Iron Overload

A resident asks....

Why would a primary care doctor want to know about the genetics of iron overload?

Key Points:

- Iron overload occurs in 1/200 to 1/400 of people. In the average primary care practice, this figure translates to about 4 to 8 patients with iron overload.
- In some patients, iron accumulation is progressive and causes serious complications such as cirrhosis, diabetes, and cardiomyopathy.
- Complications of iron overload can be prevented with phelobotomy (removal of 1-2 units of blood periodically), yet many patients are not diagnosed until organ damage has occurred.
- Early symptoms of iron overload are typically non-specific, and include common symptoms seen in primary care, such as fatigue, joint pain and palpitations.

Learning Objectives for the Iron Overload Module

Participants will be able to:

- Know the prevalence and clinical implications of iron overload
- Understand the use of serum iron measures in diagnosis of iron overload
- Understand the implications of HFE genotype data in diagnosis of hereditary hemochromatosis
- Understand the counseling and confidentiality issues that arise in family-based detection of people with hereditary hemochromatosis.

CASE # 1

A 47-year-old man presents with aching joints and fatigue. He has had the symptoms for several years. He has no other health complaints, although he notes some non-specific stomach discomfort on review of systems. He also notes 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 depressive symptoms including anhedonia, low self-esteem, and changes in appetite or sleep patterns.

Exam findings:

Exam findings include normal HEENT exam with anicteric sclera, and no facial edema noted; normal thyroid gland. There is a normal cardiac and lung exam without edema (pitting or non-pitting). Abdominal exam reveals mild hepatomegaly. Rectal exam is normal, with insufficient stool for guaiac testing. Neuro/musculoskeletal exam shows normal strength and sensation, normal reflexes and lack of inflammatory joint changes or joint tenderness. The mental status exam is normal with normal affect. No psychomotor retardation noted.

Lab work-up:

Suspecting anemia, possibly due to GI bleeding, 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.

Questions for Discussion:

1. Based on the history, what are the diagnostic considerations and how should they be evaluated?
2. How do the exam findings change the differential?
3. Based on the lab findings, what are the most likely diagnoses? What additional testing is indicated?

CASE #1 - Discussion

1. *Based on the history, what are the diagnostic considerations and how should they be evaluated?*

The differential for fatigue would include depression, hypothyroidism, anemia (possibly caused by GI bleeding given the history of non-steroidal anti-inflammatory use), CHD or other cardiovascular disease, chronic fatigue syndrome, occult chronic illness (such as liver disease or renal disease) and iron overload (see **Table 1** below). The differential for joint pain would include osteoarthritis, inflammatory arthritis, and iron overload. Additional history may be helpful at this point, including detailed history concerning mood and vegetative signs of depression, specific questions related to GI blood loss, and more information about character and duration of fatigue and joint pain.

Table 1.
Work-up of a patient with fatigue

Condition to consider	Prevalence	Risk factors	First step in diagnosis	Positive predictive value	Negative predictive value	Confirmation of diagnosis	Treatment	Evidence for outcome benefit from treatment
Depression	3-5%	Young, female, single, divorced, separated, seriously ill, past history or family history of depression	Mental status; history of vegetative signs; various screening instruments available	Average PPV for screening instruments: 84%	Average NPV for screening instruments: 72%	Clinical judgement; exclusion of other causes of fatigue	Anti-depressant therapy	RCT data
Hypothyroidism	1-4%	Female, older age, Downs syndrome	TSH	89-95%	90-96%		Synthetic thyroid replacement	Clinical observation; efficacy of treatment of subclinical hypothyroidism uncertain
Anemia	<1% - 10%	Young children, elderly & women of child-bearing age	CBC				Treatment dependent on cause of anemia	Clinical observation
Iron overload	0.3-0.5%	Male, middle age or older, family history of iron overload	TS	30-40% for TS cut-off of 60	>95% for TS cut-off of 60	Repeat TS, serum ferritin, additional measures of iron overload	Phlebotomy	Clinical observation
Chronic fatigue syndrome	0.2-0.4%	Female, middle-aged	Mental status exam, history, & physical			Exclusion of other known causes of fatigue	Treat symptoms	Clinical observation
Other chronic illness (e.g. liver disease, renal disease)	Variable		Additional history and exam to focus differential					

2. *How do the exam findings change the differential?*

There is no evidence of CHD on exam, which in addition to a negative history of related complaints argues against this as an etiology. Nothing on exam suggests hypothyroidism, but a negative exam does not rule it out. Negative joint exam reduces the likelihood of inflammatory arthritis. Hepatomegaly increases the likelihood of occult liver disease, although the physical exam is not very accurate.

