

Feature

What's New in Hereditary Hemochromatosis

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What's New in Hereditary Hemochromatosis

Introduction

The past few years have witnessed a number of developments in the field of hereditary hemochromatosis (HH) that have advanced our understanding of the natural history and pathophysiology of HH and have led to important changes in clinical practice. Several of these will be summarized in this brief review. Topics addressed will include: 1) diagnostic testing; 2) the role of liver biopsy; 3) novel genes and proteins; and 4) disease expression. This review will also provide details of the Hemochromatosis Clinic, a new clinic at Mayo for patients with suspected HH or iron overload.

Overview

Hereditary hemochromatosis is an autosomal recessive disorder characterized by increased intestinal absorption of iron with deposition in multiple organs. HH is the most common inherited, single-gene disorder in Caucasians with a prevalence of 5 per 1000 and a carrier frequency of 1 in 10. The initial description of patients with HH was "bronze diabetes" in association with cirrhosis. Currently, most persons diagnosed with HH are asymptomatic. Of those with symptoms, fatigue, arthritis, and impotence are most common. The diagnosis of HH is based on a combination of clinical, laboratory, and pathological criteria. The best initial test for HH is a fasting, morning transferrin saturation. If the transferrin saturation is >45%, it should be repeated along with a serum ferritin. If the repeat transferrin saturation and the ferritin are both elevated, genetic testing is indicated.

The gene for HH was discovered in 1996 and named *HFE*. Two point mutations were initially described and are referred to as C282Y and H63D. Approximately 85% of persons with HH have 2 copies of C282Y (homozygous). *HFE* gene testing is helpful in confirming a diagnosis of HH, screening adult family

members, and resolving ambiguous cases of iron overload. Treatment is by phlebotomy. Initially a pint of blood is removed once per week. The goal is to achieve a serum ferritin of <50 µg/L. Once depleted of excess iron stores, maintenance phlebotomy approximately every 3 months is usually required. If HH is diagnosed and treated before the development of cirrhosis or diabetes mellitus, survival is similar to age- and sex-matched controls without HH.

Diagnostic Testing

Serum Iron Studies

A diagnosis of HH is based on a combination of clinical, laboratory, and pathological criteria including an elevated serum transferrin saturation ($100 \times [\text{serum iron concentration} \div \text{total iron binding capacity}]$) and an elevated serum ferritin concentration. There is diurnal variation in serum iron values, and measurements may be affected by the ingestion of food; therefore, an elevated transferrin saturation should be repeated as a fasting early morning determination. A transferrin saturation above 45% is the earliest phenotypic abnormality in HH. Transferrin saturation testing is available from Mayo Medical Laboratories (MML) as [#9412 Iron and Total Iron-Binding Capacity, Serum](#).

Although serum transferrin saturation is the best initial screening test, the results may be normal early in the course of HH. In addition, not all cases of iron overload are due to HH. There are other hereditary and nonhereditary causes (see Table). The serum ferritin concentration and transferrin saturation may be elevated in 30% to 50% of patients with viral hepatitis, nonalcoholic fatty liver disease, alcoholic liver disease, and in end-stage liver disease of various etiologies. Serum ferritin ([#8689 Ferritin, Serum](#)) usually provides a reasonable estimate of total body iron stores,

but it is also an acute phase reactant and is elevated in a variety of infectious and inflammatory conditions in the absence of iron overload. For this reason, it should not be used as the initial screening test to detect HH.

