Commentary: Iron Metabolism in Hepatitis C Infection

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Abstract. Hepatitis C virus (HCV) infections have started to decline, but up to 10,000 deaths each year are the consequence of chronic liver disease, following the infection. Laboratory testing identifies HCV-infected individuals using positive recombinant immunoblot assays to detect the presence of the antibody; the diagnosis is confirmed by detecting HCV RNA in serum. HCV-infected patients who have large accumulations of hepatic iron have not responded well to interferon therapy, compared to patients with normal hepatic iron stores. Physicians who treat patients infected with HCV should be aware of the detrimental effect of excess liver iron on interferon therapy. The degree of hepatic iron overload should be assessed and the reason for the excess iron should be investigated. Phlebotomy is the most practical method for iron removal and is well tolerated by patients with HCV infection.

Keywords: Iron metabolism, hepatic iron overload, hepatitis C infection, liver disease

Introduction

Hepatitis C (HCV) infection is usually silent and is rarely suspected clinically. The diagnosis of HCV infection is usually made when antibody to HCV has been detected in a blood sample. Antibody testing is now routinely performed on each blood donation and this practice has markedly decreased the incidence of HCV infection in blood transfusion recipients. All newly discovered HCV-infected donors should be referred to a physician. A substantial number of individuals who have positive blood tests for HCV antibody were infected by blood transfusions before donor testing became mandatory in the USA. By retrospective review of all recipients of blood from donors who subsequently tested positive for HCV antibody, additional cases of infected recipients may be discovered [1]. Alter et al [2] has estimated that 3.9 million HCV-infected persons in the USA should be identified through blood donation. Therapy with alpha interferon is expensive and unpleasant, but it may lead to removal of HCV RNA, and if circulating hepatic enzymes remain normal, liver damage is minimized or possibly avoided altogether [2]. It is increasingly recognized that additional causes of hepatic injury may contribute to fibrosis and cirrhosis in HCV-positive subjects. One important factor appears to be hemochromatosis, since Olynyk et al [3] recently found the prevalence of genetic homozygous hemochromatosis to be 0.5% in a population of white adults of northern European ancestry who reside in Australia.

Natural History of the HCV Infection

The clinical course of HCV infection could not be evaluated until the development of reliable tests for the HCV antibody and viral RNA. The natural history of HCV infection was studied by Vogt et al [4] using a cohort of 67 children (mean age 2.6 yr). These children were transfused during heart surgery with blood suspected to be infected with HCV. These blood transfusions all occurred prior to routine testing of blood donors for HCV. The patients were observed for 12 to 27 years. Without treatment, 55% of the patients remained positive for HCV RNA. The viral load varied according to the HCV genotype (1a, 420,000 genome

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equivalents; 1b, 552,000 genome equivalents; and 3a, 5,000 genome equivalents per ml) [4]. Seventeen patients had liver biopsies that were evaluated for histologic changes. All had periportal lymphocytosis; 2 had sinusoidal lymphocytosis, and 2 had steatosis. Hepatic fibrosis was noted in 2 cases, attributed to other causes. Hepatic iron deposits were not evident [4].

Papakonstantinou et al [5] studied children suffering from thalassemia, who received many transfusions to maintain a reasonable red cell volume. Inevitably, this treatment leads to massive iron loading, unless the iron is removed. Liver iron stores were assessed by magnetic resonance imaging (MRI) to avoid liver biopsy. The patients were tested for serum ferritin level and alanine aminotransferase (ALT) activity, and their results compared with normal and HCV-infected control children. The thalassemic patients usually had very high levels of serum ferritin (> 3,000 μg/L; normal range 20-200μg/L). Their serum ALT activities were also consistently elevated (mean = 242 U/L in HCV-infected thalassemic patients; normal range, 15-35 U/L). In HCV-infected children without thalassemia, serum ALT activity (mean = 191U/L) was slightly lower than in the iron overloaded thalassemic children. In healthy controls, serum ALT activity averaged 27 U/L. HCV-infected thalassemic patients had a mean serum ferritin level of 3,517 μg/L. Thalassemic patients without HCV infection had a slightly lower mean serum ferritin level of 2,459 μg/L, and this was associated with slightly elevated serum ALT activity (mean = 41.7 U/L). Elevated ALT activity in this study confirmed the usefulness of serum ALT testing to detect hepatic inflammation. A smaller number of patients without thalassemia but infected with HCV were studied. These patients had serum ferritin levels (mean = 209 μg/L) and serum ALT activities (mean = 191 U/L) that were higher than the corresponding normal controls (mean ferritin level of 55 μg/L; mean ALT activity of 27 U/L) [5].

