Haemochromatosis

William Rosenberg

What's new?

- Hepcidin has been identified as the key regulator of iron absorption and macrophage iron release
- At least five different types of hereditary haemochromatosis are now recognized
- There is greater awareness that the common genotype of haemochromatosis has a relatively low penetrance
- The recognition that penetrance of *HFE* mutations is variable has led to a search for other genes that modify patterns of iron loading
- Transferrin receptor-2, ferroportin, haemojuvelin and hepcidin have been identified as proteins implicated in rare forms of hereditary haemochromatosis

Abstract

Hereditary haemochromatosis is the syndrome of end-organ damage due to progressive iron accumulation caused by genetic disorders. It is the commonest genetic disorder of northern Europeans. In over 90% of cases the disease is associated with mutations in the *HFE* gene. Identification of the genetic basis of rare causes of hereditary haemochromatosis has greatly increased understanding of iron metabolism. Symptoms of haemochromatosis are frequently non-specific and include abdominal pain, arthralgia and general malaise. Iron accumulates predominantly in the liver, leading to liver dysfunction, and ultimately to cirrhosis and hepatocellular cancer. Iron accumulation in the pancreas and joints result in diabetes and degenerative arthritis. Diagnosis of the common form of haemochromatosis can be made in the majority of cases using biochemical tests of iron, transferrin and ferritin combined with genetic tests for mutations in *HFE*. Liver biopsy may reveal a characteristic pattern of iron deposition in periportal hepatocytes, with relative Kupffer cell sparing and liver fibrosis that may progress to cirrhosis. Treatment with phlebotomy removes iron in haemoglobin, drawing iron out of other tissues. This can effectively reduce the morbidity and mortality of the disease if diagnosed in the pre-cirrhotic state. Due to the poor specificity of symptoms, late diagnosis remains a problem and is associated with significant morbidity and mortality. Screening with biochemical and genetic tests, particularly in families, may prevent disease.

Keywords biochemistry; cirrhosis; genetics; haemochromatosis; iron; liver; macrophages; phlebotomy

Iron is vital for many basic cellular processes, including the transport of oxygen and electrons. In excess, these potent oxidative processes can lead to tissue damage and fibrosis, resulting in organ failure. Iron overload may occur as a genetic condition termed 'hereditary haemochromatosis' (HHC) or as a secondary event (Table 1). Tight regulation of iron metabolism is vitally important. Maintenance of iron homeostasis is effected through communication between the cells that absorb iron (duodenal enterocytes), utilize iron (erythroid precursors) and store iron (hepatocytes and tissue resident macrophages). A newly identified β-defensin-like antimicrobial peptide, hepcidin,[1,2] is thought to be the molecule that controls iron absorption and macrophage iron release. The genetic and metabolic defects that cause HHC have recently been defined, increasing knowledge of the condition and making screening, testing and early diagnosis and treatment feasible.

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Causes of iron overload

Primary iron overload
- Hereditary haemochromatosis (C282Y, transferrin receptor-1, ferroportin)
- Congenital aceruloplasminaemia
- Congenital atransferrinaemia

Secondary iron overload
- Parenteral iron loading (blood transfusion, iron dextran infusions, chronic haemodialysis)
- Iron-loading anaemia (thalassaemia, sideroblastic anaemia, pyruvate kinase deficiency)
- Liver disease (post-portacaval anastomosis)
- Dietary iron overload (prolonged oral iron therapy)

Complex iron overload
- Juvenile haemochromatosis
- Neonatal haemochromatosis
- Alcoholic liver disease
- Porphyria cutanea tarda
- African iron overload (Bantu siderosis)

Table 1

Aetiology

Finch and Finch first recognized HHC as a familial disorder in 1955. In 1996, positional cloning and linkage studies isolated the responsible gene (*HFE*) on chromosome 6p; 90% of cases of classical HHC are associated with homozygous substitution of tyrosine for cysteine (C282Y) at position 282 of the *HFE* protein. A second mutation at position 63 changes histidine to aspartic acid (H63D), but this seldom appears to cause iron overload except in individuals heterozygous for H63D and heterozygous for C282Y (compound heterozygosity).

