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HFE-Associated Hereditary Hemochromatosis
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INTRODUCTION

Hereditary hemochromatosis (also called genetic hemochromatosis) is an autosomal recessive disorder associated with increased intestinal absorption of iron and deposition of excessive amounts of iron in the liver, pancreas, heart, and other organs. It is the most common single-gene disorder in the US white population. Approximately 1 in 250 to 300 white persons is homozygous for the hemochromatosis gene mutation, and at least 1 in 10 persons is a carrier for the mutation. Clinical expression varies from no symptoms to signs and symptoms of severe iron overload. Manifestations of iron overload include sexual dysfunction, joint pains, weakness, skin pigmentation, liver damage (cirrhosis), heart failure, and diabetes mellitus. The liver is the principal recipient of the majority of the absorbed iron, and the liver is always involved in hereditary hemochromatosis.

In 1889, Von Recklinghausen was the first to use the term hemochromatosis, based on the thinking that the disease was a blood disorder that caused increased skin pigmentation. Sheldon realized that hemochromatosis was an inborn error of iron metabolism and that all the pathologic manifestations of the disease were caused by increased iron deposition in the affected organs. Since the HFE gene was detected in 1996, it has been established that a single gene mutation (ie, C282Y) is responsible for most cases of hereditary hemochromatosis. The discovery of the gene has led to a blood test for the molecular genetic diagnosis of hemochromatosis. The relationship between the gene defects and the development of iron accumulation is still being explored. Disease penetrance is incomplete, and not everyone with disease-associated mutations of the gene has manifestations of iron overload. Iron overload can also occur sporadically and, in some families independent of mutations of the HFE gene; other gene mutations may interact to produce iron overload in heterozygotes. Treatment by phlebotomy is simple and efficient and can prevent the development of cirrhosis, leading to a normal life expectancy for patients with hereditary hemochromatosis.

PATHOPHYSIOLOGY

The normal iron content of the body is 3 to 4 g, with only 3 to 7 mg bound to transferrin in plasma. Approximately 2.5 g of iron exists in hemoglobin in circulating red blood cells, and 400 mg exists with iron-containing proteins in myoglobin, cytochromes, and catalase. The remainder (approximately 1 g) is stored as ferritin and hemosiderin, mostly in the liver, spleen, and bone marrow. Iron is lost in sweat, shed skin cells, and the gastrointestinal tract at a rate of 1 mg per day. Women lose another 0.5 to 1 mg per day in menstrual blood loss. A normal diet contains 10 to 20 mg of iron per day, roughly 10% of which is absorbed in the intestines, replacing the 1 mg per day of lost iron.

In patients with homozygous hereditary hemochromatosis, the absorption of heme iron is not regulated according to the amount of iron stored in the body. These patients may absorb between 2 and 4 mg of iron daily from heme and non-heme iron sources. Absorption of iron at a rate of 4 mg per day would lead to a net iron accumulation of approximately 1 g each year; in men, more than 20 g would accumulate between the end of the adolescent growth spurt and age 40 or 50 years. Individuals with this degree of iron overload are poised to develop the clinical features of hereditary hemochromatosis. Women become symptomatic approximately one decade later in life because of the extra iron losses associated with menses, child birth, and lactation.

There is no normal mechanism for increasing iron excretion. Increased iron absorption or parenteral administration of iron leads to iron overload. As the body content of iron increases, circulating transferrin becomes increasingly saturated with iron, resulting in the increased production of non–transferrin-bound iron and the off-loading of iron, especially to cells with high levels of transferrin receptors (eg, heart, liver, thyroid, gonads, and pancreatic islets). The excess iron in these cells causes the release of reactive oxygen, leading to oxidization of lipids and proteins, thereby causing tissue damage and subsequent fibrosis.
Two major hypotheses have been proposed to explain the pathogenesis of HFE-related hereditary hemochromatosis: the hepcidin hypothesis and the duodenal crypt cell-programming hypothesis. Increased expression of duodenal iron transport genes is consistent with each hypothesis.