Table. Disorders Associated with Iron Overload

<p>Hereditary Hemochromatosis</p> <p><i>HFE</i>-related</p> <ul style="list-style-type: none"> • C282Y homozygous • C282Y and H63D heterozygous (compound heterozygote) • Other <p>Non-<i>HFE</i>-related</p> <ul style="list-style-type: none"> • HH Type 2 (juvenile hemochromatosis) • HH Type 3 (TfR2 mutation) • HH Type 4 (ferroportin mutation) <p>Secondary Iron Overload</p> <p>Chronic anemias</p> <ul style="list-style-type: none"> • Thalassemia major • Sideroblastic anemia • Congenital dyserythropoietic anemia • Congenital atransferrinemia <p>Exogenous iron overload</p> <ul style="list-style-type: none"> • Chronic iron supplementation (in the absence of blood loss) • Transfusion • Iron dextran • Oral supplements (rare) <p>Chronic Liver Disease</p> <ul style="list-style-type: none"> • Cirrhosis • Viral hepatitis • Alcoholic liver disease • Nonalcoholic fatty liver disease • Porphyria cutanea tarda • Portacaval shunt <p>Miscellaneous</p> <ul style="list-style-type: none"> • Iron overload in sub-Saharan Africa • African American iron overload • Neonatal iron overload • Aceruloplasminemia • Congenital atransferrinemia

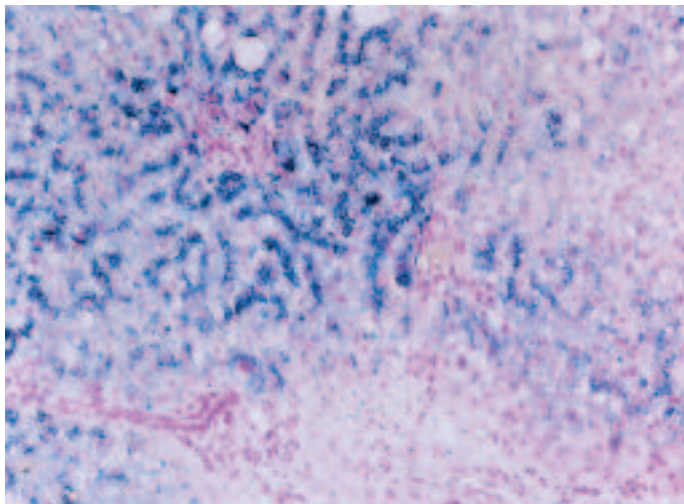
Hepatic Iron

Prior to the availability of the *HFE* gene test, a liver biopsy was often necessary to confirm a diagnosis of HH. Hepatic iron may be assessed with an iron stain such as Perls' Prussian blue. In HH, iron initially accumulates in periportal hepatocytes but is eventually distributed throughout the liver. Conversely, in secondary iron overload, iron is often present predominantly in Kupffer cells, which may help distinguish it from HH (see photos, page 3). A histologic distinction between HH and secondary iron overload is often not possible once severe iron overload has developed. Quantitation of the hepatic iron concentration can be determined by ordering #8350 [Iron, Liver Tissue](#), which utilizes inductively coupled plasma-mass spectrometry (ICP-MS).*

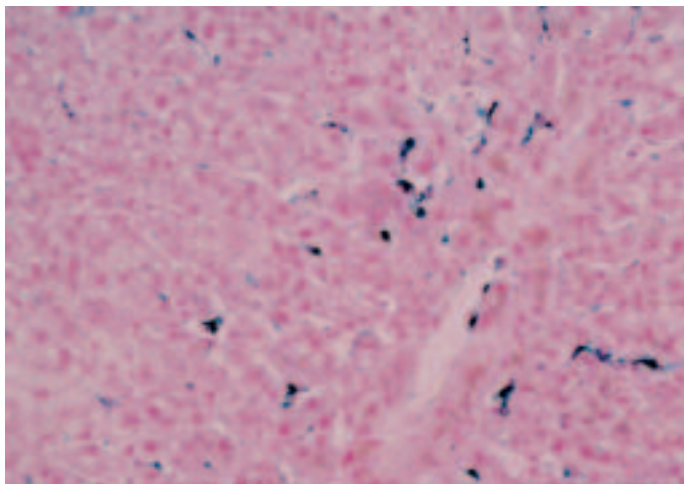
In HH there is a progressive, age-related increase in hepatic iron stores. This has led to the development of the hepatic iron index (HII), which is the hepatic iron concentration in micromoles/gram dry weight liver divided by the patient's age in years.* The HII originally was intended to distinguish HH homozygotes from heterozygotes and those with alcoholic liver disease. In the initial study, all HH homozygotes had an HII >1.9, whereas all of the HH heterozygotes or patients with alcoholic liver disease had a HII <1.9. For many years, a HII >1.9 was considered diagnostic of HH, whereas HII values <1.9 were considered inconsistent with the diagnosis. More recent studies have demonstrated that a HII >1.9 is not diagnostic of HH because patients with severe iron overload of any cause may have a HII above that level. In addition, because HH is increasingly diagnosed at an earlier stage, many patients with HH will have a HII <1.9.

