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Hereditary haemochromatosis

Diagnosis and management

Background
Hereditary haemochromatosis is a common inherited disorder in which excessive iron is absorbed and which, over time, may cause organ damage. Genetic predisposition leads to disease in some but not all cases.

Objective
This article discusses the presentation, testing, treatment and management of hereditary haemochromatosis.

Discussion
Hereditary haemochromatosis is autosomal recessive and is more common in people of Celtic or northern European descent. Although more than 90% of cases of hereditary haemochromatosis are due to C282Y homozygosity (carrying two copies of the C282Y gene) not all C282Y homozygous individuals will progress through all stages of disease development. Clinical disease is less common in females due to physiological blood loss from menstruation and pregnancy. Most importantly, early diagnosis and treatment of hereditary haemochromatosis prevents complications and results in a normal life expectancy. Venesection is a simple and effective way to both prevent and manage the potential sequelae of iron overload, which include severe fatigue, arthritis, impotence, raised alanine aminotransferase/aspartate aminotransferase, fibrosis or cirrhosis, diabetes, and cardiomyopathy.

Keywords: liver diseases; genetics; haemochromatosis

After the discovery of the HFE gene in 1996[1] it was initially believed that every individual with two abnormal copies of the gene (C282Y homozygote) would develop iron overload related disease, consistent with haemochromatosis. Haemochromatosis is defined as iron overload leading to end organ damage through the interaction between environmental and genetic factors and not the presence of genetic predisposition.

It has now been shown that although 60–80% of C282Y homozygotes develop abnormal iron indices in their lifetime, only 28% of men and less than 1% of women develop significant iron overload related disease (haemochromatosis).[2] Iron accumulation in genetically at risk individuals occurs gradually over many decades. The stages of iron loading progression are now characterised as:

- genetic predisposition without iron indices abnormality (C282Y homozygotes)
- iron overload (raised serum ferritin [SF] in the presence of a raised fasting transferrin saturation [TS]) without symptoms
- iron overload with hereditary haemochromatosis (HH) associated symptoms (such as arthritis and fatigue), and
- iron overload with organ damage, in particular cirrhosis.[3]

In patients with haemochromatosis, iron accumulation occurs because there is disordered and increased iron absorption across the intestinal mucosa, which is compounded by the fact that there are no compensatory mechanisms of iron excretion that can be activated as the body lacks an active iron excretory mechanism.

Iron depletion normally occurs through cell attrition from gastrointestinal mucosal cell turnover and through physiological and pathological mechanisms of blood loss. The basic defect in HFE associated hemochromatosis is a lack of cell surface expression of HFE (due to the C282Y mutation). The normal (wild-type) HFE protein forms a complex with beta-2 microglobulin and transferrin receptor 1 (TfR1), and the C282Y mutation completely abrogates this interaction. As a result, the mutant HFE protein remains trapped intracellularly, reducing TfR1 mediated iron uptake by the intestinal crypt cell. This impaired TfR1 mediated iron uptake leads to upregulation of the divalent metal transporter (DMT1) on the brush border of the villus cells, causing inappropriately

increased intestinal iron absorption.[4]

Hepcidin, a peptide synthesised primarily by the liver, has been identified as the central regulator in iron homeostasis, although how genetic changes in the HFE gene impact on the regulation of this key molecule remains unclear.[5]

There is recent evidence supporting a role for HFE as an important component of a larger iron-sensing complex that involves interactions with diferric transferrin, TfR1 and TfR2 at the plasma membrane of hepatocytes. Defective HFE protein prevents formation of a functional iron sensor and signal transduction effector complex leading to dysregulated hepcidin expression and the development of hereditary haemochromatosis. Genetic predisposition to HH is now frequently diagnosed in individuals who remain asymptomatic but who have been found to have abnormal iron studies, or in those with a family history of HH who have undergone family testing for the gene. Patients usually develop elevated ST saturation and SF levels before significant symptoms occur. The accumulation of iron is a slow process, is often silent in the early stages, and only when iron stores reach toxic levels does tissue injury develop. Assessment of iron overload status has traditionally been undertaken using percutaneous liver biopsy but there is now a noninvasive reasonably accurate measure of liver iron loading status through magnetic resonance imaging (MRI) of the liver using a newly patented technique called Ferriscan®.[6]

