

- Describe the etiology and pathophysiology of hereditary hemochromatosis (HH)
- Review common signs and symptoms in the clinical presentation of HH
- Explain the criteria used to establish the diagnosis of HH
- Discuss treatment options for HH and the importance of patient education

## Hereditary hemochromatosis: Iron overload as an indicator of disease

Iron accumulation occurs silently, with manifestations ranging from mild symptoms to severe disease. HH is typically discovered after routine laboratory tests in asymptomatic patients.

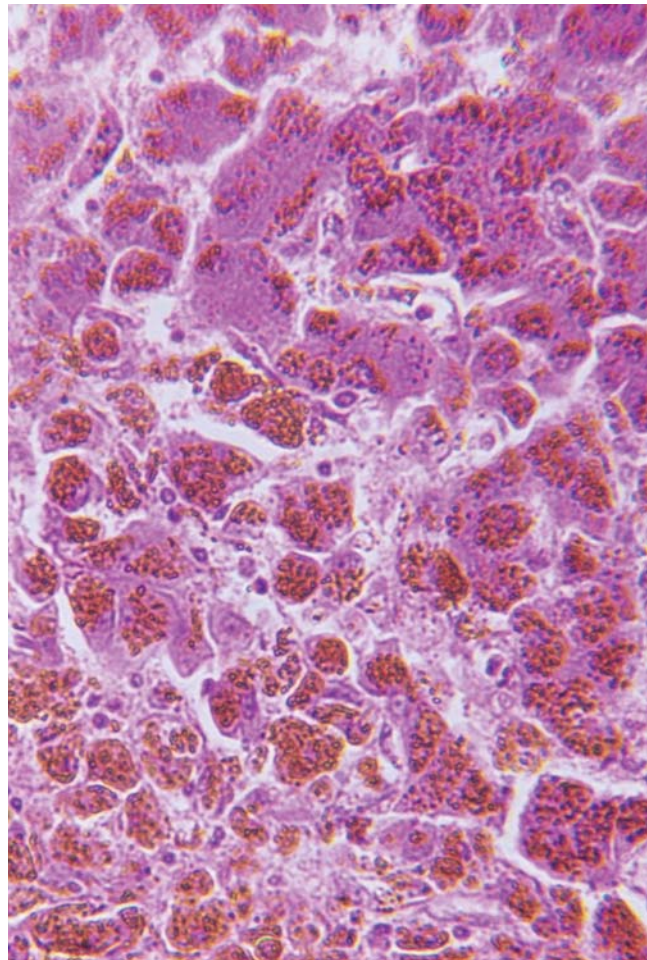
**Denise Rizzolo, PA-C, PhD; Mona M. Sedrak, PA-C, PhD**

**A** 55-year-old male presents to your office for a routine physical examination. He tells you that he has been feeling tired and his bones are achy, but he attributes this to getting old. His medical history is significant for exercise-induced asthma. Physical examination findings and an ECG are normal; however, laboratory test results reveal a serum iron level of 300 µg/dL (normal, 60-150 µg/dL) and a serum ferritin concentration of 2,000 ng/mL (normal, 15-200 ng/mL). Results of subsequent laboratory tests are serum transferrin, 200 mg/dL (normal 200-400 mg/dL), and transferrin saturation, 100% (normal 20%-55%). Liver enzymes are normal. Initially perplexed by the abnormal test results, you consult a hematologist who suggests genetic testing for hemochromatosis. One week later, genetic test results indicate that the patient has a homozygous mutation (C282Y/C282Y) of the *HFE* gene.

### EPIDEMIOLOGY

In 1865, Dr Armand Trousseau described skin pigment changes seen in patients with diabetes mellitus in the journal *Clinique Médicale de l'Hôtel-Dieu de Paris*.<sup>1</sup> However, the connection between diabetes mellitus and iron accumulation was not made until 25 years later. The German pathologist Friedrich Daniel von Recklinghausen discovered large deposits of iron in the hepatocytes of persons with discolored skin at autopsy. He coined the term *hemochromatosis* based on this discovery. Hereditary hemochromatosis (HH) is an autosomal recessive disorder of abnormal iron metabolism that causes iron accumulation and overload in various organs of the body.<sup>1</sup>

The *HFE* gene, located on chromosome 6, was identified in 1996.<sup>2</sup> The prevalence of HH in the general population is



