REVIEW

Revisiting Hereditary Hemochromatosis: Current Concepts and Progress

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ABSTRACT

Originally regarded as a rare affliction notable for its distinctive evolution to “bronze diabetes,” hereditary hemochromatosis is now recognized as the most common genetic disorder in populations of European ancestry. Recent advances in our understanding of iron metabolism, the identification of the gene responsible for hemochromatosis, and large epidemiologic studies have changed the diagnostic approach toward patients with hereditary hemochromatosis and other forms of iron overload. This article reviews the pathophysiology, epidemiology, clinical features, diagnostic testing, and management of hemochromatosis for the primary care provider. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Hemochromatosis; Iron overload; HFE; C282Y

Hereditary hemochromatosis (HH) was first identified in the late 19th century as the classic triad of glycosuria (diabetes), bronze skin pigmentation, and cirrhosis. HH is the best described of the primary iron overload syndromes that have been attributed to genetic variants in genes of iron metabolism. It is often suspected in patients with secondary causes of iron overload such as thalassemia and chronic liver disease or particularly, chronic hepatitis and alcoholic liver disease, entities that are encountered more frequently in clinical practice (Table 1). HH is an autosomal recessive disorder resulting from mutations in the HFE gene, usually manifesting in adults beginning in their 40s and 50s. Althought genetic and biochemical studies have demonstrated a high frequency of HH in various populations of Northern European descent, more recent large-scale studies suggest relatively low rates of clinical expression and have failed to demonstrate a survival disadvantage. However, certain patients with HH do progress to harmful levels of iron overload, and the genetic and environmental factors that may predispose to this have not been elucidated.

IRON METABOLISM AND THE PATHOPHYSIOLOGY OF HEMOCHROMATOSIS

Because of its ability to readily exchange electrons in aerobic conditions, iron is indispensable for basic cellular functions such as DNA synthesis, cellular respiration, and oxygen transport. Excess iron, however, damages tissue by catalyzing the conversion of hydrogen peroxide to free-radical oxygen species that attack cell membranes, proteins, and DNA.

Adult men normally have 35 to 45 mg/kg of total body iron, whereas premenopausal women have slightly lower stores (~35 mg/kg). The majority of iron (60%) is incorporated into hemoglobin, whereas lesser amounts are found in muscle myoglobin (10%-15%), enzymes, and cytochromes (10%); less than 1% circulates in plasma bound to transferrin.

Under homeostatic conditions, the 1 to 2 mg of iron that is lost daily through sweat and in the sloughed cells of the skin and intestines is balanced by dietary iron absorption. Humans have no physiologic pathway for the excretion of excess iron; thus, body stores are regulated by intestinal iron absorption in the duodenum. Improper regulation of this absorption can lead to iron overload.

The first step in this pathway is the transport of iron across the apical membrane of duodenal epithelial cells by the divalent metal transporter 1 (DMT1) protein (Figure 1).
Iron can either be stored as ferritin or exported across the basolateral membrane by ferroportin, where it is bound by transferrin and enters the circulation. Both DMT1 and ferroportin expression are dependent on cellular iron stores. However, in HH, duodenal DMT1 and ferroportin are inappropriately elevated, leading to disproportionate iron absorption over daily losses and gradual accumulation of iron.7-9

Central to the pathophysiology of HH and iron metabolism is the recently identified peptide, hepcidin. Hepcidin is a circulating hormone synthesized in the liver and regulated by iron stores and inflammation. Hepcidin, which is induced by iron, acts on ferroportin to inhibit iron transport, presumably resulting in decreased iron absorption and increased retention of iron in macrophages and Kupffer cells.10-12 In HH, hepcidin levels are inappropriately low, and in transgenic HFE-deficient mice, overexpression of hepcidin prevents the development of iron overload.