3. *Based on the lab findings, what are the most likely diagnoses? What additional testing is indicated?*

The presence of mild elevations of liver function tests raise additional diagnostic possibilities, including chronic hepatitis, hepatic drug reaction, alcoholism, and rarer conditions such as autoimmune hepatitis. Other lab tests rule out hypothyroidism and anemia. Iron overload remains a consideration.

CASE # 2

A resident presents a patient with a question about hemochromatosis (HHC). The patient is a 30-year-old woman in for a routine Pap test. However, she also wonders whether she should be tested for HHC. She reports that her brother has just been diagnosed with this condition – she is not sure what it is – and is now insisting that everyone in the family be tested. He says there is a genetic test that will determine who is affected. She is skeptical: "he's always overreacting." She reports no symptoms. She has one child, aged 5, who is healthy. Her only medication is an oral contraceptive. A hematocrit 2 years ago was 36.

Question for Discussion:

1. What additional information would be helpful in counseling her about a work-up for HHC?

Additional history:

The patient's brother arranges to have a letter sent from his doctor. The letter confirms that the brother has iron overload, diagnosed after an episode of atrial fibrillation. He has undergone the removal of 20 units of blood by phlebotomy and now has a serum ferritin <50. His HFE genotype is C282Y/H63D.

Questions for Discusion:

2. What is the patient's risk to have HHC?
3. Which testing approach is preferable in determining whether she has HHC – iron studies or testing for HFE mutations?
4. Are there additional considerations for the patient or her family as she considers her testing options?

CASE # 2 – Discussion

1. What additional information would be helpful in counseling her about a work-up for HHC?

Further information about her brother's reported diagnosis of hemochromatosis would help to determine her risk – e.g., What was the basis of the diagnosis? How was the diagnosis confirmed? If her brother's medical history confirms a diagnosis of HHC, the patient has a 25% chance of having the same HFE genotype as her brother, and therefore a genetic susceptibility to hemochromatosis. Her risk for complications of iron overload would be lower, because clinical observations indicate that penetrance of HFE mutations is less than 100% and is lower in females than males. Nevertheless, her risk for iron overload would be well above that of the population. She might benefit from testing for transferrin saturation, according to the testing pathway outlined below. She is also likely to benefit from additional information about HHC.

Testing pathway to detect people with increased risk of iron overload, based on serum iron measures:

1. Check random transferrin saturation (TS = serum iron /TIBC x 100%)
   - For TS < 45% – Iron overload is unlikely. If TS < 16 %, iron deficiency is present
   - For TS 45% to < 60% – Iron overload is possible; given the patient's family history further work-up would be appropriate
   - TS $\geq$ 60% – Iron overload is more likely; additional work-up is merited

2. If TS is elevated, re-check (fasting if possible) to confirm, and check serum ferritin (SF)
   - If SF is $\geq$ 200, iron overload is likely. Further work-up for complications of iron overload is indicated; de-ironing (removal of iron by phlebotomy) is indicated. [Note – for men, a higher serum ferritin threshold is generally used – e.g., 300.]
   - Elevated TS levels are found in 1-6% of the population, depending on the cut-off used. 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. The effect of the

TS cutoff on the detection of affected persons is illustrated in **Table 2** below (based on Bradley et al. 1996).

Table 2.
Estimates of hemochromatosis detection rates (DR), false positive rates (FPR), and odds of being affected given a positive result (OAPR) according to sex and TS cutoff level.

TS Cutoff	Males			Females		
(%)	DR (%)	FPR (%)	OAPR*	DR (%)	FPR (%)	OAPR*
50	94	6.2	1:12	82	3.3	1:8
55	91	2.3	1:5	75	1.0	1:3
60	86	0.7	2:3	67	0.2	2:1
65	79	0.2	2:1	58	<0.1	>3:1
70	72	<0.1	>4:1	48	<0.1	

[a] Assumes a prevalence of affected persons of 5 in 1000.

