BRIEF REPORT

Hereditary Hemochromatosis

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Hereditary hemochromatosis (HHC) is an inherited disease transmitted in an autosomal recessive pattern. With homozygosity occurring in up to 0.5% of the population, HHC is the most prevalent genetic disease among the white population worldwide and has the same prevalence as the sickle cell trait in the African-American population.

An asymptomatic 50-year-old white man presented at the family practice clinic and stated that HHC had been diagnosed in his mother. Laboratory findings showed markedly elevated transferrin saturation and ferritin levels. The diagnosis of HHC was made on the basis of the laboratory results and family history, and therapy was begun.

Clinical manifestations of HHC occur late and include diabetes mellitus, cirrhosis, and cardiomyopathy. As end-organ damage is preventable, optimal management involves early diagnosis and lifelong phlebotomy. Diagnosis is made by an elevated transferrin saturation level and an increased serum ferritin value.

Hereditary hemochromatosis is a genetic disorder of iron metabolism that has an excellent prognosis if diagnosed early.

KEY WORDS. Hemochromatosis; iron. *(J Fam Pract 1997; 44:304-308)*

Hereditary hemochromatosis (HHC) is a genetic disorder of iron overload that is inherited in an autosomal recessive pattern.[1-4] With homozygosity occurring in up to 0.5% of the population, it is the most prevalent genetic disorder among whites.[1-5] This case demonstrates the typical presentation of HHC with minimal symptoms early in the course of the illness. Early diagnosis and therapy is aimed at preventing end-organ damage caused by a buildup of excess iron in the body's tissues.[1,6,7] Using easily performed tests available to diagnose HHC, early intervention can significantly improve mortality and morbidity.[1,8-12]

Case Report

A 50-year-old white man presented to the family practice clinic stating that diabetes mellitus and hereditary hemochromatosis had just been diagnosed in his mother. The patient had no other complaints. His past history was negative, and he denied receiving blood transfusions. He took no medications or recreational drugs, and denied use of over-the-counter supplemental iron or vitamins. His alcohol consumption was six beers per week, usually on the weekend. Results of a physical examination were normal. Laboratory evaluation included an iron level of 174 µg/dL (normal range 38 to 180 µg/dL), a total iron-binding capacity of 253 µg/dL (normal range 20 to 255 µg/dL), and a transferrin saturation of 69% (normal range 16% to 50%). The serum ferritin level was elevated to 889 µg/dL (normal range 20 to 200 µg/dL). All other test results were normal.

The patient was referred for a liver biopsy to confirm the diagnosis of HHC, but refused to undergo this procedure. After educating the patient about his illness, venesection therapy was begun on the basis of the elevated transferrin saturation and ferritin levels. Twice-weekly phlebotomy removed 500 mL of whole blood while maintaining his hematocrit between 30% and 35%. This treatment was continued until the patient's ferritin level was less than 50 µg/dL and his transferrin saturation level less than 50%. He now has venesection every 3 months to maintain his ferritin and transferrin levels within the normal range. If therapy is continued for life, the patient has an excellent prognosis.

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DISCUSSION

Hereditary hemochromatosis is an illness caused by an autosomal recessive trait, with homozygosity affecting 0.25% to 0.77% of whites of northern European descent worldwide, and heterozygosity up to 10%.[12-17] The gene for hemochromatosis is as prevalent in white populations as the gene for sickle cell disease in African-Americans.[18,19] Symptoms only develop in persons homozygous for the gene. The gene for HHC is on the short arm of chromosome 6 closely linked to the HLA locus.[2,12,17,18,20]

Approximately 70% of patients who come to medical attention for evaluation of symptoms are between the ages of 40 and 60 years.[12] Iron absorption is consistently increased in homozygous HHC until a massive store of body iron is accumulated.[5,11] The excess iron is stored in the cells of various organs in the body. In time, the buildup of toxic iron produces clinical manifestations based on the organ involved. Table 1 shows common symptoms and signs seen with HHC. The liver is typically the first organ involved with hepatomegaly in 95% of symptomatic patients.[11,12] Fibrosis and cirrhosis are common, and 30% of these patients will develop hepatocellular carcinoma if untreated.[10-12]

The diagnosis of HHC is based on laboratory evaluations, but the history can be helpful. Important information to be elicited includes family history of hemochromatosis or diabetes mellitus, alcohol intake, and supplemental iron and ascorbic acid intake. Laboratory tests should include measurements of iron stores and evaluation of end-organ involvement. Liver function tests, serum glucose, an electrocardiogram, and films of involved joints should be checked. Parenchymal iron stores can be assessed by a number of methods. An evaluation of the serum iron level is unreliable because of a large number of false-positive and false-negative results.[11,12] The combination of an elevated transferrin saturation level and an increased serum ferritin concentration is highly sensitive (94%) for HHC and has an excellent predictive value for a negative test (97%) in uncomplicated cases.[21] Since results of these tests may be elevated in other diseases (eg, alcoholic or viral liver diseases, chronic inflammatory disease, malignancy), the results must be interpreted in the context of the clinical setting. Table 2 lists typical laboratory values in normal patients and those with HHC. The liver biopsy is the definitive test to confirm HHC.[5,11,12] An estimation of the hepatic concentration of iron can be made. The extent of fibrosis and cirrhosis can be determined as well.

