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Diagnosis and management of hereditary haemochromatosis

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Hereditary haemochromatosis is an autosomal recessive genetic disease in which increased intestinal absorption of iron causes accumulation in tissues, primarily the liver, sometimes leading to organ damage. Liver deposits may result in cirrhosis and even death. A systematic review has shown that about 0.4% of people of northern European descent have the genetic mutation that increases the risk of developing haemochromatosis, but the clinical penetrance of the mutation is much lower than the genetic prevalence. Symptoms and signs are initially non-specific, so the disease is often diagnosed at a late stage when substantial organ damage has already occurred. The challenge is to avoid both overdiagnosis and underdiagnosis. Since the discovery of the genetic mutation, new knowledge has come to light on the pathophysiology and course of the disease. This has led to new recommendations on diagnosis and treatment. In addition, new treatments are under evaluation. We review evidence from experimental and observational studies, systematic reviews, and guidelines to summarise for the general reader the clinical presentation, diagnosis, systematic reviews, and guidelines to summarise for the general reader the clinical presentation, diagnosis, including early screening options, and management of hereditary haemochromatosis.

What is hereditary haemochromatosis?

“Hereditary haemochromatosis” is a heterogeneous group of disorders (box) related to deficiency of the iron regulatory hormone hepcidin (fig 1). Organs that may be affected by iron deposits include the liver, pancreas, joints, heart, skin, and gonads. Hereditary haemochromatosis must be distinguished from secondary forms of iron overload, such as those caused by repeated red blood cell transfusions or anaemia owing to ineffective erythropoiesis (fig 2). Although all lead to raised serum iron parameters, they are treated differently. Recent consensus from the European Association for the Study of the Liver (EASL) defines hereditary haemochromatosis as “C282Y homozygosity and increased body iron stores with or without clinical symptoms.”

A meta-analysis of 2802 people of European ancestry who had clinical iron overload found that 81% were homozygous for the C282Y mutation in the HFE gene on the short arm of chromosome 6. A smaller proportion (5%) were compound heterozygous for the C282Y/H63D mutations. Several other mutations in the HFE gene have been described, but these are rare. Here, we focus on C282Y homozygous haemochromatosis with increased body iron stores, which we refer to as haemochromatosis.

A systematic review of longitudinal prognostic studies found that 38-76% of homozygous people develop higher iron parameters, such as ferritin and transferrin saturation in the blood (biochemical penetrance). However, clinical penetrance is lower—2-38% in men and 1-10% in women. The lower clinical penetrance in women is thought to result from iron loss through menstrual bleeding and childbirth, although evidence is lacking. Genetic polymorphisms, antioxidant activity, inflammation, and environmental factors—such as alcohol misuse, steatosis, and coexisting viral infections—also seem to modify the risk of developing clinically overt disease.

What are the presenting symptoms and signs?

Diabetes, bronzing of the skin, hepatomegaly, and arthropathy, especially of the second and third metacarpophalangeal joints, are typical presenting features. However, these are symptoms of advanced disease, and symptoms in early disease are non-specific. Case reports and observational studies have identified a wide range of other symptoms such as fatigue, arthropathy in other
A decrease in hepcidin production results in raised plasma iron values and accumulation of iron export by ferroportin from duodenal enterocytes and reticuloendothelial macrophages. Serum hepcidin concentrations. Hepcidin controls the plasma iron concentration by inhibiting synthesis of the iron regulatory hormone hepcidin in hepatocytes result in a decrease of and mucosal cells and from blood loss. Defects in genes encoding proteins that regulate regulated only by absorption, while iron loss occurs only passively from sloughing of skin is absorbed and lost every day. Importantly, the total amount of iron in the body can be largest flux of iron involves the recycling of iron from senescent erythrocytes out of macrophages for incorporation into erythroid precursors (all values are approximate). Liver and reticuloendothelial macrophages function as major iron stores. Only 1-2 mg of iron macrophages for incorporation into erythroid precursors (all values are approximate). Liver and reticuloendothelial macrophages function as major iron stores. Only 1-2 mg of iron

