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Wilson's disease: Hepatic manifestations

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Hepatic manifestations of Wilson's disease can be extremely variable in its presentation and uniformly fatal without early recognition and prompt medical treatment. With early diagnosis and medical treatment, almost all individuals can look forward to a good long-term outcome. For this reason, it is imperative that WD be considered in the differential diagnosis in anyone with unexplained liver disease.

Age and gender

WD should be considered in any person between the age of 3 and 55 years with typical symptoms and signs.[1] However, age should not preclude a workup for possible Wilson's disease since the spectrum of the disease can occur in the very young as well as the elderly. The youngest patient reported was a 3-year old with cirrhosis and the oldest patients with WD, diagnosed by molecular studies, were in their 70s.[2,3] Up to 4% of patients, in fact, can be diagnosed clinically and using laboratory tests after the age of 40 years.[4]

With respect to gender, in a retrospective study of 627 patients by Litwin et al.,[5] 58% of women presented with hepatic symptoms as compared to 42% of men. In this same study, women also developed the neuropsychiatric form 2 years later than men (29.4 vs 27.1, $p < 0.05$).

Clinical presentation

Presenting symptoms are highly variable, ranging from the asymptomatic individual with only mild abnormal liver function test, overt cirrhosis (compensated or decompensated), or to acute liver failure. Overall, 40–50% of affected individuals will present with liver disease.[6] Predominate hepatic symptoms usually present in the first decade of life with the average age between 10 and 13 years.[7] On an average, patients with hepatic manifestations usually present earlier than the onset of neurological symptoms by 5 years.[8] In a study of 276 patients, the most common hepatic signs and symptoms were jaundice (28%) followed by hepatomegaly (9%) and abdominal pain (5%).[9] Patients who have a history of jaundice may have previously experienced an episode of hemolysis. Other presenting signs include clinical evidence of cirrhosis such as spider angiomas, isolated splenomegaly, ascites, and gynecomastia. In a recent retrospective study of 229 patients, 62% with hepatic manifestations of Wilson's disease had liver cirrhosis.[10]

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Table 1
Hepatic features in patients with Wilson's disease.

Asymptomatic hepatomegaly
Isolated splenomegaly
Persistent elevations in serum aminotransaminases
Jaundice
Fatty liver
Resembling autoimmune hepatitis
Acute hepatitis
Compensated or decompensated cirrhosis
Acute liver failure

Furthermore, cirrhosis at diagnosis was the best predictor of death and need for liver transplantation. Asymptomatic WD patients with only mild elevation in liver function test occur between 18% and 23%.[11,12] The clinical hepatic features are summarized in Table 1.

Although many patients are diagnosed at a very young age, most have some degree of liver disease. In a study by Schmitt de Bem et al.,[13] approximately 44% (16/36) of patients show histological evidence for cirrhosis at the time of diagnosis. Over time, undiagnosed WD will invariably lead to signs of portal hypertension leading to ascites, variceal hemorrhage, hepatic encephalopathy, and renal failure. Subtle clues to disease progression from WD is the development of (1) reduced synthetic function with reduced albumin, (2) elevated international normalized ratio (INR), and (3) elevated bilirubin. Although elevations in liver function test can be a clue to Wilson's disease, it does not correlate with the severity of underlying liver disease.

The 2 major clinical hallmarks for WD is the identification of Kayser–Fleischer rings by slit-lamp examination and a low ceruloplasmin. The following 2 important points are to be made: (1) the identification of Kayser–Fleischer rings in clinically diagnosed hepatic WD is seen in only 47–52%; this in contrast to the 85–90% of patients who present with neurological symptoms and (2) a ceruloplasmin level of < 20 mg/dl is seen in only 65% of chronic liver disease patients, which compares to 85% seen in patients with neurological symptoms.[8,14] Furthermore, in young children with hepatic disease, Kayser–Fleischer rings are usually absent.[15] Therefore, an absence of Kayser–Fleischer rings and/or a low ceruloplasmin will not exclude the diagnosis of hepatic WD and may be overlooked if only strict clinical and laboratory examination findings are used as diagnostic criteria.

Radiological features in hepatic WD

In clinical practice, the use of abdominal imaging such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) is commonly performed when an individual presents for initial evaluation. Common findings associated with WD include fatty infiltration, contour irregularity, and right lobe atropy on US.[16] Recent studies have revealed images unique to individuals with WD. In a series of 28 patients using US, CT, and MRI, specific features in WD include multiple nodular lesions, presence of peri-hepatic fat layer, and an absence of caudate lobe hypertrophy.[17] Furthermore, using unenhanced CT scan in 13 patients, Li et al.[18] noted the unique findings of hyperdense nodules in 92% and honeycomb appearance in 58% of patients with WD. On MRI, the findings of multiple hypo-intense macro-nodules on T2 imaging as well as findings of contour abnormalities can be suggestive of advanced hepatic dysfunction.[19] Despite the common use of cross-sectional imaging in today's medicine, a specific diagnosis of WD as well as the severity of the liver disease cannot be made alone by cross-sectional imaging.

In the setting of cirrhosis, hepatocellular carcinoma (HCC) is rarely associated with WD. It has been hypothesized that the presence of copper in the hepatocyte may actually protect against neoplastic change.[20] In a series of 363 patients, HCC developed in 2 patients (0.5%), 31 and 38