Clinical presentation

In the majority of patients who present with overt signs of haemochromatosis, the first symptoms develop between the ages of 30–60 years. Menstruation and pregnancy account for the delayed presentation in women, which occurs more frequently after menopause. The most common symptoms of early sequelae are fairly nonspecific and include lethargy, arthralgia and loss of libido.[7]

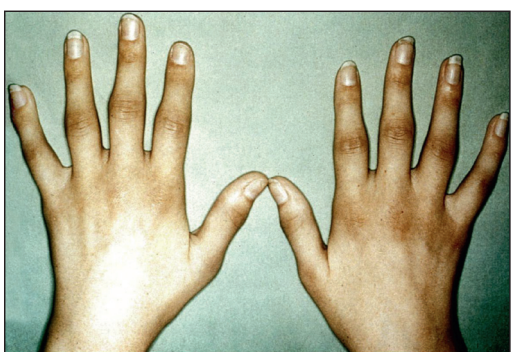

Figure 1. HH associated arthritis most usually affects the second and third metacarpophalangeal joints

Patients with more severe iron overload may develop liver disease with fibrosis or cirrhosis, arthritis, gonadal failure, diabetes mellitus, cardiac failure and arrhythmias. Hepatocellular carcinoma has been reported to develop in about 30% of patients with untreated cirrhosis due to HH. Physical examination may be normal if the predisposition to iron overload is diagnosed early, but if present, the most common physical signs are hepatomegaly or signs of cirrhosis, testicular atrophy, or joint swelling and tenderness (*Figure 1*).[7] It should be noted that HH is not a common cause of cirrhosis and that nonalcoholic steatohepatitis, alcoholic liver disease and chronic viral hepatitis each contribute more significantly to the burden of disease from cirrhosis in the Australian population.[8]

Diabetes mellitus is usually present only in patients with advanced disease.[7] 'Bronzed diabetes' (golden skin pigmentation in a newly diagnosed diabetic) was historically regarded as a classic presentation of HH before the discovery of the gene, but is rarely seen now due to early increased awareness and more aggressive testing for genetic predisposition.

Testing for hereditary haemochromatosis

Which tests on whom, and when they should be performed are outlined in *Table 1* and *2*.

Iron studies

In patients presenting with signs or symptoms suspicious of HH, a fasting TS (ratio of serum iron and iron binding capacity) and SF concentration should be undertaken. In very early disease, TS may be elevated before a rise in SF. Transferrin saturation is abnormal when it is >45% for men and >55% for women. Serum ferritin is abnormal when it is >200 µg/L in premenopausal women and >300 µg/L in men and postmenopausal women. These tests should be performed in the morning after an overnight fast.

An increased TS reflects increased absorption of Fe (the underlying biological defect of this condition) and an increased SF reflects body iron stores. However, it is also an acute phase reactant and can be elevated nonspecifically on occasions (eg. alcohol consumption, chronic inflammation and other liver diseases). Haemochromatosis is unlikely if the SF is very high but the TS is normal, and in this situation SF is more likely to be elevated as an acute phase reactant. In such cases testing the HFE gene may be helpful to exclude HH.

If both fasting TS and SF are increased, haemochromatosis should be suspected, even if there are no clinical symptoms or abnormal liver function tests. In this situation, the HFE gene test should be ordered. With the exception of arthritis, suspicious symptoms are unlikely to be due to haemochromatosis if the SF is in the normal range.

Patients with SF >1000 µg/L or elevated alanine aminotransferase/aspartate aminotransferase (ALT/AST) are at significant risk of liver cirrhosis and should be immediately referred to a hepatologist for assessment for percutaneous liver biopsy.

Genetic testing

For first and second degree relatives of an index case, HFE gene testing should be undertaken to screen for disease. Alterations in the HFE gene are the most common cause for developing haemochromatosis. Most laboratories test for two different genetic changes in the HFE genes:

- C282Y – the amino acid tyrosine is substituted for a cysteine at position 282, and
- H63D – the amino acid aspartate is substituted for a histidine at position 63.

Implications of genetic testing

No alterations found in the HFE gene

If iron studies are normal, haemochromatosis is unlikely to develop. All patients with iron overload require follow up, regardless of HFE gene test result, as in a small percentage of cases a different gene may be responsible.

C282Y homozygote (C282Y/C282Y)

Not all individuals with this genotype will develop severe iron overload related disease, however 60–80% will develop abnormal iron studies during their lifetime.[7] If iron overload is present, lifelong venesection is required. Cirrhosis is unlikely if the ferritin level is <1000 µg/L, the ALT level is normal, and there is no hepatomegaly. Liver biopsy may be performed to establish or exclude the presence of

Table 1. When should tests for HH be performed?