***HFE* Gene Test**

The *HFE* gene is located on the short arm of chromosome 6 and encodes a 343-amino acid protein, which resembles a HLA Class I molecule. Two point mutations designated C282Y and H63D were initially described. When there is a clinical suspicion of HH, approximately 85% of these patients are found to be homozygous for the C282Y mutation. In the US Caucasian population, about 1 in 200 persons is homozygous for the C282Y mutation, while 1 in 10 are heterozygous carriers. The greatest risk for iron overload exists in those who are homozygous for the C282Y mutation. Approximately 3% to 7% of the US Caucasian population are C282Y/H63D compound heterozygotes and 3% to 5% are H63D homozygotes.



Hepatocellular iron deposition in a periportal distribution in a patient with hemochromatosis.



Iron deposition in Kupffer cells in a patient with transfusional iron overload.

Only a small percentage of all C282Y/H63D compound heterozygotes or H63D homozygotes will develop iron overload and it is usually mild. One copy of the H63D mutation is present in 20% of the normal population and by itself does not increase the risk for developing iron overload.

Since discovery of the C282Y and H63D mutations, approximately 18 additional *HFE* gene mutations have been reported. In general, most of these additional mutations are uncommon and rarely of clinical significance. S65C is a mutation that occurs in 1% to 2% of the normal population. There are rare reports of iron overload occurring in patients with 1 copy of the S65C mutation, usually in association with C282Y. In most series, 5% to 10% of patients with clinically significant iron overload do not have *HFE* gene mutations. Therefore, a negative *HFE* gene test does not exclude iron overload. The Mayo Molecular Genetics Laboratory tests for the C282Y, H63D, and S65C mutations: [#81508 Hemochromatosis *HFE* Gene Analysis, Blood](#). The results for S65C are only reported for patients who also have a C282Y mutation.

The *HFE* gene test is very useful for screening adult blood relatives of a C282Y homozygous proband. Screening blood relatives is crucial because 25% of siblings and 5% of children of a proband will have HH. *HFE* gene testing should replace the more expensive HLA typing previously used to screen siblings. In addition, *HFE* gene testing often is useful in helping to resolve ambiguous cases, such as iron overload associated with hepatitis C infections, alcoholic liver disease, or other causes of end-stage liver disease. Prior to obtaining the *HFE* gene test, an individual should be counseled about the risks, benefits, and alternatives of genetic testing by a qualified professional. There is concern about the possibility of insurance, employment, or other discrimination based on *HFE* test results. For this reason, *HFE* gene testing usually is not recommended for anyone younger than 18 years old.

The Role of Liver Biopsy

HFE gene testing may eliminate the need for a liver biopsy in many cases. Traditionally, a liver biopsy was performed in patients with iron overload to confirm the diagnosis of HH and to exclude cirrhosis. Patients who are homozygous for the C282Y mutation with elevated serum iron studies do not need a liver biopsy to confirm the diagnosis of HH. Liver biopsy still remains the “gold standard” for assessing the degree of fibrosis (scarring) or cirrhosis. Definitively excluding cirrhosis is important because of the markedly increased risk of developing hepatocellular carcinoma.

*For the calculation of HII, if the hepatic iron concentration is reported in units of $\mu\text{g/gm}$ dry weight, the results must first be converted to $\mu\text{mol/gm}$ dry weight (by dividing by 56) before dividing by age.

