# Hereditary Haemochromatosis

*In May 2013 we looked at advances in diagnosing iron deficiency and anaemia of chronic disease. This month we look at what happens when the body absorbs too much iron*.

Please note: The following discussion is for educational purposes only, and cannot be applied to specific cases.

**Contents**



Hereditary haemochromatosis (HHC) is the abnormal accumulation of iron in parenchymal organs, leading to organ toxicity. It is the most common cause of severe iron overload, and the most common inherited liver disease in Caucasians.

Two mutations in the HFE gene have been described in HHC.

- The C282Y mutation involves the substitution of tyrosine for cysteine at amino acid position 282.
- The H63D mutation involves the substitution of aspartic acid for histidine at amino acid position 63.
- C282Y homozygosity or compound heterozygosity (C282Y/H63D) is found in most patients with HHC.
- Cases of homozygotic C282Y without hepatic iron overload have been reported.

Secondary haemochromatosis has been reported in patients receiving repeated blood transfusions, for example in thalassaemia major.

## Signs and symptoms

Patients with HHC may be asymptomatic or may present with general and organ-related signs and symptoms. The symptoms of HHC usually present between 30 and 50 years of age, but they can occur earlier. Despite this, many patients remain asymptomatic and are diagnosed when elevated serum iron levels are noted on routine chemistry screening or when a relative is diagnosed with HHC.

Clinical manifestations can include the following:

- Liver disease (hepatomegaly and cirrhosis)
- Skin bronzing or hyperpigmentation
- Diabetes mellitus
- Arthropathy
- Amenorrhea, impotence, hypogonadism
- Cardiomyopathy

Early symptoms include severe fatigue (74%), impotence (45%), and arthralgia (44%), with fatigue and arthralgia the most common presenting symptoms.

## Liver disease

Liver function abnormalities occur in 35-75% of patients, and can be accompanied by signs of chronic liver disease, such as abdominal pain. Right upper quadrant tenderness with hepatomegaly or splenomegaly may be present.

***Platelets and Liver Disease***

The lineage-specific cytokine thrombopoietin (TPO) links hepatocellular function and thrombopoiesis. Most TPO production takes place within the hepatocytes, so TPO production is therefore dependent on functional liver cells and is reduced when there is marked liver damage.

*From: Thrombocytopenia in liver disease by M. Peck-Radosavljevic. (Can J Gastroenterol. 2000 Nov;14 Suppl D:60D-66D.)*

Cirrhosis is caused by progressive iron deposition in the liver and is one of the most common signs of the tissue damage caused by HHC. Cirrhosis may eventually lead to liver cancer (risk > 200-fold).

Reversal of cirrhosis following iron removal has been reported, usually early in the course of liver disease, although reversal of advanced liver disease with varices has also been reported.

***Anaemia and Liver Disease***

Anaemia is a common complication of chronic liver diseases. The causes of anaemia include acute or chronic gastrointestinal haemorrhage, and hypersplenism secondary to portal hypertension. Severe hepatocellular disease can predisposes to haemorrhage due to reduced coagulation factor production by hepatocytes and/or thrombocytopenia. In patients with chronic liver disease, anaemia may be exacerbated by deficiency of folic acid and/or vitamin B12 that can occur secondary to inadequate dietary intake or malabsorption.

*From: Spectrum of anemia associated with chronic liver disease by R Gonzalez-Casas, E A Jones and R Moreno-Otero.(World J Gastroenterol. 2009 October 7; 15(37): 4653–4658.)*

Some studies show that HFE mutations in patients with hepatitis C infection are associated with higher frequencies of fibrosis and cirrhosis. Increased fibrosis was also found in patients with nonalcoholic steatohepatitis who had the C282Y mutation.

## Skin bronzing or hyperpigmentation

A combination of iron deposition and melanin causes the skin bronzing or hyperpigmentation that is typical of HHC. The classic triad of cirrhosis, diabetes mellitus and skin pigmentation occurs late in the disease, usually when total iron body content is greater than 20g (ie, > 5-times normal).

## Diabetes mellitus

Diabetes, often requiring insulin therapy, occurs due to progressive accumulation of iron in the pancreas. The damage appears to be relatively selective for the pancreatic beta cells. Most patients with haemochromatotic diabetes have other signs of HHC, such as liver disease or skin pigmentation.

## Arthropathy

Arthropathy is due to iron accumulation in joint tissues. It is associated with characteristic radiologic findings in the metacarpophalangeal (MCP) joints, particularly in the second and third metacarpal joints. Symptoms usually do not respond to iron removal.

