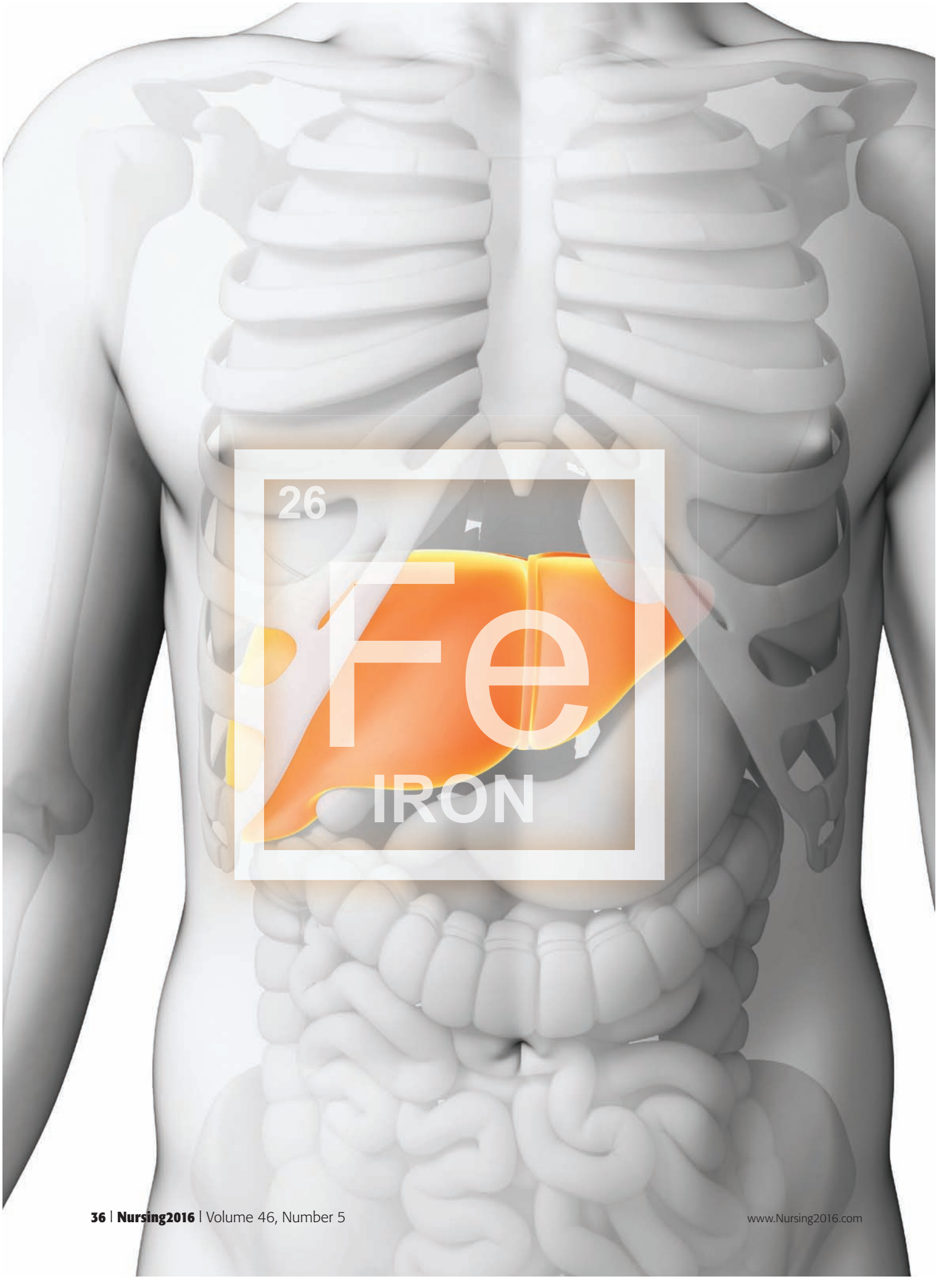

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Hereditary hemochromatosis

Dealing with iron overload

By Patricia Quigley, PhD, MNEd, BSN, RN

MR. W, A 55-YEAR-OLD White male of European descent, presents to a primary care setting with vague symptoms of unexplained fatigue, myalgia, abdominal discomfort, and bilateral knee pain. His family history includes a father who died of myocardial infarction at age 53, a sister who died at age 45 of hepatocellular carcinoma, and a deceased brother, age 52, whose liver revealed evidence of iron overload at autopsy. At age 42, a second sister is apparently healthy. Mr. W says he drinks a glass of wine with dinner every evening and doesn't take any prescription medications, over-the-counter vitamins, herbal or nutritional supplements, or illicit drugs.

