Cholelithiasis and Wilson disease

We have studied three children with Wilson disease who had clinical symptoms suggestive of cholecystitis as well as radiologic evidence of gallstones, subsequently proven at the time of laparotomy. The gallstones from the patients with Wilson disease had an appreciably higher content of cholesterol than gallstones from age-matched children with hemolytic disease. Since gallstones may be present for years before they produce clinical symptoms, young patients with Wilson disease should undergo routine investigation for the presence of stones; cholelithiasis should also be considered in the differential diagnosis of abdominal pain in such patients.


METHODS

Clinical data were gathered retrospectively from the medical records. Laboratory studies were performed as described previously. For determination of the cholesterol content of gallstones, the stones were weighed, dissolved in 100% isopropanol, and analyzed by Technicon AutoAnalyzer. Gallstones were also collected from six additional patients undergoing cholecystectomy: three children with hereditary hemolytic anemias and three adults with acute cholecystitis associated with cholelithiasis. These stones were analyzed concomitantly with those from the patients with Wilson disease.

CASE REPORTS

Case 1. A 12-year-old girl presented in May, 1973, with abdominal swelling, ankle edema, easy bruisability, and dark urine. She was found to have ascites, anasarca, splenomegaly, abnormal liver function tests, and evidence of hypersplenism (Table I). Four months later neurologic symptoms (dysarthria, mild dysdiadochokinesia) appeared, and ophthalmologic examination revealed the presence of Kayser-Fleischer rings. Treatment with penicillamine and pyridoxine was begun.

Ten months later the patient experienced severe right upper quadrant pain, and a diagnosis of acute cholecystitis was made clinically. The oral cholecystogram failed to visualize the biliary system. An intravenous cholangiogram showed a common bile duct of normal size and configuration, but the gallbladder was...
Fig. 1. A, A solitary calculus not visible roentgenographically on the plain film is coated with contrast material during oral cholecystography (arrows). B, Abdominal roentgenogram four months later shows three radio-opaque calculi (arrows) in the gallbladder region.

Table I. Laboratory data in three patients with cholethiasis

<table>
<thead>
<tr>
<th>Case</th>
<th>WBC</th>
<th>Hematocrit (%)</th>
<th>Reticulocyte Count (%)</th>
<th>Hepoglobin</th>
<th>Platelets</th>
<th>SGOT*</th>
<th>Bilirubin total/ direct (mg/dl)</th>
<th>Alkaline phosphatase</th>
<th>Ceruloplasmin % normal</th>
<th>Serum copper (µg/dl)</th>
<th>Copper metabolast†</th>
<th>Urine copper (µg/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4,700</td>
<td>39</td>
<td>3.0</td>
<td>10</td>
<td>35,000</td>
<td>420</td>
<td>4.6/-</td>
<td>112‡</td>
<td></td>
<td>15</td>
<td>45</td>
<td>240</td>
</tr>
<tr>
<td>2</td>
<td>24,050</td>
<td>26</td>
<td>3.2</td>
<td>30</td>
<td>–</td>
<td>106</td>
<td>15.3/9.5</td>
<td>1.0§</td>
<td></td>
<td>20</td>
<td>15</td>
<td>750</td>
</tr>
<tr>
<td>3</td>
<td>14,700</td>
<td>14</td>
<td>12.0</td>
<td>4</td>
<td>136,000</td>
<td>122</td>
<td>30/12.8</td>
<td>1.4§</td>
<td></td>
<td>4</td>
<td>140</td>
<td>2,200</td>
</tr>
<tr>
<td>Normal:</td>
<td>5- 10,000</td>
<td>37-47</td>
<td>&lt;1.6</td>
<td>30-160</td>
<td>150,000-300,000</td>
<td>8-36 &lt;1.0/</td>
<td>&lt;0.4 % normal</td>
<td>58-164</td>
<td>87-153</td>
<td>48 ± 16</td>
<td></td>
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</tr>
</tbody>
</table>

*Karmen Units.
†Values obtained prior to penicillamine therapy
‡Normal: 25-85 IU.
§Normal: 4-10 BU.

not seen. At surgery, a solitary, black, faceted stone was found impacted in the cystic duct, and the preoperative cholangiographic finding of a normal common bile duct was confirmed. Histologic examination of the gallbladder revealed chronic cholecystitis. Liver biopsy showed periportal inflammation, bile duct proliferation, irregular swelling of the hepatocytes, and cirrhosis. Hepatic copper level was 275 µg/gm dry weight (normal, < 50 µg/gm). Cholesterol accounted for 25% of the weight of the stones.