DUODENAL CRYPT CELL PROGRAMMING HYPOTHESIS

Duodenal crypt cells have long been thought to play a role in regulating iron absorption. Absorption of iron from blood in these cells via transferrin receptors regulates the amount of iron absorbed from intestinal lumen in the villus cells. Duodenal villus enterocytes are the primary site of iron absorption from the diet. Ferrous iron is transported into villus enterocytes by the apical transporter divalent metal transporter-1 (DMT1), and the level of DMT1 in villus cells influences the amount of iron absorbed from the diet. DMT1 synthesis is regulated by the amount of iron in duodenal crypt cells via mRNA. HFE protein is highly expressed in duodenal crypt cells, where it can be associated with transferrin receptor, and it influences the sensing of circulatory iron by these cells. Normal HFE protein facilitates uptake of iron from plasma in the crypt cells and hence inhibits secretion of mRNA, leading to decreased synthesis of DMT1 in villus enterocytes. Functional loss of HFE protein causes a decrease in the regulatory iron pool in crypt cells and increases DMT1 in villus enterocytes, leading to increased iron absorption. Recently, some investigators have challenged the importance of crypt cell sensing in regulation of iron absorption.

HEPCIDIN HYPOTHESIS

Hepcidin is a small peptide hormone secreted by the liver that works to downregulate intestinal iron absorption and macrophage iron release. Differric transferrin in portal circulation induces hepatocytes to secrete hepcidin into the blood, where it acts on target cells (reticuloendothelial macrophages and duodenal enterocytes) to decrease iron export and thereby increase iron stores in these cells. In duodenal enterocytes, this leads to a decrease in the amount of dietary iron absorbed into the circulation. Thus, circulating levels of differric transferrin are normalized and homeostasis is maintained.

HFE-related excessive iron absorption is thought to be dependent on hepcidin. Mice in which the hepcidin gene has been knocked out develop a phenotype similar to HFE knockout mice. Also, in patients with HFE-related hereditary hemochromatosis and in HFE knockout mice, there is decreased expression of hepcidin. Mutations in the hepcidin gene lead to a severe form of juvenile hereditary hemochromatosis. It is clear that hepcidin is underexpressed in HFE-related hereditary hemochromatosis, but how this occurs is not clear. HFE protein is expressed on the surface of liver cells and is thought to influence the sensitivity of transferrin receptors on the hepatocellular surface. In HFE-related hereditary hemochromatosis, with loss of hepatocellular cell surface expression of HFE, there is a consequent relative decrease in the expression of hepcidin in response to circulating transferrin. Decreased circulating hepcidin may lead to increased iron transport by ferroportin-1 and thus increased efflux of iron from the duodenal enterocytes.

NON-HFE-ASSOCIATED CAUSES OF IRON OVERLOAD

Iron overload caused by hereditary hemochromatosis should be distinguished from overload secondary to other entities and other less common familial iron overload conditions. Table 1 lists conditions associated with iron overload.

SECONDARY IRON OVERLOAD

Secondary iron overload should be suspected in patients with chronic anemia, multiple transfusions,
prolonged iron supplementation, or chronic liver disease related to alcohol abuse, nonalcoholic steatohepatitis, and viral hepatitis. In secondary iron overload, iron often accumulates in Kupffer cells rather than in hepatocytes, as typically occurs in hereditary hemochromatosis. However, severe iron overload due to hereditary hemochromatosis or secondary causes may be indistinguishable from iron overload resulting from secondary causes. In most cases of secondary iron overload, the patient has anemia with iron overload from increased iron absorption or multiple transfusions. These patients will not tolerate venesections and will require parenteral chelation therapy.