Physical assessment findings include mild hepatomegaly, tanned appearance of skin, and swelling of metacarpophalangeal (MCP) joints. His height is 6 ft, weight 200 lb (90.7 kg), and body mass index 27.1, indicating that Mr. W is overweight. Vital signs are: BP, 118/80; temperature, 98.6° F (37° C); apical pulse, regular at 86 beats/minute; and respirations, 20 breaths/minute.

Results of Mr. W's blood work show a serum ferritin level of 1,048 ng/mL (normal in men, 18 to 270 ng/mL) and transferrin (iron) saturation (TS) of 95% (normal in men, 10% to 50%).[1] The preliminary diagnosis is hereditary hemochromatosis (HH), a relatively common adult genetic disorder.[2]

The ability to anticipate the nursing care that this patient will need enables more timely treatment of his signs and symptoms as well as prevention of complications. Besides the pathophysiology of HH, this article discusses its diagnosis and treatment, along with important teaching points that nurses must address with patients and their families.

What is HH?

Known as an iron overload disorder, HH is a genetic disorder that results in increased intestinal iron absorption. Signs

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and symptoms are related to excessive iron deposits in tissues and organs such as the skin, heart, liver, pancreas, and joints.[3] Although HH can be effectively treated in its early stages, severe organ damage results if diagnosis and treatment are delayed.[4] Unfortunately, because the initial clinical presentation is vague and many clinicians are unfamiliar with genetic disorders, the diagnosis is often missed in the early stages.[5]

HH is classified into types based on factors such as the genetic mutation involved and symptom onset. More than four types have been identified, but these are the most common:[6]

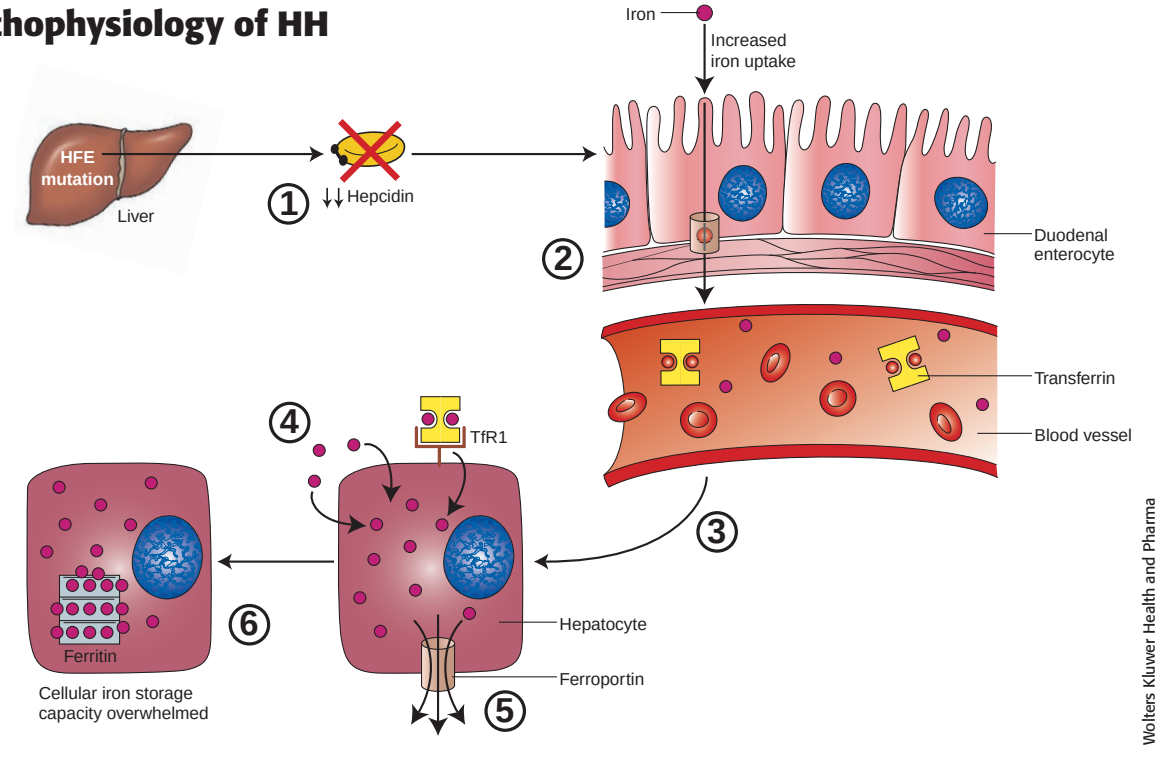
- *HFE* (type I or classical HH): caused by *HFE* gene mutation; most common type; autosomal recessive inheritance; symptom onset in adulthood.
- juvenile hemochromatosis (type II): mutations in hemojuvelin (*HJV*) in type IIA and hepcidin (*HAMP*) in type IIB; autosomal recessive inheritance; onset in childhood or young adulthood.
- transferrin receptor 2 mutation (type III): defect in transferrin receptor 2; autosomal recessive inheritance; symptom onset in young adulthood.
- ferroportin mutations (type IV): mutations in a gene encoding for ferroportin (*SLC40A1*); two different phenotypes, hepatic type and macrophage type; autosomal dominant inheritance; onset in adulthood.