GENETICS

HFE was first identified as the cause of HH in 1996.3 Two single base-pair mutations, C282Y and H63D, are responsible for most cases of HH. Approximately 70% to 100% of patients with a clinical diagnosis of HH are homozygous for the C282Y mutation.3,4,13-16 Approximately 10% are compound heterozygotes carrying a single copy each of the C282Y and H63D mutations. A small number of patients with HH are either heterozygous for C282Y or homozygous for H63D, but there does not seem to be an increased risk of iron overload with these genotypes. Novel genetic mutations in HFE and genes for ferroportin, hepcidin, and others have been described in small numbers of patients and families with iron loading syndromes and are classified on the basis of the clinical presentation and genes involved.17

EPIDEMIOLOGY

The C282Y mutation is believed to have originated in a Celtic or Viking ancestor more than 6000 years ago.2 Like many widespread genetic disorders, HH did not impose a serious obstacle to reproduction and possibly conferred some selective advantages (eg, resistance to dietary iron deficiency during periods of nutritional deficit or pregnancy), resulting in persistence of the mutation.1 Further, the relatively iron-deficient HH macrophages, where many organisms gain virulence, may also be protective against iron-dependent microbes.18

The prevalence of HH based on biochemical and genetic criteria has been well established, whereas data on the clinical prevalence of disease are not yet readily available.6 In the United States, the prevalence of the C282Y homozygous state varies among ethnic groups. In white populations, the frequency is approximately 4 per 1000 (0.4%), and the frequency of heterozygotes is approximately 100 per 1000 (9.6%).5,19 Other ethnic groups seem to have a lower prevalence, because estimates for homozygous C282Y patients are approximately 0.014% in non-Hispanic blacks, 0.027% in Mexican Americans, and 0% in Asians.20

CLINICAL FEATURES

Iron overload occurs slowly and silently. By age 40 years, patients remain asymptomatic but have accumulated 10 to 20 g of parenchymal (liver, heart, and endocrine tissue) iron stores. In men, clinically overt HH rarely presents before the fourth or fifth decade of life. In women, menstruation delays iron accumulation by approximately a decade and symptoms usually begin after menopause. This may explain why HH is found 2 to 10 times more frequently in adult men than women.

Before genetic testing and biochemical screening, HH was suspected when clinical manifestations of iron overload became apparent. Characteristic signs and symptoms have been well documented in association with HH. Early iron accumulation often starts with subtle, nonspecific symptoms and may include unexplained fatigue, joint pain, weight loss, abdominal pain, or loss of libido and can eventually progress to end-organ dysfunction (Table 2).21,22

The availability of more advanced diagnostic modalities has changed the identification of disease. The majority of patients are now identified while asymptomatic, following abnormal iron study results after testing for another disease or when screening is performed after a relative has been

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**Table 1** Secondary Causes of Iron Overload

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Thalassemia</td>
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<tr>
<td>Sideroblastic anemia</td>
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<tr>
<td>Chronic liver disease:</td>
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<tr>
<td>Hepatitis C</td>
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<tr>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Steatohepatitis</td>
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<tr>
<td>Alcohol induced liver disease</td>
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<tr>
<td>Previous portal caval shunting</td>
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<tr>
<td>Transfusion related</td>
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diagnosed with HH. Results from such testing, however, may be difficult to interpret, because studies have suggested that most individuals with the genetic abnormality do not have shortened life expectancy or progression of disease when compared with control populations. In most cases C282Y homozygosity seems to be a necessary but not sufficient factor in causing HH. However, it is still important to recognize characteristic features associated with iron overload because it is impossible to predict which patient will have progression of disease. The following reviews the most common manifestations of overt HH.

Liver

More than 95% of symptomatic patients with HH have elevated liver enzymes, hepatomegaly, or cirrhosis. Serum bilirubin and transaminases may be normal or slightly elevated, but usually not greater than twice normal. Cirrhosis or its complications account for approximately 89% of HH-related deaths. Therapeutic phlebotomy remains beneficial by improving or reversing varices in 26% of patients with HH. Survival in noncirrhotic, nondiabetic patients with HH is similar to the healthy control population, whereas those with cirrhosis have significantly increased mortality.

Screening for hepatocellular carcinoma (HCC) has been proposed for patients with cirrhosis, even after iron reduction therapy, although there are currently no data to guide the optimal method or interval for such screening. The risk of HCC is up to 200-fold more than that for the general population and is highest among men, chronic smokers, and heavy alcohol users. Overall, patients with HH have an estimated 5% annual risk for HCC after the development of cirrhosis.

