Hemochromatosis, iron, and blood donation: a short review

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Hereditary hemochromatosis (HH), an autosomal recessive disease of iron overload, is one of the most common inherited diseases. The candidate gene (HFE) for HH has been identified recently and a DNA-based test for the mutation is available. Treatment for HH patients with elevated iron stores include repeated phlebotomy. Left untreated, iron overload can lead to cirrhosis, organ failure, and a shortened life expectancy. In the past and present, blood collected for therapeutic purposes from patients with HH has been discarded. The aim of this article is to address whether blood collected from HH patients should be used for allogeneic transfusion in the future. Immunochemistry 1999;15:108–112.

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Iron is essential for human life. However, iron in excess can lead to cell injury, organ failure, and a shortened life expectancy. Iron overload can be due to a primary genetic disorder, hereditary hemochromatosis (HH); can be secondary to disorders such as sideroblastic anemia and porphyria cutanea tarda; or can be secondary to iatrogenic causes such as chronic red blood cell transfusions and excessive oral iron intake. Patients with secondary iron overload suffer the consequences of iron excess with organ damage similar to those with genetic or HH, depending on the rate of iron accumulation.1,2

HH is an autosomal recessive disease of iron overload. It is one of the most common inherited diseases, with a frequency of the homozygous state of 1 in every 200 to 400 individuals of northern European descent and a heterozygous carrier rate of 1 in 10.3,4 Although homozygosity is referred to as the disease state, not all HH individuals are equally affected, presumably due to differences in penetrance. A candidate gene for HH has been recently located on the short arm of chromosome 6. The gene, named HFE (originally designated HLA-H), is thought to code for a MHC class I-like protein. A Cys282Tyr mutation of this gene was homozygous in 83 percent of HH patients studied.5 An additional 5 percent were compound heterozygotes with a second mutation, His63Asp, of unknown significance.5,6 Other studies have shown homozygous frequencies in HH patients ranging from 90 to 100 percent.7,8 A new DNA-based test for the mutation will add to the diagnostic tools for this underdiagnosed disease.

Treatment for patients with elevated iron stores includes repeated phlebotomy, sometimes lifelong. Historically, blood collected for therapeutic purposes from patients with HH has been discarded because HH as a cause of iron storage disease was difficult to distinguish from other causes, including hepatitis-associated chronic liver disease. Today, these units are still discarded because of potential for inappropriate donor motivation as well as for specific blood labeling concerns (discussed below). However, many clinicians caring for patients with HH have long advocated the use of such therapeutic units for allogeneic blood transfusion. This review addresses the issue of whether persons with a diagnosis of HH should be included as blood donors in the United States, and whether the benefits of reducing iron stores should be used for motivating the donations of HH patients, HH heterozygotes, and even "normal donors."

Iron Overload

Iron absorption takes place primarily in the mucosal epithelium of the duodenum. The mechanism of increased uptake of iron in HH still is not well understood.9,10 However, it is thought that the mutant HFE protein disassociates with beta-2 microglobulin, leading to down regulation and poor control of iron absorption.11-15 A recent HFE gene knockout mouse model showed that HFE-deficient mice had an elevated transferrin saturation and hepatic iron concentration, supporting the theory that the HFE protein is involved in the regulation of iron homeostasis.16 Ferritin and hemosiderin accumulate in the cells, especially hepatocytes. In addition to liver injury, the pancreas and heart are adversely affected, leading to glucose intolerance and cardiomyopathy. Major causes of death of patients with HH are cirrhosis, hepatocellular carcinoma, diabetic complications, and heart failure. Other clinical features include testicular atrophy and arthropathy secondary to
Iron deposition in the pituitary gland and synovial fluid, respectively.17

Although increased iron absorption in HH patients starts at birth, tissue damage develops after years of iron accumulation. Clinical sequelae do not usually develop until the fourth decade of life. Females typically become symptomatic at a later age due to protection from excess iron deposition as a result of menstrual and gestational blood loss.