LESS COMMON FAMILIAL CONDITIONS

Juvenile Hemochromatosis

Juvenile hemochromatosis is a rare, autosomal recessive disorder characterized by accelerated iron loading. Patients typically present in the second decade of life. Genetic linkage analysis of multiple affected families provided evidence for distinct mutations on chromosomes 1q and 19q. Missense and nonsense mutations lead to decreased plasma levels of hepcidin, which in turn increases intestinal absorption and increases reticuloendothelial iron release. As a consequence, iron rapidly accumulates in target organs. In contrast to patients with HFE-associated hemochromatosis, patients who have juvenile hemochromatosis are more likely to present with endocrine failure (hypogonadism) or cardiomyopathy; hepatic disease is less prominent. If untreated, affected patients usually die of cardiac failure by age 30 years. The most effective treatment is aggressive serial phlebotomy.

Transferrin Receptor-2-Associated Hemochromatosis

Mutations in transferrin receptor-2 (TFR2) are associated with an autosomal recessive, adult-onset disorder of iron loading. The prevalence of TFR2 is low compared to HFE mutations, but it has a more global and ethnic distribution. It is thought that TFR2 may influence iron loading through regulation of hepcidin expression. The iron overload pattern resembles that in HFE-related hereditary hemochromatosis. The most effective treatment is serial phlebotomy.

Neonatal Hemochromatosis

The etiology of neonatal hemochromatosis is unclear, but it may be influenced by inherited and environmental factors. It is characterized by neonatal hepatic failure or congenital cirrhosis with intrahepatic and widespread extrahepatic iron deposition, excluding the reticuloendothelial system. The onset of hepatic iron deposition and dysfunction may begin during the third trimester in utero. Antenatal features include intrauterine growth retardation, placental edema, and oligohydramnios. Hepatocyte iron deposition predominates, and extrahepatic iron deposition follows a pattern that is similar to HFE-associated hemochromatosis. The pancreas and myocardium often are involved. The mucous membrane salivary glands, choroid plexus, and multiple endocrine glands, including the pituitary and thymus, are also affected.

Clinical presentations include stillbirth or neonatal hyperbilirubinemia, hypoglycemia, profound coagulopathy, hypoalbuminemia, and other features of fulminant hepatic failure. Biochemical evidence of iron overload, including elevated transferrin saturation (in part, a result of decreased hepatic production of transferrin) and elevated ferritin, is always present. Pathologic demonstration of iron deposition in the salivary glands of the oral mucosa often is diagnostic and may be safer than liver biopsy. Most infants die in the neonatal period. There has been limited success with medical therapy using a cocktail of the iron chelator deferoxamine, N-acetylcysteine, selenium, vitamin E, and prostaglandin 

Other Non-HFE Related Hemochromatosis

Some patients who have hemochromatosis do not have mutations in any of the known disease-related genes. It is likely that these patients harbor mutations in one or more other genes, the discovery of which will further elucidate the normal physiologic controls of iron homeostasis.

CLINICAL FEATURES

CASE PRESENTATION

A 41-year-old man presents to his physician after workplace screening showed abnormal levels of liver enzymes. The patient has no significant symptoms and has only seen his physician for routine blood pressure checks over the preceding years. His past medical history is positive for minor orthopedic surgery as a teen and borderline hypertension. The patient has no history of diabetes, jaundice, or coronary artery disease. His review of systems is positive for occasional joint pains. The family history is positive for a maternal grandfather who died of cirrhosis and an older sister who has
diabetes. The patient's mother died in her sixties of a brain tumor. The social history is positive for tobacco use (1–1 1/2 packs per day), social alcohol use, and no history of intravenous drug use or known exposure to anyone with hepatitis.

The physical examination shows blood pressure of 138/90 mm Hg, no scleral icterus, and no spider angiomas. Abdominal examination reveals a palpable liver edge that is smooth and firm but no shifting dullness or detectable splenomegaly. The laboratory values show mildly elevated alanine aminotransferase (ALT) at 55 U/L and aspartate aminotransferase (AST) at 60 U/L.