**FIGURE 1.** Brown pigmentation of hepatocytes in HH

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difficult to quantify because no set criteria exist to define what constitutes HH. Thus, researchers have estimated that the prevalence of hemochromatosis ranges from 1 in 357 persons to 1 in 625 persons in the general population.<sup>3</sup> Approximately 90% of patients with HH have mutations in the *HFE* gene. The most common mutations that cause iron overload are the *C282Y mutation*, which is a change of cysteine to tyrosine at position 282, and the *H63D mutation*, which is a change of histidine to aspartate at position 63.<sup>4</sup> Most patients (95%) with *HFE*-related HH are homozygous for *C282Y*.<sup>1</sup> The prevalence of the *C282Y* homozygous state within the United States was found to be 0.44% in whites, 0.11% in Native Americans, 0.027% in Hispanics, 0.014% in African-Americans, 0.012% in Pacific Islanders, and 0.0004% in Asians.<sup>5,6</sup>

Approximately 10% of patients with HH carry a single copy each of the *C282Y* and *H63D* mutations and are thus designated compound heterozygotes.<sup>7</sup> Patients with this mutation usually have less of an overload of iron but frequently still need treatment.<sup>1</sup> A small number of patients with HH are either heterozygous for *C282Y* or homozygous for *H63D*. Persons with these genotypes are not at increased risk of iron overload.

### **PATHOPHYSIOLOGY**

On average, 1 to 2 mg of iron are lost through skin cells, sweat, and the GI tract each day; normal Western diets supplement these iron losses. Additional iron is needed for major metabolic processes—such as adolescent growth spurts—until age 40 years. Typically, adult men have about 35 to 45 mg/kg of total body iron; women may store slightly lower levels of iron. However, iron begins to progressively accumulate after age 40 years because the body has no mechanism to excrete excess amounts once iron is absorbed. As a result, manifestations of HH often are not seen until patients are in their mid 40s. Patients with HH, particularly men, may have accumulated up to 20 g of iron in the liver, heart, and endocrine tissues by the time symptoms occur. Women typically do not present with symptoms until after menopause, when mechanisms that help excrete extra iron such as menses, lactation, or pregnancy no longer occur.

### **KEY POINTS**

- Approximately 90% of patients with hereditary hemochromatosis (HH) have mutations in the *HFE* gene. The most common mutations that cause iron overload are the *C282Y* mutation and the *H63D* mutation.
- Diagnosis of HH is made using genetic, biochemical, and clinical criteria. Persons with suspected iron overload or who are first-degree relatives of someone with a confirmed case of HH and older than 20 years are initially screened via indirect serologic markers of iron stores.
- Early manifestations of HH may be vague symptoms such as fatigue, arthralgias, loss of libido, and skin hyperpigmentation. For many patients with HH, the first sign of disease may be elevations in iron, serum ferritin, and liver enzymes seen in routine blood test results.
- Therapeutic phlebotomy should be initiated when serum ferritin levels are 300 ng/L or higher for men and 200 ng/L for women, regardless of whether the patient is symptomatic.

### **CLINICAL MANIFESTATIONS**

Early manifestations of HH may be vague, such as fatigue, arthralgias, loss of libido, and skin hyperpigmentation.<sup>8</sup> For many patients with HH, the first sign of disease may be elevations in iron, serum ferritin, and liver enzymes found in routine blood test results.<sup>9</sup> The liver is the most common site for clinical manifestations of the disease, which range from minimal effects, such as elevated aminotransferase levels, to more serious complications, such as cirrhosis<sup>9</sup> (see Figure 1). The skin pigment changes, commonly referred to as *bronzing*, are caused by increased melanin or iron deposition around the sweat glands. Skin changes can be generalized but commonly occur on the face, mucosal surfaces, forearms, hands, and lower legs. Other manifestations of the disease are found in the endocrine system (diabetes mellitus, hypogonadotropic hypogonadism, impotence, or hypothyroidism), the cardiovascular system (arrhythmias or heart failure), and the musculoskeletal system (destructive arthritis).<sup>8,10</sup> The classic presentation of HH—diabetes mellitus and cutaneous hyperpigmentation with cirrhosis—is now rare because advanced detection capabilities can identify the disease before these manifestations occur. Early recognition of the characteristic combination of features associated with iron overload is imperative because predicting which patients will experience disease progression is difficult.<sup>7</sup>

