Hereditary Hemochromatosis

Robert B. Hash, MD

Background: The understanding of hereditary hemochromatosis, along with the availability of genetic testing, is changing the approach to diagnosis of the disease.

Methods: A MEDLINE search was performed using multiple key words related to hemochromatosis and iron metabolism.

Results: Most cases of hereditary hemochromatosis are caused by a single mutation to the HFE gene, resulting in unregulated dietary iron uptake. The signs and symptoms of hereditary hemochromatosis are nonspecific and common in family practice settings. Measuring the transferrin saturation level is a cost-effective way to screen for suspected disease. Subsequent workup includes serum ferritin levels, hepatic enzyme levels, and HFE gene testing, or liver biopsy. HFE gene testing can provide a definitive diagnosis in many patients. Liver biopsy is useful and indicated when liver disease is clinically evident.

Conclusion: For many patients, hereditary hemochromatosis can be diagnosed and treated in the physician’s office. After iron mobilization with therapeutic phlebotomy, most patients will require phlebotomy 2 to 4 times each year throughout their lifetime. Treatment before organ toxicity occurs leads to a normal life span. Treatment after symptoms appear is less effective but can improve some signs and symptoms of iron toxicity. (J Am Board Fam Pract 2001;14:266–73.)

Hereditary hemochromatosis is thought to be the most common inherited disorder in whites, and perhaps the most common classically inherited disease in America. This disorder is most commonly found in persons of northern European descent, whereas it rarely occurs in Africans or Asians.1 The occurrence of the disease in Hispanics can be similar to that in whites.1,2 It is estimated that approximately 1 in 200 whites in the United States are homozygous for the gene thought to be responsible for the disease,1,3 although the frequency has been reported to be as high as 1 in 150 in some populations.3 Approximately 25% of the men and 50% of the women with hereditary hemochromatosis will develop life-threatening consequences of the disease in their lifetime.3,5 Studies suggest that the disease has been underdiagnosed, with considerable resultant reduction in both quality and quantity of life.5–7

Methods
A MEDLINE search was performed using multiple key words related to hemochromatosis and iron metabolism.

Defining the Disease
Hereditary hemochromatosis has been traditionally defined as an inherited disorder characterized by inappropriately high absorption of dietary iron, which leads to abnormal accumulation of iron in parenchymal organs.2,3 In 1996, the HFE gene was isolated on chromosome 6. Since this finding hereditary hemochromatosis has been defined by some as the presence of a homozygous defect in the HFE gene with direct or indirect evidence of iron overload.8 The requirement for evidence of iron overload to establish the diagnosis is a point of controversy in the new era of genetic testing.3,6,9–12 For this article, hereditary hemochromatosis will be defined as the phenotypic expression of iron overload in the presence of the HFE mutations known to cause the disease.

Iron overload is not synonymous with hereditary hemochromatosis. Although hemochromatosis is the most common cause of primary iron overload, there are other inheritable causes of primary iron overload, some of which occur only in the setting of
excessive iron intake. Table 1 displays the differential diagnosis of iron overload.

**Physiology of Iron Absorption**
Most Americans ingest approximately 15 to 20 mg of elemental iron daily. Of this amount, only about 1 to 2 mg are actually absorbed in the gut. For those with normal iron metabolism, daily loss of iron (menstrual losses, stool, and sweat) roughly equals absorption. Because humans have no physiologic mechanism to alter iron excretion to meet demand or availability, iron balance in the normal state is maintained through mechanisms that control absorption. Ferrous iron in the gut is then actively transported into the enterocyte and stored in the form of ferritin. Enterocyte absorption of iron is reduced by recent high dietary iron intake, by increased transferrin saturation, and by a yet-to-be-determined erythropoietic regulator from the marrow.

The HFE gene product, the HFE protein, binds to beta_2-microglobulin at the cell in a transmembrane configuration and acts as a major regulator of iron absorption by decreasing the affinity of the transferrin receptor for transferrin. HFE protein production is regulated in response to iron stores by an unknown mechanism. Iron regulatory proteins or a number of other proteins known to be involved in cellular iron metabolism might be involved.