**Fig 1 | Role of hepcidin in the pathophysiology of hereditary haemochromatosis.** The largest flux of iron involves the recycling of iron from senescent erythrocytes out of macrophages for incorporation into erythroid precursors (all values are approximate). Liver and reticuloendothelial macrophages function as major iron stores. Only 1-2 mg of iron is absorbed and lost every day. Importantly, the total amount of iron in the body can be regulated only by absorption, while iron loss occurs only passively from sloughing of skin and mucosal cells and from blood loss. Defects in genes encoding proteins that regulate synthesis of the iron regulatory hormone hepcidin in hepatocytes result in a decrease of serum hepcidin concentrations. Hepcidin controls the plasma iron concentration by inhibiting iron export by ferroportin from duodenal enterocytes and reticuloendothelial macrophages. A decrease in hepcidin production results in raised plasma iron values and accumulation of iron in the body.

How can haemochromatosis be distinguished from other diseases?

To treat patients correctly, clinicians need to distinguish haemochromatosis from other diseases that result in iron overload, from diseases that lead to high serum ferritin without iron overload, and from diseases that present in a similar way, particularly with liver dysfunction. The differential diagnoses are listed in the box.

The first tests to do in patients with suspected iron overload are measurement of iron and transferrin (which enables transferrin saturation to be calculated) and serum ferritin (fig 2). HFE genetic testing is needed only in those with increased transferrin saturation and after exclusion of common causes of hyperferritinaemia: inflammation (check C reactive protein), chronic alcohol consumption, liver cell necrosis (alanine aminotransferase), metabolic syndrome (blood pressure, body mass index, triglycerides, and glucose), anaemia (haemoglobin, mean cellular volume, and ethnic background) as recommended by international guidelines (box). If the patient is C282Y homozygous the diagnosis of HFE haemochromatosis can be established. In the absence of these mutations, perform magnetic resonance imaging to assess liver iron stores. If liver iron is high and other diseases with liver iron loading, especially iron loading anaemias, have been excluded, perform molecular analysis for rare HFE mutations and mutations in the genes that encode haemojuvelin, hepcidin, transferrin receptor 2, and ferroportin, according to clinical, laboratory, and pathological features.

People who present with symptoms of haemochromato-
sis and who are C282Y homozygous typically have higher than normal transferrin saturation and ferritin as a result of pathological features.
With high iron load ferritin is usually high, and this may correlate with the development of signs and symptoms of iron overload.10

**PATIENT’S STORY**

The first symptom was painful swelling of my hand, for which I was referred to a rheumatologist. He suspected haemochromatosis because of my bronzed skin and ordered the relevant tests. In retrospect, this explains my “fatty liver” that had been diagnosed by a screening test at work. After the diagnosis I was treated with frequent phlebotomies, which made me so tired that I could no longer work full time. Currently, my worst problem is pain in my hips and finger. None of the available painkillers is effective. Furthermore, I have fatigue, which means that I have to plan my activities carefully. Thirdly, I have erectile dysfunction. Fortunately, my wife and I have found other ways to reach intimacy. My children and my sisters have been screened for the mutation and had their iron parameters measured. Luckily, none of them are affected. I used to undergo phlebotomies biweekly. However, since I have been given esomeprazol my iron parameters remain stable and I no longer need to be bled. I worry about symptoms that might arise in the future, such as problems with my heart.

Transferrin saturation

Transferrin saturation is the proportion of the iron transport protein transferrin that is saturated with iron; it is calculated as follows: ((serum iron (μmol/L):25)/transferrin (g/L))×100%. In haemochromatosis, transferrin saturation is generally increased throughout the day, and a non-fasting measurement will detect high values. Transferrin saturation is raised as a result of innately low hepcidin, which leads to increased iron uptake from the intestine and iron release by reticuloendothelial macrophages.11

Transferrin saturation can also be high in people with iron loading anaemias, those taking iron tablets or multivitamins containing iron, patients with hepatitis, and people who misuse alcohol.12

The reference range for transferrin saturation is 15-45%; expert consensus considers 45% to be the upper limit of normal in a non-fasting situation,12 although higher cut-off values are sometimes recommended for population screening programmes.13

**SERUM FERRITIN**

Serum ferritin is an indirect measure of body iron stores and is increased in patients with iron overload, viral infections, other inflammatory conditions, the metabolic
data on interlaboratory variance of serum ferritin from about 270 Dutch laboratories in 2009). Upper reference values are about 300 μg/L and 200 μg/L for men and women, respectively.

