Hereditary Hemochromatosis (HH)

Overview

- What is Hereditary Hemochromatosis (HH)?

  Hereditary hemochromatosis (HH) is the most common form of iron overload syndromes, i.e. diseases in which too much iron builds up in one's body. This extra iron is toxic to the body and can damage organs, lead to illness or even death.

  There are three types of iron overload syndromes:

1. Hereditary hemochromatosis (HH) In this inherited disease, the genes that control the absorption of iron from the intestine are abnormal. This causes the intestine to absorb more iron than the body needs. This is the most common form of iron overload.

2. Secondary iron overload: In this condition, there is no genetic defect, but the intestine is stimulated to absorb more iron by other disorders. Examples of these disorders are anemias due to ineffective production and removal of red blood cells (thalassemia, aplastic anemia and sickle cell anemia) chronic liver disease and excessive intake of medicinal iron.

3. Parenteral iron overload: This occurs in patients who have received excessive amounts of iron either as blood transfusions or intravenous iron.

- What is the cause of HH?

  HH includes several genetic abnormalities, which cause the body to absorb excess iron from food. Since there is no way for the body to get rid of absorbed iron (other than bleeding or shedding of skin and intestinal cells), people with HH have to store the excess iron in cells of the liver, heart, pancreas, and other organs resulting in damage to these organs.

- Who gets HH?

  The most common genetic abnormality in HH is an abnormality of the *HFE* gene, which can be seen in about 90% of patients with HH. Inheritance is in an autosomal recessive pattern. Mutations in several other genes besides *HFE* are responsible for the remaining 10% of patients with HH. *HFE*related HH is one of the most common inherited disorders among Caucasians, with two copies of the *HFE* gene mutation seen in about 1 in 250 persons in the general population.

  A person who inherits the defective gene from both parents (someone who is homozygous) may develop HH. Studies indicate that about 60% of those who are homozygous for the *HFE* defect develop increased iron levels, but only some develop complications as a result of this iron overload. People who inherit the defective gene from only one parent (someone who is heterozygous) are carriers for the disease but usually do not develop it, although they may have slightly increased iron levels.

- What are the symptoms of HH?

  Symptoms may begin anywhere from 30 years to 60 years of age, although in some rare cases they can occur as early as 20 years.

  Many of the early symptoms of HH are nonspecific, including weakness and fatigue, impotence or decreased sex drive in men, early menopause in women and general muscle aches and abdominal pain. These symptoms can also be caused by a number of other medical problems unrelated to HH. With over 30 different symptoms associated with HH, the disease can be extremely difficult to diagnose. Women

usually are protected from developing symptoms until after menopause as regular menstrual blood loss depletes just enough iron to keep the disease under control.

If untreated, or not diagnosed early enough, iron will continue to build up in the organs and can lead to:

- Diabetes
- Joint pain
- Abnormal heart rhythms
- Heart failure
- Cirrhosis of the liver, liver failure, or (rarely) liver cancer

Many patients with advanced HH also have color changes in their skin giving it a bronzed appearance. This was one of the first clinical features recognized with this disorder, and is the origin of the name "hemochromatosis". This condition has also been called "bronze diabetes" for the same reason.

- How is HH diagnosed?

Blood tests can determine whether the amount of iron stored in the body is too high. The tests commonly performed are transferrin saturation and ferritin.

The transferrin saturation test determines how much iron is held by the protein that carries iron in the blood. A fasting transferrin saturation of 45 percent or higher, on at least two occasions, is considered a sign of iron overload and further tests need to be performed to confirm the condition.

The serum ferritin test acts as an indirect measure of iron storage in the body. Serum ferritin levels are considered to be in the normal range for males and postmenopausal females if they are between 20 and 300 µg/L. For premenopausal females, the normal range is between 20 and 200 µg/L. People with advanced HH may have serum ferritin levels as high as 15,000 µg/L. However, conditions other than HH can cause high serum ferritin levels, including liver disease, infection, cancer, heart disease, AIDS, metabolic disorders, and inflammatory conditions such as arthritis.