The most commonly affected joints include:

- Metacarpal joints
- Proximal interphalangeal joints
- Knees
- Feet
- Wrists
- Back
- Neck

## Amenorrhea, impotence, hypogonadism

Amenorrhea, loss of libido, impotence, and symptoms of hypothyroidism can be seen in patients with HHC, with amenorrhea in women less common than hypogonadism in men.

Hypogonadism is the most common endocrine abnormality causing decreased libido and impotence in men. It is usually due to pituitary iron deposition. Primary hypogonadism, presumably due to testicular iron deposition, can also occur but is much less common.

## Cardiomyopathy

Younger patients may present with cardiac enlargement, with or without heart failure or conduction defects. HHC with C282Y/C282Y or C282Y/H63D is not usually associated with ischaemic heart disease or myocardial infarction.

## Other manifestations

Osteopenia, osteoporosis, hair loss and koilonychia (spoon nails) may occur in patients with HHC.

Of patients with HHC, 25% have osteoporosis, while 41% are diagnosed with osteopenia. The osteoporosis is associated with hypogonadism, increase in alkaline phosphatase, increase in body weight and the severity of iron overload.

Partial loss of body hair is evident in 62% of patients. The pubic area is affected most commonly, although total loss of body hair is seen in about 12% of patients. Hair loss and thinning may be reversed by therapy in some patients.

Koilonychia, usually of the thumb and index and middle fingers, is seen in almost half of patients.

## Laboratory tests

The following discussion is of a general nature and does not reflect Clinpath policy regarding testing and diagnosis in HHC.

Laboratory studies used in evaluating suspected HHC include the following:

- Transferrin saturation.
- Serum ferritin.
- Genetic testing
    - Detection of HFE mutations C282Y and H63D.

### Transferrin Saturation

Transferrin saturation corresponds to the ratio of serum iron and total iron-binding capacity (TIBC). Transferrin saturation is influenced by inflammation and liver diseases other than HHC, so it has limitations as a diagnostic tool. The screening threshold for HHC is a fasting transferrin saturation of 45-50%, with a transferrin saturation of greater than 45% indicating the need for genetic testing for the presence of the C282Y or H63D. It should be noted that approximately 30% of women younger than 30 years who have HHC do not have elevated transferrin saturation.

### Serum Ferritin Studies

The ferritin level is less sensitive than transferrin saturation as a screening test for HHC, but may give information about disease progression. Ferritin concentration higher than 1000 µg/L suggests liver damage with fibrosis or cirrhosis. Serum ferritin levels greater than 200 µg/L in premenopausal women, and greater than 300 µg/L in men and postmenopausal women, usually indicate primary iron overload due to HHC, especially when associated with high transferrin saturation and evidence of liver disease.

### Genetic Testing

Genetic tests for the C282Y and H63D mutations are widely available, and genetic testing for the HFE mutation is recommended for all first-degree relatives of patients with HHC and also in patients with evidence of iron overload. This is particularly important in patients with known liver disease and evidence of iron overload, even if other causes of liver disease are present.

Only homozygosity for C282Y and compound heterozygosity for C282Y/H63D should be considered indicative of HHC. C282Y heterozygosity may contribute to iron overload due to other conditions, but it should not be considered the sole cause of iron overload and it should not be considered diagnostic of HHC.

HFE genotyping cannot provide information about the degree of increased body iron stores or organ damage.

## Pathophysiology

HHC is an adult-onset disorder that represents an error of iron metabolism characterized by inappropriately high iron absorption resulting in progressive iron overload. This disease is the most common cause of severe iron overload.

In the body, excess iron causes damage by production of free radicals. The presence of free iron in biologic systems can lead to the rapid formation of damaging reactive oxygen metabolites, such as the hydroxyl radical and the superoxide radical. These can result in DNA cleavage, impaired protein synthesis and impairment of cell integrity and cell proliferation, leading to cell injury and fibrosis.

Derangement of iron homeostasis is also linked to susceptibility to infectious diseases. Studies performed on Hfe knockout mice (the HHC model) showed an attenuated inflammatory response induced by lipopolysaccharide and Salmonella. Ferroportin, the macrophage iron exporter, was up regulated, and this phenomenon was linked with the presence of a decreased level of iron in macrophages.

### *Daily iron losses and absorption*

Adults preserve a constant level of body iron by efficient conservation, maintaining rigorous control over absorption to balance losses. An adult man loses approximately 1 mg of iron daily, mostly in desquamated epithelium and secretions from the gut and skin. During the childbearing years, healthy women lose an average of an additional milligram of iron daily from menstrual bleeding (40 mL blood loss) and approximately 500 mg with each pregnancy. In addition, normal daily faecal loss of approximately 0.7 mL of blood (0.3 mg of iron) occurs. Only a small quantity of iron is excreted in the urine (< 0.1 mg/day).

