

Annotated Bibliography

Batts, Kenneth MD; Brandhagen, David MD; Fairbanks, Virgil MD; Thibodeau, Stephen MD. "Update on Hereditary Hemochromatosis and the HFE Gene." Mayo. 74 (1999): 917-921.

This article describes hereditary hemochromatosis as it is commonly known, bronze diabetes. It is referred to as bronze diabetes because hereditary hemochromatosis is usually diagnosed at advanced stages. However, recent studies indicate that the disease is being diagnosed at earlier stages and as a result, 75% of patients are asymptomatic and do not have cirrhosis or diabetes. The clinical importance of the HFE gene and its discovery has contributed significantly to early detection of the disease at asymptomatic stages.

Beutler, Ernest MD; Felitti, Vincent MD; Gelbart, Terri MD; Ho, Ngoc MS. "The Effect of HFE Genotypes on Measurements of Iron Overload in Patients Attending a Health Appraisal Clinic." American College of Physicians-American Society of Internal Medicine. 113 (2000) 329-336.

This article reports on a study conducted at a health assessment clinic of 10,198 patients' genotypes. The importance of knowledge about hemochromatosis is stressed based on its prevalence. Early treatment is recommended due to the ability to prevent and reverse hemochromatosis' clinical manifestations.

Burke, Wylie MD. "Hereditary Hemochromatosis: Gene Discovery and Its Implications for Population-Based Screening." JAMA 280 (1998): 172-177.

This article focuses on the discovery of the HFE gene and its implications of genetic testing for hemochromatosis. Genetic testing for hemochromatosis is simpler, more accurate and less expensive. It provides a reliable family-based case detection in most instances. However, this article also evaluates the social consequences involved with genetic testing.

Crowe, John MD; Eustace, Stephen MD; Kenny, Dermot MD; McCarthy, Conor MD; McCarthy, Geraldine MD. "Hereditary hemochromatosis: A Common, Often Unrecognized, Genetic Disease." Cleveland Clinic Journal of Medicine. 69 (2002): 224-242.

This article raises the issue of how hemochromatosis is often misdiagnosed. Hereditary hemochromatosis in people of northern European descent is more common than most physicians realize. However, early diagnosis and proper treatment can prevent complications and provide a normal life expectancy. Environmental and dietary factors affect the risks of the disease. Dietary recommendations are provided and therapeutic phlebotomy is described as a means to manage hemochromatosis.

Deluca, Salvatore MD, and Kinney, Thomas MD. "Idiopathic Hemochromatosis." Radiographic Highlights 44 (1991): 873-875.

Deluca and Kinney explain the various causes of hemochromatosis. They highlight the pathogenesis and pathology of idiopathic hemochromatosis and the effects of this disease. They also discuss the most common treatments used to remove excess iron stores.

"Fact Sheet/ Treatment and Maintenance/Diagnosis- How Do You Find Out." Health Information on Excess Iron and Iron Overload. 2002. Iron Overload Disease Association. 22 March 2004. <<http://www.ironoverload.org/facts.html>>.

The Fact Sheet lists 17 important points and statistics that are helpful to patients diagnosed with hemochromatosis or that are concerned about the disease. The list included prevention measures, possible treatments, what diets to avoid and patient's health goals. The Diagnosis section describes three possible tests physicians use for diagnosing the disease. The Treatment and Maintenance section describes the current most popular form of treatment and its duration.

"Hemochromatosis." Digestive Diseases Home. Aug. 2002. National Digestive Diseases Information Clearinghouse. 22 March 2004. <<http://www.digestive.niddk.nih.gov/ddiseases/pubs/hemochromatosis/index.htm>>.

This article provides a brief and informative synopsis of hemochromatosis. Causes, risk factors, symptoms, diagnosis, treatment, tests for hemochromatosis, and hope through research are explained simplistically. The causes and risk factors are the greatest area of interest.

Iron Disorders Institute. "Disorders: Hemochromatosis Introduction." 22 Sept. 2003. 20 March 2004 <<http://www.irondisorders.org/disorders/hem/>>.

This article defines Hemochromatosis (HHC) as a genetic disorder of metabolism. An individual with hemochromatosis absorbs too much iron. The excess iron cannot be excreted and it builds to toxic levels in the tissues of major organs. The organs that may be affected are identified as well as what those affects may be. This article also discusses the severity of undiagnosed and untreated HHC. The gene known as HFE was discovered in 1996 and is responsible for hemochromatosis. This article discusses patients who are most at risk and the signs and symptoms of hemochromatosis. It also provides possible tests to determine if one has hemochromatosis.

"Iron Overload and Hemochromatosis." Nutrition & Physical Activity. 4 Feb. 2004. National Center for Chronic Disease Prevention and Health Promotion. 22 Mar. 2004. <<http://www.cdc.gov/hemochromatosis/>>.

This article distinguishes the genetic and non-genetic causes of hemochromatosis.

In the United States the majority of cases are genetic and are referred to as hereditary hemochromatosis. This article identifies the signs and symptoms of various stages of hereditary hemochromatosis and the ages that these symptoms generally occur. Diagnosis and treatments are briefly discussed. The issue of whether donating blood is safe is also addressed.

“Will the Real Hemochromatosis Please Stand Up?” 15 June 1999. *Annals of Internal Medicine*. 19 March 2004. <<http://www.acponline.org>>.

This is an editorial from the perspective of a patient diagnosed with hemochromatosis and it indicates the importance of prevention care. The two HFE gene mutations associated with hereditary hemochromatosis are identified as C282Y and H63D. This article raises the issue of whether genetic testing should be done for all patients with elevated transferrin saturation.

