Haemochromatosis: Information for General Practitioners

In the 'pre-genetic' era, haemochromatosis was recognised as 'bronze diabetes'. With the advent of easy and rapid genotyping, haemochromatosis has been transformed into a potentially trivial condition detectable in its pre-symptomatic stages using appropriate lab tests. The overt clinical manifestations of diabetes, cirrhosis, pigmentation and cardiomyopathy are now rare.

Now, most use the term 'Hereditary Haemochromatosis' to describe a genetic predisposition - the consequences of which are trivial provided excess iron is not allowed to accumulate (or is removed). Note that some still reserve the expression 'haemochromatosis' to describe the disease manifestations of iron overload rather than the genetic predisposition.

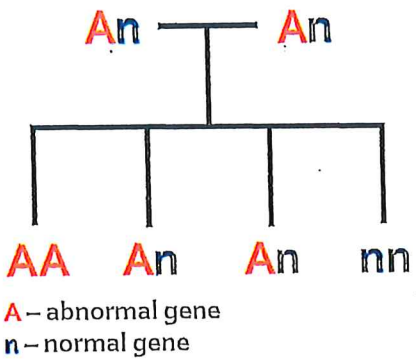
What causes the iron overload?

Iron overload occurs as a result of increased iron absorption in the gut. The impaired regulation of iron absorption is attributable to a genetic variant in the HFE protein which was discovered in 1996.

The haemochromatosis mutation

The haemochromatosis gene (*HFE*) produces a protein involved in the regulation of iron absorption in the gut and its distribution in the tissues. The HFE protein is thought to be involved with sensing the body's iron status. About 99% of cases of haemochromatosis in New Zealand are caused by a mutation at amino acid position 282 in the HFE protein that changes a cysteine to a tyrosine and is referred to as: 'C282Y'.

Haemochromatosis is an autosomal recessive condition. This means that in order to develop haemochromatosis, both chromosomes of an affected individual must contain the abnormal gene (i.e. homozygous for the C282Y mutation). Individuals carrying one copy of a mutation are heterozygotes (carriers) and don't suffer iron overload as a consequence.



There is a 1 in 4 chance that the children of parents heterozygous for the C282Y mutation will have a child who is homozygous (i.e. may develop haemochromatosis). 1 in 4 are likely to be completely unaffected and 2 out of 4 will be carriers.

The haemochromatosis mutation is very common

One in seven New Zealanders is a carrier (heterozygote) of the C282Y mutation and 1 in 200 New Zealanders is a homozygote (i.e. potentially affected). The mutation is so common that it is likely to have provided some evolutionary advantage. Patients with haemochromatosis are evolutionary survivors, with increased levels of "fitness".

Penetrance

Penetrance of the disease is thought to be low – i.e. not all C282Y homozygotes will develop evidence of haemochromatosis. This is probably due to the effect of environmental and genetic differences between individuals. The most obvious example of this is the effect of menstruation in women. Up to the menopause this protects women from the deleterious effects of iron loading. In women, the clinical and biochemical effects of haemochromatosis are more likely to become evident after the menopause.

What are the signs and symptoms of genetic haemochromatosis?

Currently the most common symptom of haemochromatosis is chronic fatigue. The next most common manifestation is arthritis, often atypical, and often affecting the MCP joints of the hand. Occasional patients present with liver disease (including cirrhosis). Other rare signs, which may indicate advanced disease, include endocrine changes, excessive skin pigmentation, diabetes and cardiomyopathy. An important feature of haemochromatosis is that much of the organ damage is irreversible (especially arthritis).

Diagnosis of hereditary haemochromatosis

The most common diagnostic abnormality is raised transferrin saturation. Persons with haemochromatosis usually have a transferrin saturation >50%, often 80-100%. Serum ferritin is also usually increased, but in children and menstruating women the ferritin can be normal. It is important that there are many other causes of increased ferritin (e.g. inflammation, other liver disease). However, these other causes are not usually associated with elevated transferrin saturation. So, measurement of iron, transferrin and ferritin are all required when assessing iron status in possible iron overload.

