HEREDITARY haemochromatosis (HH) is a common inherited disorder in which excessive iron is absorbed from the intestine, which may cause organ damage over time. Although more than 90% of cases of HH in Australia are due to HFE C282Y homozygosity (that is, having two copies of the C282Y amino acid substitution in the HFE protein) not all C282Y homozygous individuals will progress through all stages of disease development. Clinical disease is less common in females due to increased iron requirements and blood loss from pregnancy and menstruation.

Early diagnosis and treatment of HH 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, impotence, raised AST/ALT, liver fibrosis or cirrhosis, diabetes and cardiomyopathy.

HH is autosomal recessive and is more common in people of Celtic or northern European descent. It is the most common genetic condition of Caucasian populations with more than one in 200 individuals at genetic risk for this disease. Tens of thousands of people in Australia are at risk of disease development although only several hundred each year will develop signs of organ damage as a result of iron overload.

cont’d next page
How To Treat - Hereditary haemochromatosis

Serum ferritin can be elevated in the absence of iron overload in conditions such as neoplasia, inflammation ... and autoimmune disease.

The most common symptoms are non-specific and include lethargy, arthralgia and loss of libido.

Individuals with more severe iron overload may develop liver disease with fibrosis or cirrhosis, arthritis, gonadal failure, diabetes, cardiac failure and arrhythmias. Hepatocellular carcinoma has been reported to develop in about 30% of individuals with untreated cirrhosis caused by 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, systemic signs of cirrhosis, testicular atrophy and joint swelling and tenderness. Diabetes is usually present only in individuals with advanced disease. ‘Bronzed diabetes’ (golden skin pigmentation in a newly diagnosed patient with diabetes) was historically regarded as a classical presentation of HH but is now rarely seen, owing to increased awareness of HH and more aggressive testing for genetic predisposition.

The diagnosis of HH is divided into stages, with iron loading progression being categorised as follows:

AFTER the discovery of the HFE gene in 1996, it was initially believed that every individual with a mutation in each copy of the gene would develop iron-overload-related disease consistent with HH. However, more recently it has been shown that only 60-80% of C282Y homozygotes develop abnormal iron indices in their only, with only one third of men and one in 100 women developing significant iron-overload-related disease, that is, HH. Iron accumulation in genetically at-risk individuals occurs gradually over many decades. The stages of iron loading progression can be categorised as follows:

Stage 1: Genetic predisposition

Stage 2: Raised transferrin saturation (TS) with normal serum ferritin (SF).

Stage 3: Iron overload (raised SF in the presence of a raised fastings iron saturation) but liver biopsy is not diagnostic of HH.

Stage 4: Iron overload with HH-associated symptoms (such as arthritis and fatigue).

Stage 5: Iron overload with organ damage, in particular cirrhosis. Discovering the genetic predisposition to HH frequently now occurs in patients who remain asymptomatic but have been found to have abnormal iron studies or who have a family history of HH and have undergone testing for HFE mutations. Individuals usually develop elevated TS and SF levels before significant symptoms occur. The accumulation of iron is a slow process. It is often silent in the early stages, with tissue injury only occurring when iron stores reach toxic levels.

In individuals who present with overt signs of HH-related iron-overload-related disease, the first symptoms usually develop between the ages of 30 and 60 years. Menstruation and pregnancy account for the delayed presentation of the disorder in women, which occurs more frequently postmenopausally.
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of HH are entirely preventable by normalisation of iron indices, there should be a low threshold for investigating an individual for this disorder.

Indications for testing for HH include liver disease, abdominal pain, fatigue, arthralgia, unexplained arrhythmias and/or cardiac failure and impotence as well as a positive family history of the condition. If an individual has symptoms that may be due to HH then the first-line testing is fasting TS and SF. If these indices are raised then genetic testing for HFE mutations is the next step (figure 1). The rationale to begin investigation in symptomatic individuals with iron studies is to ascertain whether symptoms are secondary to iron overload. Those with normal SF are highly unlikely to be symptomatic due to HH.

The Medicare rule for provision of a Medicare rebateable HH genetic test is as follows (see Online resources, page 28):
- the patient has an elevated transferrin saturation or elevated serum ferritin on testing of repeated specimens;
- the patient has a first-degree relative with haemochromatosis; or
- the patient has a first-degree relative with homozygosity for the C282Y genetic mutation, or
- the patient has compound heterozygosity for c282y/H63D compound heterozygous.

