The American Journal of Medicine (2006) 119, 391-399

ELSEVIER

THE AMERICAN JOURNAL of MEDICINE®

REVIEW

Revisiting Hereditary Hemochromatosis: Current Concepts and Progress

Andrew W. Yen, MD, Tonya L. Fancher, MD, MPH, Christopher L. Bowlus, MD

University of California, Davis Medical Center, Department of Internal Medicine, Sacramento, Calif.

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.

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.[3] Although genetic and biochemical studies have demonstrated a high frequency of HH in various populations of Northern European descent,[1,2,4] more recent large-scale studies suggest relatively low rates of clinical expression and have failed to demonstrate a survival disadvantage.[5,6] 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.

Requests for reprints should be addressed to Andrew W. Yen, MD, University of California, Davis Medical Center, Department of Internal Medicine, 4150 V Street #3116, Sacramento, CA 95817.

E-mail address: andrew.yen@ucdmc.ucdavis.edu

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2005.10.041

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.[7]

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.[7]

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 Kuppfer 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.

CLINICAL SIGNIFICANCE

- Secondary causes of iron overload are more common than primary iron overload syndromes.
- In most cases of HH, possessing the C282Y/C282Y genetic abnormality is a necessary but not sufficient factor in causing disease.
- Hepcidin may play a significant role in the development of HH, as well as explain the variability of disease presentation and progression.
- Diagnostic strategies for HH are not standardized, making clinical suspicion and judgment crucial.

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]

Table 1 Secondary Causes of Iron Overload

Thalassemia
Sideroblastic anemia
Chronic liver disease:
Hepatitis C
Hepatitis B
Steatohepatitis
Alcohol induced liver disease
Previous portal caval shunting
Transfusion related