**Pathophysiology and Genetics of Hereditary Hemochromatosis**
The clinical disease of hereditary hemochromatosis is usually caused by a homozygous autosomal recessive mutation in the HFE gene. In approximately 60% to 90% of cases, the defect is a single missense mutation at position 282 where cysteine is replaced by tyrosine (C282Y). The C282Y mutant HFE protein is unable to bind to beta_2-microglobulin, with the result being unregulated transferrin receptor-mediated iron uptake in the gut.

The prevalence of the homozygous C282Y mutation ranges from 1 in 200 for whites to 1 in 4,000 for those of African-American heritage. There appears to be variable expression of iron overload in persons with the homozygous C282Y mutation, with as many as 30% to 50% of those homozygous for the defect showing no signs of phenotypic expression at the time of discovery. As much as 10% of the US white population is heterozygous for the C282Y mutation.

Persons affected with hereditary hemochromatosis absorb 3 to 4 mg/d of iron, instead of the normal 1 to 2 mg/d. The net result is a positive iron balance in the range of 400 to 1,000 mg/y. Ninety percent of the excess iron stores are retained in the liver. As ferrous iron accumulates in the parenchymal tissues, the intracellular iron-binding sites are overwhelmed, which results in lipid peroxidation, cellular injury, and fibrosis.

In addition to the mutation at the 282 position, a second mutation has been found at position 63, where histidine is replaced by aspartate (H63D). The H63D mutation, while able to bind to transferrin receptors, appears to lack the normal high degree of inhibitory effect on the transferrin receptor. Persons homozygous for the H63D mutation and those who are compound heterozygotes (with the C282Y mutation) have a low rate of phenotypic expression, accounting for approximately 5% and 15% cases of hereditary hemochromatosis, respectively.

<table>
<thead>
<tr>
<th>Types of Iron Overload</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Iron Overload</td>
<td></td>
</tr>
<tr>
<td>HFE gene mutation-</td>
<td>C282Y homozygotes</td>
</tr>
<tr>
<td>associated hemochromatosis</td>
<td>C282Y simple</td>
</tr>
<tr>
<td>(hereditary hemochromatosis)</td>
<td>heterozygotes</td>
</tr>
<tr>
<td></td>
<td>H63D homozygotes</td>
</tr>
<tr>
<td></td>
<td>Compound heterozygotes</td>
</tr>
<tr>
<td>Non-HFE-associated</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>hemochromatosis</td>
<td>(South Pacific region)</td>
</tr>
<tr>
<td></td>
<td>Sporadic familial clusters</td>
</tr>
<tr>
<td></td>
<td>Nonhereditary</td>
</tr>
<tr>
<td></td>
<td>African iron overload</td>
</tr>
<tr>
<td></td>
<td>Juvenile hemochromatosis</td>
</tr>
<tr>
<td></td>
<td>Atransferrinemia</td>
</tr>
<tr>
<td></td>
<td>Acerauloplasminemia</td>
</tr>
<tr>
<td></td>
<td>Friedreich ataxia</td>
</tr>
<tr>
<td>Secondary iron overload</td>
<td>Ineffective erythropoiesis</td>
</tr>
<tr>
<td>and miscellaneous causes</td>
<td>Chronic anemias</td>
</tr>
<tr>
<td></td>
<td>(thalassemia major, sideroblastic anemia)</td>
</tr>
<tr>
<td></td>
<td>Multiple transfusions</td>
</tr>
<tr>
<td></td>
<td>Primary liver diseases</td>
</tr>
<tr>
<td></td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic (parenteral or oral)</td>
</tr>
<tr>
<td></td>
<td>Chronic hemodialysis</td>
</tr>
</tbody>
</table>

Table 1. Classification of Iron Overload
Physical Findings and Symptoms of Hemochromatosis