When the ferritin is below about 200 µg/L the transferrin saturation is often only slightly elevated but when ferritin exceeds about 300-500 µg/L, the saturation is often >70%.

	Transferrin Saturation	Ferritin
Early	55%	200 µg/L
Advanced	90%	2000 µg/L

Because of the influence of diet and diurnal variation on serum iron, abnormal iron studies should always be rechecked with a fasting blood specimen taking in the morning. If the elevated transferrin saturation persists, HFE gene testing is recommended. If the individual is homozygous for the C282Y mutation then the diagnosis is confirmed and no additional diagnostic studies are needed.

If any other gene result is obtained, and the iron studies continue to indicate possible iron overload, then the case should be reviewed with a clinical pathologist or physician with expertise in this area.

The role of the liver biopsy

While no longer a diagnostic test for haemochromatosis (except in rare cases with an atypical genotype), the liver biopsy does have a role in assessing prognosis and determining future management. Patients with cirrhosis have an increased risk of hepatocellular carcinoma. Patients without cirrhosis have a completely normal life expectancy provided excess iron is removed.

If the probability of cirrhosis is very low, liver biopsy is no longer recommended. A liver biopsy is recommended only if the ferritin is >1000 µg/L, if hepatomegaly is present or if the liver enzymes are persistently abnormal.

Treatment

Treatment is straightforward - venesection. The issues relate to the frequency and targets of venesection.

For patients with very high ferritin and/or symptoms or signs (including abnormal LFTs or arthritis) weekly venesection is strongly recommended (one unit [450 mL] per week equates to the removal of 250 mg iron). Some older patients may need to commence with half-unit venesections, building up if possible to one unit per week when their bone marrow responds. In young patients with extremely high ferritin and evidence of organ damage, excess iron should be removed as soon as possible, i.e., up to two units per week.

For patients with lower ferritin (perhaps <1000 µg/L) and no symptoms, a slower rate of venesection is reasonable (perhaps every 2-4 weeks). After excess iron stores have been removed, venesection 3-6 times annually should be sufficient to maintain ferritin levels between 50 - 100 µg/L (while avoiding anaemia).

Maintenance Targets

The aim of treatment is to reduce iron stores. The goal of treatment is to reduce the ferritin to between 50 and 100 ug/L. There is no need to induce iron deficiency.

Although transferrin saturation varies throughout the day (because of variation in serum iron) high values (especially >75%) may be associated with the presence of free iron in the blood. This free iron is thought to be toxic and may be responsible for the chronic fatigue and arthritis often seen in haemochromatosis.

Who needs treatment?

Organ damage due to iron overload is not likely when serum ferritin is <1000 ug/L (although some individuals may experience the more common symptoms below this level). While venesection is recommended for those with serum ferritin >1000 ug/L, the decision to offer venesection below this value should be based on the presence or otherwise of symptoms and signs due to iron overload.

For those with a ferritin between 500 and 1000 µg/L, the transferrin saturation can be used as a guide – venesection can be offered if the transferrin saturation (using morning, fasting blood specimens) is persistently >75%.

In most centres, haemochromatosis patients are being accepted as regular volunteer blood donors (after appropriate counselling). If appropriate this option could be discussed with the patient and the local director of the blood bank.

Dietary modification?

Raw oysters should be avoided. They can carry *Vibrio vulnificus*, which can cause fatal septicaemia in patients with high iron levels and in immune-compromised patients.

The mainstay of treatment for haemochromatosis is venesection. Other attempts to control iron absorption should only be used in conjunction with venesection. Avoidance of foods high in iron will reduce iron absorption slightly, but is by no means necessary for adequate therapy. Many patients choose a low meat diet to minimise venesection requirements. Alcohol intake should be moderated, since it increases iron absorption, and contributes to the pancreatic and liver damage induced by haemochromatosis.