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

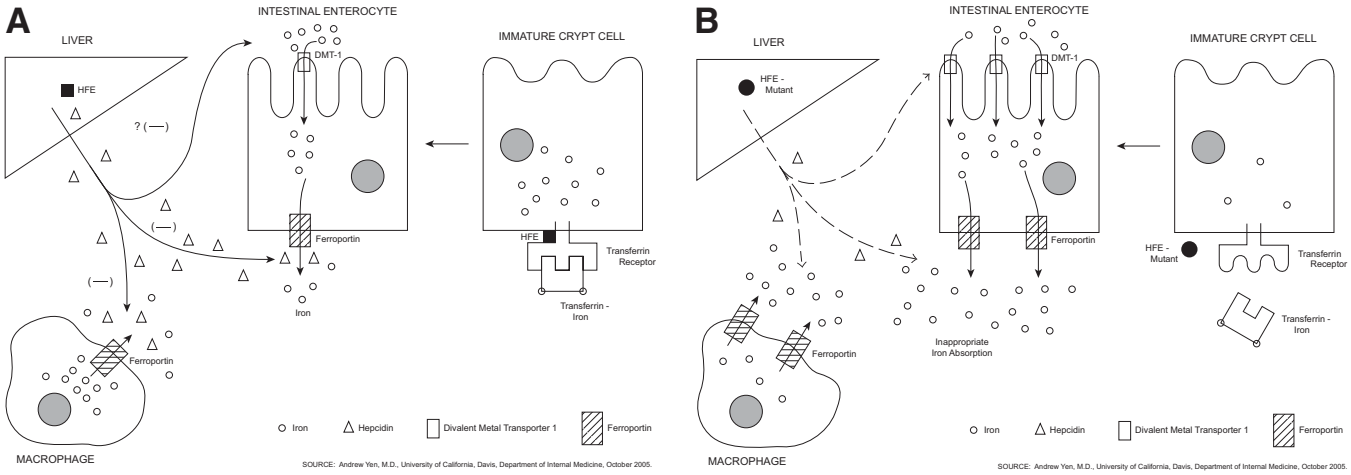

Figure 1 Iron regulation. Under normal conditions (A), immature crypt cells sense body iron requirements through the uptake of circulating transferrin-bound iron, which is mediated by the normal interaction between transferrin-receptor and the *HFE* gene product (*HFE*). Crypt cells are programmed by this information as they mature into absorptive enterocytes, modifying the activity of luminal divalent metal transporter 1 (DMT1) and basolateral ferroportin to absorb appropriate amounts of iron to compensate for daily losses. The proposed role of hepcidin, which is thought to increase (decrease) when iron levels are high (low), is to slow (hasten) the influx of iron from enterocytes and macrophages when plasma levels of iron are elevated (depressed). Hepcidin may also down-regulate the absorption of iron at the luminal surface of enterocytes. In classic HH (B), the mutant *HFE* gene product is unable to interact with transferrin-receptor, preventing circulating iron from being taken up by crypt cells, leading to relative intracellular iron deficiency. As they mature, enterocytes inappropriately express DMT1 and ferroportin to compensate for this presumed deficiency, resulting in inappropriate iron absorption and subsequently iron overload. *HFE* is also thought to play a role in regulating hepcidin as well, and a mutant gene product may disrupt the normal function and regulation of this protein, contributing to inappropriate release of iron from enterocytes and macrophages.

diagnosed with HH.[23] 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.[6] 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.

Table 2 Frequency of Signs and Symptoms in Overt HH from Population Studies Prior to Genetic and Biochemical Screening Tests[21,22]

Sign or Symptom	Frequency
Prior to clinical diagnosis	
Fatigue	46%
Arthralgia	44%
Loss of libido	26%
Skin bronzing	26%
At the time of clinical diagnosis	
Liver function abnormalities	75%
Weakness and lethargy	74%
Skin hyperpigmentation	70%
Diabetes mellitus	48%
Impotence in males	45%
Arthralgias	44%
Electocardiographic abnormalities	31%

Liver

More than 95% of symptomatic patients with HH have elevated liver enzymes, hepatomegaly, or cirrhosis.[24-27] 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.[25] Therapeutic phlebotomy remains beneficial by improving or reversing varices in 26% of patients with HH.[25] Survival in noncirrhotic, nondiabetic patients with HH is similar to the healthy control population, whereas those with cirrhosis have significantly increased mortality.[27]

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.[28,29] Overall, patients with HH have an estimated 5% annual risk for HCC after the development of cirrhosis.[30]

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.[28]

Cardiac

HH can lead to a mixed dilated-restrictive or dilated cardiomyopathy and conduction disturbances, such as atrial fibrillation or sick sinus syndrome.[31] 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.[32,33] Cardiac dysrhythmias and cardiomyopathies are the most common cause of sudden death in iron overload states.[34]

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.[35,36] 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.[37]

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.[38,39] 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.[40] 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.[41]

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.[41] 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.[21]

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.[5] 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.[42] Pigmentation is likely secondary to increased melanin or iron deposition around sweat glands.[24] 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 *HFE* gene mutation being studied include possible linkage to amyotrophic lateral sclerosis,[43] porphyria cutanea tarda,[44] and Alzheimer and Parkinson diseases.

DIAGNOSTIC TESTING

The discovery of the *HFE* 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.[26] Biochemical methods are simple, fast, and inexpensive (Table 3).[45] 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.[46] 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.[34] 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.[34]

More recent large-scale population studies have yielded variable results,[47] 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-

Table 3 Serum Iron Studies for the Biochemical Detection of C282Y Homozygotes[45]

Serum Marker	Screening Cutoff*	Sensitivity	Specificity	PPV†	NPV‡
Transferrin saturation (TS)§ [20–45%]	≥45%	94%	94%	6%	99.96%
Ferritin (body iron stores) [40–200 μg/L]	≥300μg/L	50%	87%	2%	99.69%

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

dently compared serum iron studies with the gold standard (liver biopsy or quantitative phlebotomy),[48] making determination of sensitivity and specificity for serum testing highly variable and comparison of data impractical. The lack of compelling data supporting optimal cutoffs for iron studies reinforces 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 diagnosis 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] 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]

Noninvasive testing, such as computed tomography or magnetic resonance imaging, is currently not widely recommended for diagnostic purposes, although emerging research has shown possible utility for assessing liver fibrosis with improving magnetic resonance imaging techniques.[52]

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).

A certain index of suspicion is necessary for the primary care provider to identify individuals with HH. Initial diagnostic studies can and should be undertaken by general practitioners, with referral to hepatologists and/or hematologists when diagnosis is made, or when HH is highly suspected and more invasive or definitive genetic testing is needed. Specific clinical manifestations may also necessitate referral to appropriate specialists if organ dysfunction is severe or refractory.

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 Physicians[53] 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.