The treatment of HHC is twofold: the removal of excess iron, and support of the damaged tissues. Weekly to twice-weekly phlebotomy of 500 mL of whole blood is performed to remove about 25 mg of iron over a 2- to 3-year period. The hematocrit is maintained in the 30% to 35% range. When the serum ferritin level is less than 50 µg/dL and the serum iron is in the normal range, the patient enters the maintenance phase.[1,11,12] Phlebotomy is done every 3 months to maintain the ferritin and iron in the normal range. If levels begin to rise, the interval between phlebotomies is shortened until the iron and ferritin results return to normal. Deferoxamine mesylate is an iron chelator that is more expensive, less effective, and less convenient. It should be used only when phlebotomy is impractical.[11,12,15]

Without treatment, the prognosis of HHC is poor. Death occurs within 4 to 10 years due to cardiac failure in 30%, hepatocellular carcinoma in 30%, and hepatocellular failure or portal hypertension in 25% of patients.[6,7,10,11] Patients without cirrhosis whose disease was diagnosed and treated early are expected to have a normal life span.[10,22] Phlebotomy therapy may prevent the onset of hepatic fibrosis and cirrhosis. Unfortunately, patients with advanced disease and signs of liver failure and portal hypertension

TABLE 1

Common Signs and Symptoms of Hereditary Hemochromatosis, in Order of Decreasing Frequency

Symptoms	Signs
Weakness	Hepatomegaly
Abdominal pain	Pigmentation
Diabetes mellitus	Loss of body hair
Arthralgia	Splenomegaly
Loss of libido or potency	Peripheral edema
Amenorrhea	Jaundice
Dyspnea on exertion	Gynecomastia
Neurologic symptoms	Ascites

usually do not respond well to iron removal. Non–insulin-dependent diabetes may be improved by iron removal; insulin-dependent diabetes, however, is usually not reversed, although the insulin dose can be reduced in some patients.[7] Cardiac symptoms may be reduced as a result of phlebotomy therapy. Once severe left ventricular dysfunction develops, the chance of survival is poor.[6,12]

Currently, there is no program for generalized screening of the white population. Screening has been recommended for the following groups[12,23,24]:

1. All first- and, if possible, second-degree relatives of a patient with newly diagnosed HHC should be screened for elevated serum ferritin levels and transferrin saturation. HLA typing is recommended for the patient and his or her siblings only as part of a family study.

2. Unless both parents are homozygotes or both are heterozygotes, screening of children should begin at age 10. If the tests are normal, they should be repeated at 3-year intervals until the children are adults over 40 years old. Other recommendations have been made to begin screening at the age of 4 years.[25]

Several authors have proposed screening of the population at large.[10-12] Cost-effectiveness analyses are appearing in the literature.[8,26-28] One study has demonstrated that screening for hemochromatosis is the strategy preferred over waiting for symptoms to develop, in terms of both mortality and cost.[1]

TABLE 2

Typical Laboratory Values in Normal Subjects and Patients with Hereditary Hemochromatosis

Test Test	Normal Range	HHC Patients
Serum iron (µg/dL)	38-180	180-300
Serum unsaturated iron-binding capacity	>50%	<50%
Serum transferrin ((µg/dL)	220-410	200-300
Transferrin saturation [(serum iron [µg/dL] divided by TIBC [µg/dL])] ×100	16%-50%	55%-100%
Transferrin index (serum iron [µmol/L] divided by serum transferrin [µmol/L])	0.1-0.8	1.5-1.9
Serum ferritin (µg/dL)		
Male	20-200	300-6000
Female	15-150	300-6000
Hepatic iron concentration		
(µg/g dry wt)	300-1500	5000-30,000
(µmol/g dry wt)	5-27	89-550
Hepatic iron index (hepatic iron concentration [µmol/g dry wt] divided by patient age, y)	<2	>2

HHC denotes hereditary hemochromatosis; TIBC, total iron-binding capacity.

Conclusions

Hereditary hemochromatosis is the most common genetic disease among whites throughout the world. The pathogenesis of the disease involves the deposition of toxic excess iron in the tissues of the liver, heart, endocrine glands, and skin. Early identification and appropriate treatment prevent the clinical manifestations of the disease. Patients who undergo adequate phlebotomy before the onset of signs and symptoms of the overt disease have the same survival rate as the general population. Screening of the at-risk population may be cost effective.

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