Earn CPD points on page 38

Complete How to Treat quizzes online (www.australiandoctor.com.au/cpd) or in every issue.

HEREDITARY haemochromatosis

Background

HEREDITARY haemochromatosis is a unique group of inherited diseases that cause total body iron loading. HFE-gene-related haemochromatosis is the most common inherited disorder in our population, with a carrier frequency rate of about 1:200-300.

Hereditary haemochromatosis is predominantly a disorder affecting people of northern European descent. The mutation may have offered a previous survival advantage in populations who had a diet low in iron. This has now become a survival disadvantage, as First World diets are iron rich.

Untreated, affected persons have an increased lifetime risk of chronic liver disease as well as other systemic diseases including diabetes mellitus. As a consequence of these long-term complications, developing

cont'd next page

inside

Iron physiology

Clinical presentation

Investigation and diagnostic methods

Management

The authors

DR CHRISTOPHER HAIR, advanced trainee registrar, gastroenterology, Barwon Health, Geelong Hospital, Victoria.

DR JONATHON WATSON, consultant gastroenterologist, Geelong, Victoria.

from previous page
methods to allow early identification of asymptomatic carriers is warranted.

In 1996, the HFE gene was described. Since then there has been much debate regarding the mass population screening for HFE-related hereditary haemochromatosis.

One feature of HFE-related hereditary haemochromatosis is the phenomenon of incomplete penetrance. This means that not all people who are homozygous for the genotype will develop iron overload. We have no method of identifying which homozygotes will develop iron overload.

The expense of identifying all homozygotes, and the lack of a way of identifying whom we should treat, has been the major argument against mass population screening for haemochromatosis. High-risk individuals (see page 35) can access Medicare rebatable genetic test screening.

This article reviews iron physiology and the pathophysiology of iron-loading conditions, and examines the genetics and differential diagnosis of hereditary haemochromatosis. Most of the article focuses on the investigation and management of hereditary haemochromatosis, with several case studies to allow a better understanding of current treatment.

Iron physiology

EACH day 1-2mg of iron is absorbed into the body, which has a normal iron storage of about 3-4g. Iron is absorbed from the GI tract, circulated and stored in the liver and the reticuloendothelial system. It is used for the production of haem, as a cofactor of various metabolic pathways and is present in myoglobin.

Iron loss of about 1.0-1.5mg/day occurs through the GI tract, skin and sweat. In females, menstrual losses account for another 0.5-1.0mg/day.

People with haemochromatosis typically absorb 2.0-4.0mg/day — twice that of unaffected individuals. As net losses are not increased, iron is cumulatively stored in end organs, leading to grossly increased iron stores over time.

Most iron absorption occurs in the duodenum. Ferrous iron is transported into the cytoplasm of the enterocyte, where it may be stored as ferritin. Iron circulates in the plasma bound to transferrin.

The patho-biochemistry of hereditary haemochromatosis is complex and incompletely understood. The protein hepcidin appears to be important in regulating the iron-storage pathway. Its major effect is to decrease the amount of dietary iron absorbed at the duodenal enterocyte as well as reducing iron release by macrophages. It is therefore a negative regulator protein in the iron-absorption pathway.

Hepcidin is synthesised by the liver and appears to be regulated by the HFE protein. In patients with HFE-related haemochromatosis, hepcidin levels are reduced. This may lead to a loss of regulation of the storage pathway, with the ultimate consequence of increased iron absorption and storage.

Mutations in the HFE protein may not be enough to account for the increase in iron absorption seen in patients homozygous for the C282Y mutation. It may be that other mutations affecting iron-regulatory proteins need to be present for significant iron overload to occur. In the absence of these mutations a milder form of disease may be present.