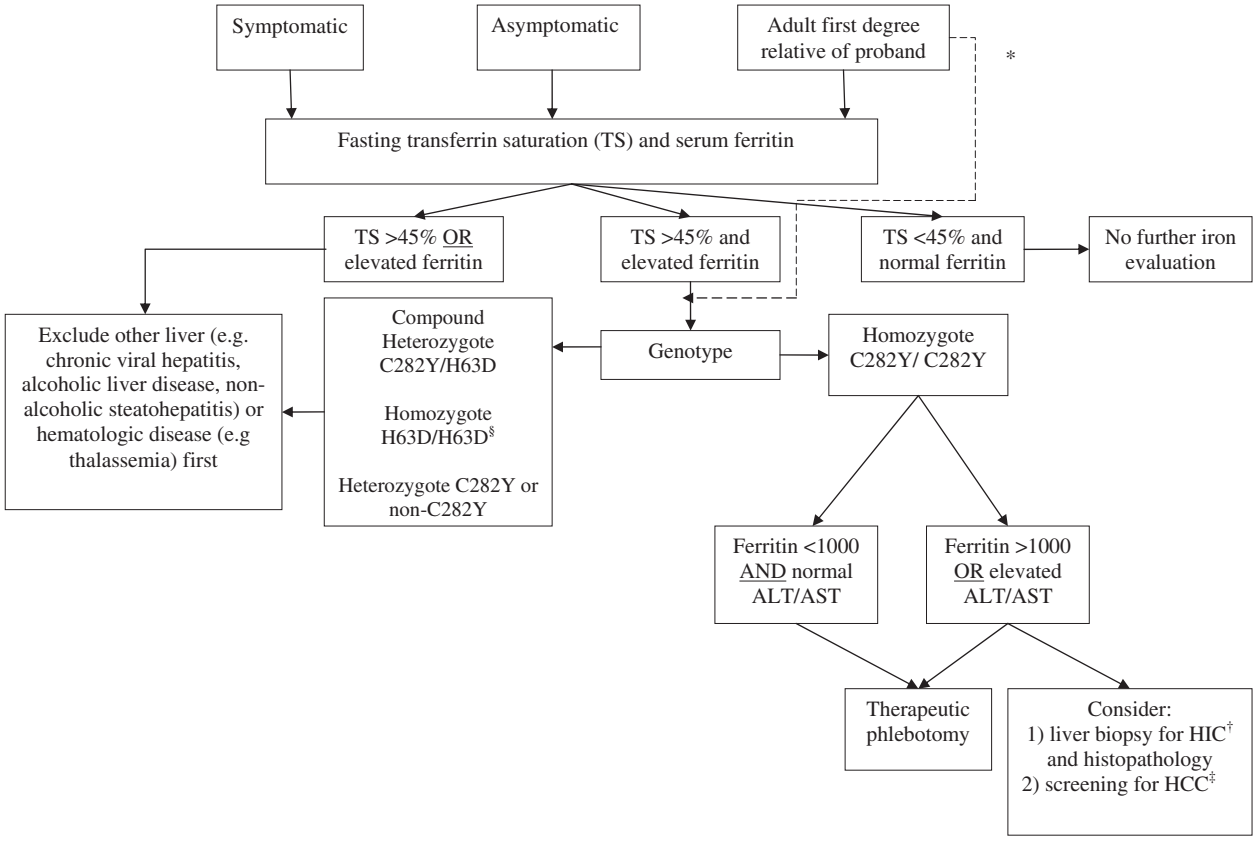

Figure 2 Modified from the American Association for the Study of Liver Disease diagnostic algorithm, 2001.[34]
*direct testing of first degree probands is an acceptable alternative
†hepatic iron concentration
‡hepatocellular carcinoma
§Although H63D homozygosity is thought to lead to hemochromatosis in some individuals, this is more the exception, rather than the rule. Since the H63D mutation has a higher prevalence than the C282Y mutation, [20] 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.