Case 2. A 12-year-old boy presented with a one-month history of malaise, vomiting, and abdominal pain. He was jaundiced and had evidence of hemolysis. Liver function tests were abnormal (Table I). The diagnosis of Wilson disease was confirmed by the presence of Kayser-Fleischer rings. Treatment with penicillamine and pyridoxine was begun. Within the next six months, the patient experienced four episodes of right upper quadrant pain, without signs of cholangitis, and a radiographic diagnosis of cholelithiasis was made (Fig. 1). At surgery, 25 ml of greenish brown sludge and multiple brownish black variegated stones were found in the gallbladder. Liver biopsy revealed moderate periportal inflammation and necrosis, mild cholestasis, and cirrhosis. Hepatic copper level was 537 µg/gm dry weight. Cholesterol accounted for 20% of the weight of the stones.

Case 3. A 12-year-old girl presented with jaundice and hemolytic anemia in 1970. Kayser-Fleischer rings confirmed the diagnosis of Wilson disease and the liver function tests were abnormal (Table I). Penicillamine therapy was started. At age 13 the patient began to have intermittent attacks of sharp right upper quadrant pain following meals. An oral cholecystogram and intravenous cholangiogram revealed the presence of gallstones and dilated common bile duct (Fig. 2). At surgery, the gallbladder was found to be filled with sludge and approximately 25 soft, multifaceted brownish black stones. Liver biopsy revealed chronic active hepatitis and cirrhosis. Hepatic copper
DISCUSSION

The three children in this study demonstrated two well-known complications of Wilson disease—cirrhosis and hemolysis—both predisposing to the development of cholelithiasis. In patients with cirrhosis, the increased prevalence of gallstones appears to be dependent primarily upon the presence of pigmented stones. Consequently, hemolysis has been cited as the primary pathogenetic mechanism for cholelithiasis in such patients. In Wilson disease, hemolysis may occur as a result of hypersplenism with diminished red cell survival or may be due to copper-induced red blood cell injury, indeed either may provide the basis for a potential increase in content of biliary pigment. The mechanisms of stone formation, however, in patients with hemolysis is unknown. It has been postulated that increased quantities of unconjugated bilirubin might serve as a nidus for stone deposition.

Standard criteria are available which relate color, size, and shape of gallstones to the content of cholesterol and pigment. On the basis of these criteria, the stones in the present study would be classified as “mixed,” and indeed, their content of cholesterol supports this classification. Our preliminary observations of gallstones in children with hemolytic disease have demonstrated that they are more uniform in appearance, dark green in color, and have a mean cholesterol content approximately half that found in those of our three patients with Wilson disease. Adult patients with symptomatic cholelithiasis have had larger, yellowish, faceted stones containing predominantly cholesterol (> 95% of total weight).

The composition of biliary lipid in Wilson disease has not been extensively investigated. The bile of such patients is said to contain distinctly less copper than normal bile. The available data, however, do not provide a mechanism for the formation of gallstones in Wilson disease apart from that dependent upon cirrhosis or hemolysis or both. Conceivably, an alteration in the heavy metal content of gallbladder bile in Wilson disease might increase nidation; this hypothesis is currently being tested in our laboratory.

Because of the strikingly high association of gallstones and Wilson disease in our patients, this complication should be looked for in every young patient in whom the diagnosis is made. Patients particularly at risk are those who have had episodes of hemolysis. Cholelithiasis must always be considered in patients with Wilson disease who develop abdominal pain. Even when stones are not identified, sequential observations with ultrasound techniques should be obtained to identify patients at risk prior to the onset of clinical symptoms.

REFERENCES

9. McIntyre N, Clink HM, Levi AJ, Cummings JN, and