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Understanding Hereditary Hemochromatosis

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Introduction

One of the most common genetic diseases, hereditary hemochromatosis is a disruption of iron regulation in the body. Its geographic distribution is worldwide, but it is most common in those of northern European origin. (Roach and Di Palma, 2012). Occurrence is rare in other racial or ethnic groups. (Emanuele, Tuason, & Edwards, 2014).

Symptoms are due to significant iron overload, normally as a result of HFE gene mutation. (Centers for Disease Control and Prevention, 2010). The HFE gene plays an important role in regulating iron absorption in the GI tract, transport, and storage. (Emanuele, et al., 2014).

If excess iron accumulates in vital organs, cirrhosis, bone and joint disease, diabetes, other endocrine disorders and heart disease can result. (Crownover & Covey, 2013).

Although penetrance (exhibition of phenotype, or clinical symptoms) varies in those with the genetic mutation, those who have the HFE mutation are much more genetically susceptible to iron overload as it manifests in hereditary hemochromatosis.

Patients can present with nonspecific complaints such as weakness, fatigue, changes in mental status, and arthralgia, so hereditary hemochromatosis can be missed or misdiagnosed if iron study testing is not performed. The most common route to diagnosis is through routine office visits or investiation of common complaints. (Brissot, Ball, Rofail, Cannon, & We Jin, 2011). In some cases, but not all, genetic testing may be appropriate. Other forms of iron overload must be considered as well when making a differential diagnosis.

Hereditary hemochromatosis has an autosomal recessive pattern; a carrier father and carrier mother have a 1 in 4 chance of having a homozygous child and a 50% chance of having a heterozygous (carrier) child. About 75% of homozygotes have expression of the disease with elevated serum ferritin levels, although there is some controversy as to the proportion which develops clinically significant disease. Environmental and genetic factors may interact to influence expression of hereditary hemochromatosis.(Roach & DiPalma,2012). Approximately 1 million people in the United States are homozygous for the mutation. (National Heart Lung and Blood Institute, 2011). According to Emauele, et al., (2014), 1 in 8 to 1 in 10 whites in the United States may be carriers of the affected HFE gene.

Signs and Symptoms

- Slow progression. Many are asymptomatic.
- Age of presentation typically 40-60 in men, post-menopause in women.
- Early signs and symptoms tend to be general and may include:
  - Weight loss
  - Fatigue
  - Joint discomfort
  - Abdominal discomfort
  - Weakness
  - Restless leg syndrome
  - Hair loss
  - Loss of libido
  - Changes in mental status/depression

  (Rojas-Roldan & Wilkins, 2014).
- With untreated advanced disease, patients may present with:
  - Hepatitis
  - Hepatomegaly
  - Hepatocellular cancer
  - Cirrhosis
  - Arrhythmias
  - Arthritis, particularly of the second or third metacarpophalangeal joints.
  - Cardiomyopathy
  - Bronzed, hyperpigmented skin
  - Diabetes Mellitus
  - Hypogonadism
- Laboratory findings:
  - Transferrin Saturation >45%
  - Serum ferritin levels > 300 ng/mL
  - Serum ferritin >200 in premenopausal females

  (Centers for Disease Control and Prevention, 2010).

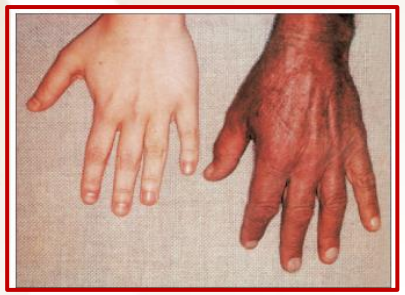

Figure 1. The hand on the right shows hyperpigmentation, or bronzing of the skin, due to iron overload in hereditary hemochromatosis.
Image Courtesy of Consultant 360.com

Underlying Pathophysiology

Hereditary hemochromatosis encompasses a range of iron overload disorders which are due to genetic misregulation of iron acquisition. (Vujic, 2014).

The specific mutation which accounts for most cases of hereditary hemochromatosis occurs at the major histocompatibility complex (MHC) region on the short arm of chromosome 6. A missense mutation is found at this locus in 80% of hereditary hemochromatosis patients. The mutation results in a cysteine to tyrosine substitution at amino acid 282 of the HFE protein (C282Y). (Vujic, 2014). This form of the disease is known as "hemochromatosis type 1". (Cherfane, Hollenbeck, Go, & Brown, 2013).

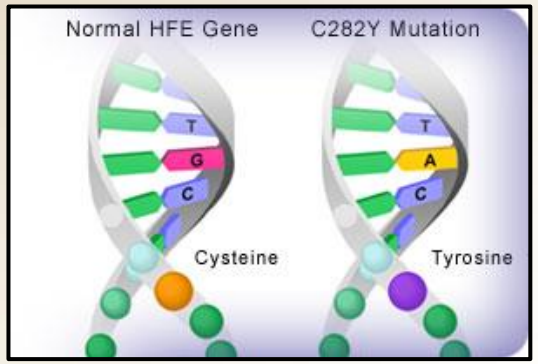

Figure 2. Normal HFE Gene Compared to C282Y Mutation in Hemochromatosis Type 1
www.CDC.gov