Although vitamin C is thought to increase the absorption of iron, reduction of vitamin C intake cannot be recommended. Fruits and vegetables obviously have many beneficial effects which may well be more important than their potential effect on iron absorption. Furthermore, secondary scurvy has been described in patients with haemochromatosis as a result of the oxidative damage from the excessive tissue iron. Obviously dietary supplements containing iron and high dose vitamin C should be avoided.

Anecdotally, some sportsmen and women find an improvement with active training; getting and keeping fit may be a great way to help control the iron levels.

Counselling and monitoring patients

Haemochromatosis is common and can easily be managed by general practitioners, in conjunction with a local venesection service if available. However, patients with disease manifestations should be referred to the appropriate specialist. Provided it is detected early, this is a very positive diagnosis and counselling can reflect this. Those homozygous for the mutation are "fitter" than others and they will probably have slightly above average haemoglobins. They are very unlikely to be iron deficient (they could become super blood donors if appropriate) and now that a diagnosis has been established, have a normal life expectancy. Furthermore, through this diagnosis they may allow a normal life expectancy for other members of their family.

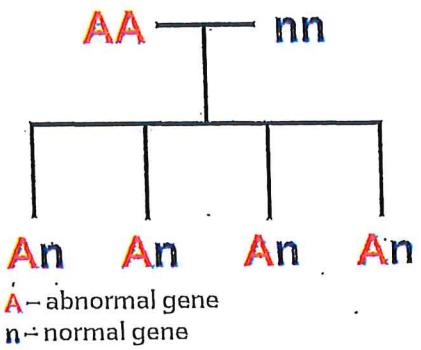
Occasional patients have encountered problems with insurance companies. Commencement of venesection before significant tissue injury results in normal life expectancy and the use of the diagnosis to load premiums or refuse insurance is unjustifiable.

Testing of special groups

1. Family members

Being a recessive condition, each sibling has a 1 in 4 chance of being affected. Parents and offspring of homozygotes must be carriers at least, but because the mutation is so common among the population, they have a one in 14 chance of being a homozygote. Thus all first degree family members of affected individuals should be screened. Full iron studies and gene studies should be carried out in first degree relatives.

With regards to children, when one parent is diagnosed as being a homozygote, it may be more effective to test the other parent rather than offering genotyping to the offspring. If the second parent doesn't carry a C282Y mutation then genetic testing of their offspring is not required. In general it may be best not to test children until their late teens to avoid reinforcing anxieties. Significant iron overload is unlikely due to the demands of growth. However, in some situations, testing of children may be the appropriate course of action, and if so both iron studies and gene testing should be used. It is important that an iron restricted diet is not imposed in childhood.



Where 1 parent is homozygous for the HFE mutation and the other has no mutations, all of their offspring will be carriers (i.e. unaffected).

2. Symptomatic individuals

Remember that genetic haemochromatosis is very common (1 in 200). Iron studies should be included in the work up of all patients with chronic fatigue, degenerative arthritis, atypical arthritis, unexplained upper abdominal pain, idiopathic cardiomyopathy, idiopathic atrial fibrillation, testicular atrophy, excessive skin pigmentation, and adult onset diabetes.

3. Following up other laboratory abnormalities

Full iron studies should be included in the workup of unexplained elevation of liver enzymes and for unexplained macrocytosis (the average MCV in those with haemochromatosis is 95 fL compared to 90 fL in others).

Support and more information:

The New Zealand support group for people with haemochromatosis is sponsored by Leukaemia & Blood Cancer New Zealand. Their webpage for haemochromatosis can be found at http://www.leukaemia.org.nz/page/387. Contact details are: PO Box 99-182, Newmarket, Auckland. Tel: (09) 638 3556. Toll Free: 0800 15 10 15. Fax: (09) 638 3557.

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