In healthy adults, losses are balanced by absorption of sufficient dietary iron (1-2 mg) to maintain a relatively constant amount of body iron throughout life. Although excretion is quantitatively as important as absorption in the maintenance of iron balance, absorption usually plays the more active regulatory role. In HHC, dysregulation of intestinal iron absorption occurs, allowing iron to be absorbed despite a significant elevation of body iron stores.

### *HFE gene missense mutations*

The gene associated with most cases of HHC is called HFE and is located within the human leukocyte antigen (HLA) class I region on chromosome 6, between the genes coding for HLA-A and HLA-B. This gene is mutated in most individuals with HHC, and the 2 missense mutations (C282Y and H63D) of the HFE gene are responsible for most cases of HHC in patients of European descent. The clinical significance of other rarer forms of compound heterozygosity, such as heterozygosity for C282Y and a mutation in which cysteine replaces serine at position 65 (S65C) or heterozygosity for H63D and S65C, is controversial.

### *HHC types 2 and 3*

The gene for HHC type 1 (HFE1), the result of the C282Y and H63D mutations, is located at band 6p22 and encodes a protein containing 343 amino acids. Two other types of HHC have been identified:

- Juvenile HHC (JH), also called type 2 (gene HFE2), with the gene mapped to band 1q21. (This gene may also be referred to as HJV as its product is hemojuvelin.)
- An adult form designated HHC type 3 (gene HFE3) which results from mutations of the transferrin receptor 2 gene (TfR2) located on band 7q22.

Since the clinical appearance of the different types of HHC may be similar, patients with HHC who lack the HFE1 type mutations should be evaluated for other possible types of HHC.

### HAMP gene mutation

Rare cases of juvenile HHC have been linked to a homozygous mutation in the HAMP gene, which encodes hepcidin, a peptide that plays a key role in human iron metabolism. However, most juvenile-onset cases have been mapped to chromosome 1q, where the gene that produces hemojuvelin, HJV (also called HFE2), has been identified.

### Hepcidin deficiency

Evidence indicates that certain forms of HHC are caused by hepcidin deficiency. Studies suggest that the product of the TfR2 gene (see above) is a modulator of hepcidin production, as hepcidin was low or undetectable in most patients homozygous for the TfR2 mutation.

In May 2013 the Haematology Case Study looked at the article "Diagnosis of Iron Deficiency and Anaemia of Chronic Disease" by Julie Fielding. (This article is in the May 2013 Case Study folder on the T drive.) One of the assays that has the potential for routine diagnostic use is Hepcidin. To quote Fielding's article:

"*Hepcidin is now recognized as the major systemic (negative) regulator of iron through its ability to degrade ferroportin and subsequently to inhibit extracellular iron transit. An increase in hepcidin levels leads to reduced dietary iron absorption in intestinal enterocytes and also a blockade of iron export from the RES. Hepcidin has been shown to respond rapidly to changes in haematological status with anaemia, hypoxia and erythropoiesis all suppressing hepcidin expression. Synthesis of hepcidin is stimulated by iron overload, an increase in BMPs or the presence of inflammatory cytokines such as interleukin-6 (Il-6), interleukin-1 (Il-1), tumour necrosis factor (TNF β) or interferon gamma (If γ).*"
(*Page 3*)

## Epidemiology

The worldwide frequency of the C282Y mutation is about 1.9% and that of the H63D mutation is about 8.1%. HHC has the same prevalence in Europe, Australia, and other Western countries, with the highest prevalence being noted in people of Celtic origin. The frequency of the C282Y mutation is much lower among Hispanic persons (0.27 per 1000 population), Asian Americans (< 0.001 per 1000 population), Pacific Islanders (0.12 per 1000 population), and black persons (0.14 per 1000 population) than among persons of northern European descent. The frequencies of the C282Y and H63D mutations vary in black individuals from different geographic regions of the United States as a result of white admixture.

### Sexual differences in the incidence of iron overload

Men are affected with clinical HHC nearly 2-3 times as often as women, with an estimated ratio of 1.8:1 to 3:1.