There may be a subset of HH patients who have very high or low probability of cirrhosis such that a liver biopsy would be unnecessary. Several recent studies have confirmed that cirrhosis is extremely uncommon in C282Y homozygotes with serum ferritin levels lower than 1000 µg/L and normal aspartate aminotransferase (#8360 Aspartate Aminotransferase [AST], Serum) values. A serum ferritin of <1000 µg/L seems to be the best predictor of the absence of cirrhosis in C282Y homozygotes. However, the positive predictive value of a serum ferritin >1000 µg/L is poor, since only about 50% of those with serum ferritin values >1000 µg/L have cirrhosis. A recent study examined noninvasive predictors of cirrhosis in C282Y homozygotes and found that cirrhosis was present in approximately 80% of subjects who had a serum ferritin >1000 µg/L, platelet count less than $200 \times 10^9/L$ and an elevated AST.

The figure provides a screening algorithm for HH (page 6).

Novel Genes and Proteins

A number of proteins of iron metabolism have recently been discovered that have furthered our understanding of the pathophysiology of HH. Of all the proteins, the one that has generated the most interest is hepcidin. Hepcidin is a small polypeptide produced in the liver. Hepcidin inhibits iron absorption in the small intestine and prevents release of iron from macrophages. Hepcidin may function as an iron stores regulator. Levels of hepcidin are markedly elevated in infectious and inflammatory conditions. Hepcidin may be responsible for the development of anemia of inflammation (anemia of chronic disease). Hepcidin levels are inappropriately low in HH and hepcidin knockout mice develop iron overload in a pattern similar to human HH. Preliminary studies have found that mutations in hepcidin may influence disease expression in HH. This has led to rethinking of the pathophysiology of iron metabolism. Previous models emphasized the role of enterocyte crypt cells in sensing body iron stores. It may be that the liver is the primary site that senses the body iron stores and responds by increasing or decreasing the production of hepcidin. Future studies of hepcidin and other proteins of iron metabolism will undoubtedly further our understanding of the pathophysiology of iron metabolism and HH.

Disease Expression

There is currently disagreement among experts regarding the utility of screening for HH in the general population. Despite the fact that HH fulfills many of the criteria of a condition appropriate for population screening, many public health experts are not advocates. They cite a lack of information about burden of disease and disease expression in those with *HFE* mutations as reasons why they do not endorse population screening for HH. Unfortunately, the natural history of HH in an asymptomatic patient identified by population screening may never be known since many would consider it unethical to withhold treatment once a patient develops iron overload.

A recent study screened for hemochromatosis in over 41,000 patients attending a health appraisal clinic. All subjects underwent a history and physical and completed a detailed symptom questionnaire. They also had serum iron studies and the *HFE* gene test performed. Although the majority of C282Y homozygotes had an elevated serum transferrin saturation and ferritin, symptoms did not differ among the 152 C282Y homozygotes compared to the non-C282Y homozygotes. The authors concluded that less than 1% of C282Y homozygotes develop clinical evidence of hemochromatosis.

There are several potential problems with this study. The study population may have been biased toward a less symptomatic group since patients attending a “health appraisal clinic” might be expected to be healthier. The authors also excluded many patients who had already been diagnosed with HH, thereby potentially selecting out a less symptomatic group. Finally, liver biopsies were not performed. Plasma collagen IV, a surrogate marker of fibrosis, was measured. Of interest, median levels of plasma collagen IV were statistically higher in the group with HH compared to those without HH. Although it is probably true that the majority of C282Y homozygotes will not develop serious problems with iron overload, the true prevalence of clinically relevant disease manifestations in HH remains unknown. It is, therefore, premature to conclude that the prevalence of important clinical manifestations in HH is less than 1%. With the information currently available, it seems reasonable to screen for iron overload in persons with a family history of HH, chronic liver disease, or symptoms or signs suggestive of HH.