End-stage liver disease can be treated with transplantation, although HH alone is an uncommon indication for organ exchange. Those who do undergo transplantation have reduced survival compared with those undergoing transplantation without HH, especially when HCC is present. Survival at 1, 3, and 5 years posttransplant was 72%, 62%, and 55%, respectively, and death was secondary to perioperative cardiac or infection-related complications.
HH can lead to a mixed dilated-restrictive or dilated cardiomyopathy and conduction disturbances, such as atrial fibrillation or sick sinus syndrome. The severity of myocardial involvement varies widely and does not correlate with the severity in other organs. Electrocardiographic abnormalities include a decrease in QRS amplitude and T-wave flattening or inversion. Cardiac abnormalities may or may not be permanent, and reversal of left ventricular dysfunction with therapy has been observed. Cardiac dysrhythmias and cardiomyopathies are the most common cause of sudden death in iron overload states.

Endocrine
Iron can lead to diabetes by 2 distinct mechanisms: (1) Iron accumulation in pancreatic β-cells decreases insulin production, and (2) iron impairs insulin sensitivity. A recent study of healthy women showed higher iron stores were associated with an increased risk of type II diabetes independent of known diabetes risk factors.

Hypogonadism is the most common nondiabetic endocrinopathy in HH and can present as impotence, amenorrhea, loss of libido, or osteoporosis. It is usually secondary to iron accumulation in pituitary cells leading to impaired gonadotropin secretion, although primary hypogonadism has also been observed. Even with iron depletion, most patients continue to require hormone replacement therapy.

Thyroid dysfunction in men has also been observed in HH and occurs at a rate of approximately 80 times over unaffected males in the general population. Iron accumulation in thyroid tissue causes fibrosis and leads to the development of antithyroid antibodies, resulting in hypothyroidism. Affected individuals typically require lifelong supplementation for thyroid dysfunction.

Arthropathy
Classic HH arthropathy occurs in one-third to one-half of patients and resembles noninflammatory osteoarthritis involving the second and third metacarpophalangeal joints and proximal interphalangeal joints. The wrists, knees, hips, and shoulders are less frequently affected. Hand radiographs show squared-off bone ends and hook-like osteophytes, joint space narrowing, sclerosis, and cyst formation resembling calcium pyrophosphate dehydrate disease.

Iron itself may not even be the primary cause of joint pain, but may instead moderate the effects of or interact with genes associated with arthritis. Although less than 10% of patients improve after therapy for HH, it is important to note that arthropathies are extremely common clinical entities and the extent to which the HH mutation contributes to symptomatic disease is not clear.

Dermatologic
Skin pigment changes (melanoderma) may not occur at an increased rate, although most patients will admit to skin changes, or “bronzing,” at the time of diagnosis. When severe, it is often grey or brown and slate-grey mucosal patches that can be seen in the mouth. Pigmentation is most often generalized but can sometimes be limited to the face, neck, extensor aspects of the lower forearms, dorsum of the hands, lower legs, genital region, and old scars. Pigmentation is likely secondary to increased melanin or iron deposition around sweat glands. Cutaneous atrophy, flattening of the nails, and loss of body hair are also common.

Other
Other clinical manifestations that can be seen include unexplained weight loss, fatigue, abdominal pain, or depression. Implications for iron overload and/or the HH gene mutation being studied include possible linkage to amyotrophic lateral sclerosis, porphyria cutanea tarda, and Alzheimer and Parkinson diseases.

Diagnostic Testing
The discovery of the HH gene has profoundly modified diagnostic and screening approaches, but recall that the C282Y homozygous state alone does not confer disease. The phenotypic manifestation of HH is determined by genetic, biochemical, and clinical markers. There remains no consensus on which factor or combination of factors is needed to define HH. The presence of the genetic abnormality and clear biochemical evidence of iron overload makes the diagnosis indisputable, but this combination is not always present.

