

Iron Overload (Hereditary Hemochromatosis)

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Key Points

- Elevated transferrin saturation (TS), a serum iron measure, occurs in more than 2% of the population. A small proportion of these people will experience progressive iron accumulation and iron overload in body tissues.
- Most people who develop iron overload have *HFE*-related hereditary hemochromatosis (HHC), an autosomal recessive genetic condition caused by mutations in the *HFE* gene.
- Iron overload can cause serious complications such as cirrhosis, diabetes mellitus, cardiomyopathy, and liver cancer.
- Complications of iron overload can be prevented with phlebotomy (periodic removal of 1-2 units of blood), yet many individuals with clinically significant iron overload are not diagnosed until organ damage has occurred.
- Early symptoms of iron overload are typically nonspecific, and include common symptoms such as fatigue and joint pain.
- Biological relatives of a person with *HFE*-related HHC are at increased risk of having HHC themselves. Risk is highest for siblings of an affected person.

Learning Objectives

Participants will be able to:

- Understand the use of serum iron measures in diagnosis of *HFE*-related HHC;
- Understand the implications of *HFE* mutations in diagnosis of HHC;
- Understand treatment options for *HFE*-related HHC.

Family History Issues

A family history of iron overload or hereditary hemochromatosis (HHC) confers an increased risk for the condition. Siblings are at highest risk.

Most people with clinically significant HHC have two copies of the *HFE*

mutation C282Y; conversely, population-based studies indicate that only a minority of people with this genotype (C282Y/C282Y) develop clinical disease. The *HFE* mutation H63D also contributes to risk for *HFE*-related HHC, but to a lesser degree than C282Y.

The carrier rate for the C282Y mutation is approximately 10% among people of northern European descent; it is lower in other populations. Siblings of an affected person have a 25% chance of inheriting the genotype associated with HHC. The risk to offspring of an affected individual is 5% or lower, depending on ethnicity.

Red Flags

Several nonspecific symptoms and clinical problems can be seen in early iron overload, including fatigue, joint pain, elevated liver function tests, cirrhosis, arrhythmias, cardiomyopathy, diabetes mellitus, and hypogonadism with impotence or amenorrhea. All of these symptoms and clinical problems have other more common causes. However, iron overload secondary to HHC should be a consideration if other treatable causes of these symptoms have been ruled out.

Case 25. Fatigue in a 47-Year-Old Man

A 47-year-old man presents with fatigue. He also complains of persistent aching joints. He has had the symptoms for several years. He has no other health complaints, although he notes some nonspecific stomach discomfort on review of systems. He also reports a past history of excess alcohol use. He has seen two other doctors for his joint pain and fatigue. He has been advised to exercise regularly and take non-steroidal anti-inflammatory medications for his joint symptoms, but these measures have not provided symptomatic relief. He has not had any chest pain or shortness of breath. He denies symptoms of depression such as anhedonia, low self-esteem, or changes in appetite or sleep patterns.

Physical examination findings

- **HEENT:** Sclerae anicteric; no facial edema noted; normal thyroid

gland; no adenopathy

- **Cardiac:** Normal heart sounds; normal pulses; no edema
- **Lung:** Clear to percussion and auscultation
- **Abdomen:** Mild hepatomegaly
- **Rectal:** Normal, with insufficient stool for guaiac testing
- **Musculoskeletal:** No inflammatory joint changes or joint tenderness
- **Mental status:** Normal affect; no psychomotor retardation

Lab workup. Suspecting anemia, possibly due to GI bleeding from use of non-steroidal anti-inflammatory medications, his new physician orders stool cards and a hematocrit. Because of the mild hepatomegaly, he also orders liver function tests. In addition, he orders a TSH to rule out hypothyroidism. Stool cards are negative, TSH is 2.0, hematocrit is 45, and AST and ALT are mildly elevated.

Clinical Care Issues

The patient has a nonspecific complaint of fatigue and moderately elevated liver function tests. Potential causes that might be considered for workup are listed in [Table 1](#). In this case, laboratory results suggest that the patient does not have hypothyroidism or anemia as a cause of his fatigue. Additional history may be helpful at this point, including a more detailed history concerning mood and vegetative signs of depression, more information about the character and duration of the fatigue, and specific questions related to the finding of elevated liver function tests. In addition, further assessment of risk factors is indicated, as an aid in planning the workup.

Table 1. Potential Causes of Fatigue and Elevated Liver Function Tests

	Potential Causes	Risk Factors
Fatigue	Depression	Young; female; single, divorced, or separated; seriously ill; personal or family history of depression
	Hypothyroidism	Female; elderly; Down syndrome

	Anemia	Young children; elderly & women of child-bearing age
	Iron overload	Male; middle age or older; family history of iron overload
	Chronic fatigue syndrome	Female; middle-aged
	Other chronic illness (e.g., liver or renal disease)	Various lifestyle factors; family history
Elevated Liver Function Tests	Chronic hepatitis	Exposure to blood products; shared needles
	Hepatic drug reaction	Exposure to drugs with known hepatic effects
	Alcoholism	Male; young adult; personal or family history of alcoholism
	Iron overload	Male; middle age or older; family history of iron overload
	Autoimmune hepatitis	Female; other autoimmune disorders

Risk Assessment

Risk factors for the potential causes of fatigue and elevated liver functions should be assessed ([Table 1](#)).

Family history may sometimes be helpful in pointing to a particular diagnosis. For example, family history is a risk factor for depression, alcoholism, and iron overload. In the case of depression and alcoholism, family history may reflect shared environment as much as genetic factors. In the case of iron overload, family history of complications seen in iron overload may be an indicator of HHC.