Diagnostic algorithm for raised serum ferritin (SF) and/or transferrin saturation (TS).

<table>
<thead>
<tr>
<th>Raised SF</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF &lt;1000µg/L</td>
</tr>
<tr>
<td>Normal fasting TS</td>
</tr>
<tr>
<td>SF &gt;1000µg/L</td>
</tr>
<tr>
<td>Seek other cause for SF (eg, neoplasia, inflammation, infection)</td>
</tr>
<tr>
<td>HFE gene test</td>
</tr>
<tr>
<td>Diagnosis of type 1 HH confirmed</td>
</tr>
<tr>
<td>C282Y homozygous or C282Y/H63D compound heterozygous</td>
</tr>
<tr>
<td>One or no copy of C282Y or H63D</td>
</tr>
<tr>
<td>Refer for liver biopsy (may have quantitative phlebotomy or liver MRI instead if SF &lt;1000 µg/L)</td>
</tr>
<tr>
<td>Hepatic iron index &gt;1.9</td>
</tr>
<tr>
<td>Diagnosis of HH confirmed</td>
</tr>
<tr>
<td>Consider referral to clinical genetics for testing for other genetic causes of HH</td>
</tr>
<tr>
<td>Liver cirrhosis/ severe fibrosis</td>
</tr>
<tr>
<td>Refer to a hepatologist for management</td>
</tr>
</tbody>
</table>

Liver iron is only very rarely seen, occurring with very elevated iron levels.

Symptoms and signs
Many individuals with iron overload due to HFE mutations are asymptomatic or have non-specific symptoms. Non-specific symptoms that have been associated with iron overload include fatigue, arthralgia, depression and reduced libido. The classic description of individuals with HH having bronzed skin is only very rarely seen, occurring with very elevated iron levels.

Endocrine manifestations
Diabetes occurs more frequently in HH, with 20-30% of those with symptomatic disease having this complication. In general it occurs in those with severe iron overload (ie, SF >1000µg/L). There is no evidence that screening for iron overload in those with type 2 diabetes will identify a large number of individuals with HH. Nevertheless, those in whom HH is diagnosed, in particular those with severely elevated SF, should have testing for diabetes. Diabetes in HH is managed in the same way as diabetes from other causes. Hypogonadotropic hypogonadism may occur, and again this is particularly the case where SF on liver biopsy, tests for other causes of liver damage should be undertaken. This includes testing for hepatitis B and C. Echocardiography and electrocardiography should be considered in those with very high SF if there are any symptoms or signs of cardiac involvement. Tests of pituitary dysfunction should be conducted if there are symptoms such as reduced libido or if there is a very high SF.

Cardiac manifestations
Cardiac manifestations of HH are rare and generally occur in individuals with severe iron overload (SF >1000µg/L). Cardiac manifestations include arrhythmias and congestive cardiac failure due to dilated or restrictive cardiomyopathy. There should be a low threshold for undertaking cardiac investigations including ECG and echocardiography, particularly in those with very high SF levels.

Hepatocellular carcinoma occurs between 20-100 times more commonly in individuals with hereditary haemochromatosis than those in the general population.

Organ system manifestations

Hepatic manifestations
LIVER: fibrosis and liver cirrhosis may occur in HH. Fibrosis in the absence of cirrhosis is generally reversible through normalisation of body iron stores. Cirrhosis is not reversible by this treatment.

There are several non-invasive methods that can give some indication as to the presence or absence of fibrosis. One approach is to undertake testing for one of various combined scores such as Hepscore and Fibrometer. Here a selection of blood indices such as alpha-2 macroglobulin, platelet count and hyaluronic acid are combined with the person’s age. Those with a score above a certain level are more likely than those with scores below that level to have significant hepatic fibrosis. Another method that can be used is transient elastography (Fibroscan). This method utilises ultrasound to measure the elasticity of the liver. Those with higher levels are more likely to have fibrosis than those with lower levels. Nevertheless, the gold standard for diagnosing fibrosis and cirrhosis is liver biopsy.

Hepatocellular carcinoma occurs between 20-100 times more commonly in individuals with HH than those in the general population. While this generally occurs in individuals with cirrhosis, it can occasionally occur in non-cirrhotic individuals.

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Some studies have identified an increased rate of hypertrophy in HH but others have not. The need for testing of thyroid function should be made on a case-by-case basis.

