present with symptoms at any age, although most cases are diagnosed before age 55 years.[2] Most pediatric patients present with hepatic manifestations, while adults have hepatic manifestations with or without psychiatric or neurologic manifestations.

In Wilson disease, the spectrum of liver disease at presentation can range from mild biochemical abnormalities to acute liver failure or cirrhosis. Common neurologic symptoms include dystonia, tremor or ataxia, while psychiatric symptoms can resemble paranoia, depression or schizophrenia.[3] Kayser–Fleischer rings, which represent copper deposits in the Descemet membrane of the cornea, are a pathognomonic finding of Wilson disease.[3] However, they can be absent in around 50% of patients with Wilson disease.[3] Wilson disease should be considered in the differential diagnosis for patients with unexplained acute liver injury and must be excluded in patients with liver disease presenting with neurologic or psychiatric disorders. Wilson disease can resemble autoimmune hepatitis both clinically and histologically on liver biopsy. Both can present with elevated serum immunoglobulins and nonspecific autoantibodies, as seen with our patient. Patients presenting with apparent autoimmune hepatitis in childhood, or those presenting with apparent autoimmune hepatitis that is not responsive to therapy in adulthood, should be evaluated for Wilson disease.[4]

Wilson disease occurs because of sequence variations in the hepatocyte transport protein *ATP7B* gene, which impairs biliary copper excretion and leads to copper accumulation in tissue. At least 380 variations have been confirmed to cause symptomatic Wilson disease.[5] Defective ATP7B also impairs the binding of copper to its main transport protein ceruloplasmin. Specific tests include serum ceruloplasmin, which is generally decreased in Wilson disease because of the shorter half-life of non–copper-bound ceruloplasmin, and 24-hour urinary copper excretion, which is universally elevated in untreated patients. Other initial investigations include liver biochemical tests, a complete blood count, serum ceruloplasmin, 24-hour urinary copper excretion and slit lamp examination for Kayser–Fleischer rings. If a baseline neurologic evaluation is abnormal, further imaging with magnetic resonance imaging should be considered to evaluate for signal changes and to exclude other potential causes. Liver biopsy can aid in diagnosis through quantification of hepatic copper deposition and assessment of the stage of liver injury. Finally, genetic testing for *ATP7B* variations can provide diagnostic confirmation if biochemical testing is not definitive.[2] The American Association for the Study of Liver Diseases provides a diagnostic algorithm to facilitate the diagnosis of symptomatic Wilson disease, which can be used in combination with scoring systems such as the modified Leipzig score to determine if additional testing is required. A score greater than 4 suggests likely Wilson disease;[3] our patient's score was 7.

Initial treatment for stable symptomatic Wilson disease uses a copper-chelating agent such as D-penicillamine or trientine. We did not treat our patient with copper chelators as they would not be effective, given that she had cirrhosis with synthetic dysfunction. Asymptomatic patients may be treated with lower doses of copper-chelating agents or with zinc salts that lower intestinal copper absorption. Lifelong maintenance therapy and clinical monitoring is required when patients are managed with chelating agents or zinc. The New Wilson Index has been shown to predict risk of death better than the Model for End-Stage Liver Disease (MELD) score for Wilson disease.[2] A score of 11 or higher is a strong predictor of death without liver transplant;[2] our patient's score was 11. In patients who present with acute liver injury, liver transplantation is curative as it corrects the underlying metabolic defect. First-degree relatives of patients with Wilson disease should be screened either through genetic testing, if disease-specific mutations are identified in the proband, or by clinical and biochemical assessment for signs and symptoms of Wilson disease.[2]

Conclusion

We present a case of Wilson disease with the classic clinical picture of a teenaged patient with acute liver injury, decreased serum ceruloplasmin and detectable Kayser–Fleischer rings. This case highlights the importance of maintaining clinical suspicion for Wilson disease in a young adult with unexplained liver injury, especially when more common causes of acute liver injury are excluded.

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