In 1977-78, HCV-contaminated anti-D immune globulin was administered to 62,667 women in Ireland. The Irish Hepatology Research Group followed these patients for 17 years, and found that only 56% were positive for HCV RNA [6]. On liver biopsy, 98% had only slight to moderate inflammation and no iron deposits were recorded. The absence of liver iron may have reflected the fact that women are commonly iron depleted, compared to men, and have marginal hepatic iron stores.

Lichtman et al [7] reported that bone marrow transplants performed to cure patients with hematologic malignancies may lead to long-term complications of iron overload. Some of these patients are infected with HCV. This situation requires evaluation and treatment, including iron removal. Iron removal may be difficult if red cell regeneration is inadequate. But the administration of erythropoietin restores normal red cell proliferation in the presence of large iron stores [7]. The present author has treated such a patient with a ferritin level of 9,000 μg/L, using regular phlebotomy, made possible by administration of erythropoietin to maintain normal red cell production.

The cited clinical studies substantiate that increased risk is associated with the presence of elevated hepatic iron stores in patients with HCV infection. Irreversible liver damage can occur in patients who have the combination of HCV infection and excess iron in the liver [5], in contrast to HCV-infected patients with low or normal iron stores [4,6]. The cited studies also confirm the value of clinical laboratory tests, including serum transferrin saturation, ferritin, and ALT assays. Liver biopsy permits an assessment of the presence or absence of fibrosis in response to the combined viral and iron overload damage [4].

Bassett [8] infected a small group of chimpanzees with HCV. Both the infected group and an uninfected control group were fed a diet supplemented with iron. Only the infected animals showed histologic evidence of liver injury. However, the small number of animals did not permit statistical validation of these findings.

HCV and C282Y Mutation: a Sinister Synergism?

Hereditary hemochromatosis is commonly associated with homozygosity for a point mutation in the HFE gene (the substitution of tyrosine for cysteine at position 282, or C282Y) [9]. Since reliable genetic testing for hemochromatosis is now available, it is
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tempting to screen HCV-infected patients for the homozygous C282Y mutation, searching for potential synergism of HCV and C282Y [10]. However, HCV-infected patients seldom require expensive genetic tests for hemochromatosis. Rather, their tests should include (1) serum transferrin saturation, (2) serum ferritin levels, and, if indicated, (3) a liver biopsy to evaluate liver iron stores and possible fibrosis. These tests generally suffice for patient evaluation, management, and therapy [10].

The first important step in the evaluation of HCV-infected patients is the quantitative assessment of the iron stores. The serum transferrin saturation may be as high as 90% in HCV-infected patients. A serum ferritin level of 300 μg/L or higher indicates significantly elevated liver iron stores. The recognition that excess hepatic iron induces inflammation and cell damage, and that the presence of HCV results in greater liver damage, makes iron removal important [9].

The lesson learned from studies of HCV-infected patients is that oral iron intake needs to be restricted. Enhancers of iron absorption, such as alcohol and the easily absorbed heme from red meat, should be avoided. Close observation of HCV-infected patients and careful assessment of their iron stores are essential to shield the liver from severe damage [11].

Phlebotomy removes red cells and, over time, depletes the hepatic iron stores, even in highly iron overloaded individuals. Phlebotomy is well tolerated by HCV-infected patients. Returning the iron stores to normal may increase the likelihood of successful antiviral treatment, with disappearance of HCV RNA.

Summary

Excess iron stores are often demonstrated in patients infected with HCV. The toxic effect of iron on the HCV-infected liver can lead to liver cirrhosis, which contributes to morbidity. Excess iron stores may be already present in persons with the homozygous hemochromatosis gene mutation. Excess iron stores may also be acquired by high iron intake, which is enhanced by alcohol consumption. Low iron stores are found in children and women, who consequently have little damage to the liver, and cirrhosis rarely develops. Extreme iron loading and HCV infection can be found in patients with thalassemia and in patients who have received bone marrow transplantation. Such patients should be treated for iron overloading, whether or not they have HCV infection, to avoid hepatic cirrhosis.

References