At-risk individuals who do not initially exhibit biochemical markers indicative of iron overload require follow-up for early detection of disease progression.[54] 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,[55] 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).[56]

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.[57]

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.[58] 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.[58] Typically, this is done by removing 1 to 2 units of blood per week until the patient has mild

Table 4 Additional Topics, Questions, and Tests to Pursue in Patients with Evidence of Genetic Iron Overload

Gastrointestinal
Discussion of hepatic symptoms at each office visit
Iron studies as dictated by treatment schedule if undergoing phlebotomy, otherwise annually if not yet requiring iron depletion therapy
LFTs* and AFP† every 6 months
Abdominal ultrasound once a year
Cardiac
Baseline EKG‡
Clinical assessment of cardiac function at each visit with further workup as guided by history
Echocardiogram, especially if abnormal EKG or clinical symptoms to suggest cardiac dysfunction
Endocrine
Discussion of endocrinopathies including manifestations of hypogonadism at each office visit
Fasting blood glucose and/or glucose tolerance test at regular screening intervals if diabetes not yet present
Thyroid function tests
Testosterone levels in males, FSH/LH§ levels in females, especially if symptoms to suggest hypogonadism
Bone density scan if evidence of hypogonadism
Rheumatologic
Assessment of arthralgias
Plain radiographs of painful joints and other rheumatological testing as dictated by clinical manifestations and exam
Other
Advise patients to
avoid iron supplementation
minimize alcohol consumption
avoid shellfish rich in facultative bacteria
consume a normal, balanced diet without excess red meat

*Liver function tests
†Alpha-fetoprotein
‡Electrocardiogram
§Follicle-stimulating hormone/luteinizing hormone

hypoferritinemia. Men may tolerate removal on the higher end of this schedule, whereas the elderly or those with other comorbidities may tolerate only a ½ unit removal per week. The majority of patients undergoing venesection achieve iron depletion, although adherence with therapy wanes over time.[59]

The end points for adequate treatment have not been strictly established. A 1998 National Institutes of Health consensus conference suggested weekly phlebotomy until serum ferritin concentration is less than 50 μg/L and transferrin saturation is less than 50%. Maintenance phlebotomies, on average 3 to 4 phlebotomies per year for men and 1 to 2 phlebotomies per year for women, should keep serum ferritin concentration between 25 and 50 μg/L.[34] Hemoglobin and hematocrit should be measured before each phlebotomy, ferritin levels should be measured every 10 to 12 phlebotomies, and transferrin saturation can be measured each year after initial iron depletion. Blood from these therapeutic draws has been shown to safely and significantly augment the allogeneic donor supply, thereby accomplishing the dual purpose of therapy and providing contribution to regional or national blood banks.[60]

Chelation therapy with deferoxamine is almost never necessary because of the ease, cost, and efficacy of phlebotomy.[33] However, a daily 2-g 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.

ACKNOWLEDGMENTS

The authors thank Dr. Mark C. Henderson for his critical review of the article and Mark Biegaj for his graphics expertise.

References

1. Distante S, Robson KJ, Graham-Campbell J, Arnaiz-Villena A, Brissot P, Worwood M. The origin and spread of the HFE-C282Y haemochromatosis mutation. *Hum Genet.* 2004;115(4):269-279.
2. Lucotte G, Dieterlen F: A European allele map of the C282Y mutation of hemochromatosis: Celtic versus Viking origin of the mutation? *Blood Cells Mol Dis.* 2003;31(2):262-267.
3. Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet.* 1996;13(4):399-408.
4. Nielsen P, Carpinteiro S, Fischer R, Cabeda JM, Porto G, Gabbe EE. Prevalence of the C282Y and H63D mutations in the HFE gene in patients with hereditary haemochromatosis and in control subjects from Northern Germany. *Br J Haematol.* 1998;103(3):842-845.
5. Waalen J, Felitti V, Gelbart T, Ho NJ, Beutler E. Penetrance of hemochromatosis. *Blood Cells Mol Dis.* 2002;29(3):418-432.
6. Waalen J, Nordestgaard BG, Beutler E. The penetrance of hereditary hemochromatosis. *Best Pract Res Clin Haematol.* 2005;18(2):203-220.
7. Andrews NC. Disorders of iron metabolism. *N Engl J Med.* 1999; 341(26):1986-1995.
8. Pietrangelo A. Hereditary hemochromatosis—a new look at an old disease. *N Engl J Med.* 2004;350(23):2383-2397.
9. Stuart KA, Anderson GJ, Frazer DM, et al. Duodenal expression of iron transport molecules in untreated haemochromatosis subjects. *Gut.* 2003;52(7):953-959.

10. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood.* 2003;102(3):783-788.
11. Nicolas G, Viatte L, Lou DQ, et al. Constitutive hepcidin expression prevents iron overload in a mouse model of hemochromatosis. *Nat Genet.* 2003;34(1):97-101.
12. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroprotein and inducing its internalization. *Science.* 2004;306(5704):2090-2093.
13. Beutler E, Gelbart T, West C, et al. Mutation analysis in hereditary hemochromatosis. *Blood Cells Mol Dis.* 1996;22(2):187-194; discussion 194a-194b.
14. Carella M, D'Ambrosio L, Totaro A, et al. Mutation analysis of the HLA-H gene in Italian hemochromatosis patients. *Am J Hum Genet.* 1997;60(4):828-832.
15. Jazwinska EC, Cullen LM, Busfield F, et al. Haemochromatosis and HLA-H. *Nat Genet.* 1996;14(3):249-251.
16. Jouanolle AM, Gandon G, Jezequel P, et al. Haemochromatosis and HLA-H. *Nat Genet.* 1996;14(3):251-252.
17. Medicine M-NIfG: Hemochromatosis: Online Mendelian Inheritance in Man (OMIM). 2000. Available at www.nslij-genetics.org/omim.html.
18. Moalem S, Weinberg ED, Percy ME. Hemochromatosis and the enigma of misplaced iron: implications for infectious disease and survival. *Biometals.* 2004;17(2):135-139.
19. Steinberg KK, Cogswell ME, Chang JC, et al. Prevalence of C282Y and H63D mutations in the hemochromatosis (HFE) gene in the United States. *JAMA.* 2001;285(17):2216-2222.
20. Adams PC, Reboussin DM, Barton JC, et al. Hemochromatosis and iron-overload screening in a racially diverse population. *N Engl J Med.* 2005;352(17):1769-1778.
21. McDonnell SM, Preston BL, Jewell SA, et al. A survey of 2,851 patients with hemochromatosis: symptoms and response to treatment. *Am J Med.* 1999;106(6):619-624.
22. Niederau C, Strohmeyer G, Stremmel W. Epidemiology, clinical spectrum and prognosis of hemochromatosis. *Adv Exp Med Biol.* 1994;356:293-302.
23. Adams PC, Kertesz AE, Valberg LS. Clinical presentation of hemochromatosis: a changing scene. *Am J Med.* 1991;90(4):445-449.
24. Adams PC, Deugnier Y, Moirand R, Brissot P. The relationship between iron overload, clinical symptoms, and age in 410 patients with genetic hemochromatosis. *Hepatology.* 1997;25(1):162-166.
25. Fracanzani AL, Fargion S, Romano R, et al. Portal hypertension and iron depletion in patients with genetic hemochromatosis. *Hepatology.* 1995;22(4 Pt 1):1127-1131.
26. Franchini M, Veneri D. Recent advances in hereditary hemochromatosis. *Ann Hematol.* 2005;84(6):347-352.
27. Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology.* 1996;110(4):1107-1119.
28. Crawford DH, Fletcher LM, Hubscher SG, et al. Patient and graft survival after liver transplantation for hereditary hemochromatosis: implications for pathogenesis. *Hepatology.* 2004;39(6):1655-1662.
29. Elmberg M, Hultcrantz R, Ekbom A, et al. Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. *Gastroenterology.* 2003;125(6):1733-1741.
30. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol.* 2001;35(3):421-430.
31. Rivers J, Garrahy P, Robinson W, Murphy A. Reversible cardiac dysfunction in hemochromatosis. *Am Heart J.* 1987;113(1):216-217.
32. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 31-1994. A 25-year-old man with the recent onset of diabetes mellitus and congestive heart failure. *N Engl J Med.* 1994;331(7):460–446.
33. Nielsen P, Fischer R, Buggisch P, Janka-Schaub G. Effective treatment of hereditary haemochromatosis with desferrioxamine in selected cases. *Br J Haematol.* 2003;123(5):952-953.
34. Tavill AS. Diagnosis and management of hemochromatosis. *Hepatology.* 2001;33(5):1321-1328.
35. Nelson RL, Baldus WP, Rubenstein AH, Go VL, Service FJ. Pancreatic alpha-cell function in diabetic hemochromatotic subjects. *J Clin Endocrinol Metab.* 1979;49(3):412-416.
36. Hramiak IM, Finegood DT, Adams PC. Factors affecting glucose tolerance in hereditary hemochromatosis. *Clin Invest Med.* 1997;20(2):110-118.
37. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA.* 2004;291(6):711-717.