Because HH is most commonly due to mutations in the *HFE* gene (type I),[3] it's the focus of this article and will be referred to as HH.

Genetics of HH

The most common genetic mutation causing HH, an autosomal recessive disorder, is a mutation in the *HFE* (for **h**ereditary **Fe** [iron]) gene with homozygosity for the C282Y mutation on chromosome 6.[6-10] This C282Y mutation disrupts the regulatory mechanism for intestinal iron absorption.

Pathophysiology of HH



1. The genetic defect in HH leads to decreased hepatic production of hepcidin. Hepcidin is considered the "master" iron regulatory hormone. Hepcidin is produced by the liver and it determines how much iron is absorbed from the diet and released from storage sites in the body. 2. As a consequence, when iron in the duodenal lumen enters enterocytes, its export through ferroportin (a specialized protein crucial to the proper export of iron from cells) isn't regulated appropriately and too much iron is absorbed and transported through the enterocytes into the blood. 3. Normally, iron is transported in the blood bound to transferrin (Tf), and Tf is usually about one-third saturated with iron. In HH, not only is Tf iron-carrying capacity saturated (100%), but free iron (unbound to Tf) is also abundant in the blood. 4. Iron enters hepatocytes both as Tf-bound iron and as free iron. Tf-bound iron enters via the transferrin receptor 1 (TfR1) pathway. Free iron enters via a different, poorly understood pathway. 5. Lacking inhibition by hepcidin, ferroportin export of iron is very active. 6. However, probably because of overwhelming entry of free iron into hepatocytes, iron storage and export capacities are overwhelmed and excess iron accumulates.

A person must acquire two mutated genes (one from each parent, homozygosity) to develop HH. (See *Glossary of genetic terms*.) If a person inherits only one copy of the mutated gene (heterozygosity), he or she is a carrier, usually with no signs or symptoms—one copy of the unaffected gene is normally sufficient to regulate iron absorption. As a "silent carrier," this person could pass the mutated gene on to a child. If both parents are carriers, each child has a 25% chance of inheriting two copies of the mutated gene and would probably develop the disorder as an adult.[9]

Penetrance refers to the proportion of people in a population who have the genotype and the corresponding phenotype or who exhibit symptoms of the disorder.[11] In HH, penetrance is incomplete or less than 100%, meaning that not all individuals who have the genetic mutation will exhibit the symptoms. Research is ongoing to explore the relationship between the genetic mutation and iron accumulation.[12]

The ethnic population most affected by HH is White, with the highest risk in those of northern European descent. In the United States, HH affects about one million people.[9]

In evolutionary terms, having HH may have once provided a genetic advantage. Women who were heterozygous (having one mutated and one unaffected gene) may have had a reproductive advantage because they were less likely to develop iron deficiency anemia, and both men and women could have had a survival advantage in times of starvation.[8]

Clinical manifestations

Patients with two copies of the most common genetic mutation, C282Y, will usually, but not always, have signs and symptoms of HH, related to penetrance. Most patients are

Glossary of genetic terms[11,19]

Allele: one of two or more versions of a gene responsible for hereditary variation. Individuals inherit two alleles for each gene, one from each parent. If the alleles are different, the dominant allele will be expressed and the recessive allele's effect will be masked. In order to develop a recessive genetic disorder, an individual must inherit two copies of the mutated allele.