Serum iron measures can be use to evaluate the diagnosis of HHC [[CDC Testing Protocol](#)].

Genetic Counseling and Testing

If the patient's workup results in a diagnosis of HHC, genetic counseling would be appropriate to discuss genetic testing and address the risk of HHC in family members.

The most common form of HHC is associated with mutations in the *HFE* gene. HHC is usually diagnosed on the basis of serum iron measures, but genetic testing can provide information that could be valuable to family members. If the patient's *HFE* genotype is known, other family members can be tested to determine whether they have inherited the same *HFE* genotype. The clinical value and personal implications of *HFE* testing may vary, and pre-test genetic counseling can assist the patient or family members in deciding whether to proceed with genetic testing [[CDC Genetic Testing & Basic Counseling](#)].

Interventions


If the patient's workup reveals HHC, "de-ironing" is indicated. This procedure consists of the removal of one to two units of blood per week until the serum ferritin concentration (SF) reaches a low normal range. After the initial treatment, phlebotomy is done periodically (usually 3-4 times per year), to maintain a low SF. Regular monitoring for complications of HHC is also indicated, with the frequency based on the clinical status of the patient.

Ethical/Legal/Social/Cultural Issues

The diagnosis of *HFE*-related HHC may have adverse social consequences. Anecdotal reports of discrimination in insurance and employment have been reported after a diagnosis of HHC [[Alper et al 1994](#)]. Loss of self-worth or increased concerns about health may occur when a genetic risk state is identified [[Markel 1992](#)]. The likelihood of these responses or the scope of these risks is unknown, and they need to be weighed against the clinical benefits of early diagnosis and treatment of iron overload.

Because of the risk of discrimination, clinicians should be cautious about applying the diagnosis of HHC to individuals who do not have evidence of iron overload. For example, an expert panel has recommended that the diagnosis of *HFE*-related HHC should not be made on the basis of genotype in the absence of clinical evidence of iron overload [[Adams et al 2000](#)].

Resources

- **CDC: Hemochromatosis for Health Care Professionals**
- **American Liver Foundation**
75 Maiden Lane, Suite 603
New York, NY 10038
Phone: 800 GO LIVER (465-4837)
Fax: 212-483-8179
Email: info@liverfoundation.org
- **Iron Overload Diseases Association, Inc**
433 Westwind Drive
North Palm Beach, FL 33408
Phone: 561-840-8512
Fax: 561-842-9881
Email: iod@ironoverload.org
- **National Library of Medicine Genetics Home Reference**
[Hemochromatosis](#)
- **GeneReview: *HFE*-Associated Hereditary Hemochromatosis**
- **GeneTests Resources for *HFE*-Associated Hereditary Hemochromatosis** 

References

Adams P, Brissot P, Powell LW (2000) EASL international consensus conference on haemochromatosis. *J Hepatol* 33: 485-504 [[Medline](#)]

Alper JS, Geller LN, Barash CI et al (1994) Genetic discrimination and screening for hemochromatosis. *J Publ Health Pol* 15: 345-58 [[Medline](#)]

Andersen RV, Tybjaerg-Hansen A, Appleyard M, Birgens H, Nordestgaard BG (2004) Hemochromatosis mutations in the general population: iron overload progression rate. *Blood* 103: 2914-9 [[Medline](#)]

Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T (2002) Penetrance of 845G→A (C282Y) *HFE* hereditary haemochromatosis mutation in the USA. *Lancet* 359:211-8 [[Medline](#)]

Kowdley KV, Hassanein T, Kaur S, Farrell FJ, Van Thiel DH, Keeffe EB, Sorrell MF, Bacon BR, Weber FL Jr, Tavill AS (1995) Primary liver cancer and survival in patients undergoing liver transplantation for hemochromatosis. *Liver Transpl Surg* 1:237-41 [[Medline](#)]

Lapham EV, Kozma C, Weiss JO (1996) Genetic discrimination: perspectives of consumers. *Science* 274:621-4 [[Medline](#)]

Markel H (1992) The stigma of disease: implications of genetic screening. *Am J Med* 93:209-15 [[Medline](#)]

McCune CA, Al-Jader LN, May A, Hayes SL, Jackson HA, Worwood M (2002) Hereditary haemochromatosis: only 1% of adult *HFE* C282Y homozygotes in South Wales have a clinical diagnosis of iron overload. *Hum Genet* 111:538-43 [[Medline](#)]

McDonnell SM, Preston BL, Jewell SA, Barton JC, Edwards CQ et al (1999) A survey of 2851 patients with hemochromatosis: symptoms and response to treatment. *Am J Med* 106:619-24 [[Medline](#)]

McDonnell SM and Parrish RG (2003) Hereditary hemochromatosis and its elusive natural history. *Arch Intern Med* 163:2421-3 [[Medline](#)]

Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G (1996) Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 110:1107-19 [[Medline](#)]

Phatak PD, Sham RL, Rabuertas RF, Dunnigan K, O'Leary MT, Braggins C, Cappuccio JD (1998) Prevalence of hereditary hemochromatosis in a sample of 16,031 primary care patients. *Ann Int Med* 129:954-61 [[Medline](#)]

Witte DL, Crosby WH, Edwards CQ, Fairbanks VF, Mitros FA (1996) Practice guideline development task force of the College of American Pathologists. Hereditary hemochromatosis. *Clin Chim Acta* 245:139-200 [[Medline](#)]