Diagnostic strategies can include serum iron studies, genetic testing, liver biopsy, and assessment of the response to phlebotomy or chelation therapy. Now that genetic testing is widely available, it should be performed in all patients in whom HH is highly suspected. Currently, diagnosis is most often based on biochemical tests first, followed by genetic testing. Biochemical methods are simple, fast, and inexpensive (Table 3). Transferrin saturation is generally regarded as the best single screening test for HH. Measuring a morning fasting transferrin saturation eliminates 80% of false-positive results. Values of 60% or greater in men and 50% or greater in women have an approximate sensitivity of 92%, specificity of 93%, and positive predictive value of 86% for detecting homozygous individuals with HH. However, there is no agreed on cutoff for the optimal detection of disease. We use a lower threshold of 45% or greater to identify individuals with potential iron overload. Decreasing the cutoff presumably increases the sensitivity for the detection of C282Y homozygotes but at the expense of specificity and positive predictive value. Opponents of this lower threshold point to the inappropriate identification of individuals with relatively minor degrees of secondary iron overload.

More recent large-scale population studies have yielded variable results, but data comparisons are complicated by populations selected for study, differences in screening protocols, and definitions of iron overload. There has been no prospective, randomized study that blindly and indepen-
since the discovery of the HFE gene, genetic testing has greatly changed the approach for diagnosing HH. All patients in whom there is a strong suspicion for iron overload should have C282Y and H63D mutation analysis completed. Figure 2 is a modification of recent recommendations from the American Association for the Study of Liver Disease in the workup of individuals with suspected iron overload, using the methods discussed above.34

Patients with recently diagnosed HH, or in whom HH is highly suspected, should also have a thorough history and review of systems performed, focusing on disease manifestations of various organ systems, including gastrointestinal, cardiac, endocrine, and rheumatologic symptoms (Table 4).

SCREENING

Although HH meets many of the criteria for screening as set by the World Health Organization and the U.S. Preventive Services Task Force, the variability of disease presentation and progression makes population screening a topic of debate. Proponents cite the prevalence of the HFE mutation and simplicity of therapy. Opponents cite the cost of genetic testing and the scarcity of data on the significance ascribed to genetic susceptibility.49 Recent guidelines set forth by the American College of Physicians55 state that there is insufficient evidence at this time to recommend for or against population screening. There is, however, general agreement that first-degree relatives of patients with HH should be screened, as well as those with suspicious organ involvement. The implications for screening relatives of C282Y heterozygotes have not been explored, but presumably a lower threshold for performing serologic testing in these individuals may be warranted.

Table 3 Serum Iron Studies for the Biochemical Detection of C282Y Homozygotes

<table>
<thead>
<tr>
<th>Serum Marker</th>
<th>Screening Cutoff*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV†</th>
<th>NPV‡</th>
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<tr>
<td>Ferritin (body iron stores) [40–200 μg/L]</td>
<td>≥300 μg/L</td>
<td>50%</td>
<td>87%</td>
<td>2%</td>
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<td>Transferrin saturation (TS)§ [20–45%]</td>
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Biostatistics for serum iron markers vary widely from study to study based on populations selected and screening protocols, which are not agreed upon. Values listed above represent only one study and may markedly differ from others.

Normal values appear in []

*Optimal cutoffs have not been established
†Positive predictive value
‡Negative predictive value
§TS = (serum iron/total iron binding capacity) × 100

Research has shown possible utility for assessing liver fibrosis with improving magnetic resonance imaging techniques.52

Noninvasive testing, such as computed tomography or magnetic resonance imaging, is currently not widely recommended for diagnostic purposes, although emerging research has shown promising results in detecting and quantifying hepatic fibrosis or cirrhosis.48 Making determination of sensitivity and specificity for serum testing highly variable and comparison of data impractical. The serum iron studies reinforce the physician’s need to incorporate sound clinical judgment and thorough investigation of abnormal results.

Serum ferritin estimates total body iron stores. Ferritin values greater than 300 μg/L in men and greater than 200 μg/L in women provide further support for iron overload. However, ferritin can be falsely elevated as an acute phase reactant and does not become abnormal until iron loading has advanced to liver involvement.49,50 Bridging fibrosis or cirrhosis is rarely seen when levels are less than 1000 μg/L in the setting of normal transaminases.51 Causes other than HH should be considered in patients with high serum ferritin levels if transferrin saturation is not elevated.

Before the advent of mutation analysis, liver biopsy had been the definitive test to diagnose iron overload, document the presence of fibrosis or cirrhosis, and investigate other possible causes of liver disease.34 In addition, the hepatic iron index, the ratio of hepatic iron concentration to the age of the patient, can be calculated from a liver biopsy.49,50 Hepatic iron index values greater than 1.9 are highly supportive of HH. Biopsy is now generally reserved for settings in which genetic testing is unavailable or when serum iron studies are abnormal and genetic testing is normal.