Autosome: any of the numbered chromosomes, as opposed to the sex chromosomes. Humans have 22 pairs of autosomes and one pair of sex chromosomes (the X and Y). Autosomes are numbered roughly in relation to their sizes. That is, Chromosome 1 has approximately 2,800 genes, while chromosome 22 has approximately 750 genes.

Autosomal Dominant: a pattern of inheritance characteristic of some genetic diseases. *Autosomal* means that the gene in question is located on one of the numbered, or nonsex, chromosomes. *Dominant* means that a single copy of the disease-associated mutation is enough to cause the disease. This is in contrast to a recessive disorder, where two copies of the mutation are needed to cause the disease. Huntington disease is an example of an autosomal dominant genetic disorder.

Carrier: an individual who carries and is capable of passing on a genetic mutation associated with a disease and may or may not display disease symptoms. Carriers are associated with diseases inherited as recessive traits. In order to have the disease, an individual must have inherited mutated alleles from both parents. An individual having one normal allele and one mutated allele doesn't have the disease. Two carriers may produce children with the disease.

Chromosome: an organized package of DNA found in the nucleus of the cell. Different organisms have different numbers of chromosomes. Humans have 23 pairs of chromosomes—22 pairs of numbered chromosomes, called autosomes, and one pair of sex chromosomes, X and Y. Each parent contributes one chromosome to each pair so that offspring get half of their chromosomes from their mother and half from their father.

Gene: a sequence of DNA occupying a specific location on a chromosome; considered the basic unit of heredity.

Genetics: the study of a particular gene

Genome: the entire set of genetic instructions found in a cell. In humans, the genome consists of 23 pairs of chromosomes, found in the nucleus, as well as a small chromosome found in the cells' mitochondria. Each set of 23 chromosomes contains approximately 3.1 billion bases of DNA sequence.

Genotype: an individual's collection of genes. The term also can refer to the two alleles inherited for a particular gene.

Heterozygous: refers to having inherited different forms of a particular gene from each parent. A heterozygous genotype stands in contrast to a homozygous genotype, where an individual inherits identical forms of a particular gene from each parent.

Homozygous: a genetic condition in which an individual inherits the same alleles for a particular gene from both parents.

Mutation: a change in DNA sequence that can result from radiation, viral infections, chemical exposure, or mistakes during cell division. Germ line mutations occur in eggs and sperm and can be passed on to offspring; somatic mutations aren't passed on as they occur in body cells.

Penetrance: The probability of a gene or genetic trait being expressed. *Complete* penetrance means the gene or genes for a trait are expressed in all the population who have the genes. *Incomplete* penetrance means the genetic trait is expressed in only part of the population. The penetrance percentage also may change with the age range of the population.

Phenotype: an individual's observable traits, such as height, eye color, and blood type. The genetic contribution to the phenotype is called the genotype. Some traits are largely determined by the genotype, while other traits are largely determined by environmental factors.

adults after age 40 when they become symptomatic and seek medical attention. Men may be affected sooner than women, as menstruation reduces the accumulation of iron and delays symptoms until after menopause.[12,13] Symptom onset may also be delayed in people who routinely donate blood, which removes excess iron.

In early stages, a patient with HH can be asymptomatic. Nonspecific clinical manifestations develop as iron accumulates in tissues and organs. Examples include weakness, abdominal pain, and unintentional weight loss. More serious disorders associated with advanced disease include cirrhosis, diabetes mellitus, cardiomyopathy, arthritis, and hypogonadism.