Additional biochemical evidence of iron overload is typically required for the diagnosis of HHC. Usually an elevated serum ferritin and liver function tests (e.g., AST, ALT, alkaline phosphatase and bilirubin) are obtained; if both are abnormal, a liver biopsy may be recommended, to confirm HHC by measurement of the hepatic iron index and to assess for the presence of liver fibrosis or cirrhosis. If the serum ferritin is elevated but liver function tests are normal and no hepatomegaly is present, many experts recommend quantitative phlebotomy: the removal of 1-2 units of blood per week until the serum ferritin reaches a low normal range. Removal of a defined amount of iron (e.g., 3-4gms) by this procedure confirms the diagnosis of HHC.

2. What is the patient's risk to have hemochromatosis?

Her brother's medical history confirms HHC. Her risk is to have a hemochromatosis genotype is 25%. Her risk to have complications of iron overload is substantially lower, partly because penetrance is lower in women and partly because her brother's genotype is associated with much lower penetrance than the more common HFE genotype seen in affected patients (C282Y/C282Y), as discussed under question 4 below.

3. Which testing approach is preferable in determining whether she has hemochromatosis – iron studies or testing for HFE mutations?

Her brother's HFE genotype is known, so HFE testing can be used to identify other affected siblings. However, it should be noted that the penetrance of the C282Y/H63D genotype is much lower than that of the C282Y/C282Y genotype. This lower penetrance can be inferred from the fact that case control studies demonstrate relatively few cases with this genotype (about 5% of cases - see **Table 2** above), yet this genotype is about four times more common in the population than the C282Y/C282Y genotype. As a rough estimate, the penetrance of the C282Y/H63D genotype is in the 1% range (Burke et al. 2000).

As a result, HFE mutation testing would be a means to identify whether the patient has inherited an increased risk for iron overload, but a positive genetic test result would still be associated with a low risk of iron overload. Serum iron measures (TS, followed by serum ferritin) are a more accurate way to determine whether the patient has iron overload.

In planning work-up 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 2-3 years. The genotype test could be used to determine the value of such a surveillance program, that is, the surveillance program would not be needed if she had a normal HFE genotype. Conversely, a positive genotype 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.

4. Are there additional considerations for the patient or her family as she considers her testing options?

Once an individual is diagnosed with iron overload, and the work-up reveals that the cause is HHC, work-up of all biological relatives is appropriate. Family-based detection is an efficient way to detect people with an increased risk of iron overload, but requires careful attention to

patient confidentiality and preferences. Genetic studies reveal that the relationship between genotype and phenotype is complex. Two mutations have been shown to be associated with disease, one of which, C282Y, is more severe than the other, H63D. Iron overload has also been observed in mutation carriers and in people without HFE mutations (see **Table 3** below).

Table 3.
HFE genotypes in patients with iron overload and in control populations
Pooled data - studies of people of European descent (Hanson et al. 2001)

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%

Although the genotype-phenotype relationship is complex, most people with HHC carry two *HFE* mutations are present. An affected person has thus usually inherited an *HFE* mutation from each of his/her parents. The parents can be either carriers, who are usually without evidence of iron overload, or can be themselves affected. The most important family history is of disease suggestive of HHC – e.g. primary liver cancer or cirrhosis and diabetes in the same relative; HHC may not always be recognized as the cause of disease in family members.

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. When an affected person marries a carrier, their children each have a 50% chance of inheriting a genotype predisposing to iron overload. Since about 10% of people in the general population carry the C282Y mutation, children of a person with hemochromatosis 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 this inheritance pattern.

As shown in **Table 3**, about 7% of persons with HHC carry no known *HFE* mutations; clinical findings consistent with HHC are also sometimes seen in C282Y and H63D heterozygotes. As a result 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 useful and efficient means to detect others at risk in the family. Other HFE genotypes may be less useful for this purpose. Even when genotype data is informative, iron studies are necessary to determine the need for medical management.

Health care providers can facilitate family detection 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 counseling available to family members. In this way, information can be provided about hemochromatosis, the procedures involved in family screening and the potential of screening to identify family members who may benefit from phlebotomy treatment.

The diagnosis of hemochromatosis 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 or scope of these risks is unknown. However, careful attention to the confidentiality of information, and respect for individual preferences regarding testing, are important issues as information is provided to the family about HHC.

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