Disease related to iron overload is more likely to develop in men who are homozygous for the C282Y mutation, rather than women, especially when serum ferritin levels are 1000 µg/L or more. The increased prevalence of iron overload related disease in C282Y homozygous men, when compared with that in women, is usually ascribed to recurrent physiologic blood loss and the resultant slower accumulation of iron in women. In a study of relatives of HHC patients who are homozygous for the C282Y mutation, iron overload was seen in 85% of males and 69% of females.

Men have also been reported to have a higher incidence of serious complications of HHC, primarily diabetes mellitus and cirrhosis. In men, the incidence of cirrhosis was 25.6% (13.8% in women), and the incidence of diabetes mellitus was 15.9% (7.4% in women). Women complained more often of fatigue 64.8% (42% in men) and skin hyperpigmentation 48% (44.9% in men).

### Age-related differences in the incidence of iron overload

In women, symptoms of HHC usually appear later, probably because menstruation causes physiologic blood loss, which increases iron removal.

## Treatment

Early diagnosis is essential in HHC. The goal of therapy in patients with iron overload disorders is to remove the iron before it can produce irreversible damage.

### Phlebotomy

Once diagnosed, HHC is usually treated by phlebotomy to rid the body of excess iron and to maintain normal iron stores. Phlebotomy is the preferred treatment for HHC and should be performed until iron-limited erythropoiesis develops, identified by failure of the haemoglobin level and/or haematocrit to recover before the next phlebotomy. It should be continued until transferrin saturation is less than 50%.

Most patients require maintenance phlebotomy with 1 unit of blood removed every 2-3 months. Therapeutic phlebotomy may improve or even cure some of the manifestations and complications of the disease, such as fatigue, elevated liver enzymes, hepatomegaly, abdominal pain, and hyperpigmentation. Other complications usually show little or no change after phlebotomy.

Regular monitoring of haematocrit, haemoglobin, and serum ferritin levels is necessary in patients undergoing phlebotomy. Genetic testing for HHC should also be performed in family members of patients with HHC.

### Iron chelation therapy

Patients affected with anaemia cannot be treated with phlebotomy. In these cases, use of iron chelating agents (eg, desferoxamine, deferiprone, deferasirox) is recommended.

## Prognosis

Increased diagnostic awareness has improved early diagnosis of HHC with the early detection and treatment resulting in a normal lifespan in patients with HHC.

The most important prognostic factor at the time of diagnosis is the presence or absence of hepatic fibrosis or cirrhosis. Patients without significant hepatic fibrosis may be expected to have a normal life expectancy if they undergo adequate phlebotomy therapy.

Mortality is estimated to be 1.7 cases per 10,000 deaths. The death rate associated with HHC increased from 0.5 persons per million population in 1968 to 0.9 persons per million population in 1992 probably due to improved recognition of the disease.

## Screening

The American Association for the Study of Liver Diseases (AASLD) guidelines recommend screening of high-risk groups such as those with suggestive organ involvement, a familial history of HHC and those with biochemical or radiologic abnormalities suggestive of iron overload.

## Dietary Considerations and Prevention

Dietary factors may influence the expression of HHC by altering iron absorption, however these dietary changes may not be feasible for all patients.

Patients should not consume foods that contain large concentrations of bioavailable iron, such as red meats and organ meats. In addition, they should not use iron supplements, including multivitamins with iron.

Substances in foods and drinks, including tannates (in tea), phytates, oxalates, calcium, and phosphates can bind iron and inhibit its absorption.

Alcohol abuse may accelerate disease progression. Ethanol may increase iron absorption, and certain alcoholic drinks, especially red wine, contain relatively high concentrations of iron. Activity of hydroxyl free radicals is elevated by iron-containing diets combined with alcohol intake, and this is implicated in hepatocarcinogenesis. Ingestion of 30 g or more of ethanol daily potentiates hepatic injury due to iron overload and increases the relative risk for primary liver cancer in persons with cirrhosis. Patients with evidence of hepatic injury should consume little or no ethanol. Other patients should consume ethanol in moderation.

Vitamin C (ascorbic acid) increases intestinal absorption of inorganic iron. No reason exists to discourage patients from eating fresh fruits and vegetables containing vitamin C, but ingestion of vitamin C supplements should be limited to no more than 500 mg/day. Ideally, mineral supplements should be used for specific deficiencies only.

Seafood from potentially contaminated waters must be cooked thoroughly. Raw or improperly cooked shellfish is sometimes contaminated with *Vibrio vulnificus* and can cause sepsis in patients with HHC.

## Reference

Duchini, A., Sfeir, H. E. & Klachko, D. M. (2013). *Hemachromatosis*. Downloaded from emedicine http://emedicine.medscape.com/article/177216-overview on 16/8/2013.