A late and unusual presentation is "bronze diabetes," characterized by the triad of cirrhosis, diabetes, and skin hyperpigmentation, which gives the skin a bronze color.[7] This presentation has become less common because most patients today are diagnosed and treated before these complications develop.[3,12]

Signs and symptoms of HH reflect accumulation of iron in various tissues and organs:[3]

- Iron accumulation in the liver can cause hepatomegaly, fibrosis, and cirrhosis, which can lead to liver failure, hepatocellular carcinoma, and death.
- Iron accumulation in the pancreas can cause diabetes mellitus, which is present in about 50% of patients with HH who present with symptoms.[12]
- Joint pain isn't completely understood but may be related to excess iron resulting in calcium crystals in joint tissues, which causes joint pain and deformity, especially in the MCP joints.
- Iron accumulation in heart tissues can cause dilated cardiomyopathy, conduction defects, and heart failure.
- Iron accumulation in pituitary cells can cause decreased sex hormone levels, resulting in hypogonadism and impotence in men and amenorrhea in women.
- Iron accumulation in the thyroid gland can result in reduced

Patient teaching: Share this information with patients and their families[12,16,20]

You've been diagnosed with hemochromatosis, a disease that causes your body to absorb too much iron. The condition is usually passed through genes and runs in families. Your blood relatives need to speak with their healthcare provider about getting a simple blood test to determine if they have the same condition. A letter is available from the CDC that can inform them about the condition (see www.cdc.gov/ncbddd/hemochromatosis/training/pdf/hemo_family_letter.pdf). Give the letter to blood relatives: sisters, brothers, mother, father, adult children (inform the healthcare provider about young children), and both grandparents on both sides of the family. Family members need to understand that if they've inherited the genes that cause the disease, iron can build up in the heart, joints, liver, or pancreas and cause permanent damage—even if they feel fine now. Early diagnosis and treatment can prevent complications.

To manage your condition and prevent complications, follow these guidelines:

- Monitor iron levels and continue to undergo therapeutic phlebotomies as directed by the healthcare provider. Hemochromatosis can't be treated with dietary changes alone.
- Don't take iron pills or any nutritional supplements or multivitamins that contain iron. Read product labels carefully.
- Don't take vitamins or supplements containing more than 500 mg of vitamin C daily because vitamin C increases the amount of iron your body absorbs. Eating foods containing vitamin C is fine.
- Don't eat raw fish or raw shellfish because it may contain germs that can be harmful to people with iron overload. But eating well-cooked fish and shellfish is fine because cooking destroys these germs.
- Drink very little alcohol if you choose to drink (no more than 1 drink/day for women or 2 drinks/day for men). If you have liver problems, avoid alcohol altogether.
- For more information and resources, visit the CDC website at www.cdc.gov/ncbddd/hemochromatosis/index.html.

Phlebotomy pointers[13,15,16,20]

Someone with HH can donate blood from a therapeutic phlebotomy because HH isn't a blood disease: Erythrocytes and other blood cells aren't affected and HH isn't transmitted by blood. The patient may schedule therapeutic phlebotomies at hospitals, clinics, bloodmobiles, community blood centers, and hospital-based donor centers. Advise the patient to choose a center or site that can perform phlebotomies at the frequency prescribed by the healthcare provider.

Before and after a therapeutic phlebotomy, the patient should drink water, milk, or fruit juice to help increase blood flow during phlebotomy and replenish fluids afterward. Advise the patient to avoid vigorous physical activity for 24 hours after a treatment.

The patient will continue to need therapeutic phlebotomies as needed for his or her lifetime. Emphasize the importance of monitoring iron accumulation as directed by the healthcare provider and undergoing phlebotomies as prescribed to prevent complications and premature death.

Resources for patients regarding hemochromatosis donor programs are available from the Iron Disorders Institute at www.irondisorders.org.

thyroid hormone levels, causing hypothyroidism.

• Accumulation of iron and melanin in the skin may cause skin hyperpigmentation, causing a tanned or bronze skin tone.

Weakness, fatigue, and lethargy are present in about 75% of people with symptoms at time of diagnosis.[12] Because effects on normal physiologic mechanisms are so significant, early diagnosis is important to avoid development of serious health problems.