The symptoms and signs in patients with symptomatic hemochromatosis are very common in the family practice setting. Common symptoms include weakness, fatigue, arthralgias and arthritis, intermittent abdominal pain, loss of libido, and impotence. The most common symptoms are arthralgias and fatigue. Physical and laboratory findings include skin hyperpigmentation, hepatomegaly, evidence of heart failure, testicular atrophy, elevated liver enzymes, hyperglycemia, low testosterone levels, and hypothyroidism. The symptoms usually begin to appear in the third to sixth decade of life. Symptoms appear, on average, 10 to 15 years earlier in men, presumably because women lose iron during menstruation and pregnancy in the reproductive years. The classic triad of skin bronzing, cirrhosis, and diabetes is found in only a small percentage of patients at the time of diagnosis. Hepatic involvement manifested by elevated liver enzymes occurs in up to 65% of affected patients at the time of diagnosis. The expression and severity of hepatic disease is dependent on concurrent toxins, such as alcohol, viruses, and medications. Hepatic fibrosis eventually leads to cirrhosis in many untreated patients. The hepatic fibrosis resulting from hereditary hemochromatosis is a causative factor in approximately 3% of cases of hepatic cirrhosis and 10% to 30% of cases of hepatocellular carcinoma. Cardiac involvement occurs in 5% to 50% of the cases. Diastolic dysfunction, dilated cardiomyopathy, ST-T segment changes, atrial and ventricular arrhythmias, and conduction abnormalities can occur.

Pancreatic involvement, with beta cell damage and decreased insulin production, usually follows liver involvement. The result can range from glucose intolerance to frank diabetes that requires insulin for control. There is also evidence of insulin resistance in patients with hereditary hemochromatosis, implying damage to insulin-responsive mechanisms. Although hemochromatosis can be the cause of diabetes, only a small percentage of diabetic patients will be found to have hereditary hemochromatosis. Clinical findings suggesting iron overload or liver disease in diabetic patients should prompt screening for iron overload.

Other endocrine abnormalities in patients with hereditary hemochromatosis can result from hypothalamic dysfunction or glandular involvement or both. For example, testicular atrophy is due both to testicular fibrosis and decreased gonadotropin production. Thyroid gland involvement is manifest by thyroid tissue inflammation and fibrosis, with initial hyperthyroid function followed by low thyroid output.

The arthritis seen with hereditary hemochromatosis mimics osteoarthritis clinically and radiographically. The metacarpophalangeal and the proximal interphalangeal joints of the hands are usually affected first, followed by the large joints of the lower extremities and spine.

Diagnosis

Considering how commonly the above signs and symptoms occur in typical primary care practice, a low-cost method to evaluate for hereditary hemochromatosis is essential. Screening for hemochromatosis has resulted in earlier diagnosis. In some studies 75% of new cases are diagnosed during the clinically asymptomatic stage of the disease. Figure 1 displays an algorithm for the evaluation of patients with suspected hereditary hemochromatosis.

When clinical findings warrant evaluation, the best phenotypic screening tool is the serum transferrin saturation. A newer test, the unsaturated iron-binding capacity, shows promise as a more cost-effective screening test for the general population, but it is not yet widely available. Elevated transferrin saturation is usually the earliest phenotypic expression of the disease; its sensitivity for iron overload is 94% to 98%, with a specificity of 70% to 98%. In the white population, the sensitivity and specificity yield a positive predictive value of approximately 20%, and a negative predictive value of 99.9%. The test costs approximately $20.

Transferrin saturation is a calculated value (serum iron divided by total iron-binding capacity) that can be affected by other factors. If a screening transferrin saturation is high, the test should be obtained after an overnight fast, as serum iron levels can vary considerably after an oral dose. The iron-binding capacity is affected by acute and chronic disease states, oral contraceptives, and acute hepatitis. Normal transferrin saturation is
less than 45%, and elevations above this level warrant further evaluation. In men and postmenopausal women, transferrin saturations of 45% to 54% should be monitored at 1- to 2-year intervals. If the transferrin saturation exceeds 45% in premenopausal women or 55% in men and postmenopausal women, the workup should proceed with determination of serum ferritin and hepatic enzyme levels.

