

Educational Case: Iron Overload and Hemochromatosis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289518779944>.

Keywords

pathology competencies, organ system pathology, hematopathology, anemia, iron overload, hemochromatosis, genetic mechanisms, inheritance patterns

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Primary Pathology Learning Objective

Objective HRC1.3: Hepcidin Regulation, Iron Overload, and Anemia of Chronic Disease: Discuss the role of hepcidin as an iron regulator and describe how different types of alterations in the hepcidin pathway can produce anemia of chronic disease or iron overload.

Competency 2: Organ System Pathology; Topic HRC: Hematopathology - Red Cell Disorders; Learning Goal 1: Anemia.

Secondary Pathology Learning Objective

Objective GM1.2: Inheritance Patterns: Compare and contrast the inheritance patterns of different types of Mendelian disorders and give examples of each type of pattern.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Patient Presentation

A 50-year-old Caucasian male presented for evaluation concerned that he may be at risk of developing hemochromatosis based on his family history. His father presented at age

Table 1. Iron and Genetic Studies of the Patient and His Father.

Lab Test	Father—Age 60	Patient—Age 50	Normal Range
Serum iron	232	106	65-170 µg/dL
Transferrin	284	230	200-400 mg/dL
Total iron binding capacity	355	288	250-450 mg/dL
% saturation	65	37	20%-55%
Ferritin	1518	217	10-300 ng/mL
HFE genotype C282Y	Homozygous	Heterozygous	

60 with bronzed skin and diabetes; he was found to have iron overload and subsequently has been undergoing therapeutic phlebotomies. The patient's medical history is unremarkable with the exception of hypercholesterolemia, for

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Table 2. Iron and Genetic Studies of the Father and the Brother of the Patient.

Lab Test	Father—Age 60	Brother—Age 46	Normal Range
Serum iron	232	176	65-170 µg/dL
Transferrin	284	230	200-400 mg/dL
Total iron binding capacity	355	266	250-450 mg/dL
% saturation	65	65	20%-55%
Ferritin	1518	611	10-300 ng/mL
HFE genotype C282Y	Homozygous	Homozygous	

which he takes a statin. You decide to do some diagnostic blood work. In addition, the patient has provided you with results of blood work from his father.

Diagnostic Findings, Part I

Results of iron studies and *HFE* studies are presented in Table 1.

Questions/Discussion Points, Part I

Interpret the Father's and the Patient's Iron Studies

The father has elevated serum iron associated with increased transferrin saturation and an elevated ferritin indicative of both increased iron absorption and iron storage. The son has normal iron studies.

Do the Patient's Iron Studies Support the Diagnosis of Hemochromatosis?

No. He does not have evidence of either increased absorption or increased iron stores. Additionally, he is only a carrier of the *HFE* mutation, making it highly unlikely that he has a genetic predisposition to iron overload.

Ferritin and Serum Iron Reflect Different Aspects of an Individual's Iron Metabolism. What Is the Major Difference in the Type of Information Obtained From Each of These?

Ferritin is a measure of long-term iron storage, while serum iron (and transferrin saturation) better reflect daily iron absorption. Interpretation of ferritin testing can be misleading with only a single measurement because it is an acute phase reactant.

Diagnostic Findings, Part 2

After obtaining the results above, the patient consults his brother and recommends that he also undergo testing. Results from his brother, again in comparison to those of his father, are shown in Table 2.

Questions/Discussion Points, Part 2

Does His Brother Have Iron Overload? Why Is His Brother's Ferritin So Much Lower Than His Father's?

Yes, he has evidence of iron overload. He is younger than his father was at the time of his iron studies, and the degree of iron overload is a function of time.

Should Other Siblings Be Tested? What Would Be the Best Approach for Further Molecular Testing? If You Had Had the Opportunity to Evaluate the Father at the First Sign of Potential Iron Overload, What Testing Would You Have Done on Him?

Taking the brother's and father's genotypes together (and assuming the brothers have the same father!), mother must be a carrier, and other children have a 50% chance of being homozygotes also. *HFE* C282Y homozygotes in general will have an increased risk of significant iron overload. However, because there are significant modifiers of iron absorption beyond the *HFE* gene (age, gender, diet, and polymorphisms in other genes affecting iron absorption), not all homozygotes will have iron overload.¹ In this family, however, homozygotes do appear to have an increased risk of iron overload, so they should be identified. Because we know the mutation in this case, targeted mutation analysis for *HFE* C282Y is the only analysis needed.

If you had seen the father early in his course and had had no family history of hemochromatosis, it would be appropriate to do targeted analysis for both the *HFE* C282Y and H63D mutations, and if these were negative, sequence analysis could be used to identify other less common mutant alleles associated with *HFE*.

Which Genes Can Cause Hemochromatosis When Mutated? Describe the Inheritance Patterns Seen

The *HFE* C282Y on chromosome 6p22.2, as present in this case, is the most common mutation seen in classic (type 1 or *HFE*1) hemochromatosis and is associated with autosomal recessive inheritance. This mutation accounts for >80% of hemochromatosis cases.^{2,3} Another common mutation in *HFE* (H63D) may be seen as a compound heterozygous (C282Y/H63D) genotype in some patients with hemochromatosis; patients with homozygous H63D rarely have clinically significant iron overload.^{2,3} Four additional iron overload disorders labeled hemochromatosis have been identified²:

Juvenile hemochromatosis is the term given to clinically similar autosomal recessive diseases caused by mutations in 2 different genes:

HFE2A: the hemojuvelin (HJV) gene on chromosome 1q21.

HFE2B: the hepcidin (HAMP) gene on chromosome 19q13.

HFE3, also autosomal recessive, is caused by a mutation in transferrin receptor 2 gene on chromosome 7q22.

HFE4, is autosomal dominant and caused by a mutation in *SLC40A1* gene on chromosome 2q32.

Discuss the Pathophysiology of How Iron Overload Occurs in Hemochromatosis

Patients with hemochromatosis have in common low hepcidin levels. Hepcidin normally binds ferroportin in both duodenal enterocytes and reticuloendothelial macrophages, which in turn blocks release of iron from these cells. Thus, hepcidin serves to keep iron from being absorbed from the gut or being released from storage macrophages back into circulation. In the absence of hepcidin, this process is reversed, with increased iron absorption and increased turnover of iron from reticuloendothelial macrophages leading to high levels of both serum ferritin and saturation of transferrin and ultimately to iron deposition in tissues.³

Teaching Points

- Iron overload can be suspected from serum iron studies, in particular elevated serum iron and transferrin, and increased transferrin saturation.
- In the absence of a historical explanation for iron overload (such as multiple blood transfusions), patients with iron overload should be investigated for genetic disorders, and in particular for hereditary hemochromatosis.

- If hereditary hemochromatosis is identified, family members should be tested for evidence of iron overload as well.
- Other factors modify the effects of the abnormal gene so that affected family members may vary significantly in their clinical and laboratory presentations.
- The most common form of hereditary hemochromatosis is called type 1 and is due to a mutation in the *HFE* gene. It is inherited as an autosomal recessive.

Declaration of Conflicting Interests

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