Clinical suspicion of haemochromatosis (signs and symptoms suggestive of iron overload)

The most useful initial tests are iron studies, which include fasting transferrin saturation and serum ferritin. If the fasting transferrin saturation is >45% for men or >55% for women in the context of an elevated serum ferritin, then the HFE gene test should be ordered to confirm HH

Family history of haemochromatosis

For first and second degree relatives of an index case, HFE gene testing should be undertaken to screen for disease. Iron studies should be also ordered if there are any signs or symptoms suggestive of HH. If the individual is not C282Y homozygous HH is highly unlikely to occur. Patients should be counselled that rarely HH can occur from other genetic mutations

The Medicare rebate only applies to the HFE gene test if the ferritin or transferrin saturation are abnormal or a first degree relative has been diagnosed with haemochromatosis

Table 2. Who should be tested for genetic predisposition to HH?

- Family members of patients with haemochromatosis
- Family members of patients shown to have an altered HFE gene
- Patients with symptoms which may be early manifestations of haemochromatosis:
  - tiredness
  - arthralgia
  - loss of libido
  - upper abdominal discomfort
- Patients with liver disease of unknown cause, including patients with suspected alcoholic liver disease
- Patients with conditions which could be complications of haemochromatosis
  - arthritis, especially involving metacarpophalangeal (MCP) joints, but also wrist, shoulders, knees and feet
  - cardiomyopathy
  - impotence
  - diabetes mellitus in association with liver disease

cirrhosis if blood tests are suggestive of cirrhosis. Those without iron overload require iron studies every 2–5 years.

Testing of all first degree family members is recommended once they have reached the age of 18 years. Those who are C282Y homozygotes who wish to test offspring under the age of 18 years, should first test their partner, as offspring will not be affected by HH if the partner does not carry the C282Y gene.[8] There have been no reports of iron overload from C282Y homozygosity occurring before the age of 18 years, therefore children should be tested after they have turned 18 years[9] and can self manage any preventive measures.

Compound heterozygote (C282Y/H63D)

Only about 1% of people with this genotype develop haemochromatosis.[10] Monitoring of iron status every 2–5 years may be indicated. Elevated SF may also be due to acute phase reactants and therefore other causes should be investigated if SF is persistently elevated over 6 months in the absence of elevated fasting TS.

C282Y and H63D heterozygote or H63D homozygote

Carrier status is common (1 in 8 of the general population) and has not been shown to be associated with disease.[11] Some may have minor abnormalities in iron studies.[12] There is no need to monitor iron studies unless symptoms or abnormal iron studies are present.

Treatment and prevention

Treatment for haemochromatosis consists of lifelong venesection and monitoring of iron indices, in particular SF.[13] Venesection therapy depletes the body of iron by removal of iron in haemoglobin and is highly effective.[14]

The prevention of haemochromatosis for asymptomatic individuals identified through family studies is through regular blood donation (approximately three times per year). Medically directed venesections are accepted by the Australian Red Cross Blood Bank (ARCBB) and are of benefit to the community by increasing the scarce supply of blood. There are no specific contraindications other than those specified by ARCBB for the general population.

Patients should be encouraged to inform family members that they may be at increased risk of haemochromatosis and to discuss this with their own GP. An initial course of 1–2 venesections per week is performed until the excess iron stores are removed. Once this is achieved, patients usually require one venesection every 3–4 months to keep iron stores at low-normal levels without rendering the patient iron deficient. It is rare for patients not to tolerate venesection therapy. An alternative method of treatment is with desferrioxamine, a chelating agent, but this is costly and in practice is rarely needed. There is no value in a low iron diet in the management of haemochromatosis.[14] Patients can choose to reduce their red meat intake if they wish, as this may reduce the frequency of venesections.

There is currently controversy as to an ideal target range for SF from venesection therapy. Previous guidelines have suggested that venesection should continue until SF is <50 µg/L.[14] Earlier guidelines suggested an even more aggressive target of actual iron depletion with SF <20 µg/L. However, with genetic testing and less severe disease on presentation due to earlier detection, some experts now recommend normalisation of SF to <300 µg/L for men and postmenopausal women, and <200 µg/L for women.[15] This latter approach is based on the premise that iron loading is less likely to be severe and is appropriate for patients who present with SF <1000 who are at low risk of cirrhosis. More aggressive management may be required for those presenting with more severe iron overload and SF >1000 µg/L when the risk of cirrhosis is higher and the aim is to iron deplete extrahepatic organs in addition to the liver to minimise risk of haemochromatosis. Recent research[16] suggests that disease expression in those presenting with

SF <1000 µg/L is lower than previously believed and as such, less aggressive management is indicated with the aim of normalisation of iron indices and not actual iron depletion. Long term follow up to monitor for and prevent progression of SF to >1000 µg/L should be initiated with SF levels every 3–5 years.