Serum ferritin concentration is linearly related to total body iron stores. Serum ferritin levels are normally less than 300 µg/L in men and postmenopausal women, and less than 200 µg/L in premenopausal women. In patients with an elevated transferrin saturation but normal serum ferritin levels and normal liver enzyme levels, it is prudent to monitor these values yearly. An elevated serum ferritin level defines the point at which treatment should be initiated in patients with a confirmed diagnosis. Serum ferritin is an acute phase reactant and can be elevated in the absence of iron overload. Elevated levels of the serum ferritin generally occur later in the course of iron overload than elevated transferrin saturation. For these reasons, serum ferritin is less useful as an initial screening test for hereditary hemochromatosis.

Hepatic enzymes are useful to gauge the likelihood of hepatic iron toxicity, but they are not useful as a screening tool. Studies have shown, however, that up to 3.4% of patients with elevated hepatic enzymes might have hereditary hemochromatosis. Also, because concurrent hepatic toxins

Figure 1. Algorithm for evaluation of suspected hereditary hemochromatosis. If cirrhosis is present, consider periodic α-fetoprotein measurements and hepatic sonography.

* Some authorities use 40 years as the age cutoff.
† Positive indicates HFE gene test shows homozygous C282Y mutation.
‡ Negative indicates HFE gene test shows no mutation or mutation other than homozygous C282Y mutation.
accelerate the hepatic toxicity of iron overload, it is recommended to screen for iron overload in patients with evidence of liver disease.2

Elevated serum ferritin or elevated hepatic enzyme levels in patients with an elevated fasting transferrin saturation indicate the need for further evaluation with HFE gene testing or liver biopsy. HFE gene testing is readily available in the United States. The test is performed on a whole blood specimen, and the cost to the patients is about $180. A much less costly method for identifying both mutations has recently been described.18 This lower cost test might eventually affect the role of genetic testing in both suspected persons and for general population screening. Currently, the appropriate use of HFE gene testing is being debated and refined.5,6,19,26,39,40 HFE gene testing will not distinguish the 10% to 40% (depending on the population) of whites with non-HFE iron overload, nor will it determine the cause of iron overload in most African-Americans or Asians.5 Thus, the HFE gene test is not recommended as a screening test for iron overload. At present, one well-defined use of HFE gene testing is to diagnose hereditary hemochromatosis in relatives of patients who have a confirmed diagnosis. First-degree relatives should be screened with HFE gene testing to determine risk and need for further evaluation and treatment.1,2,22

In the pre-HFE testing era, liver biopsy was considered the reference standard for diagnosis of hereditary hemochromatosis, but this concept has recently been challenged. Liver biopsy has a low complication rate in properly selected patients. Mortality ranges from 0.01% to 0.1%, and the risk of hemorrhage is 0.3%.18 The traditional criteria for diagnosis based on hepatic iron stores are listed in Table 2. These criteria are not exclusive for hereditary hemochromatosis, as these levels of iron can be found in end-stage liver disease of other causes.2,41 Periportal iron deposition is usually seen in hereditary hemochromatosis as opposed to other patterns of iron deposition in other disease states.1,5 Liver biopsy establishes the presence and severity of iron overload as well as the presence or absence of hepatic fibrosis, which has important implications for future evaluation.22 Some authorities state that liver biopsy is not necessary in selected patients aged 30 to 40 years or younger with homozygous C282Y defect and no laboratory or physical evidence of liver disease.1,10,18,19 A serum ferritin level of less than 1,000 μg/L has also been shown to predict the absence of liver fibrosis and is included in the decision process by some authorities.1,3,10,18

Because liver disease itself can cause elevated serum transferrin saturation and ferritin levels, biopsy combined with HFE gene testing is often necessary in patients with evidence of iron overload and suspected coexistent liver disease (such as viral hepatitis or ethanol-induced disease) to establish a definitive diagnosis. In these cases HFE gene testing can confirm hereditary hemochromatosis as the cause of the iron overload1,19,22,42 and can help in the risk stratification of family members.