Causes of iron overload

Hereditary haemochromatosis

HFE related:
- C282Y homozygosity
- C282Y/H63D heterozygosity

Non-HFE related:
- Juvenile haemochromatosis
- Transferrin-receptor-2 mutations
- Ferroportin-1 mutations
- Hepcidin mutations

Chronic liver disease
- Non-alcoholic fatty liver disease
- Alcoholic liver disease
- Chronic viral hepatitis

Iron-loading anaemias
- Haemolytic anaemia
- Thalassaemia major
- Sideroblastic anaemia

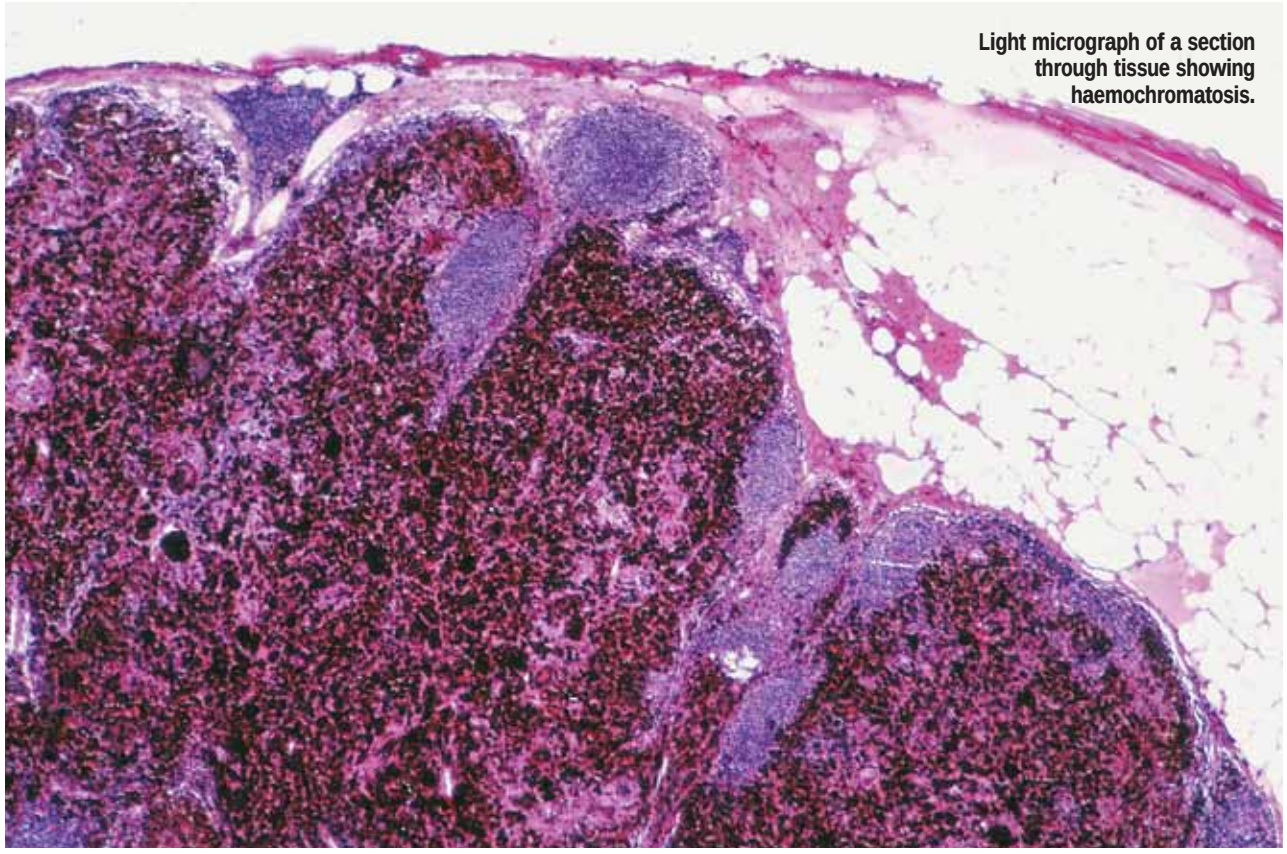
Acaeruloplasminaemia

Parenteral iron overload

Dietary iron overload

Genetics of haemochromatosis

- Missense mutations in the HFE gene cause most haemochromatosis.
- The C282Y mutation is the most common (90%), followed by H63D.
- Homozygosity of C282Y occurs when two copies of mutant C282Y are inherited.
- Patients with C282Y/H63D mutations are called compound heterozygotes.
- A large majority of patients with HFE mutations, including C282Y homozygosity, may not develop clinically significant iron overload.