The standard screening markers, serum ferritin and transferrin saturation, are both elevated in untreated HH. Historically, the definitive test for iron overload disease has been liver biopsy with a Prussian blue stain for iron. The availability of genetic testing for the mutation in the HFE gene has decreased the necessity of a liver biopsy. However, tissue diagnosis may be helpful for determining whether a patient has progressed to cirrhosis. In addition, liver biopsy can aid in diagnosis of the 5-15 percent of patients who lack the Cys282 to Tyr282 mutation. Hepatic iron index (HII), defined as micromoles of iron per gram dry weight of liver divided by age in years, is markedly elevated in HH (> 2.0; normal: < 1.7) and is helpful in distinguishing HH patients from alcoholic cirrhotic patients who may also have elevated biochemical markers. Patients with alcoholic cirrhosis typically have HII values between 1.7 and 2.0.

If treated before the development of cirrhosis, patients have a normal life expectancy. Typical initial treatment consists of weekly phlebotomy of one unit of blood until a low-to-normal ferritin level is achieved. Thereafter, maintenance phlebotomy every few months may be required in order to prevent iron accumulation.

**Iron and Coronary Artery Disease**

Several controversial studies have linked iron stores to coronary artery disease (CAD). The "iron hypothesis" states that iron can catalyze free radical production, thereby inducing lipid oxidation and subsequent atherosclerosis.18-21 This hypothesis is supported by the fact that the risk of CAD for females after menopause approaches that of males. Thus, iron loss from menses may provide a protective effect for the heart.20 However, most believe that hormonal explanations (endogenous estrogen) suffice to explain why females have a lower risk of CAD prior to menopause.22

Can phlebotomy promote better health by reducing the risk of CAD in males? Two studies have concluded that male blood donors have a decreased risk of CAD20,23 Despite the fact that well-matched case controls were used, these studies may be challenged because, as a whole, blood donors may be healthier individuals who already have a decreased risk of CAD. Other studies have not found an association between iron stores and CAD.24,25

Heterozygous carriers for HH have increased iron absorption compared with normal individuals.26 Thus, if the iron hypothesis is valid, males in this group would be at an increased risk for CAD, and would therefore receive a protective benefit from donating blood two to three times a year. Miller and Hutchins24 examined the prevalence of CAD in almost 48,000 autopsies of patients with hemochromatosis and multiorgan hemosiderosis and did not find an association between iron overload and increased prevalence of CAD. Their results did not support the theory that lowering iron stores lowers the risk for CAD in males. Consequently, a relationship between iron stores and risk of CAD remains unproven.22,24,25

**Screening**

As noted above, symptomatic HH is readily diagnosed with screening tests, followed by liver biopsy and genetic testing.20 Nevertheless, HH may still be a significantly underdiagnosed disease. HH is a prime candidate for universal screening because the initial screening tests (transferrin saturation and serum ferritin) are inexpensive and sensitive, and treatment is available and relatively common. Screening a selected population at a higher risk of inheriting the disease of the population at large (e.g., blood donors) has been proposed to be cost effective.27 However, a recent consensus conference concluded that genetic testing for HH is not recommended at this time for population-based screening. The major reasons against genetic population screening included uncertainties about prevalence and penetrance of the HFE gene mutation and management of asymptomatic patients carrying the mutation.28 In addition, others have expressed concern about prejudicial denial of insurance based on the diagnosis of HH.29 Nevertheless, most agree that genetic testing may play a role in the diagnoses of family members of HH patients known to have the HFE gene mutation and confirming the diagnosis of HH in suspected patients with elevated iron studies.28