For patients who cannot or will not receive liver biopsy, HFE gene testing should definitely be performed. In these patients, serum markers of iron overload, in combination with homozygous C282Y mutation, are sufficient for the diagnosis and to initiate treatment. For patients 30 to 40 years or younger with no evidence of liver involvement and serum ferritin levels of less than 1,000 μg/L, a similar strategy is recommended.22,23

The diagnostic criteria for hereditary hemochromatosis listed in Table 2 were developed in the pre-HFE gene testing era and thus do not include HFE gene status. The availability of this technology will likely result in changes in these criteria in the foreseeable future.

One potential diagnostic criterion for hereditary hemochromatosis (Table 2) is the finding of 4 g or more of mobilizable iron (approximately 16 U of blood) through a weekly or biweekly phlebotomy schedule. Scheduled phlebotomy without inducing iron-limited erythropoiesis is considered diagnostic

---

Table 2. Traditional Diagnostic Criteria for Hereditary Hemochromatosis.

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Observation of elevated transferrin saturation &gt;60% on at least 2 occasions in the absence of other known causes of elevated transferrin saturation</td>
</tr>
<tr>
<td>B. Diagnosis of iron overload: 1 plus 2, or 1 plus 3, below</td>
</tr>
<tr>
<td>1. Elevated serum ferritin not explained by another cause</td>
</tr>
<tr>
<td>2. Increased hepatic iron by either a or b, below</td>
</tr>
<tr>
<td>a. Increased stainable hepatocellular iron (Scheuer grade 3 or 4)</td>
</tr>
<tr>
<td>b. Increased hepatic iron concentration (&gt;80 μmol/g) and hepatic iron index (&gt;1.9)</td>
</tr>
<tr>
<td>3. Increased mobilizable iron (removal of 4 g of iron without development of iron-limited erythropoiesis)</td>
</tr>
</tbody>
</table>

for parenchymal iron overload in lieu of tissue biopsy. For patients showing evidence of iron overload with heterozygous C282Y results, isolated H63D homozygous mutations, or concurrent liver disease, liver biopsy and consultation with an expert can be helpful in defining the cause of the problem.9,10

The role and method of population screening are currently being debated. At present, the most cost-effective general population screening test might be the an unbound iron-binding capacity or transferrin saturation at age 20 to 30 years.1,2,12,35

**Treatment**

The recommended treatment for most patients is therapeutic phlebotomy.9 Therapeutic phlebotomy includes an induction phase to induce iron depletion and a maintenance phase (see below) to prevent excess iron reaccumulation. Therapeutic phlebotomy can be performed safely in the physician’s office or even in the patient’s home.9 Therapy should not be delayed until symptoms develop, as the goal of therapy is to prevent irreversible organ damage.9,26

Care must be taken to assure optimal pre- and post-phlebotomy hydration.9 Precautions to avoid postphlebotomy orthostatic hypotension should be observed after each treatment. Adequate dietary protein, vitamin B12, and folate intake should be encouraged to support the accelerated erythropoiesis that occurs with therapy. For patients who find venipuncture uncomfortable, comfort can be enhanced by prescribing a topical anesthetic preparation for use before each treatment.

Patients should be counseled to maintain a diet with only moderate amounts of high–iron-content foods.9 Iron supplementation in any form should be strictly avoided. There is no reason to discourage vitamin C intake, with the exception of limiting those patients who choose to take supplements to 500 mg/d.9,26 Ethanol should be avoided completely in patients with liver disease.43

Patients should be advised to avoid uncooked seafood, because they have a unique susceptibility to *Vibrio vulnificus* infection. Similarly, these patients are at increased risk of infection with this organism if they expose open wounds to warm coastal seawater. Therapeutic phlebotomy treatment does not reduce susceptibility to *V. vulnificus* infection.9

Erythropoietin therapy can be used for patients with iron overload and hypoproliferative anemias, such as in renal disease and anemia of chronic disease.9 In such cases with complicating hematopoietic disease, balancing therapies can be difficult, and appropriate consultation is suggested.