Vitamin C supplements should be avoided as vitamin C can increase iron absorption, and for obvious reasons iron supplements should be avoided. Alcohol consumption should be kept to a minimum if the SF remains elevated but abstention is not required once iron levels have been normalised by venesection. Patients should be counselled that iron deficiency can still develop, particularly if venesection is overzealous. This appears to be an important point to make for female C282Y homozygotes who are less likely to have severely elevated SF levels at diagnosis. Patients in whom iron deficiency occurs for no apparent reason should be referred for assessment of occult blood loss.

What is the prognosis for patients with HH?

Noncirrhotic patients diagnosed and treated early have a normal life expectancy provided they continue treatment. The response to venesection treatment depends on the presenting symptoms and the stage of disease at the time of diagnosis. Those with SF <1000 µg/L are at low risk of cirrhosis and do not require a liver biopsy. A normal lifespan can be expected if venesection to normalise iron levels is implemented.[8]

Early symptoms and signs are completely reversible with normalisation of iron indices, including elevated aminotransferases and liver fibrosis. However, cirrhosis rarely regresses to normal despite venesection therapy, nor does it develop if the patient is noncirrhotic at diagnosis and is adequately treated. Patients with cirrhosis have a risk of primary liver cancer even when complete iron depletion is achieved. These patients should be screened every 6 months with hepatic ultrasound and serum alpha-fetoprotein levels. It is not yet known whether HH associated arthritis is reversible with venesection, and it is the only HH associated condition for which prophylactic venesection may not prevent disease progression.

Author

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Conflict of interest: none declared.

References

1. Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. Nat Genet 1996;13:399–408.
2. Allen KJ, Gurrin LC, Osborne NJ, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med 2008;358:221–30.
3. Pietrangelo A. Hereditary hemochromatosis. Ann Rev Nutr 2006;26:251–70.
4. Giannetti AM, Björkman PJ. HFE and transferrin directly compete for transferrin receptor in solution and at the cell surface. J Biol Chem 2004;279:25866–75.
5. Bridle KR, Frazer DM, Wilkins SJ, et al. Disrupted hepcidin regulation in HFE-associated haemochromatosis and the liver as a regulator of body iron homoeostasis. Lancet 2003;361:669–73.
6. St Pierre T, Clark PR, Chuaq-anusorn W, et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. Blood 2005;105:855–61.
7. Adams PC, Barton JC. Haemochromatosis. Lancet 2007;370:1855–60.
8. The Australia and New Zealand Liver Transplant Registry 20th report. Available at www.anzltr.org/thisYear/report.pdf.
9. Delatycki MB, Powell LW, Allen KJ. Hereditary hemochromatosis genetic testing of at-risk children: what is the appropriate age? Genet Test 2004;8:98–103.
10. Gurrin LC, Bertalli NA, Dalton GW, et al HealthIron Study Investigators. HFE C282Y/H63D compound heterozygotes are at low risk of hemochromatosis-related morbidity. Hepatology 2009;50:94–101.
11. Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med 2008;358:221–30.
12. Adams PC, Reboussin DM, Barton JC, et al. Hemochromatosis and iron-overload screening in a racially diverse population. N Engl J Med 2005;352:1769–78.
13. Tavill AS. Diagnosis and management of hemochromatosis. Hepatology 2001;33:1321–8.
14. Adams PC, Barton JC. How I treat hemochromatosis. Blood 2010;116:317–25. Epub 2010 Mar 22.
15. Allen KJ, Bertalli NA, Osborne NJ, et al. HFE Cys282Tyr homozygotes with serum ferritin concentrations below 1000 microg/L are at low risk of hemochromatosis. Hepatology 2010;52:925–33.
16. Allen KJ, Bertalli NA, Osborne NJ, et al for the HealthIron Study Investigators. HFE-C282Y homozygotes with elevated SF less than 1000 µg/L are not at increased risk of iron overload-related clinical features. Hepatology 2010; in press.

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