HFE encodes a class 1 HLA-like protein which, when associated with β_2-microglobulin, is transported to the basolateral cell surface where it binds to transferrin receptor-1. The C282Y mutation prevents HFE from associating with β_2-microglobulin, but how this leads to HHC remains to be elucidated. In 10% of cases the cause of HHC cannot be attributed to mutations in *HFE* mutations. The search for other causes of hereditary iron overload has led to the identification of rare gene defects that effect iron metabolism to produce distinct syndromes of hereditary iron overload. Mutations in the haemojuvelin gene[3] (HJV) and hepcidin gene[2] (HAMP) cause iron overload in the first two decades of life leading to cardiac damage (juvenile haemochromatosis). Mutation in the transferrin receptor 2 gene[4] (TFR2) and ferroportin gene[5] (SLC40A1) have also been shown to account for rare causes of HHC.

In the UK, homozygosity for C282Y is found in 1/300 population, but only a minority of homozygotes have iron overload. Expression of the disease is influenced by environmental factors including dietary iron intake, alcohol and blood loss (e.g. menstruation). The heterozygote carrier frequency rate of 1/10 makes HHC the most common human recessive genetic disorder in Northern Europeans, suggesting selection pressure for the mutation (perhaps via protection from anaemia or an infectious agent). The C282Y mutation is almost exclusively found in populations of Celtic origin.

Clinical features

HHC is usually asymptomatic in the early stages, but as iron deposition progresses, end-organ damage may lead to:

- skin pigmentation
- liver failure
- maturity-onset diabetes mellitus
- arthopathy (commonly affects metacarpophalangeal joints, wrists and knees and may be complicated by chondrocalcinosis and pseudogout)
- cardiac failure or cardiac dysrhythmia
- anterior pituitary dysfunction (loss of libido may antedate other clinical manifestations).

Clinical manifestations usually become overt at age 40–50 years. Women are protected by iron loss through menstruation and pregnancy and thus often present later than men.

Liver disease is the most common clinical manifestation of HHC. Iron accumulates preferentially in hepatocytes (initially periportal), with relative sparing of Kupffer cells (in contrast to secondary iron overload). With progressive iron loading, fibrosis leads to cirrhosis despite the absence of an overt necro-inflammatory reaction. Cirrhosis carries a risk of hepatocellular carcinoma; most tumours are multifocal and/or metastatic by the time they are symptomatic.

Juvenile haemochromatosis (JH) typically presents in the second decade of life, and in contrast to HHC commonly presents with abdominal pain, hypogonadatrophic hypogonadism, cardiac arrhythmias, intractable cardiac failure and impaired glucose tolerance, Two causes of juvenile haemochromatosis have been identified.

- *HJV* exists in membrane bound and soluble forms. JH is associated with mutation in HJV located in the region that encodes the membrane binding part of the molecule and are associated with low or unmeasurable levels of hepcidin. It has been suggested that excess soluble HJV binds to neogenin in the liver to down regulate hepcidin leading to iron overload.
- The first gene identified as a cause of JH was hepcidin antimicrobial peptide (HAMP). Identification and subsequent study of this important peptide has greatly advanced understanding of the biology of iron regulation.

Transferrin receptor 2 deficiency – TFR2 is expressed predominantly in the liver and erythroid precursors. Genetic haemochromatosis linked to mutations in the TFR2 gene is rare and appears to be clustered in families of Southern European origin. It is thought that TFR2 is the sensor of plasma transferring saturation in the signalling pathway that regulates hepcidin, accounting for the low levels of hepcidin found in patients with TFR2 mutations.

Ferroportin disease – ferroportin is expressed mainly in Kupffer cells and splenic macrophages, at the basolateral border of enterocytes and to a lesser extent in hepatocytes. It functions as an iron exporter and is tightly regulated by hepcidin. Hepcidin binds to ferroportin in epithelial cells and macrophages and induces internalization and degradation of ferroportin, thus blocking iron export. Mutations in SCL40A1 appear to render ferroportin unresponsive to hepcidin. Ferroportin disease differs from classical HHC. Young patients present with isolated hyperferritinaemia and normal or slightly elevated transferring saturation. Marked hepatic iron overload develops with characteristic accumulation of iron in Kupffer cells (in contrast to classical HHC). Therapeutic phlebotomy is often poorly tolerated, leading to iron deficiency anaemia.

Investigations

Genetic testing is widely available. In its absence, HHC may be diagnosed using clinical tests to detect iron overload (Table 2). When clinical suspicion is high, patients should be managed on the basis of clinical criteria irrespective of genetic results (10% lack the common *HFE* mutations). With the advent of genetic testing, it is anticipated that, in future, HHC will be diagnosed most commonly in asymptomatic individuals. Other genetic forms of HHC are very rare, particularly amongst patients of northern European origin. Investigation of these patients requires access to specialist genetic services.

Liver biopsy is often useful to confirm the diagnosis, to exclude other pathology and to assess prognosis. Biopsy is unnecessary