**Blood Donation**

Blood obtained for therapeutic purposes from HH patients has usually been discarded, because most clinicians refuse to use these units as long as other blood is available. However, some clinicians caring for HH patients have advocated using these units for allogeneic
transfusion. The prevalence of HH in the United States is approximately 1 in 400 or 0.25 percent. If one assumes that this population is similar to the general population without HH, 40 percent of this total population meet the criteria to make allogeneic donations. In one group of 208 adult Canadian HH patients, 67 percent were judged to be otherwise eligible for blood donation. If HH patients donate on a regular basis (four times a year), then almost one million additional blood units could be available in the United States (250 million people) per year. This number does not reflect the additional units available from more frequent phlebotomy of newly diagnosed HH patients. If the units obtained during initial treatment of HH patients and blood from some heterozygous donors were included, the number of additional units would increase even more. The number of additional units would be fewer if one takes into account that only a fraction of individuals with HH have been diagnosed and are therefore undergoing therapeutic phlebotomy.

If blood from patients with HH were to be used for allogeneic transfusion, no additional screening questions or tests would be necessary, because if donors meet existing criteria, there is unlikely to be harm to the donor or recipient. Furthermore, there is no direct data to suggest that units from donors with HH, meeting all allogeneic donor criteria, would be less safe for transfusion. Besides expanding the donor pool and reducing costs to the health care system by decreasing the cost of therapeutic phlebotomy and making available units that are now discarded, there is another theoretical advantage of transfusing some of the blood from HH patients. The blood from HH patients who are bled aggressively, during the early phase of treatment, contains an elevated number of neocytes or young red blood cells. These cells would have a prolonged survival and, potentially, could benefit patients requiring chronic transfusion (e.g., beta thalassemia) by decreasing the frequency of transfusion.

A major concern about the use of blood from patients with HH for allogeneic transfusion is the fear that these patients may misrepresent historical information (such as high-risk behavior) during the blood donation interview process in order to avoid the costs of therapeutic phlebotomy. The charge for therapeutic phlebotomy can be as costly as $200 or more per unit. Financial motivation has been known to increase infectious disease marker frequency of the population of those motivated. This motivation can be addressed by bleeding all HH patients at no cost, whether or not they qualify as blood donors. Since 1991, Canada has allowed healthy HH patients to be voluntary blood donors. However, Canadian and other governments subsidize health care and thus eliminate the financial motive to serve inappropriately as allogeneic donors. Although current infectious disease testing has made the volunteer blood supply essentially safe, it is not absolutely safe. The additional protection of a careful health history from a donor, motivated primarily by altruism, remains an important part of blood supply safety.

The Code of Federal Regulations (Title 21, 640.3) states that units of blood from patients can be transfused, as long as they are labeled with the patient's disease. However, as noted, this limits usefulness of this blood, because patients and physicians do not wish to use such "labeled" blood. American Association of Blood Banks Standards (C2.000) were changed in 1996 to discourage transfusion of blood collected by therapeutic phlebotomy because of the concern about donor motivation and the complexity of the recipient informed consent process.

Donor Motivation

Should patients with hemochromatosis be included as volunteer blood donors in the United States if they otherwise meet standard donor criteria? Should blood collection agencies promote blood donation as a health benefit to male donors? One approach to these questions is related to the issue of donor motivation. Donors are motivated to give blood for many reasons: some donors are purely altruistic, whereas others seek benefits ranging from time off from work to health-related testing. Some donors with factors associated with a higher HIV risk have donated blood in order to obtain infectious disease testing.

Blood from some groups of donors with less than altruistic motivation (e.g., commercial donors) have a higher frequency of infectious disease markers, and presumably, less safe marker-negative blood. Avoiding the cost of therapeutic phlebotomy can be seen as such an incentive, potentially reduced with free phlebotomy. Similarly, the self-interest of a normal healthy male wishing to lower his risk of CAD could theoretically make our blood supply less safe.

Summary

Both avoiding the cost of therapeutic phlebotomy by serving as a volunteer blood donor and donating to reduce the risk of CAD represent questionable motivations for donation. Although donors with these motiva-
tions have not been shown to have increased infectious disease marker frequency, existing data relating donor motivation to blood safety should cause blood collectors to proceed cautiously with regard to acceptance of blood donations from individuals with HH for transfusion purposes.33

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