### **DIAGNOSTIC TESTING**

The discovery of the *HFE* gene profoundly impacted the diagnostic and screening approaches for HH. The *C282Y* homozygous state alone does not translate into disease.<sup>3,11</sup> Diagnosis of HH is made using a combination of genetic, biochemical, and clinical criteria<sup>12</sup> (see Figure 2, page 20). Diagnostic testing is based on the recommendations of the Practice Guidelines Committee of the American Association for the Study of Liver Diseases.<sup>12</sup> These guidelines provide data-supported, peer-reviewed recommendations for the care of patients with HH. Persons with suspected iron overload and those who are first-degree relatives of someone with a confirmed case of HH and older than 20 years are initially screened via indirect serologic markers of iron stores.<sup>12</sup>

Initial laboratory tests to confirm a diagnosis of HH are serum transferrin saturation (TS), serum ferritin concentra-

### **COMPETENCIES**

●●●● Medical knowledge

● Interpersonal & communication skills

●●●● Patient care

●●● Professionalism

●●● Practice-based learning and improvement

● Systems-based practice

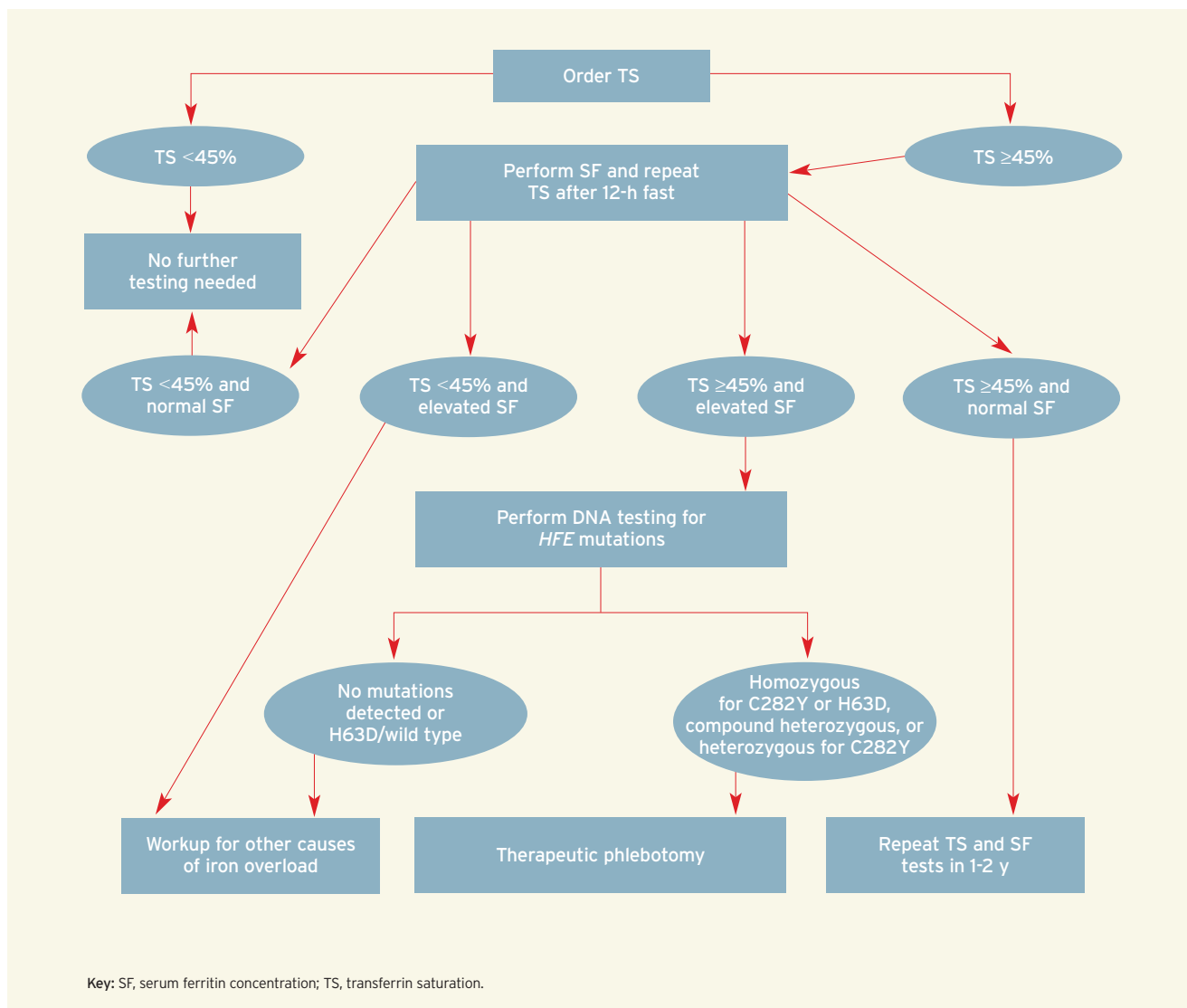
tion, and biochemical tests. These tests are simple, fast, and inexpensive. TS level is the best single screening test for HH. Serum iron concentrations vary throughout the day and are affected by food consumption; therefore, measuring TS level from a morning fasting blood sample can eliminate 80% of false-positive results.<sup>13</sup> TS levels of 60% or higher in men and 50% or higher in women are approximately 92% sensitive and 93% specific, with an 86% positive predictive value, for detecting HH in homozygous persons.<sup>12</sup>