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Rheumatological manifestations
Arthritis occurs more often in people with HH. The typical pattern is symmetrical polyarthritis involving the metacarpophalangeal joints (classically but not always the second and third metacarpophalangeal joints), proximal interphalangeal joints, wrists, hips and knees. Unlike other manifestations of HH, the presence of arthropathy in HH is not related to SF levels.
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The risk of disease

A STUDY of 30,000 individuals tested for the presence of C282Y and H63D identified the risk of disease in individuals homozygous for C282Y (C282Y/C282Y) and compound heterozygous for C282Y and H63D (C282Y/H63D). The study found that among C282Y homozygotes, a minimum of 28% of males (up to 45%) and 1% of females (up to 9%) have iron-overload-related disease.

The risk of symptoms is much lower in those who are compound heterozygous for C282Y and H63D, with only one in 80 exhibiting signs of iron overload and none having cirrhosis. About 20% of the population are heterozygous for H63D compared with 10% for C282Y. Despite the higher population frequency of compound heterozygotes than C282Y homozygotes, this genotype accounts for only 5-10% in published case series of individuals with HH.

C282Y heterozygosity is not associated with liver disease or elevated liver enzymes and again an alternative pathology should be entertained if this combination is identified.

Prevention and treatment

MOST morbidity in HH can be prevented by reversal or maintenance of total body iron in the normal range. Treatment guidelines recommend that any individual with HFE-related HH and SF above the upper limit of normal iron overload should have treatment to normalise iron indices. If there is raised TS but normal SF, treatment is not required as TS is only raised if there is evidence of raised total body iron levels. In C282Y homozygotes with normal SF, iron indices should be measured annually and treatment instituted if and when SF becomes elevated.

In almost all individuals with iron overload, regular venesection will normalise iron indices. Each 450mL unit of blood removes about 250mg of iron. Removal of a 450mL unit of blood reduces SF by about 50µg/L.

The frequency of venesection depends on the initial SF. In those with very high SF (>1000µg/L), removal of one or even two units of blood each week may be necessary. In those with lower initial SF, fortnightly venesection may suffice. Venesection should continue until SF is 50-100 µg/L, although there is no evidence base to inform what the lower limit should be. Each venesection should be preceded by measurement of haemoglobin and haematocrit. Venesection should only go ahead if the haematocrit is within 20% of the previous measurement and haemoglobin is greater than 11g/dL. SF should be measured every 10-12 phlebotomies but more often when SF approaches 100µg/L, as it is important to avoid iron deficiency. TS will generally remain elevated until iron stores are reduced to normal. It is not necessary to normalise TS.

Once SF is reduced to about 100µg/L, lifelong maintenance venesection is generally required. This needs to be assessed in each individual. Some require no further venesection treatments while others require monthly venesection. The average requirement is venesection every 3-4 months. Some choose to forgo maintenance venesection and instead have venesection treatment once their SF reaches the abnormal range. Treatment with proton-pump inhibitors reduces iron absorption and may reduce the requirement for maintenance venesection.

Most individuals tolerate venesection therapy. Occasionally however, people do not tolerate the therapy and experience vasovagal reactions. In these individuals, iron chelation therapy can be used. Here blood is centrifuged, separating the red blood cells from plasma. The red cells are removed while the plasma is returned to the treated individual.

In addition saline can be infused during the process to minimise the risk of vasovagal symptoms. Very occasionally iron chelation therapy is required. In this setting the treatment of choice is deferasirox, an oral iron chelator.

Venesection treatment can be performed through the Red Cross Blood Service. If an individual has no contraindications, the blood obtained can be used for donation purposes. The Red Cross Blood Service will undertake therapeutic venesection on individuals even if there are contraindications to the use of their blood for donation purposes. For more information on this service, see Online resources.

Prognosis of HH

STUDIES have shown that if an individual maintains iron indices in the normal range, their lifespan is not diminished by the genetic predisposition to HH. If an individual with elevated iron indices as a result of HH is treated and does not have diabetes or liver cirrhosis then lifespan is also unaffected.

There is clear evidence that if SF is >1000µg/L then normalisation of iron indices is necessary to minimise the risk of permanent morbidity from liver cirrhosis, diabetes and hepatic cellular carcinoma. There is no clear evidence of benefit of treatment when SF is <1000µg/L, although guidelines recommend treatment for individuals in this range. A research project, the Mi-iron Study, is currently underway, which is investigating how much iron removed in hereditary haemochromatosis should be treated. For more information on this trial and inclusion and exclusion criteria as well as how people can be referred, see Online resources.