If either of these tests shows higher than normal levels of iron in the body, doctors can order a test called "*HFE* mutation analysis" to detect the HFE gene mutations, which will confirm the diagnosis. The test "*HFE* mutation analysis" determines mutations identified in the HFE gene. These are called C282Y and H63D. When patients have two copies of C282Y (one from each parent), they have HH. If they only have one copy of the C282Y, they are a carrier. Most patients with either one or two copies of the H63D mutation have no evidence of iron overload. If the mutation is not present, HH is not the reason for the iron buildup and the doctor will look for other causes.

Because HH is easily detected through tests for blood iron levels and by looking for mutations in the hemochromatosis gene (HFE), more doctors are diagnosing individuals with the disease before they have symptoms.

Doctors sometimes perform a liver biopsy in patients in order to determine the extent of liver damage and to distinguish between HH and other liver diseases. A liver biopsy is the only test that can tell whether cirrhosis is present, which is the only complication that affects the lifespan of someone with HH, since it increases the risk for liver cancer. A liver biopsy should be recommended for anyone with HH who has a ferritin level over 1000 µg/L and/or abnormal liver function test results.

Outside of those two conditions (ferritin > 1,000 µg/L or elevated liver tests) the likelihood of cirrhosis is so low it does not usually justify the risk of the procedure (2% chance of minor complications such as transient pain/low blood pressure and <0.1% chance of bleeding). A liver biopsy can also provide a clearer picture of the amount of iron that is being stored in the liver, which is known as hepatic iron concentration. Liver biopsy is also used in cases of apparent iron overload with a negative genetic test result and no other family history of HH.

- How is HH treated?

Treatment is simple, inexpensive, and safe. The first step is to rid the body of excess iron. This process is called phlebotomy, which means removing blood the same way it is drawn from donors at blood banks. Based on the severity of the iron overload, a pint of blood is taken once or twice a week for several months to a year, and occasionally longer. A phlebotomy of one unit of blood usually drops the ferritin

level by about 30 µg/L. Blood ferritin levels are tested periodically to monitor iron levels. The goal is to bring blood ferritin levels to the low end of normal and to keep them there. That means bringing the ferritin down to less than 50 µg/L.

Once iron levels return to normal, maintenance therapy begins, which involves removing a pint of blood every 2 to 4 months for life. Some people may need phlebotomies more often. Many patients who are having maintenance phlebotomy do so as blood donors. An annual blood ferritin test will help determine how often blood should be removed. Regular follow-up with a specialist who has an interest in hemochromatosis or iron overload disorder is also necessary. This may be a hematologist or a gastroenterologist/hepatologist.

If treatment begins before organs are damaged, associated conditions—such as liver disease, heart disease, arthritis, and diabetes—can be prevented. The outlook for people who already have these conditions at diagnosis depends on the degree of organ damage. For example, treating HH can stop the progression of liver disease in its early stages, which leads to a normal life expectancy. However, if cirrhosis, or scarring of the liver, has developed, the person's risk of developing liver cancer increases, even if iron stores are reduced to normal levels. People with diabetes resulting from damage to the pancreas usually see an improvement if not a reversal of their diabetes, depending on how much damage has occurred. Treatment cannot cure the conditions associated with established HH, but it will help most of them improve. The main exception is arthritis, which usually does not improve even after excess iron is removed.

People with HH should not take iron or vitamin C supplements. And those who have liver damage should not drink alcoholic beverages because they may further damage the liver or eat raw seafood because of a risk for a serious infection.

- Who should receive screening and counseling for HH?

Screening for HH—testing people who have no symptoms—is not a routine part of medical care or checkups. However siblings of patients who have HH should have their blood tested to see if they have the disease or if they are carriers. First degree relatives of patients who have the disease should be offered testing. Testing should include transferrin saturation, ferritin, and *HFE* mutation analysis (gene test). When considering testing of children of a patient, it may be easier to test the other parent first and if he/she is negative for any *HFE* mutations, then the children can only be carriers. However, if the other parent has a gene mutation, then the children should be offered gene testing. Whenever genetic testing is done, a certified genetic counselor should be available and informed consent should be obtained.

Doctors should counsel patients to have their close relatives be tested and consider testing people who have joint disease, severe and continuing fatigue, heart disease, elevated liver enzymes, impotence, and diabetes because these conditions may result from HH.

Since the genetic defect is common and early detection and treatment are so effective, some researchers and education and advocacy groups have suggested that widespread screening for HH would be cost-effective and should be conducted. However, there are concerns about possible genetic discrimination that could come about by identifying someone who never is going to have any disease progression.

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