The Importance of Hereditary Hemochromatosis Awareness

Idiopathic or Hereditary hemochromatosis is a severe disease in which most physician and Americans are not well-educated. It is a genetic disorder of metabolism in which the body absorbs iron in amounts greater than required for maintenance, generally about four times the normal amount, (Deluca and Kinney). One's inability to excrete the excess iron results in iron deposition predominately in parenchymal organs--the pancreas, liver, and heart. The spleen, kidney and skin also may contain about five times the normal amount of iron, (Deluca and Kinney, 1991). The iron deposits damage these organs and tissues and can be fatal, (Crowe, 2002). Hemochromatosis can develop into diseases such as diabetes, hepatic cirrhosis, heart trouble, arthritis, liver disease, neurological problems, depression, impotence, infertility, and cancer, ("Disorders: Hemochromatosis Introduction," 2003). Thirty-two million people in America (1 in 10) have the hemochromatosis gene mutation and are carriers of the disease. One and a half million people (1 in 250) have the double mutation and have hereditary hemochromatosis.

Although hereditary hemochromatosis is one of the most common genetic diseases affecting people of Northern European descent, it is under-diagnosed due to clinician's lack of sufficient awareness of the disease's prevalence, its long latency period and its nonspecific symptoms, (Crowe, 2002). Symptoms of hemochromatosis may mimic symptoms of other diseases. Doctors may then focus on these conditions caused by the disease rather than hemochromatosis itself, ("Hemochromatosis," 2002). Hereditary hemochromatosis is a very serious disease that if left untreated, it progresses from iron over-absorption to iron overload to

organ damage. “At least 50% of men and 25% of women with the disease are likely to develop life-threatening complications,” (Crowe, 2002).

In 1996 it was discovered that defects in the HFE gene, which help regulate the amount of iron absorbed from food, were associated with hereditary hemochromatosis, (“Will the real Hemochromatosis Please Stand Up?” 1999). The most common genotype associated with the disease is homozygous C282Y mutation. Most patients of European descent with hereditary hemochromatosis are homozygous for the C282Y mutation and have elevated transferrin saturation and serum ferritin levels (Beutler, 2000). This discovery has enabled physicians to detect hereditary hemochromatosis at much younger ages and has eliminated the need to conduct a liver biopsy to confirm the disease, (Batts, 1999). Patients can now be tested for mutations of the HFE gene by a whole blood sample or a cheek sample.

Iron build up in patients with classical heredity hemochromatosis is slow and may take years to build to destructive levels. Symptoms may not occur until one is in their 30’s, 40’s and 50’s. Men generally develop problems from excess iron at a younger age than women. Diagnosis generally occurs in later stages of one’s life, and therefore the disease has been misidentified as an older male’s disease. As a result, men are five times more likely than women to be diagnosed with the disease, (“Hemochromatosis,” 2002). However, it can affect males, females, and adolescents. No race, age, or sex is free from this disorder. However those of Northern European descent are most at risk, (“Disorders: Hemochromatosis Introduction,”2003). Early symptoms are nonspecific and may include weakness, fatigue, weight loss, abdominal pain, and arthralgia. Advanced stages can include liver cancer, liver cirrhosis, arthritis, diabetes, and heart failure, (“Iron Overload and Hemochromatosis,” 2004).

Currently most routine medical checkups do not include testing for iron overload, which is why many hemochromatosis cases remain undetected. Early detection of hemochromatosis is important because early diagnosis and treatment can prevent complications and provide a normal life expectancy. People who have symptoms congruent with the signs and symptoms of hemochromatosis and/or have blood relatives with hemochromatosis should be evaluated and monitored yearly. ("Fact Sheet," 2002). The disease is diagnosed with two simple and inexpensive blood tests that measure iron levels. Transferrin saturation determines how much iron is bound to the protein that carries iron in the blood. A safe range is between 12-44%. Serum ferritin measures the level of iron in the liver. A safe range is between 5-150ng/ml, ("Diagnosis," 2002). Danger zones include a percent saturation over 45% and or a serum ferritin over 150 ng/ml, ("Treatment and Maintenance," 2002).

If either the transferrin saturation or serum ferritin shows higher levels of iron in the body, then a blood test can determine an HFE mutation. Patients who fall within this danger zone should be treated to unload the body of excess iron as fast as possible. Therapeutic phlebotomy is the preferred treatment to reduce iron stores. Phlebotomy is the process of removing a full unit of blood, 500 mls., from a patient. This should be administered at least one or twice a week until serum ferritin levels fall below 10. This treatment may take six months to three years depending on the iron levels. Once a patient's ferritin level is reduced below 10, they are de-ironed. The phlebotomy schedule is changed to two to six times a year for the rest of the patient's life. Phlebotomy can decrease symptoms and improve life expectancy. Arthritis is the main exception, in which conditions cannot be improved even after excess iron is removed, ("Hemochromatosis," 2002).

Patients with hemochromatosis should not take iron supplements or vitamin C because it may cause them to experience symptoms earlier and experience more serious complications. Those with liver damage should also not consume alcoholic beverages because it may further damage the liver. Hereditary hemochromatosis is one of the few genetic diseases for which simple effective therapy exists, (Burke, 1998). Because an effective therapy is available, especially at early stages of the disease, the awareness of this disease and advocacy of population screening is important.

Based on physician's unawareness and misdiagnosis of hereditary hemochromatosis, I would encourage patients, on my web site, to ask their doctors to test their iron levels. If a blood relative of someone has hemochromatosis, I would recommend that the whole family be tested for the disease. I would assess the effectiveness of my Web site by examining the number of visitors to my site. I would also conduct further research to determine whether the number of misdiagnosed cases of hereditary hemochromatosis increases or decreases.