Most clinical laboratories calculate TS levels by determining the ratio of serum iron to the total iron-binding capacity; however, unsaturated iron-binding capacity (UIBC) is used in some laboratories in order to reduce the overall costs of testing. UIBC values lower than 28  $\mu\text{mol/L}$  are indicative of iron overload.<sup>12</sup>

A test for serum iron or ferritin lacks specificity when used alone. Serum ferritin is an acute-phase reactant that is elevated by a number of infectious and inflammatory conditions in the absence of iron overload. In addition, serum ferritin levels do not become abnormal until iron overload advances to the liver.<sup>14,15</sup> However, the combination of serum ferritin and TS levels has a negative predictive value of 97%.<sup>12</sup> In a confirmed case of HH, a serum ferritin level higher than 1,000 ng/mL accurately correlates with the degree of hepatic fibrosis.<sup>16,17</sup>

A diagnosis of hemochromatosis should be confirmed by genetic testing in all patients suspected of having the disease. If iron overload is highly suspected, C282Y and H63D mutation analysis should be performed.<sup>12</sup> However, mutation analysis cannot reveal whether increased iron stores or organ damage is present.<sup>18,19</sup> Although not routinely recommended,

**FIGURE 2.** Algorithm for screening for hereditary hemochromatosis



genetic testing should be used to screen first-degree relatives of patients with confirmed HH.<sup>720</sup> Once HH is diagnosed, referral to a hematologist or a gastroenterologist who specializes in hemochromatosis management should be made.

Liver biopsy confirms the presence of cirrhosis when investigating other causes of liver disease or to rule out significant iron overload when iron markers are equivocal. Biopsy is recommended for all homozygous persons with clinical evidence of liver disease, serum ferritin concentration higher than 1,000 ng/mL, and persons older than 40 years with other risk factors for liver disease.<sup>12</sup> Biopsy should also be considered for patients with compound or C282Y heterozygosity with elevated TS levels, especially those who have had abnormal liver enzyme levels or clinical evidence of liver disease.<sup>12</sup>

Histopathology and staging of fibrosis is determined with a hematoxylin-eosin and Masson trichrome stain. Biopsy is helpful when documentation of hepatic iron concentration (HIC) and stage of fibrosis are necessary.<sup>12</sup> Normal HIC is less than 1,800 µg/g dry weight (equivalent to 32 µmol/g).<sup>12</sup> Perls' stain should also be performed to obtain a qualitative hepatic iron determination. If this result suggests increased iron stores, the diagnosis should be confirmed with a quantitative measurement of iron in stored tissue.

The hepatic iron index (HII) as a measure of the iron accretion rate was developed to distinguish HH from other clinical conditions, particularly alcohol-induced liver disease.<sup>1</sup> A rate in excess of 1.9 is strong evidence for homozygous hemochromatosis. However, studies have recently shown that up to 15% of genotypic homozygotes for HH do not meet this rate. Thus, an elevated HII is no longer considered essential for diagnosis.<sup>1,21</sup> However, patients with partial expression of homozygous HH have an HIC at least 3 times the upper limit of normal if they are older than 20 years.<sup>12</sup> Although HII has lost some of its importance for a diagnosis of HH, the correlation between HIC and age determines the age at which fibrosis will develop.