- **What is the typical initial presentation for a patient with hereditary hemochromatosis?**

  Most patients with hereditary hemochromatosis are identified by iron studies performed as routine blood chemistry tests or by screening studies in family members of patients diagnosed with hereditary hemochromatosis. Common clinical manifestations are listed in Table 2. In early case series, weakness, lethargy, abdominal pain, arthralgias, and loss of libido were the most common symptoms at presentation, and approximately 9% of patients were asymptomatic. In more recent case series, up to 73% of patients were asymptomatic. Similarly, cirrhosis, hepatomegaly, ascites, jaundice, bronze or slate gray skin pigmentation, and clinical diabetes were found in 55% to 75% of cases in earlier series, but in recent series these features were seen in only 5% to 13% of the cases at presentation. Symptomatic patients typically present when they are 40 to 50 years of age. In most clinical series, men were identified 2 to 8 times more frequently than women. As the defective gene is distributed equally between men and women, female patients are underestimated based on phenotypic expression.

  Hepatic manifestations range from elevation in serum ALT and AST levels to advanced cirrhosis and hepatocellular carcinoma. Right upper quadrant pain is common and is caused by hepatic capsular distention. Elevations in serum ALT and AST levels are usually mild and are present in 30% to 50% of patients. With regular phlebotomy and depletion of excess iron stores, liver enzyme abnormalities typically return to normal. Once cirrhosis has developed, there is an increased risk for the development of hepatocellular carcinoma. Carcinoma may occur even with successful phlebotomy, although the risk may be lowered by iron depletion.

  Endocrine abnormalities include loss of libido and impotence from testicular failure and pituitary dysfunction. Diabetes from pancreatic iron loading is rarely seen these days. Adrenal and thyroid dysfunction is rare with hereditary hemochromatosis. Iron loading of the myocardium leads to cardiomyopathy, congestive heart failure, and atrial and ventricular dysrhythmias. The threshold for development of cardiac disease is unknown, but this appears to be prevented with early diagnosis and treatment. The arthropathy of hereditary hemochromatosis is characterized most commonly by changes in the second and third metacarpophalangeal joints, including joint space narrowing, chondrocalcinosis, subchondral cyst formation, osteopenia, and swelling of the joints.

  Both hemochromatosis with cirrhosis and transfusional iron overload in dialysis patients appear to be risk factors for infection with *Listeria* and *Yersinia enterocolitica*. The latter organism is siderophoric (iron-loving) and possesses several pathways to facilitate iron uptake, which is essential for its growth. Septicemia from *Vibrio vulnificus*, another siderophoric bacterium, can occur in patients with hereditary hemochromatosis who ingest uncooked seafood that contains this organism. Accordingly, it has been recommended that patients with hereditary hemochromatosis avoid consumption of uncooked seafood.

### Table 2. Common Clinical Manifestations

<table>
<thead>
<tr>
<th>Stage</th>
<th>Manifestations</th>
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</thead>
<tbody>
<tr>
<td><strong>Early</strong></td>
<td>Arthritis, especially in hands</td>
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<tr>
<td></td>
<td>Chronic fatigue</td>
</tr>
<tr>
<td></td>
<td>Loss of libido or impotence</td>
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<tr>
<td></td>
<td>Amenorrhea</td>
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<tr>
<td></td>
<td>Abdominal pain</td>
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<tr>
<td></td>
<td>High blood glucose levels</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Abnormal liver function tests</td>
</tr>
<tr>
<td><strong>Advanced</strong></td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrhythmias</td>
</tr>
</tbody>
</table>

**NONEXPRESSING HOMOZYGOTES**

As genetic testing becomes more widespread, an increasing number of people with the hemochromatosis gene but without iron overload have been identified. Patients homozygous for the C282Y mutation should be considered at risk for developing iron overload, but if there are no abnormalities in transferrin saturation or...
elevation of ferritin in adulthood, they may be phenotypically normal. Their risk for developing iron overload later in life is uncertain but most likely is reduced compared to those individuals manifesting iron loading at an earlier age. Pooled estimates from 14 studies have suggested that up to 50% of C282Y homozygotes may not develop iron overload, and other long-term follow-up studies are now demonstrating that many C282Y homozygotes do not appear to be accumulating iron over time. There is no general recommendation regarding these patients, but following them with serum ferritin and transferrin saturation assessments every 5 years seems reasonable and will also improve our understanding of their natural history.

