

HOSPITAL PHYSICIAN®

GASTROENTEROLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Gastroenterology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in gastroenterology. Each manual reviews a topic essential to the current practice of gastroenterology.

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HFE-Associated Hereditary Hemochromatosis

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HFE-Associated Hereditary Hemochromatosis

Sanjay Jain, MD, and Anthony Martin, MD

INTRODUCTION

Hereditary hemochromatosis (also called genetic hemochromatosis) is an autosomal recessive disorder associated with increased intestinal absorption of iron and deposition of excessive amounts of iron in the liver, pancreas, heart, and other organs. It is the most common single-gene disorder in the US white population. Approximately 1 in 250 to 300 white persons is homozygous for the hemochromatosis gene mutation, and at least 1 in 10 persons is a carrier for the mutation.¹ Clinical expression varies from no symptoms to signs and symptoms of severe iron overload. Manifestations of iron overload include sexual dysfunction, joint pains, weakness, skin pigmentation, liver damage (cirrhosis), heart failure, and diabetes mellitus. The liver is the principal recipient of the majority of the absorbed iron, and the liver is always involved in hereditary hemochromatosis.

In 1889, Von Recklinghausen² was the first to use the term *hemochromatosis*, based on the thinking that the disease was a blood disorder that caused increased skin pigmentation. Sheldon realized that hemochromatosis was an inborn error of iron metabolism and that all the pathologic manifestations of the disease were caused by increased iron deposition in the affected organs.² Since the HFE gene was detected in 1996,³ it has been established that a single gene mutation (ie, C282Y) is responsible for most cases of hereditary hemochromatosis. The discovery of the gene has led to a blood test for the molecular genetic diagnosis of hemochromatosis. The relationship between the gene defects and the development of iron accumulation is still being explored. Disease penetrance is incomplete, and not everyone with disease-associated mutations of the gene has manifestations of iron overload. Iron overload can also occur sporadically and, in some families independent of mutations of the HFE gene; other gene mutations may interact to produce iron overload in heterozygotes. Treatment by phlebotomy is simple and efficient and can prevent the development of cirrhosis, leading to a normal life expectancy for patients with hereditary hemochromatosis.

PATHOPHYSIOLOGY

The normal iron content of the body is 3 to 4 g, with only 3 to 7 mg bound to transferrin in plasma. Approximately 2.5 g of iron exists in hemoglobin in circulating red blood cells, and 400 mg exists with iron-containing proteins in myoglobin, cytochromes, and catalase. The remainder (approximately 1 g) is stored as ferritin and hemosiderin, mostly in the liver, spleen, and bone marrow. Iron is lost in sweat, shed skin cells, and the gastrointestinal tract at a rate of 1 mg per day. Women lose another 0.5 to 1 mg per day in menstrual blood loss. A normal diet contains 10 to 20 mg of iron per day, roughly 10% of which is absorbed in the intestines, replacing the 1 mg per day of lost iron.

In patients with homozygous hereditary hemochromatosis, the absorption of heme iron is not regulated according to the amount of iron stored in the body.⁴ These patients may absorb between 2 and 4 mg of iron daily from heme and non-heme iron sources. Absorption of iron at a rate of 4 mg per day would lead to a net iron accumulation of approximately 1 g each year; in men, more than 20 g would accumulate between the end of the adolescent growth spurt and age 40 or 50 years. Individuals with this degree of iron overload are poised to develop the clinical features of hereditary hemochromatosis. Women become symptomatic approximately one decade later in life because of the extra iron losses associated with menses, child birth, and lactation.

There is no normal mechanism for increasing iron excretion. Increased iron absorption or parenteral administration of iron leads to iron overload. As the body content of iron increases, circulating transferrin becomes increasingly saturated with iron, resulting in the increased production of non-transferrin-bound iron and the off-loading of iron, especially to cells with high levels of transferrin receptors (eg, heart, liver, thyroid, gonads, and pancreatic islets). The excess iron in these cells causes the release of reactive oxygen, leading to oxidization of lipids and proteins, thereby causing tissue damage and subsequent fibrosis.^{5,6}