Patients with HH who have established cirrhosis are at an increased risk for hepatocellular carcinoma (HCC). The relative risk for HCC is 20 and the standardized incidence ratio in cirrhotic HH is 92.9.<sup>22</sup> Therefore, alpha-fetoprotein testing and ultrasonography examination every 6 months are recommended for these patients.<sup>23</sup>

## TREATMENT

Hemochromatosis treatment has remained quite simple despite the advances in genetic testing technology. Therapeutic phlebotomy should be initiated when serum ferritin levels are 300 ng/L for men and 200 ng/L for women, regardless of whether the patient is symptomatic. Typically, 500 mL of whole blood is removed per week, as tolerated. The goal is to remove excess iron without causing anemia. Phlebotomy should continue until transferrin saturation is less than 50% and the ferritin level is below 50 ng/mL.<sup>24</sup> Most patients require maintenance phlebotomy with reassessment of iron status every 2 to 4 months; however, a few patients may not reaccumulate excess iron.<sup>24</sup>

## PROGNOSIS AND PATIENT EDUCATION

The majority of patients with HH are identified while asymptomatic as a result of advances in diagnostic testing. Abnormal iron levels are detected in laboratory tests for another medical problem or when screening is performed after HH has been diagnosed in a relative.<sup>20,25</sup> Most persons with the genetic disorder do not have a shortened life span or progression of disease when compared to a control population.<sup>26</sup> Survival of the noncirrhotic, nondiabetic patient with HH is similar to that of a healthy person.<sup>27</sup> However,

“Patients should try to limit their intake of foods that contain large concentrations of bioavailable iron such as red meats.”

more than 95% of symptomatic patients have elevated liver enzymes, hepatomegaly, or cirrhosis. Furthermore, cirrhosis and/or its complications account for 89% of all HH-related deaths.<sup>5,27</sup> Patients with HH who develop cirrhosis have an increased annual risk for developing HCC.<sup>28</sup> The risk for developing HCC is higher for patients with HH than for the general population and is the highest in men older than 55 years who are heavy alcohol users.<sup>29</sup>

Proper dietary management can reduce the rate of iron reaccumulation and reduce or eliminate the complications of hepatic disorders and diabetes mellitus. Patients with HH need to limit their intake of foods that contain large concentrations of bioavailable iron such as red meats and organ meats.<sup>30</sup> Furthermore, they should not take iron supplements or multivitamins with iron. Patients with HH should also be advised not to consume more than 500 mg/d of vitamin C (ascorbic acid) from supplements because vitamin C increases intestinal absorption of inorganic iron.<sup>31</sup> However, there is no rationale for discouraging these patients from consuming fresh fruits and vegetables that contain vitamin C.

Alcohol also has the potential to increase iron absorption, and some alcoholic drinks, such as red wine, contain high levels of iron.<sup>31</sup> Excessive ingestion of alcohol can potentiate hepatic injury, increasing the risk for HCC in patients with cirrhosis.<sup>32</sup> Patients with evidence of hepatic injury should consume little or no alcohol, whereas others should be encouraged to limit their intake.

However, foods and drinks that contain tannates, phytates, oxalates, calcium, and phosphates can bind iron and thereby inhibit its absorption. For example, consuming large quantities of tea, which contains tannates, can decrease iron absorption.<sup>33</sup> Patients do not need to alter their diet in an attempt to inhibit iron absorption unless they are unable to tolerate therapeutic phlebotomy.

Patients with HH should avoid consuming or even handling raw seafood because of an increased risk of *Vibrio vul-*

*nificus* and *Salmonella enteritidis* infections.<sup>34</sup> *V vulnificus* occurs naturally in many warm coastal waters, including along the US shore and in the Gulf of Mexico. The bacteremia that results when *V vulnificus* is introduced into the blood stream through an open wound when handling contaminated seafood may be related to the availability of iron for microbial metabolism or the presence of cirrhosis and can be fatal. Patients should be advised to ensure that seafood from potentially contaminated waters is thoroughly cooked before eating it.

## CONCLUSION

Advances in screening technology have led to HH being diagnosed much more frequently and before the onset of multiorgan iron overload. Once a diagnosis is made, prompt referral and treatment is indicated to avoid the negative consequences of iron accumulation. Early therapeutic phlebotomy decreases iron overload, thereby increasing longevity and quality of life. **JAAPA**

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