Diagnostic testing

Diagnosis of HH depends on the presence of increased iron stores with or without symptoms. Initially, serum ferritin and TS levels are obtained. Ferritin is a protein that stores iron in the body. Serum ferritin production increases when excess iron is absorbed. Serum ferritin levels are the most reliable indicator of total-body iron stores.[14]

Transferrin is a transport protein that picks up iron absorbed by the intestines and transports it within the body. When iron absorption is abnormally high, transferrin proteins become more saturated with iron, so an elevated TS level indicates increased iron absorption.[14]

If either value is abnormal (TS ≥ 45% or ferritin above the upper limit of normal, >300 ng/mL for males), then *HFE* gene mutation analysis should be performed to confirm the diagnosis.[2,14]

In the past, a liver biopsy was required for a definitive HH diagnosis. However, *HFE* gene mutation analysis has reduced the need for liver biopsy, although it may be indicated in certain patients to determine disease severity or an underlying liver disease such as hepatitis C virus infection.[3,13]

Genetic testing can also identify carriers, which can be helpful to couples planning a family. Each of two asymptomatic individuals who are carriers could contribute a mutated gene copy to a child who could develop the disease. Early intervention is important to prevent organ damage in affected individuals, so identifying a child at risk is important to prevent complications.[2,9]

Lifelong management

Patients with symptomatic iron overload are treated with phlebotomy to remove excess iron. After iron overload is corrected, patients are monitored and treated with phlebotomy as needed.

Initially, during the induction phase, fixed amounts of blood are removed twice weekly, weekly, or monthly depending on the patient's clinical status. The duration of aggressive treatment depends on the patient's ferritin level, gender, and other patient factors.[15]

When ferritin levels fall below a target level, such as 500 ng/mL, phlebotomy may be performed less frequently, such as monthly. During this *transition phase*, the goal is to reduce ferritin levels gradually to normal levels. Treatment then moves into the *maintenance phase*, in which phlebotomy is performed as needed to maintain safe iron levels.[15]

The Iron Disorders Institute recommends achieving a serum ferritin level below 50 ng/mL at least once during the transition phase of treatment, then tailoring treatment to maintain levels in the range of

Resources for keeping current

- The American Nurses Association (ANA) has defined competencies for all levels of nursing in the *Essentials of Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indicators*, 2nd Edition. https://www.genome.gov/Pages/Careers/HealthProfessionalEducation/geneticscompetency.pdf.
- The ANA and the International Society of Nurses in Genetics (ISONG) published the *Essential Genetic and Genomic Competencies for Nurses with Graduate Degrees* to define a higher level of expertise for nurses prepared at the master's and doctoral levels. www.genome.gov/Pages/Health/HealthCareProvidersInfo/Grad_Gen_Comp.pdf.
- ISONG is a global nursing specialty organization dedicated to genomic healthcare, education, research, and scholarship. Webinars and other educational opportunities are available at www.isong.org/index.php.
- The Genetics/Genomics Competency Center offers genetic and genomic resources for use in the classroom or practice. Visit http://g-2-c-2.org.
- The National Coalition for Health Professional Education in Genetics (NCHPEG) is an interdisciplinary resource to promote collaboration among a diverse group of leaders. The ANA joined with the American Medical Association and the National Human Genome Research Institute to establish NCHPEG with the goal of promoting education and access to information about advances in human genetics. Learn more at www.nchpeg.org.
- The *National Human Genome Research Institute Talking Glossary of Genetic Terms* is a free resource, available for download to mobile devices or computer. Genetic and genomic terms are defined via text and audio versions. Learn more at www.genome.gov/glossary.
- Telling Stories is a web-based multimedia education resource that uses real-life stories from the public and professionals to promote knowledge and understanding of genetics and how it affects people's lives. The collection of 100 stories from individuals, patients, caregivers, and professionals in text and video formats is mapped to education frameworks for nurses, midwives, medical students, and primary care physicians. Visit www.tellingstories.nhs.uk.