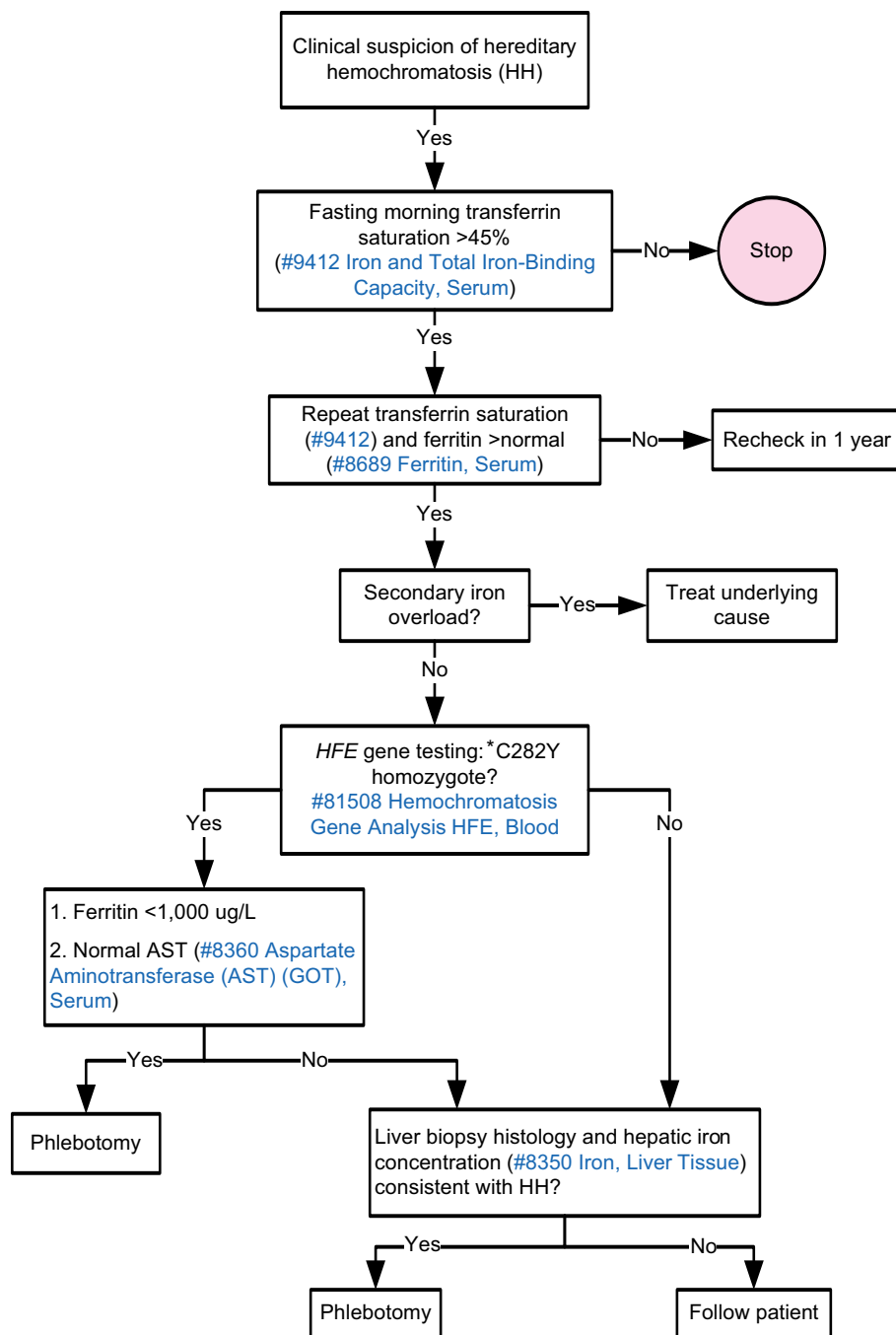
The Hemochromatosis Clinic

A multidisciplinary Hemochromatosis Clinic has recently been developed at Mayo Clinic. Consultants in Gastroenterology/Hepatology and Hematology with an interest and expertise in HH and iron overload staff the clinic. Patients referred to the Hemochromatosis Clinic are seen within 24-48 hours of the consult request. Referring physicians can request consults to the Hemochromatosis Clinic by calling (507)538-4183.