Light micrograph of a section through tissue showing haemochromatosis.

Iron-loading conditions

Hereditary haemochromatosis is a term used to describe all inherited disorders of iron metabolism causing increased iron deposition in tissues and increased iron absorption from the intestine. HFE-related hereditary haemochromatosis is the most common form, although other hereditary forms exist, including juvenile haemochromatosis (hemojuvelin mutations).

Secondary iron overload can occur in acquired conditions causing increased iron liberation or absorption. These include some cases of chronic liver disease, iron-loading anaemias, increased oral iron intake or excessive intravenous iron loading.

Genetics and expression of disease

Your patient is found to be homozygous for the C282Y mutation after screening in the setting of a first-degree relative who has been recently diagnosed with haemochromatosis. She wants to know what the chance is that she will also develop clinically significant disease.

Hereditary haemochromatosis can result from a mutation in at least five genes. The most common genotype encountered in clinical practice is type 1 hereditary haemochromatosis relating specifically to the HFE gene.

C282Y is the most common mutation and is present in about 12% of the Australian population. It accounts for about 90% of all cases of hereditary haemochromatosis. H63D is the next most common mutation.

Homozygosity for the C282Y mutation occurs in about 1:200-300 people. These people may exhibit iron overload, although many will remain asymptomatic throughout life because of incomplete penetrance.

It is possible to acquire a single copy of each mutation — the so-called C282Y/H63D compound heterozygote. This genotype also confers an increased risk of disease expression. About 5% of compound heterozygotes develop significant iron overload requiring phlebotomy.

It is not clear whether patients who are homozygous for H63D develop clinically significant disease. Raised transferrin saturation levels have been reported in this cohort.

About 10% of patients do not carry the described mutations but still exhibit the disease, presumably as a result of expression of as-yet undescribed mutations.

It is of great interest that not all persons who are homozygous C282Y or compound heterozygote C282Y/H63D will develop iron overload. Because of incomplete penetrance, fewer than 1% of homozygous patients will exhibit iron overload at the time of diagnosis. It is not understood what proportion will progress to serious long-term disease such as organ failure.

While incomplete penetrance helps explain the observed disparity between genotype and disease expression, there may be other factors that contribute to this effect. These may include the modifying effects of diet, sex, various environmental agents and other conditions that contribute to blood loss.

Screening

A young couple present to your office for prenatal counselling. One of the pair is known to carry the C282Y mutation, having had a mother with symptomatic haemochromatosis. They wish to know their risk of producing a child with haemochromatosis.

As a consequence of incomplete penetrance leading to variable disease expression, and our inability to predict which patients with the susceptible genotype will express the disease, mass genotype screening is not recommended and is unlikely to occur in the near future.

It is our practise to recommend screening of first-degree relatives of a patient with hereditary haemochromatosis, and of patients with symptoms or signs that suggest iron overload.

While screening patients with iron studies is a useful initial test, some patients with haemochromatosis may be missed, as iron overload may have not as yet occurred. HFE gene analysis is a confirmative and definitive test, and is a more reliable screening tool.

The optimal age group for screening has not been established, but generally first-degree relatives under 18 are unlikely to have significantly altered iron studies.

Screening issues

- Although the genotype of HFE-related haemochromatosis is well established, population screening is not currently recommended because of incomplete penetrance.
- Heterozygotes for C282Y are not at risk of iron overload. The chance of offspring being homozygous for C282Y if both parents are carriers is 50%.
- First-degree relatives of a patient with HFE-related haemochromatosis should be offered genotype testing and appropriate education and counselling

In order for this couple to know their risk of producing a child with genetic haemochromatosis, the carrier's partner would have to be screened. However, as haemochromatosis is an entirely treatable condition, and also has incomplete phenotypic penetrance, I would not advocate genetic counselling or prenatal screening. In my opinion therefore the carrier's partner should not undergo screening.