**DIAGNOSTIC TESTING**

**FURTHER EVALUATION OF CASE PATIENT**

The differential diagnosis of the case patient included hepatitis B and C infection, autoimmune hepatitis, α1-antitrypsin deficiency, Wilson’s disease, and hemochromatosis. Work-up revealed a serum ferritin level of 1500 ng/mL and a serum iron saturation greater than 80%, findings highly indicative of iron overload. Work-up for other etiologies for abnormal liver tests including hepatitis B and C, autoimmune hepatitis, α1-antitrypsin deficiency, and Wilson’s disease were negative. The physician considers the diagnosis of hereditary hemochromatosis.

- How is hereditary hemochromatosis diagnosed?

Hereditary hemochromatosis should be considered in any patient with unexplained manifestations of liver disease or a presumably known cause of liver disease with abnormality of one or more indirect serum iron markers. It should also be considered in patients with type 2 diabetes mellitus, particularly in the presence of hepatomegaly or elevated liver enzymes, atypical cardiac disease or early-onset atypical arthropathy, cardiac disease, and male sexual dysfunction. Individuals with abnormal serum iron markers discovered during routine testing and all asymptomatic individuals who are first-degree relatives of a confirmed case of hemochromatosis should be evaluated for hereditary hemochromatosis. An algorithm for management of hereditary hemochromatosis is shown in the Figure.

**SERUM IRON STUDIES**

A serum iron concentration and total iron-binding capacity (TIBC), or transferrin concentration, with calculation of the transferrin saturation along with a serum ferritin level should be obtained as the first step in the evaluation of patients suspected for hereditary hemochromatosis by clinical presentation. Because serum iron levels can be elevated in the fed state, and there is a diurnal variation in serum iron concentration, blood should be drawn from fasting patients in the morning. Normal values for serum iron studies are shown in Table 3. The combination of a transferrin saturation greater than 45% and an elevated ferritin level in an otherwise healthy person has a sensitivity rate of 93% for hereditary hemochromatosis. In a person older than 35 years, the combination of a normal ferritin level and a normal transferrin saturation has a negative predictive accuracy of 97%, indicating that there is only a 3% chance of missing a diagnosis of hereditary hemochromatosis in a patient of this age or older with normal iron studies. Transferrin saturation is more sensitive and specific than the serum ferritin level. Serum ferritin can be normal in young persons with hereditary hemochromatosis or elevated for a variety of reasons other than hereditary hemochromatosis, including various types of necroinflammatory liver disease (eg, chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease), certain malignancies, and other inflammatory conditions. In most cases, a person with an elevated ferritin level but a normal transferrin saturation and another inflammatory disorder does not have hereditary hemochromatosis. However, elevated transferrin saturation with a normal ferritin level in a young person do not exclude hereditary hemochromatosis.

- How is the diagnosis of hereditary hemochromatosis confirmed?

**GENETIC TESTING**

The HFE gene test is a polymerase chain reaction-based test that is usually performed on a whole blood sample. The test is widely available at an average charge of approximately US $200. The HFE gene test is helpful in confirming hereditary hemochromatosis in suspected cases, screening adult family members of an identified proband (up to 25% of siblings and 5% of children of a proband have hereditary hemochromatosis), and resolving ambiguous situations such as iron overload associated with hepatitis C, alcoholic liver disease, and other causes of end-stage liver disease. It is not recommended as a tool for general screening of the population for hereditary hemochromatosis and is not recommended for anyone younger than 18 years of age.
Hereditary hemochromatosis is associated with 2 gene mutations.20 The C282Y mutation involves the substitution of tyrosine for cysteine at the 282 amino acid position of the protein product of the HFE gene located on the short arm of chromosome 6. Another mutation (H63D) in which aspartic acid is substituted for histidine at position 63 has also been associated as a cofactor in some cases of hemochromatosis. Three common patterns are commonly recognized:

1. C282Y homozygotes. These patients account for approximately 95% of typical cases of hereditary hemochromatosis. Expression of disease ranges from no evidence of iron overload to massive iron overload with organ dysfunction. Siblings have a 1 in 4 chance of being affected and should have genetic testing. For children to be affected, the other parent must be at least a heterozygote. If iron studies are normal, false-positive genetic testing or a nonexpressing homozygote should be considered.