Individuals with HH are at increased risk of hepatic cellular carcinoma. This is usually, but not always, in the setting of the presence of liver cirrhosis. It is recommended that individuals with liver cirrhosis from HH be monitored for hepatocellular carcinoma by regular ultrasound examinations. The use of alpha fetoprotein for screening is controversial. Monitoring for hepatocellular carcinoma is not necessary in those without proven cirrhosis.

Arthritis, hypogonadism, cirrhosis and type 1 diabetes are unlikely to be reversed by normalisation of total body iron. Nevertheless, it is important to treat people with these complications. Firstly this will prevent other morbidity and secondly it can improve some of these complications, for example reducing the daily insulin requirement.

Liver transplantation is indicated if an individual has decompensated liver failure. If at all possible it is important to normalise body iron before transplantation, as this has been shown to improve the prognosis of the transplant.

Individuals with HH should be vaccinated against hepatitis A and B since the presence of viral hepatic hepatitis can severely exacerbate liver disease in those with hepatic iron deposition caused by HH.

Dietary advice

It is recommended that individuals limit alcohol intake while they have very high iron indices. If there is no evidence of liver damage and iron indices are reduced to the normal range, there are no different recommendations in relation to alcohol intake than for the general community.

There is no need to prescribe a low-iron diet in individuals with increased iron levels who are being treated with venesection since the amount of iron that can be reduced by venesection is far greater than that present in even a high-iron diet.

Individuals should, however, be advised to avoid vitamin C supplementation when iron indices are high. Vitamin C increases absorption of dietary iron and also facilitates release of iron from storage and is occasionally responsible for inducing lethal cardiac failure.

Those with elevated body iron should also be advised to avoid raw shellfish, due to the risk of sepsis from Vibrio vulnificus.
Population screening

SINCE the major complications of HH are preventable by maintenance of normal iron levels in the body, some have called for the introduction of population screening for this disorder. Such screening can be by measurement of iron indices (so-called phenotypic screening) or testing for HFE C282Y and H63D (genotypic screening). The arguments for and against population screening for HH are presented in table 2.

Studies where screening for C282Y was offered in the workplace and to high-school students found that individuals shown to be homozygous for this mutation were not made anxious by this information and those with raised SF took steps to normalise iron indices. There is a pressing need for thorough health economic evaluation of population screening for HH.

Insurance implications of genetic testing for HH

Some individuals refuse to have genetic testing for HH due to concerns about the insurance implications of being identified as being at risk of this disorder. Genetic testing of an asymptomatic individual has no implications for health insurance since this is offered to all at the same rate (so-called “community rated”). It has no implications for existing life and disability insurance policies.

Familial implications of genetic testing for HFE C282Y and H63D.

No alterations found in the HFE gene

• If iron studies are normal, HH is exceedingly unlikely to develop
• All individuals with iron overload require follow-up regardless of HFE gene test result because in a small percentage of cases of HH, mutations in a different gene are responsible

a) C282Y homozygote (C282Y/C282Y)
• >80% of Australians with HH have this genotype
• Not all individuals with this genotype will develop severe iron-overload-related disease but 60-80% will develop abnormal iron studies during their lifetime
• If iron overload is present, lifelong venesection is required
• Cirrhosis is unlikely if the SF is less than 1000 µg/L, the ALT level is normal and there is no hepatomegaly
• Liver biopsy may be performed to exclude the presence of cirrhosis if blood tests are suggestive of cirrhosis
• Those without iron overload require iron studies no more frequently than annually
• Elucidation of the genetic status of all first-degree family members is recommended
• If a person with HH has more than one child, it is recommended that the other parent of the children is tested first and only if that parent has one or two HFE mutations do the children need be tested
• There have been no definite reports of significant morbidity due to C282Y homozygosity before adulthood and therefore children should be tested once they have reached an age when they can provide informed consent and can self-manage any preventive measures

b) Compound heterozygote (C282Y/H63D)
• Only about 1% of people with this genotype develop HH
• Those without iron overload require iron studies no more frequently than annually

c) C282Y heterozygote, H63D heterozygote or H63D homozygote
• Carrier status is common (>1 in 5 of the general population) and has not been shown to be associated with disease
• Some may have minor abnormalities in iron studies
• There is no need to monitor iron studies unless symptoms or abnormal iron studies are present.