Genetic testing
When symptoms and serum iron parameters suggest haemochromatosis genetic testing is indicated. A systematic review found sensitivity and specificity of C282Y homozygosity to be above 90% and almost 100%, respectively, for the presence of an iron overload phenotype in white northern Europeans. 19

A recent prospective population based cohort study showed that documented iron overload disease is rare among C282Y/H63D compound heterozygotes. 20 An advantage of genetic testing in patients with signs of increased iron stores is the certainty of the diagnosis, and this has important implications for treatment and counselling of first degree relatives. If a symptomatic patient is a C282Y homozygote, screening of first degree relatives for the presence of the genotype may be indicated. 21

Magnetic resonance imaging and liver biopsy
If the diagnosis is still unsure after blood analysis and testing for the C282Y and H63D polymorphisms of the HFE gene, magnetic resonance imaging might be helpful. A reliable, quantitative imaging technique for the detection of iron in the liver is available. 22 23 If the expertise or facilities to offer the technique is lacking, tissue from a liver biopsy may be analysed to look for iron deposits. If the concentration of iron deposits is below the cut-off value, haemochromatosis can be excluded, but if it is above, genetic testing for rare haemochromatosis mutations is indicated. 9

What is the prognosis for patients with haemochromatosis?
A meta-analysis found that C282Y homozygous patients with clinically ascertained haemochromatosis have an increased risk of developing liver disease (odds ratio 3.9, 99% confidence interval 1.9 to 8.1) and hepatocellular carcinoma (11, 3.7 to 34). 11 A population screening survey of 65 238 people showed that the absolute risk of liver damage is about 5% in homozygous men and less than 1% in women. 22 Patients with either of these complications have a reduced life expectancy. However, observational studies of patients who received adequate and timely treatment, of people identified by population screening, and of previously undiagnosed family members of patients with haemochromatosis show that overall mortality is not higher than in the general population. 24 25

Is screening indicated?
Population screening
The relatively high prevalence of the C282Y homozygous genotype in European populations led several authors to recommend population screening. 26 27 However, the low clinical penetrance means that many people would be incorrectly diagnosed with haemochromatosis when not clinically unwell, which could be harmful and could lead to problems with obtaining medical insurance. A systematic review therefore concluded that population screening for haemochromatosis is not indicated in any population.
Screening is not recommended because the harms exceed the benefits.28

Screening those with haemochromatosis related diseases
New EASL guidelines recommend considering genetic testing for patients with porphyria cutanea tarda, well defined chondrocalcinosis, hepatocellular carcinoma, late onset type 1 diabetes, and those presenting with a combination of unexplained chronic liver disease and raised transferrin saturation. Although the evidence is limited, these diseases are associated with a higher prevalence of C282Y homozygosity.1

Screening people with a positive family history
Screening first degree relatives of patients diagnosed with haemochromatosis is another option. A modelling study showed that for patients with two or more children, the most cost effective approach is to test the patient’s spouse first and test the children only if the spouse is heterozygous. For one child or siblings, direct testing for the mutation is the most cost effective strategy.11 The value of testing for the C282Y mutation is still unclear because of the unknown risk of developing biochemical or clinical signs of haemochromatosis even in homozygotes. This is even more the case when testing for C282Y/H63D compound heterozygosity. This is because the chance of finding this genotype in relatives of a C282Y homozygous proband is relatively high (the population frequency of the H63D mutation is 20%); documented iron overload in people with this genotype is rare21; and disease penetrance in the absence of comorbid factors is low, as is shown in an observational study.29

However, an observational study of first degree relatives of C282Y homozygous patients found that haemochromatosis related symptoms are more common than in controls and that their level of iron overload may be predicted by disease severity in the index patient.25 30 Because the first symptoms develop during adulthood, the choice of whether or not to test can be postponed until children are grown up and can decide for themselves.