Iron chelation therapy is reserved for patients who are severely anemic.9,26 Deferoxamine is generally well tolerated, but it has serious adverse side effects and is inconvenient and expensive.2,26 Oral agents are being investigated, but they are also associated with higher costs and undesirable side effects.2

**Induction Phase**

Effective initial treatment requires removal of 5 to 20 g of iron for most patients.18 Each unit of whole blood (500 mL) contains approximately 250 mg of iron.9,26 The frequency of phlebotomy depends on the severity of iron overload symptoms as well as the patient’s overall state of health. For patients with average or better body mass and evidence of ongoing iron toxicity, aggressive treatment with twice weekly phlebotomy is indicated and generally well tolerated.9 For those patients with iron overload and little or no evidence of toxicity, a less aggressive schedule of weekly or biweekly phlebotomy is sufficient. Erythroid hyperplasia occurs after a few weeks of treatment, which can permit acceleration of the treatment schedule in some patients.9,29 In general, because of sex differences and the effects of time on the extent of iron accumulation, men require more phlebotomies than women, and older patients require more treatments than younger patients.

During the induction phase, most authorities recommend that the hematocrit be measured before every other phlebotomy. For patients on a less aggressive treatment schedule, the hematocrit can be measured before every third or fourth treatment as long as the patient is asymptomatic.2 The target hematocrit during therapy is 35% to 40%.29 The serum ferritin level is the most reliable and least expensive measure of the response to treatment.9 Serum ferritin should generally be measured after each month of treatment until it falls below 100 μg/L. Thereafter, it should be measured after every other treatment.9 Iron depletion occurs when serum ferritin decreases to 20 to 50 μg/L or when the hematocrit fails to rise above 33% for more than 3 weeks after treatment.8,9,26,29
Maintenance Phase

After completion of the induction phase, maintenance therapy is required indefinitely to maintain normal iron stores. This phase usually requires two to four phlebotomy sessions each year with a goal of maintaining the serum ferritin level at less than 50 µg/L.26

Response to Therapy

Although the end points for the treating physician are easily measurable, the responses perceived by the patient might not be so evident. Most patients report improvements in strength and pigmentation. Cardiomyopathy, if not severe, is likely to improve through the process of remodeling once the tissue toxin is removed. Hyperglycemia often improves with treatment. Liver congestion and liver enzymes are likely to improve. Unfortunately, the arthritic symptoms, hypogonadism, and hypothyroidism do not improve with treatment.9 The endocrinopathies and arthritis caused by hereditary hemochromatosis might even continue to worsen despite treatment.7 Cirrhosis, if present, is not likely to improve,29 although treatment might result in slowing the progression of cirrhosis in a few affected patients.9 Cirrhosis is the most reliable predictor of survival. If there is no cirrhosis at the time of diagnosis, patients have a normal survival with treatment. If cirrhosis is present, 5- and 10-year survivals with treatment are 72% and 62%, respectively.29

The most dreaded outcome of hereditary hemochromatosis in patients with evidence of cirrhosis is developing hepatocellular carcinoma.37 The risk of developing this cancer is as high as 19% if cirrhosis is present, and 5% if cirrhosis is not present.20 Many authorities recommend monitoring the α-fetoprotein level or scheduling a hepatic sonogram every 6 months for patients with cirrhosis, but effectiveness of this strategy is unclear.9,26,29

Conclusion

Family physicians are likely to encounter patients with undiagnosed hereditary hemochromatosis in their practices. Considering the prevalence of the disease, it is important for physicians to consider it in the differential diagnosis when patients complain of the common signs and symptoms. For most patients hereditary hemochromatosis can be successfully treated in the physician’s office. Early diagnosis and treatment, before signs of iron toxicity, if possible, can result in improved quality and quantity of life for many patients.

References