2. Compound heterozygotes with C282Y/H63D. These patients carry one copy of each mutation. Most patients with this genetic pattern have normal iron...

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**Figure.** Proposed algorithm for management of hereditary hemochromatosis. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HH = hereditary hemochromatosis; HIC = hepatic iron content; TS = transferrin saturation. (Adapted with permission from Tavill AS. Diagnosis and management of hemochromatosis. American Association for the Study of Liver Diseases, American College of Gastroenterology, American Gastroenterological Association. Hepatology 2001;33:1321.)
### Table 3. Normal Serum Iron Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma (or serum) iron concentration</td>
<td>60–150 µg/dL</td>
</tr>
<tr>
<td>Transferrin concentration (plasma total iron-binding capacity)</td>
<td>300–360 µg/dL</td>
</tr>
<tr>
<td>Transferrin saturation (the ratio of plasma iron to transferrin)</td>
<td>20%–50%</td>
</tr>
<tr>
<td>Plasma ferritin</td>
<td>40–200 ng/mL</td>
</tr>
</tbody>
</table>

Normal Serum Iron Values

– Transferrin saturation (the ratio of plasma iron to transferrin)

The iron load in most patients can be estimated by determining the number of weekly 500 mL phlebotomies required to produce iron deficiency anemia. In patients with normal iron stores, quantitative phlebotomy will be important to further characterize this group of patients. If the patient is younger than 40 years of age, serum ferritin levels of less than 1000 ng/mL, normal liver enzymes, and no hepatomegaly. These patients can be safely started with phlebotomy without prior liver biopsy.

### LIVER BIOLOGY

Liver biopsy is helpful for determining hepatic iron content (HIC) for diagnosis of hereditary hemochromatosis or to rule out other causes of liver disease. Biopsy was the method of choice before genetic testing was available. HIC should be qualitatively determined by Perls’ staining. If staining suggests increased iron stores, quantitative measurement of iron in stored tissue should be done. Normal values for HIC are less than 10% of the white population and is usually associated with normal iron studies. In rare cases, the iron studies are high in the range expected in a homozygote rather than a heterozygote.

A negative C282Y test should alert the physician to question the diagnosis of genetic hemochromatosis and reconsider secondary iron overload related to cirrhosis, alcohol abuse, viral hepatitis, insulin resistance, or iron-loading anemias. If no other risk factors are found, the patient should begin venesection treatment similar to any other hemochromatosis patient. The decision to classify this group of patients as non-HFE hemochromatosis or idiopathic iron overload is a matter of semantics and ideology surrounding case definition. Quantification of iron burden by hepatic iron concentration or quantitative phlebotomy will be important to further characterize this group of patients.

- Is liver biopsy indicated in all patients with hereditary hemochromatosis?

### RESPONSE TO QUANTITATIVE PHLEBOTOMY

One can clinically confirm the presence of iron overload in most patients by determining the number of weekly 500 mL phlebotomies required to produce iron deficient erythropoiesis, with each phlebotomy removing 200 to 250 mg of iron. Quantitative phlebotomy is useful in patients who cannot undergo liver biopsy but are suspected for iron overload. Iron stores in normal men are approximately 1 g. Thus, 4 to 5 phlebotomies over 4 to 8 weeks will produce an iron deficient state characterized by microcytic, hypochromic anemia. In contrast, patients with significant iron loading usually have at least 5 g of iron stores, requiring at least 20 units of phlebotomy to induce iron deficiency. The iron loss required to achieve iron deficiency is then calculated.
OTHER TESTS

CT scanning and MRI are usually not reliable in early hereditary hemochromatosis in mildly iron-loaded persons, and magnetic susceptibility is available only as a research tool. As iron loading advances, MRI may be used to noninvasively estimate HIC. The pattern of iron deposition may also yield diagnostic information: In primary hemochromatosis, the liver is the main organ for abnormal iron deposition, consisting of ferritin and hemosiderin. In secondary iron overload, iron is deposited in the reticuloendothelial cells of the liver, spleen, and bone marrow.