How is hereditary haemochromatosis treated?
Phlebotomy
Haemochromatosis is usually treated with phlebotomy. Each 500 mL of blood contains 0.25 g of iron. The concentration of iron above which phlebotomy is indicated is not clear. A meta-analysis has shown that serum ferritin concentrations above 1000 µg/L may cause cirrhosis of the liver.11 A consensus based approach is to start treatment when serum ferritin rises above local reference values (about 300 µg/L and 200 µg/L for men and women, respectively).1 However, not all patients with raised serum ferritin show further increases.11 Therefore, for patients with moderately raised serum ferritin a “watchful waiting” approach, with phlebotomy only when their serum ferritin increases progressively, might be an alternative to regular phlebotomy.32

The optimum frequency of phlebotomy and quantity of blood taken are unclear, but expert consensus suggests that 500 mL of blood should be taken each week in the depletion stage, guided most usually by serum ferritin and haemoglobin values.1 9 The procedure used is similar to that for blood donations. If phlebotomy results in anaemia, or adverse consequences of hypovolaemia, frequency of bleeding or volumes of blood taken can be adjusted.

No evidence is available to help set a target value for serum ferritin. Some authors recommend aiming for 50 µg/L or even lower.1 However, it might be better to aim for values within the normal range because these might be better tolerated by patients, result less often in anaemia, and prevent an increase in intestinal iron uptake caused by further lowering of hepcidin as a result of intensive blood letting.13 The maintenance stage is reached when serum ferritin drops below the target value. The optimum frequency of phlebotomy will depend on the patient’s symptoms and response to treatment, the serum ferritin value at diagnosis, and patient preferences.

An observational study reported that adherence to phlebotomy was greater than 90%.36 The main negative effects were problems with venous access and the time consuming nature of the treatment.35 Observational studies have shown that fibrosis of the liver may be reversed by phlebotomy. The effects on symptoms have not been evaluated extensively, and reviews show that treatment can improve some symptoms, such as fatigue and skin pigmentation, but not others, such as arthralgia.1 9 36 In addition, evidence that treatment improves survival is limited because the low absolute risk of death from cirrhosis or hepatocellular carcinoma makes it difficult to show an effect using observational data.23 A randomised clinical trial to evaluate the effect of phlebotomy would probably be considered unethical and would be complicated because of variable penetrance.

Iron chelation
Currently, the only routinely available alternative to phlebotomy is iron chelation, which is more costly and has more side effects. In iron chelation with desferrioxamine ferric ions are bound into ferrioxamine complex and eliminated from the body via the urine. Side effects include gastrointestinal symptoms, dizziness, visual and auditory impairments, muscle cramps, tachycardia, and thrombopenia. Experts recommend chelation with desferrioxamine only when phlebotomy is contraindicated—for example, when venous access cannot be obtained and in patients with circulatory problems (such as heart failure or anaemia).

Therapeutic erythrocytapheresis
Therapeutic erythrocytapheresis is the removal of erythrocytes only rather than whole blood that could become an alternative to phlebotomy. Preliminary results show that erythrocytapheresis leads to a fourfold reduction of phlebotomy sessions. More than twice as much iron can be removed per session and side effects are reduced.37

What can patients do to influence the disease?
Whether avoiding dietary iron reduces iron storage has not been investigated. Expert consensus opinion is that patients should avoid iron containing food supplements.1 Patients might want to limit alcohol consumption,
How do we monitor patients with haemochromatosis?

Patients are monitored mainly to guide the timing of treatment and detect liver damage. Serum ferritin is the main parameter used because an observational study found that it correlates with symptoms and the risk of complications. A cross-sectional study showed that when serum ferritin is less than 1000 µg/L the risk of serious liver damage is below 1%. Serum ferritin levels above 1000 µg/L are, according to international consensus, an indication for liver biopsy because of the risk of cirrhosis. When a liver biopsy shows cirrhosis, periodic screening for hepatocellular carcinoma becomes mandatory. This can be done with echography or magnetic resonance imaging.

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