38. Iyer R, Duckworth WC, Solomon SS. Hypogonadism in idiopathic hemochromatosis. Endocrine studies. *Arch Intern Med.* 1981;141(4):517-518.
39. Kelly TM, Edwards CQ, Meikle AW, Kushner JP. Hypogonadism in hemochromatosis: reversal with iron depletion. *Ann Intern Med.* 1984;101(5):629-632.
40. Edwards CQ, Kelly TM, Ellwein G, Kushner JP. Thyroid disease in hemochromatosis. Increased incidence in homozygous men. *Arch Intern Med.* 1983;143(10):1890-1893.
41. Jordan JM. Arthritis in hemochromatosis or iron storage disease. *Curr Opin Rheumatol.* 2004;16(1):62-66.
42. Gochee PA, Powell LW. What's new in hemochromatosis. *Curr Opin Hematol.* 2001;8(2):98-104.
43. Wang XS, Lee S, Simmons Z, et al. Increased incidence of the Hfe mutation in amyotrophic lateral sclerosis and related cellular consequences. *J Neurol Sci.* 2004;227(1):27-33.
44. Mehrany K, Drage LA, Brandhagen DJ, Pittelkow MR. Association of porphyria cutanea tarda with hereditary hemochromatosis. *J Am Acad Dermatol.* 2004;51(2):205-211.
45. Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW. A population-based study of the clinical expression of the hemochromatosis gene. *N Engl J Med.* 1999;341(10):718-724.
46. Edwards CQ, Griffen LM, Goldgar D, Drummond C, Skolnick MH, Kushner JP. Prevalence of hemochromatosis among 11,065 presumably healthy blood donors. *N Engl J Med.* 1988;318(21):1355-1362.
47. Beutler E, Felitti V, Gelbart T, Ho N. The effect of HFE genotypes on measurements of iron overload in patients attending a health appraisal clinic. *Ann Intern Med.* 2000;133(5):329-337.
48. Schmitt B, Golub RM, Green R. Screening primary care patients for hereditary hemochromatosis with transferrin saturation and serum ferritin level: systematic review for the American College of Physicians. *Ann Intern Med.* 2005;143(7):522-536.
49. Dooley JS. Diagnosis and management of genetic haemochromatosis. *Best Pract Res Clin Haematol.* 2002;15(2):277-293.
50. Edwards CQ, Kushner JP. Screening for hemochromatosis. *N Engl J Med.* 1993;328(22):1616-1620.
51. Morrison ED, Brandhagen DJ, Phatak PD, et al. Serum ferritin level predicts advanced hepatic fibrosis among U.S. patients with phenotypic hemochromatosis. *Ann Intern Med.* 2003;138(8):627-633.
52. Olynyk JK, St Pierre TG, Britton RS, Brunt EM, Bacon BR. Duration of hepatic iron exposure increases the risk of significant fibrosis in hereditary hemochromatosis: a new role for magnetic resonance imaging. *Am J Gastroenterol.* 2005;100(4):837-841.
53. Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Screening for hereditary hemochromatosis: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2005;143(7):517-521.
54. Olynyk JK, Hagan SE, Cullen DJ, Beilby J, Whittall DE. Evolution of untreated hereditary hemochromatosis in the Busselton population: a 17-year study. *Mayo Clin Proc.* 2004;79(3):309-313.
55. Andersen RV, Tybjaerg-Hansen A, Appleyard M, Birgens H, Nordestgaard BG. Hemochromatosis mutations in the general population: iron overload progression rate. *Blood.* 2004;103(8):2914-2919.
56. Delatycki MB, Powell LW, Allen KJ. Hereditary hemochromatosis genetic testing of at-risk children: what is the appropriate age? *Genet Test.* 2004;8(2):98-103.

57. Hover AR, McDonnell SM, Burke W. Changing the clinical management of hereditary hemochromatosis: translating screening and early case detection strategies into clinical practice. *Arch Intern Med.* 2004;164(9):957-961.
58. Barton JC, McDonnell SM, Adams PC, et al. Management of hemochromatosis. Hemochromatosis Management Working Group. *Ann Intern Med.* 1998;129(11):932-939.
59. Hicken BL, Tucker DC, Barton JC. Patient compliance with phlebotomy therapy for iron overload associated with hemochromatosis. *Am J Gastroenterol.* 2003;98(9):2072-2077.
60. Leitman SF, Browning JN, Yau YY, et al. Hemochromatosis subjects as allogeneic blood donors: a prospective study. *Transfusion.* 2003; 43(11):1538-1544.