If you have questions about the appropriate laboratory tests to order for your patient, please call Mayo Laboratory Inquiry at 800-533-1710.

Recommended Reading

1. Tavill AS: Diagnosis and Management of Hemochromatosis. *Hepatology* 2001;33:1321-28
2. Beutler E, Felitti VJ, Koziol JA, et al: Penetrance of the 845GÆA (C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet* 2002;359:211-18
3. Morrison ED, Brandhagen DJ, Pradyumna PD, et al: Serum ferritin level predicts advanced hepatic fibrosis among U. S. patients with phenotypic hemochromatosis. *Ann Intern Med* 2003;138:627-633
4. Beaton M, Guyader D, Deugnier Y, et al: Noninvasive prediction of cirrhosis in C282Y-linked hemochromatosis. *Hepatology* 2002;36:673-78
5. Ganz T: Heparin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood* 2003;102:783-88
6. Pietrangelo A: Hereditary Hemochromatosis-A New Look at an Old Disease. *NEJM* 2004;350:2383-2397



* Prior to genetic testing, consider referral to a specialist.

Figure. Screening Algorithm for Hereditary Hemochromatosis in Adults

2005 Education Calendar

Interactive Satellite Programs . . .

Obesity Management

April 12, 2005

Presenter: *Maria L. Collazo-Clavell, MD*

Moderator: *Robert M. Kisabeth, MD*

Drug Cautions in the Elderly

May 10, 2005

Presenter: *David G. Bell, MD*

Moderator: *Robert M. Kisabeth, MD*

Congestive Heart Failure

June 1, 2005

Presenter: *Allan S. Jaffe, MD*

Moderator: *Robert M. Kisabeth, MD*

Laboratory and Clinical Collaboration in the Diagnosis and Management of Thyroid Disease

June 14, 2005

Presenter: *Bryan McIver, MBChB, PhD*

Moderator: *Robert M. Kisabeth, MD*

Alzheimer's: An Update on Treatment and Research

September 6, 2005

Presenter: *Ronald C. Petersen, MD, PhD*

Moderator: *Robert M. Kisabeth, MD*

Genomics & Proteomics – An Update

November 1, 2005

Presenter: *David B. Schowalter, MD, PhD*

Moderator: *Robert M. Kisabeth, MD*

What's New in Hereditary Hemochromatosis

December 13, 2005

Presenter: *David J. Brandhagen, MD*

Moderator: *Robert M. Kisabeth, MD*

Upcoming Education Conferences . . .

Quality Phlebotomy: Back to the Basics

April 20, 2005

Location to be determined • Chicago, Illinois

12th International Surgical Pathology Symposium

May 3-6, 2005

Sofitel Victoria Hotel • Warsaw, Poland

Integration Through Community Laboratory Insourcing

May 18-20, 2005

Sofitel Philadelphia • Philadelphia, Pennsylvania

4th Biennial Symposium – Pulmonary Pathology Society

June 15-17, 2005

L'Imperial Palace • Annecy, France

Coagulation Testing Quality: Lessons and Issues from Quality Assessment, Standardization and Improvement Programs & Studies

June 15-17, 2005

The Kahler Grand Hotel • Rochester, Minnesota

How the Practice of Medicine Informs Technology

July 23, 2005

Rosen Centre Hotel • Orlando, Florida

Practical Surgical Pathology

September 29-October 1, 2005

Mayo Clinic, Siebens Building • Rochester, Minnesota

Quality Phlebotomy: Back to the Basics

September 27, 2005

Airport Marriott • Los Angeles, California

Practical Spirometry

November 17-18, 2005

Mayo Clinic, Siebens Building • Rochester, Minnesota

Real-Time PCR for the Clinical Laboratory

November 17-18, 2005

Mayo Clinic, Siebens Building • Rochester, Minnesota

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