TREATMENT

DIAGNOSIS OF CASE PATIENT

Demonstration of a C282Y/C282Y mutation in the HFE gene confirms a diagnosis of hereditary hemochromatosis in the case patient. Liver biopsy shows 4+ iron (primarily in the hepatocytes) and stage 4 fibrosis (cirrhosis). The hepatic iron index is greater than 1.9.

• How is hereditary hemochromatosis treated?

PHLEBOTOMY

The mainstay of hemochromatosis treatment remains phlebotomy. Initiation of treatment should begin as soon as iron overload is recognized to prevent the development of fibrosis or cirrhosis. If treatment is initiated before cirrhosis develops, the patient will have a normal life span. All patients with the C282Y/C282Y HFE genotype should be treated for hereditary hemochromatosis if they have direct or indirect markers of increased iron stores (increased transferrin saturation, plasma or serum ferritin, hepatic iron index, or HIC above the upper limit of normal). Patients with C282Y/H63D should be considered as possibly having a significant degree of iron loading. If direct or indirect markers of increased iron stores are present, these patients should probably undergo a liver biopsy with quantitative iron determination, followed by repeated weekly phlebotomy to render them iron deficient, or quantitative phlebotomy.

Weekly phlebotomy of 500 mL (1 unit) of whole blood should be performed, checking the hematocrit before each phlebotomy. The hematocrit should not fall more than 20% below the prior level. Transferrin saturation and ferritin levels should be checked at 2- to 3-month intervals to monitor response. Once iron stores are depleted (ferritin <50 ng/mL; transferrin saturation <50%), maintenance phlebotomy is done at an interval determined by the rate at which iron reaccumulates. This rate may vary between patients, but typically 1 unit of whole blood is removed every 2 to 3 months.

Phlebotomy can effectively prevent or resolve certain complications of hemochromatosis but not others. Often, the duration of the complication has a role in the effectiveness of phlebotomy. Phlebotomy can prevent complications of iron overload in those without complications and can help ensure a normal life expectancy. For example, phlebotomy can help prevent the potentially life-threatening complications of cirrhosis and liver cancer. Phlebotomy can resolve or markedly improve weakness, fatigue, and lethargy; darkening of the skin; and high blood ferritin levels. It can also resolve or greatly improve poor liver function, liver enlargement, and liver pain. Phlebotomy is most likely to reverse liver disease when it is in an early stage, but phlebotomy can still improve liver function in people who have developed cirrhosis.

Phlebotomy may also resolve joint pain, varices, and heart disease. Studies suggest that phlebotomy improves joint symptoms in about 20% of people with hemochromatosis and improves or resolves varices in about 26% of people with hemochromatosis who have cirrhosis. Phlebotomy is most likely to reverse heart disease when it is in an early stage. Phlebotomy only rarely improves joint deformity, pituitary disease, elevated blood iron levels, and susceptibility to certain infections, diabetes, and thyroid disease. It is most likely to restore normal levels of sex hormones in men under the age of 40 years. Phlebotomy does not reverse advanced cirrhosis and may not lessen the risk of liver cancer that is associated with cirrhosis.

ORTHOTOPIC LIVER TRANSPLANTATION

Orthotopic liver transplantation is an option in patients with end-stage liver disease due to hereditary hemochromatosis. Post-transplant deaths are usually related to infectious or cardiac complications. Unfortunately, hereditary hemochromatosis or secondary iron overload often is not diagnosed before transplantation. A high index of suspicion for iron overload in patients with end-stage liver disease should lead to improved diagnosis and allow for prompt institution of either phlebotomy or iron-chelation therapy before transplantation. It is anticipated that improved management will reduce post-transplantation complications and improve long-term survival.

