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 phelobotomy (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 the genetic counseling and confidentiality issues that arise in the assessment of risk for HHC among relatives of an affected person.

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 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 26. Patient with a Question about Hemochromatosis

A resident presents a patient with a question about hereditary hemochromatosis (HHC). The patient is a 30-year-old woman in for a routine Pap test. However, the resident also wonders whether the patient should be tested for HHC. The patient reports that her brother has just been diagnosed with this condition — she is not sure what it is — and that he is now insisting that everyone in the family be tested. He says that a genetic test will determine who is affected. The patient is skeptical: "He's always overreacting." She reports no symptoms. She has one child, aged five, who is healthy. Her only medication is an oral contraceptive. A hematocrit two years ago was 36%.

Clinical Care Issues

Further information about her brother's reported diagnosis of HHC would help to determine her risk. For example, is the diagnosis really HHC? If so, is it the common form, caused by mutations in the *HFE* gene? What was the basis of the diagnosis? How was the diagnosis confirmed? HHC is an inherited disorder in which end organ complications occur as a result of iron overload. Most cases occur in people who have two copies of the C282Y mutation of the *HFE* gene; this genotype is associated with increased absorption of iron from the gastrointestinal tract. Complications of HHC include cirrhosis; liver cancer; cardiomyopathy; joint pain; diabetes mellitus; and hypogonadism, resulting in impotence in men and amenorrhea in women. Complications can be prevented by regular phlebotomy to maintain low-normal serum ferritin concentration.

Risk Assessment

If her brother's medical history confirms a diagnosis of *HFE*-related HHC, the patient has a 25% chance of having the same *HFE* genotype as her brother, and therefore a genetic susceptibility to HHC. Her risk for clinical complications of iron overload is more difficult to estimate. Even though most people with HHC have a C282Y/C282Y genotype, most people with a C282Y/C282Y genotype do not develop HHC. Furthermore, women are less likely to develop clinical symptoms of iron overload than men. Nevertheless, the patient's risk for iron overload is well above that of the population.

Serum iron measures: testing pathway to determine whether iron overload is present [CDC Testing Protocol]

- Check random transferrin saturation (TS = serum iron concentration / TIBC x 100%)

  Elevated TS is found in 1-6% of the population, depending on the cut-off used. For a cut-off of 55%, a little over 2% of the population will have an elevated level. Persistently elevated TS is an indicator of significantly increased risk of iron overload if other causes (such as liver disease and iron-loading anemia) are absent.

  - TS <45%: iron overload is unlikely. TS <16%: iron deficiency is present.

  - TS = 45%-<60%: iron overload is possible; given the patient's

positive family history, further workup would be appropriate.

- TS ≥60%: iron overload is more likely.

- If TS is elevated, re-check (fasting if possible) to confirm, and check serum ferritin (SF)

  - If SF concentration is ≥200 ng/mL in a premenopausal woman, or ≥300 ng/mL in a man or postmenopausal woman, iron overload is likely.
    - Further workup for complications of iron overload is indicated

      AND

    - The procedure referred to as "de-ironing" is indicated. This procedure consists of the removal of 1-2 units of blood per week until the SF concentration reaches a low normal range. If 12 units of blood are removed before a low normal SF concentration is achieved, iron overload is confirmed.

Genetic Counseling and Testing

If the patient's brother's diagnosis of HHC is confirmed, and his *HFE* genotype is known, *HFE* testing can be used to determine whether the patient has the same genotype. There are pros and cons to genotype testing. In favor of testing, this single test can determine whether the patient has inherited a risk for iron overload. For example, if she is found to have a C282Y/C282Y genotype, her increased risk for iron overload is confirmed. Regular assessment of her iron status would be recommended.

Most people with HHC have two copies of the *HFE* mutation C282Y. However, genetic studies reveal that the relationship between genotype and phenotype is complex (Table 1); as a result, genotype results can sometimes be difficult to interpret. Iron overload has been observed in people who have only one *HFE* mutation and in people without identifiable *HFE* mutations.

Table 1. *HFE* Genotypes in Patients with Iron Overload and in Control Populations: Pooled Data - Studies of People of European Descent

Genotype	% of Cases	% of Controls
C282Y/C282Y	77.5%	0.4%
C292Y/H63D	5.3%	1.8%
H63D/H63D	1.5%	2.0%
C282Y/+	3.6%	9.2%
H63D/+	5.2%	21.6%
+/+	6.9%	65.1%

Hanson et al 2001

In addition, the implications of a "positive" result are not always straightforward because population-based studies indicate that only a small proportion of people with a C282Y/C282Y genotype progress to clinical symptoms [Beutler et al 2002, Asberg et al 2001, McCune et al 2002, Gleeson et al 2004]. Thus a diagnosis of HHC should not be made on the basis of genotype alone [Adams et al 2000].

Genetic testing in relatives of a patient with HHC

Siblings of affected persons have a 25% chance of inheriting the same genotype as their affected sibling and thus of having an increased risk of iron overload. The offspring of an affected person will inherit one *HFE* mutation from that parent. If the other parent is an *HFE* mutation carrier, the offspring will each have a 50% chance of inheriting a genotype predisposing to iron overload. Since about 10% of people in the general population have the C282Y mutation, offspring of a person with *HFE*-related HHC have about a 5% chance of inheriting the predisposition to iron overload. Genetic counseling may help an affected person and his/her family members to understand their risks and testing options.

The value of genetic testing as a means to detect affected family members

depends on the genotype of the index case: if the index case has a C282Y/C282Y genotype, testing may be a useful and efficient means to detect others at risk in the family. Other *HFE* genotypes may be less useful for this purpose because they are associated with a lower risk of iron overload than the C282Y/C282Y genotype. Even when genotype data are informative, iron studies are necessary to determine the need for medical management.

Health care providers can facilitate detection of family members at risk by counseling a patient with HHC about the value of informing family members, by providing letters and information sheets to be passed on to family members, and by making genetic counseling available to family members. In this way, information can be provided about HHC, the procedures involved in family evaluation, and the potential of testing to identify family members who may benefit from [CDC Genetic Testing & Basic Counseling].

Interventions

In planning the workup and monitoring of the patient, it is important to take into account that iron overload occurs over time. If the patient's serum iron measures are normal now, she may benefit from repeat testing every two to three years.

Ethical/Legal/Social/Cultural Issues

Potential for stigma. As discussed above, genetic testing could be used to determine the need for periodic surveillance of iron status. Conversely, a positive genetic test in the setting of normal iron measures could be stigmatizing, or cause the patient to believe herself to be ill, or make her vulnerable to loss of insurance options.

Identification of family members at risk. Once an individual is diagnosed with iron overload, and the workup reveals that the cause is HHC, workup of all biological relatives is appropriate. Family-based detection is an efficient way to identify people with an increased risk of iron overload, but requires careful attention to patient confidentiality and preferences.

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**

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