Iron and liver diseases

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A well-defined relation between iron excess and liver damage occurs in hereditary hemochromatosis (HHC). However, recently an excess of iron has also been found in people with chronic liver diseases apparently unrelated to HHC, and it has been suggested that iron may play a role in these conditions by affecting their natural history.

HEPATITIS B VIRUS AND HEPATITIS C VIRUS CHRONIC LIVER DISEASE

In the 1970s, Lustbader et al (1) reported that hemodialysis patients with elevated levels of serum ferritin had a higher likelihood of developing hepatitis B virus (HBV) infection than those with lower levels of serum ferritin. Later, increased values of transferrin saturation, serum ferritin and liver iron concentration (LIC) were found in a high proportion of patients with hepatitis C virus (HCV)- and HBV-related chronic liver disease (2-5). These findings motivated the use of phlebotomy in the therapy of patients with chronic hepatitis, because it was thought that iron depletion could improve liver function and possibly the natural history of the patients. However, phlebotomies were followed by a reduction of alanine aminotransferase that, in some cases, reached normal values, but HCV RNA concentration did not appear to be markedly affected by iron depletion (6-9).

Iron has been included among the factors that are able to influence the response to alpha-interferon (IFN) therapy. Only 5% to 15% of patients with increased iron parameters have a response to IFN therapy versus 50% of those with normal iron status. A significant difference in LIC values between responders and nonresponders to IFN therapy was found, although the LIC of the majority of the nonresponders was in the upper part of the normal range (10-13). Recently, a correlation between the grade of hepatic iron deposits and histological severity was found (14,15), suggesting that liver iron deposition could facilitate the evolution to cirrhosis.

Key Words: Genetic hemochromatosis; Hepatitis C virus; Iron; Liver disease

Le fer et les maladies du foie

RÉSUMÉ : On observe, chez les patients atteints d’une hépatopathie, une surcharge légère ou modérée en fer, sans liens apparents avec l’hémochromatose génétique. Le fer semble modifier l’évolution naturelle des maladies chroniques du foie, liées au virus de l’hépatite C, des hépatopathies alcooliques et de la stéatohépatite non alcoolique en menant à une fibrose encore plus marquée du foie, d’où formation d’un terrain propice à la cirrhose. Les mutations du gène HFE, le gène responsable de l’hémochromatose héréditaire, se rencontrent plus souvent chez les patients souffrant de maladies du foie et chez ceux qui ont une surcharge ferrique. Les patients présentant un surplus de fer sont plus prédisposés que les autres à l’hépatome. Au contraire, la déplétion martiale pourrait générer l’installation de la fibrose et réduire ainsi les risques de cancer du foie.

Key Words: Gene HFE; Hepatitis C virus; Iron; Liver disease
TABLE 1
Frequency of carriers of HFE mutations among patients with porphyria cutanea tarda

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Number of patients</th>
<th>C282Y</th>
<th>H63D</th>
<th>Patients with HFE mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Great Britain (26)</td>
<td>41</td>
<td>44% (11%)</td>
<td>31% (29%)</td>
<td>68% (37%)</td>
</tr>
<tr>
<td>The Netherlands (27)</td>
<td>15</td>
<td>67% (17%)</td>
<td>33% (NA)</td>
<td>87% (NA)</td>
</tr>
<tr>
<td>Italy (29)</td>
<td>68</td>
<td>3% (1.5%)</td>
<td>51% (24%)</td>
<td>53% (25%)</td>
</tr>
<tr>
<td>Australia (28)</td>
<td>27</td>
<td>44% (12%)</td>
<td>44% (NA)</td>
<td>70% (NA)</td>
</tr>
</tbody>
</table>

Numbers in brackets indicate the frequency of control individuals from the same population. NA Not applicable.

Porphyria cutanea tarda (PCT) is a liver disease in which the pathogenic role of iron is better defined. The C282Y and H63D mutations of the HFE gene are associated with PCT, although patients with HCV-related chronic liver disease and PCT may have increased iron stores. A meta-analysis of 113 Italian patients with HCV-related chronic liver disease and PCT revealed that the frequency of both H63D and C282Y mutations was higher in patients with more severe liver damage. These results suggest a direct relation between iron and alcohol-related liver disease but suggest a possible role for HFE mutations in the susceptibility to alcohol toxicity.
hyperferritinemia (39), suggesting that the mutations of the HFE gene may affect the natural history of patients with fat accumulation in the liver.

**LIVER CANCER**

Finally, iron has been suggested to facilitate liver cancer occurrence, although its role in cancer development is still a matter of debate. Numerous clinical investigations have suggested that patients with excess iron have a greater than normal risk of developing cancer, and several experimental studies in animals have confirmed a relation between iron and cancer (40). Indirect support of the role of iron in cancer comes from recent findings in French patients who underwent orthotopic liver transplantation for liver cancer. The concentration of iron in extrahepatic, non-neoplastic tissue was markedly higher than in control patients without liver cancer. Increased liver iron stores were present in both patients with hepatocellular carcinoma that developed on a cirrhotic or noncirrhotic liver (41). In a similar series of Italian patients undergoing orthotopic liver transplantation for liver cancer, the values of LIC compatible with a diagnosis of HHC were found in 8% of the patients – a 20-fold higher frequency than expected in the Italian population (42). The absence of severe cirrhosis rules out the possibility that the high LIC could be only secondary to liver cirrhosis, as recently reported (43,44). In addition, in two patients, hepatocellular carcinoma occurred in the absence of a pre-existing cirrhosis. Very recently a high prevalence of the HFE gene mutations has been reported in patients with liver cancer, in those with both normal and cirrhotic livers (45,46). These results suggest that the increased iron in the liver may act as a promoter of neoplastic transformation in the presence of carcinogenic factors.

**CONCLUSIONS**

Excess iron is present in many patients with chronic liver disease, and mutations of the gene associated with HHC are often found in these patients. Evidence suggests that iron may affect the natural history of different liver diseases independent of etiology. Iron depletion therapy may improve the prognosis of patients with chronic liver disease and possibly reduce the risk of liver cancer.

**REFERENCES**

1. Lustbader ED, Hann HWL, Blumberg BS. Serum ferritin as a predictor of host response to hepatitis B virus infection. Science 1983;220:423-5.


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