Disparate Hepatic Imaging with Technetium-99m Sulfur Colloid and Disofenin in Wilson’s Disease

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A 10-yr-old boy presented with fulminant hepatic failure. Technetium-99m sulfur colloid images showed absent reticuloendothelial function in the liver. A [99mTc]-disofenin hepatobiliary scan visualized liver parenchyma and biliary excretion. Disparate appearance of the liver may be seen in other hepatic diseases, but should be remembered as a possible pattern in Wilson’s disease.


Wilson’s disease is an uncommon, but potentially treatable, cause of fulminant hepatic failure. There is excessive copper accumulation in the liver, attributed to an underlying defect in biliary copper excretion. The exact biochemical defect is not established. The radionuclide appearance of the liver has received little mention, although the computed tomography (CT) and magnetic resonance imaging (MRI) appearances of the liver have been reported in this disease. Disparity between the hepatic accumulation of technetium-99m sulfur colloid ([99mTc]SC) and technetium-99m disofenin ([99mTc]DISIDA) has not previously been reported in Wilson’s disease to our knowledge, although this observation has been reported in other hepatic disorders.

We report Wilson’s disease in a child in whom there was nonvisualization of the liver with [99mTc]SC and intact accumulation and excretion of [99mTc]-DISIDA.

CASE REPORT

A previously well 10-yr-old white male presented with a 2-wk history of vomiting, diarrhea, and fever. Jaundice and increasing abdominal girth were noted by the family. Intermittent epistaxis began 1 wk prior to admission. No other family members reported illness.

Physical examination at the time of admission revealed a small, thin, markedly jaundiced white male with protuberent abdomen. Nontender hepatosplenomegaly and ascites were present. Neurologic examination was normal. Kayser-Fleischer rings and subconjunctival hemorrhages were noted on ophthalmologic examination. Laboratory findings revealed the following: SGOT 540 International units (IU); SGPT 133 IU; alkaline phosphatase 118 IU; total bilirubin 20.1 mg/dl; direct bilirubin 7.3 mg/dl; prothrombin time 20.1 sec; partial thromboplastin time 55.6 sec; hemoglobin 9.8 g/dl; hematocrit 28.6%; platelet count 164,000. The white blood cell count was 9.5 × 10^3 with 65% neutrophils and two bands. Hepatitis B (surface) antigen and Hepatitis B (core) antibody titers were negative. Serum ceruloplasmin was 21 mg/dl (normal 20 to 40 mg/dl). 24-hr urine copper was 1,131 μg/ml (normal <40 μg/ml).

A [99mTc]SC liver spleen scan (50 μCi per kg) was performed on the second hospital day (Fig. 1). There was absence of activity within the liver on all views, with localization of the radionuclide confined to the spleen and the bone marrow. Hepatobiliary imaging with [99mTc]DISIDA (50 μCi per kg) performed 6 days later showed homogenous hepatic parenchymal accumulation of the radionuclide with excretion into the extrahepatic biliary system and bowel (Fig. 2). Computed tomography (CT) of the abdomen revealed evidence of hepatosplenomegaly. The CT attenuation values of both liver and spleen were in the range of 52–55 Hounsfield units (Fig. 3). No intrahepatic space occupying lesions were demonstrated.

Hyperbilirubinemia and intermittent bleeding episodes continued. Treatment with penicillamine and a low copper diet were instituted, but severe hemolysis and obtundation were noted on the 16th day. The bilirubin rose to 66.0 mg/dl, with direct bilirubin 40.9 mg/dl. Despite plasmapheresis and supportive measures, the patient’s neurologic status continued to
deteriorate. Generalized seizures, pulmonary hemorrhage, and gastrointestinal bleeding worsened. The patient expired on the 26th hospital day.

Postmortem examination was performed. Hepatic copper concentration was 991.0 mg/g of dried tissue (normal 20 to 50 mg/g). The liver weighed 874 g. It appeared shrunken and finely nodular. On microscopic examination, islands of hepatocytes were separated by wide bands of fibrous tissue. Severe bile duct proliferation and formation of pseudoacini was present. Remaining nodules of liver cells contained many round eosinophilic hyaline-like bodies. A diffuse inflammatory infiltrate was present within the septae and surrounded the hepatocytes. Severe bile stasis and iron deposition were seen. Copper was demonstrated within the hepatocytes by rubeonic acid staining. The spleen showed congestive changes and weighed 390 g.

DISCUSSION

The classic form of Wilson's disease is described as the coexistence of neurologic symptoms, chronic liver disease, disturbances of renal function, and corneal Kayser-Fleischer rings. In Wilson's original description, young siblings of some patients were found to die of cirrhosis without manifesting neurologic symptoms. Since that time there have been numerous descriptions of children and adult patients presenting with liver disease in the absence of neurologic symptoms (1–4). He-
Hepatosplenomegaly and hepatic manifestations varying from asymptomatic organ enlargement followed by slowly appearing jaundice and ascites to an acute fulminant hepatitis-like picture have been observed (5–8). In many instances, the presentation mimics subacute or chronic hepatitis. Thus, no single pattern of liver disease is sufficient for diagnosis. Neither Kayser-Fleischer rings nor ceruloplasmin levels are pathognomonic for the disease (2,3). Kayser-Fleischer rings may be absent in young patients in whom copper has not yet been transferred from hepatic storage sites to the cornea. Similar rings have been described in biliary cirrhosis and in intrahepatic cholestasis. Although most patients with Wilson’s disease will have low ceruloplasmin levels, elevated levels have been found in a minority of patients. With fulminant hepatitis, massive liver cell necrosis may also result in low ceruloplasmin levels. Although hepatic copper is elevated on biopsy specimens and urinary copper excretion is high, these studies are also not pathognomonic of Wilson’s disease (9,10). More importantly, they are unlikely to be obtained until the possibility of Wilson’s disease is seriously considered. Since treatment with chelating agents has been shown to be beneficial in Wilson’s disease and is different from the treatment of other forms of fulminant hepatitis, it is important to establish this diagnosis.