Normally, hepatocytes secrete the regulatory hormone hepcidin in response to excess iron intake. Hepcidin, a peptide hormone, decreases intestinal iron absorption by enterocytes and decreases iron release by macrophages, contributing to whole-body iron homeostasis. The HFE genetic defect alters expression of the protein which regulates hepcidin. (Crownover and Covey, 2013). Patients with hereditary hemochromatosis have insufficient hepcidin concentrations, resulting in unregulated iron absorption, mobilization, distribution, and storage. (Emanuele, et al., 2014). A major means of iron export from the body is the ferroportin-hepcidin pathway. Hepcidin binds with ferroportin, which is located on enterocytes (GI tract), macrophages, and hepatocytes, and regulates release of cellular iron. This pathway is disrupted due to low hepcidin levels. (Emanuele, et al., 2014).

Iron begins to enter the plasma at a high rate, leading to increased transferrin saturation and ferritin levels, and over time builds up in body tissues and organs, causing damage. (Emanuele, et al., 2014). Major organs adversely affected by iron deposition are the liver, pancreas, heart, pituitary gland, testicles, joints, and skin. Many of the presenting signs and symptoms are due to disruption of the normal function of these organs.

Main pathological findings in the liver are fibrosis and cirrhosis. Iron overload may contribute to the risk of diabetes, as it is associated with increased hepatic glucose production and metabolic inflexibility, both characteristics of type II diabetes. (Huang, et al., 2011).

Less common forms of hereditary hemochromatosis (types 2-4) are caused by mutations in genes other than HFE which help control iron regulation. (Cherfane, et al., 2013). A less common form of the type 1 mutation is at H63D, another locus of the HFA gene. Compound heterozygotes (those carrying the C282Y defect and another autosomal recessive mutation which could affect iron regulation) are susceptible to developing iron overload. accounting in part for variability in expression. Non-genetic factors such as alcoholism may contribute to disease progression.

Significance of Pathophysiology

Iron is "essential for cell metabolism and is a constituent of hemoproteins, such as hemoglobin, myoglobin, and cytochrome." (Crownover & Covey, 2013, p. 183). Any pathological process which disrupts the carefully regulated iron balance of the body will eventually affect entire body systems. Hereditary hemochromatosis, with an insidious onset and often generalized presenting systems, could slide under the radar or be misdiagnosed until more severe manifestations of iron overload appear. End-organ damage or clinical manifestations of hereditary hemochromatosis occur in approximately 10 percent of persons homozygous for C282Y. (Crownover & Covey, 2013). Considering the number of those homozygous for the disease, this is a significant portion of the population.

Hereditary hemochromatosis is associated with an increased risk for malignancies, such as hepatocarcinoma and breast cancer. "Approximately 6 percent of patients with hemochromatosis and cirrhosis develop hepatocellular carcinoma; this represents a 20-fold increased lifetime risk over the general population…" (Crownover & Covey, 2013, p. 183).

If untreated, hereditary hemochromatosis can lead to irreversible organ damage. Prognosis is worsened in those who develop cirrhosis, diabetes, or cardiomyopathy. "The 5-year survival rate in those who have untreated hereditary hemochromatosis and cirrhosis is reduced by 50 percent compared with those who do not have cirrhosis." (Crownover & Covey, 2013, p. 184.)

It is important to understand the progression of the disease, the broad spectrum of phenotypical expression, and the underlying genetic, hormonal, and environmental interplay at work in this disease in order to recognize and anticipate how body systems may be affected.

Implications for Nursing Care

Although patients may rarely present with the classic triad of symptoms described by Trousseau (bronzed skin, diabetes mellitus, and hepatomegaly), practitioners should also consider hereditary hemochromatosis in patients with nonspecific symptoms such as fatigue, arthralgia, weakness, cognition changes, or depression in conjunction with elevated transferrin saturation and ferritin levels. Medical professionals should be aware that expression of the disease is influenced not only by genetics but also by other factors such as alcoholism, iron rich diet, menstruation, age, and other diseases of iron malabsorption such as celiac disease.

If a patient is of northern European ancestry, this genetic disorder may be of particular concern in those with relevant symptoms.

There is debate among researchers about the usefulness of genetic testing. Population screening for the HFE mutation is not recommended by the Centers for Disease Control and Prevention, but should be performed in first degree relatives of those with HFE hemochromatosis. (Crownover & Covey, 2013). According to the Centers for Disease Control and Prevention, iron status testing is considered more clinically relevant than genetic testing for identifying those who have hemochromatosis (2010). Many times this disease is diagnosed in patients after routine office visits, so general practitioners should be aware of its nuances.

Conclusion

Hereditary hemochromatosis is the most common genetic disorder affecting whites in the United States. Most of those who are homozygous for the mutation are asymptomatic. Manifestation of symptoms correlates with body iron content, with symptoms worsening as iron levels increase. At the beginning of disease progression, patients may have nonspecific complaints, but may progress to signs of organ damage and early death.

Treatment for iron overload in hereditary hemochromatosis includes decreasing dietary iron intake and phlebotomy to decrease serum ferritin to the desired level. It is imperative that health practitioners know how to recognize and respond to hereditary hemochromatosis, preferably before irreversible organ damage occurs.

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