Quantitative phlebotomy can also diagnose iron overload, but unlike a liver biopsy, it provides no information on the cellular location of iron or the extent of hepatic fibrosis. Quantitative phlebotomy confirms the presence of excess iron by determining the number of phlebotomies required to induce iron deficiency. Calculated storage greater than 5 g is considered abnormal.24

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Since the discovery of the HFE gene, genetic testing has greatly changed the approach for diagnosing HH. All
At-risk individuals who do not initially exhibit biochemical markers indicative of iron overload require follow-up for early detection of disease progression. A recent Danish study recommends that C282Y homozygotes identified during population screening, and not because of clinically overt hemochromatosis, at most need to be screened for manifestations of disease every 10 to 20 years, although more frequent follow-up with iron studies is easy and comes at a relatively low cost for preventing the potentially devastating sequelae of iron overload.

Children of C282Y homozygotes pose a dilemma, as problems of consent and the low prevalence of phenotypic disease in classic HH arise. Genetic testing of the unaffected parent has been suggested, and if that parent does not carry an HFE mutation, then no further testing of their children is required unless they have symptoms that could be attributable to HH. Screening in offspring may be delayed until late teenage years (although there is a subtype of HH that is of juvenile onset that may need to be considered).

Because of the lack of consensus, the best screening continues to be education. Education of health care providers and insurers about an “iron-avid” state increases vigilance and aids in early recognition and therapy.

**TREATMENT**

Ideally, treatment is initiated before the development of symptoms when serum ferritin levels exceed 200 µg/L in premenopausal women or 300 µg/L in men and postmenopausal women. Patients with manifestations of late disease should also receive treatment because some of the sequelae are reversible.

The easiest, cheapest, and most effective way to remove iron is by therapeutic phlebotomy, also known as venesection. Most patients with the phenotype consistent with HH, regardless of genotype, will benefit from therapeutic phlebotomy. Iron depletion can be initiated and monitored by general practitioners, but lack of experience with phlebotomy and nonstandardized guidelines commonly prompts specialty referral. The optimum regimen for venesection has not been determined, but patients should be depleted of iron as quickly as possible. Typically, this is done by removing 1 to 2 units of blood per week until the patient has mild

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**Figure 2** Modified from the American Association for the Study of Liver Disease diagnostic algorithm, 2001.  
*direct testing of first degree probands is an acceptable alternative  
†hepatic iron concentration  
‡hepatocellular carcinoma  
§Although H63D homozygosity is thought to lead to hemochromatosis in some individuals, this is more the exception, rather than the rule. Since the H63D mutation has a higher prevalence than the C282Y mutation, but accounts for a significantly smaller portion of those with clinically relevant hemochromatosis, abnormal iron studies with H63D homozygosity should prompt further evaluation into other disease processes first, with a diagnosis of hereditary hemochromatosis only after other avenues have been explored.
augment the allogeneic donor supply, thereby accomplishing the dual purpose of therapy and providing contribution to regional or national blood banks.\textsuperscript{50}

Chelation therapy with deferoxamine is almost never necessary because of the ease, cost, and efficacy of phlebotomy.\textsuperscript{53} However, a daily 2-gram subcutaneous dose infused over 8 hours has been shown to be effective.

**SUMMARY**

HH is a common genetic disorder but uncommon clinical entity, whose progression to multiorgan failure can be halted with simple and effective therapy. HH should be suspected in any individual with unexplained liver, heart, or endocrine dysfunction, and diagnostic testing to detect iron overload should be performed, bearing in mind the distinction between primary and secondary causes of abnormal results. Genetic testing should also be pursued in individuals in whom HH is highly suspected. Variable penetrance of the disease has been a point of contention for recommending universal screening. The identification of the genetic abnormality provides evidence of susceptibility to developing the phenotype but does not itself make the diagnosis. Because it is currently impossible to determine which individuals will develop serious clinical consequences, it is prudent for physicians to take a more conservative approach and implement therapy or frequent monitoring sooner, rather than later.

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