Early metabolism studies and hepatic imaging using copper-64 (64Cu) and copper-67 (67Cu) have shown decreased hepatic accumulation of copper with progressive liver disease (11,12). Little attention has been given to the radionuclide appearance of the liver with current reticuloendothelial cell function and newer hepatocyte imaging agents. Nazer et al. described diminished liver activity with increased spleen and vertebral uptake in a 13-yr-old boy with acute liver failure (13). Chajek’s report of a colloidal gold-198 (198Au) liver scan in a 14-yr-old indicates a similar pattern of nonvisualization of the liver with a colloid radiopharmaceutical (14). Serial scans in this patient showed improvement as therapy with penicillamine progressed. A single case reported by Yamamoto et al., demonstrated patchy inhomogeneity of the liver and spleen with [99mTc]phytate in a 29-yr-old woman (15).

Discrepancies between hepatic visualization with [99mTc]colloid and hepatobiliary agents have been described in many patients with chronic liver disease (16–21). However, in most cases the hepatobiliary function shows greater disturbance than the reticuloendothelial function (16,17). Alcoholic cirrhosis has previously been identified as a cause for reduced sulfur colloid accumulation in the liver with relatively preserved [99mTc]IDA accumulation (19). In other studies of alcoholics, reduced sulfur colloid with preserved [67Ga]-citrate and iodine-131 rose bengal accumulation were observed (20). The greater disturbance in reticuloendothelial cell function of the liver has been described in radiation therapy, following intestinal bypass, with infestation by Schistosomiasis and with familial erythrophagocytic lymphohistiocytosis (21). Reticuloendothelial cell saturation in systemic disorders has also been cited as a cause of diminished sulfur colloid accumulation with intact IDA-compound accumulation (18).

The radionuclide appearance we report is particularly interesting in view of the pathophysiology of Wilson’s disease and the brief duration of clinically overt disease.
Excess copper accumulates in the hepatocytes, not in the reticuloendothelial cells. Accumulation of copper within the hepatocytes is postulated to occur slowly in most patients, with redistribution of the metal from the cytoplasm to the lysosomes without clinical consequences (6). Ultimately, copper saturation and toxicity would result in hepatic cell necrosis, with resultant liver failure and release of large amounts of copper from the hepatic tissues (22). One consequence of the severe hepatocyte necrosis would be diffuse hepatic injury, followed by hepatocyte regeneration. Since reticuloendothelial cell regeneration cannot occur, the replaced liver would consist primarily of hepatocytes. Alternatively, as postulated in cases of chronic liver disease and cirrhosis, intrahepatic shunting of blood could result in diminished hepatic reticuloendothelial cell visualization and relatively greater splenic and marrow accumulation of the radionuclide (23). Greater reticuloendothelial cell activity in the spleen could also be expected as the result of hepatic inflammation.

The hepatic computer tomographic (CT) attenuation values of 52–55 Hounsfield units in our patient are within the normal range of 45–75 Hounsfield units (24–26). The splenic CT attenuation values were also 52–55 Hounsfield units. The normal range of liver-spleen CT attenuation differences is 0 to +19 Hounsfield units. The normal hepatic CT attenuation values in our patient with Wilson’s disease are thus in accordance with the series of Dixon and Walshe in which no correlation was found between hepatic copper concentration and CT attenuation values in ten patients with Wilson’s disease (27). Similar findings were also reported by Smevik et al. and Lawler et al., although increased CT attenuation values of the liver associated with an elevated hepatic copper level has recently been described in one patient (28–30).

Magnetic resonance imaging of the liver is considered by Lawler et al. to offer considerable potential in the diagnosis of Wilson’s disease. In their series, abnormalities on MRI study were detected in two patients with normal CT scans. In two additional patients with abnormal CT scans the MRI study demonstrated more extensive involvement. In this series of 13 patients the $T_1$ measurements of the liver were within normal limits (210–270 ms) including patients with elevated hepatic copper levels at the time of magnetic resonance imaging.

There is at present no single imaging modality for the definitive diagnosis of Wilson’s disease. There are insufficient reported cases of radionuclide studies in Wilson’s disease to determine the incidence of the combination of scan appearances we report. It could be speculated that hepatobiliary imaging performed later in this patient’s course would have demonstrated greater hepatocyte impairment with concordant decrease in reticuloendothelial and hepatobiliary function. The possibility of Wilson’s disease should be considered in patients displaying decreased reticuloendothelial cell activity in the liver with relatively greater hepatocyte visualization, since this may reflect an earlier and potentially treatable stage of this disorder.

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REFERENCES