Familial implications of HH

Because HH-related HH is autosomal recessive, siblings of individuals diagnosed with this should have genetic testing for HFE mutations along with iron indices (see box, right). Because about one in 10 Caucasians are heterozygous for C282Y (ie, have one copy of this mutation) and one in five are heterozygous for H63D, it is relatively common for the child of a person with HH to also have the genetic predisposition.

If an individual has more than one child it is recommended as a first step that their partner should be tested for their genetic status. If the partner has no HFE mutations then, assuming the individual has no suspicious symptoms, their children do not need any further testing. If the partner has one or two HFE mutations then their children should be offered testing. It is recommended that this testing is done no earlier than late teenage years. The rationale for this is that there is no evidence that significant morbidity occurs in HFE-related HH before adulthood. By testing individuals in late teenage years that individual can be involved in the decision whether or not to have testing, and if found to be at high risk, can take part in decision-making concerning monitoring and preventive therapy.

The Financial Services Council, the peak body for the Australian insurance industry, recently released a policy that means individuals with HH will only be penalised in obtaining life and disability insurance if they have evidence of organ damage from HH (see Online resources). That is, individuals who are found to be C282Y homozygous or C282Y/H63D compound heterozygous, and who have normal iron indices or who have raised iron indices without organ damage, and who are also having treatment to normalise their iron levels, will not be penalised when obtaining new life and disability insurance policies on the basis of their HFE genetic test result.
How To Treat – Hereditary haemochromatosis

Author’s case study

LAWRIE, a 56-year-old businessman, went to see his GP because of fatigue and generally feeling unwell. He found completing work tasks more onerous than he had in the past and he noticed that looking after his young grandchildren was more and more exhausting. He could no longer play 18 holes of golf as he had done each Saturday for the past 30 years. He also complained of reduced libido.

Llawie’s GP could find no cause for his symptoms on history or examination. Lawrie’s past history included mild hand arthritis treated with NSAIDs.

Investigations were conducted to look into the cause of Lawrie’s symptoms including an FBC, ESR, thyroid function tests, EUC, CRP, LFTs, iron studies and an electrocardiograph.

Lawrie was found to have a number of abnormalities including a SF of 2127µg/L, T5 of 98% and AST and ALT raised to about three times the upper limit of normal.

Because of the raised SF and TS, Lawrie’s GP arranged detection of the HFE gene. This revealed Lawrie to be homozygous for the C282Y mutation.

Lawrie was referred to a hepatologist for further investigation and management. He had a liver biopsy that revealed stage II fibrosis but no cirrhosis. Lawrie had an echocardiogram that was normal. He had reduced serum testosterone and raised FSH and LH. He had twice-weekly venesection for three months then weekly venescence for nine months and this normalised his SF to 120µg/L.

A repeat liver biopsy at the end of treatment revealed a reduction in the severity of fibrosis to stage I.

By the end of treatment Lawrie was less tired and was able to resume a healthy round of golf. His joint pain was somewhat worse than it had been 12 months before treatment but his libido was much improved following prescription of testosterone. Lawrie subsequently required venesection every four months to maintain normal SF.

Conclusion

EARLY diagnosis and treatment of HH 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.

Genetic testing of relatives of individuals diagnosed with HH is important and physicians should be aware of the ethical implications of screening for disease in this era of personalised genomics medicine.

Population genetic screening for HH may become routine in the future but is currently considered too costly, despite the benefits of ascertaining early preventable disease.

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

How to Treat Quiz

Hereditary haemochromatosis

12 April 2013

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points.

GO ONLINE TO COMPLETE THE QUIZ


CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2011-13 triennium. You can complete this online along with the quiz at www.australiandoctor.com.au. Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

NEXT WEEK

Gallstones are a leading cause of hospital admissions related to gastrointestinal disease. The Western diet and lifestyle have been implicated in the risk factors for gallstones. The next How to Treat gives a guide to the presentation and management of this condition. The authors are Dr Tony Speer, gastroenterologist, Royal Melbourne Hospital and Western Hospital, Melbourne; and Professor Robert Gibson, deputy head, department of radiology, University of Melbourne and Royal Melbourne Hospital, Melbourne, Victoria.

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