25 to 75 ng/mL.[15] Having reached this point, the patient may need to undergo phlebotomy only a few times a year.[15,16]

The patient's hematocrit/hemoglobin levels are checked before each phlebotomy. The Iron Disorders Institute Advisory Board recommends against phlebotomy (with a few exceptions) when hemoglobin is below 12.5 g/dL to prevent iron deficiency anemia.[15]

Another possible treatment is chelation therapy with deferoxamine or deferasirox. The benefit of chelation therapy is that the drug tightly binds iron and removes it from the body, reducing iron stores. However, this treatment is rarely used to treat HH because phlebotomy is simpler and equally effective.[12]

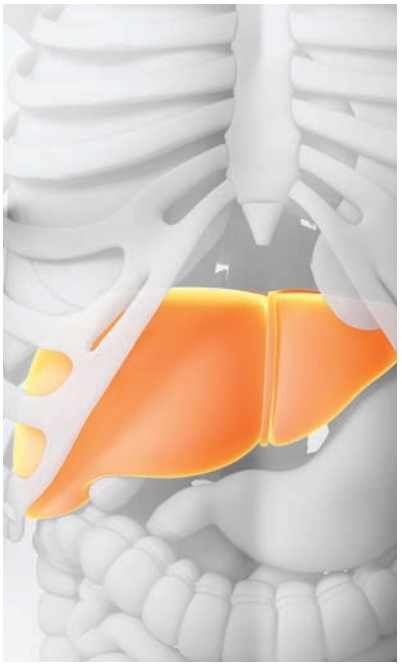
Dietary guidelines

Although dietary instruction is an important part of the treatment plan for a patient with HH, no special diet is required: Moderate amounts of iron-rich foods don't worsen the condition. However, the patient should be instructed to avoid vitamins or supplements containing iron or vitamin C, which can increase iron absorption. Alcohol in moderation is permissible unless liver disease has been diagnosed; in that case, the patient must avoid alcohol.

The patient should also avoid uncooked seafood because it may contain bacteria that grow well in an iron-rich environment. A bacterium found in raw shellfish and oysters, *Vibrio vulnificus*, thrives in iron-rich blood and organs and can be fatal if ingested; deaths have been reported from ingestion of raw oysters by people with HH.[8,13,17]

Preventing complications

In recent years, the number of patients who develop serious HH-related complications has been reduced due to such factors as more attention to abnormal routine blood test results, more widespread testing of those who have a relative diagnosed with the disease, and identification of patients with HH at a younger age. As a result, most people don't have complications at time of diagnosis.[12]



Symptom onset may be delayed in people who routinely donate blood, which removes excess iron.

Because the genetic mutation is passed from both parents to a child, clinicians recommend that first-degree relatives (parents, siblings, and children) of people with HH be screened. The purpose of the screening is to detect HH before symptoms or complications occur. The brother or sister of a person diagnosed with HH has a 1-in-4 chance of having the disorder from having inherited two copies of the C282Y mutation.

Ideally, first-degree relatives should be screened between ages 18 and 30, before serious tissue damage occurs. The recommendation for the first phase of screening is to order blood work for TS and serum ferritin. If results indicate increased iron stores consistent with HH, the healthcare provider will recommend genetic testing for *HFE* mutation.[2] If a couple has or plan to have children, testing the spouse of the affected person may also be recommended to determine if he or she carries the *HFE* mutation. Resources for patients and their families are available online from the CDC at www.cdc.gov/ncbddd/hemochromatosis/materials.html.

The case study continued

A literature search about HH by the nurse caring for Mr. W reveals that his risk factors include age, gender, ethnicity, family history, and no history of blood donation. Analysis of the physical assessment data indicates that his vague symptoms of fatigue, muscle aches, abdominal discomfort, and knee pain are consistent with HH pathophysiology. The medical treatment plan is established to include phlebotomy with monitoring of serum ferritin, hemoglobin, and hematocrit values.

Discharge teaching encompasses pre- and postphlebotomy instructions and discussion of dietary modifications; for example, education to avoid iron supplements or multivitamins with iron. Also important is the need for the patient to inform his blood relatives about their risk for this disorder. (For details, see *Patient teaching: Share this information with patients and their families,* and *Phlebotomy pointers.*)

The nurse's commitment to learning more about Mr. W's diagnosis is in accord with the nursing responsibility to provide competent care for patients with genetic disorders.[18] (See *Resources for keeping current*.) By achieving and maintaining competence in caring for patients

with genetic disorders, nurses help integrate the scientific advances of genetics and genomics into clinical practice. ■

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