• What other measures are recommended?
DIETARY RECOMMENDATIONS

A normal balanced diet is advised. There is no need to avoid foods containing iron; however, dietary supplements containing iron should be avoided. Dietary substances that bind iron or inhibit absorption of iron are ineffective in hereditary hemochromatosis and are unnecessary in patients undergoing therapeutic phlebotomy. Patients with hemochromatosis should not consume uncooked seafood, which may contain bacteria that grow well in an iron-rich environment.

Alcohol consumption is associated with a 9-fold increase in the likelihood of developing cirrhosis in hereditary hemochromatosis patients and should be avoided. Patients in the high-alcohol group also had a higher incidence of hepatocellular carcinoma and developed cirrhosis at a lower mean HIC and at a younger age than those with less alcohol consumption. Patients should not abuse alcohol, but occasional social drinking is permissible in those without significant liver disease.

Ingestion of large quantities of vitamin C has been rarely associated with fatal cardiac arrhythmias in patients with iron overload, presumably due to a rapid release of iron stores that leads to oxidative injury. Thus, it may be reasonable to advise patients to avoid vitamin C supplements until they are rendered iron depleted.

SCREENING FOR HEPATOCELLULAR CANCER

Hepatocellular cancer accounts for about 30% of all deaths in hereditary hemochromatosis, whereas other complications of cirrhosis account for an additional 20%. Hepatocellular cancer is usually seen only in patients who already have cirrhosis. Recommended screening and surveillance for hepatocellular carcinoma in patients with hereditary hemochromatosis and cirrhosis includes abdominal ultrasound and measurement of serum α-fetoprotein every 6 months.

SCREENING OF FAMILY MEMBERS

All first-degree relatives (parents, siblings, children) of people with known hemochromatosis should undergo screening. There is 25% chance that a sibling will also have hereditary hemochromatosis. If the spouse of a C282Y homozygote is a C282Y heterozygote, there is a 50% chance that a child of the couple will be homozygous for C282Y. The optimal age for screening is between 18 and 30 years; during this age range, the condition can be detected, but serious tissue damage has not yet occurred.

Before an HFE gene test is performed, a qualified professional should provide counseling about the benefits and risks of genetic testing, as well as the alternatives to such testing. The possibility of insurance, employment, or other discrimination based on HFE test results is a concern. For this reason, HFE gene testing is usually not recommended for anyone younger than 18 years of age.

HFE mutation analysis in children can eliminate the need for subsequent serum iron testing if a genotype of C282Y/C282Y or C282Y/H63D is not found. In children who are C282Y homozygotes or compound heterozygotes, ferritin levels should be measured yearly and phlebotomy instituted when ferritin levels become elevated. There is no need for liver biopsy for asymptomatic C282Y homozygotes and compound heterozygotes (C282Y/H63D) identified by HFE mutation analysis.

MANAGEMENT OF CASE PATIENT

Phlebotomy is instituted every 1 to 2 weeks until the patient shows a serum ferritin level of less than 50 ng/mL and a transferrin saturation of less than 50%. Monitoring of serum ferritin is continued and phlebotomy is performed at intervals with a goal of keeping serum ferritin below 50 ng/mL. The patient is currently stable but continues to have laboratory evidence of portal hypertension (thrombocytopenia).

SUMMARY

Hemochromatosis is a common and often underdiagnosed disease. Early diagnosis and treatment result in an excellent long-term prognosis. The development of a diagnostic genetic test has made it possible to test for the disease in individuals even prior to iron accumulation; however, measurement of serum iron and TIBC and ferritin are still useful for population screening for iron overload. Early diagnosis has reduced the morbidity and mortality from hemochromatosis, but the long-term survival for those with cirrhosis is reduced compared to those without cirrhosis at the time of diagnosis. Questions remain about the natural history of untreated disease since some patients with hereditary hemochromatosis do not develop iron overload. The impact of other genes in the iron metabolic pathway that may alter the phenotypic expression of the disease is an area of great interest.

REFERENCES


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