Clinical presentation

A 63-year-old man is referred with a raised ferritin level (1535µg/L) after a recent ventricular fibrillation arrest. Echocardiography revealed dilated cardiomyopathy. On examination there are six spider naevi across the chest, gynaecomastia, testicular atrophy and evidence of left ventricular failure. Ultrasound reveals a nodular liver suspicious of cirrhosis. Genotype testing reveals C282Y/C282Y homozygous state. A fasting glucose test is consistent with diabetes mellitus. Male sex hormones are below normal ranges.

Broadly speaking, haemochromatosis presents in two ways. First, an asymptomatic patient can request genetic screening because of a first-degree relative with hereditary haemochromatosis. Typically, those found to be homozygous will have a low incidence of iron overload and end-organ disease.

Secondly, symptomatic persons with previously undiagnosed disease may present with fatigue and lethargy, arthralgia or a loss of libido.

Symptoms relating to hereditary haemochromatosis and iron overload typically do not occur in people under 40. Iron accumulation is minimal before age 20 because child and adolescent growth accounts for a greater iron utilisation than in adults. From age 20 to 40 a progressive accumulation of iron may result in an asymptomatic state of iron overload (about 20g/L). Clinical features may not develop in men until after age 40, and even later in women as a result of lifetime menstrual iron losses and iron utilisation during pregnancy.

Typically, further iron accumulation above 20g/L may result in major organ dysfunction such as liver disease and pancreatic endocrine dysfunction.

Liver disease

Liver-related symptoms are secondary to the underlying liver dysfunction, which may occur in later life when iron overload is severe. Progressive hepatic iron accumulation may cause hepatic inflammation, elevated LFT results and cirrhosis (figure 1). Fatigue and lethargy are common. In advanced liver disease other symptoms may include weight loss, hypogonadism, male breast swelling, hair loss and palmar erythema.

Several conditions may complicate the course of cirrhosis, including portal hypertension and variceal bleeding, encephalopathy and ascites. Patients with suspected chronic liver disease should be referred to a gastroenterologist for management.

Hepatic iron accumulation may worsen the natural history of several other liver diseases, including hepatitis C infection and alcoholic liver disease. It would seem logical that iron overload would also worsen the disease process of non-alcoholic fatty liver disease, but the evidence is not as yet clear. Although the precise mechanism is unclear, there is an increased risk of developing significant liver fibrosis and ultimately cirrhosis in the presence of iron overload (figure 2).

The most serious hepatic complication of haemochromatosis is the development of hepatocellular carcinoma. The risk is increased 20-200 times relative to the normal population and, once diagnosed, the clinical course of hepatocellular carcinoma is not improved by a reduction in iron levels.

Extrahepatic manifestations

The extrahepatic manifestations of hereditary haemochromatosis reflect the progressive deposition of iron in various organs, including the pituitary gland, myocardium, pancreas, skin and joints.

Arthralgia presenting as pain in the second and third metacarpophalangeal joints is suggestive of haemochromatosis, although arthritis in this setting can also occur in other conditions. The arthropathy of haemochromatosis does not typically improve with iron reduction.

Iron deposition in cardiac tissue may cause a dilated cardiomyopathy, left ventricular dysfunction and arrhythmia, including sick sinus syndrome. Cardiac disease alone may be the presenting feature in a small number of patients with haemochromatosis, and screening with fasting iron levels should be considered.

A wide array of endocrine

cont'd page 35

Symptoms and signs of haemochromatosis

Symptoms

- Fatigue and lethargy
- Arthralgia
- Impotence and loss of libido
- Skin pigmentation

Signs

- Cirrhosis
- Hepatomegaly
- Skin pigmentation
- Tenderness of the second or third metacarpophalangeal joints
- Testicular atrophy
- Dilated cardiomyopathy and left ventricular failure

Other findings

- Elevated blood glucose
- Elevated LFT results
- Abnormal ECG

Figure 1: Liver cirrhosis due to hereditary haemochromatosis. (Image courtesy of Dr S Wallace, Pathcare Consulting Pathologists, Geelong, Victoria.)

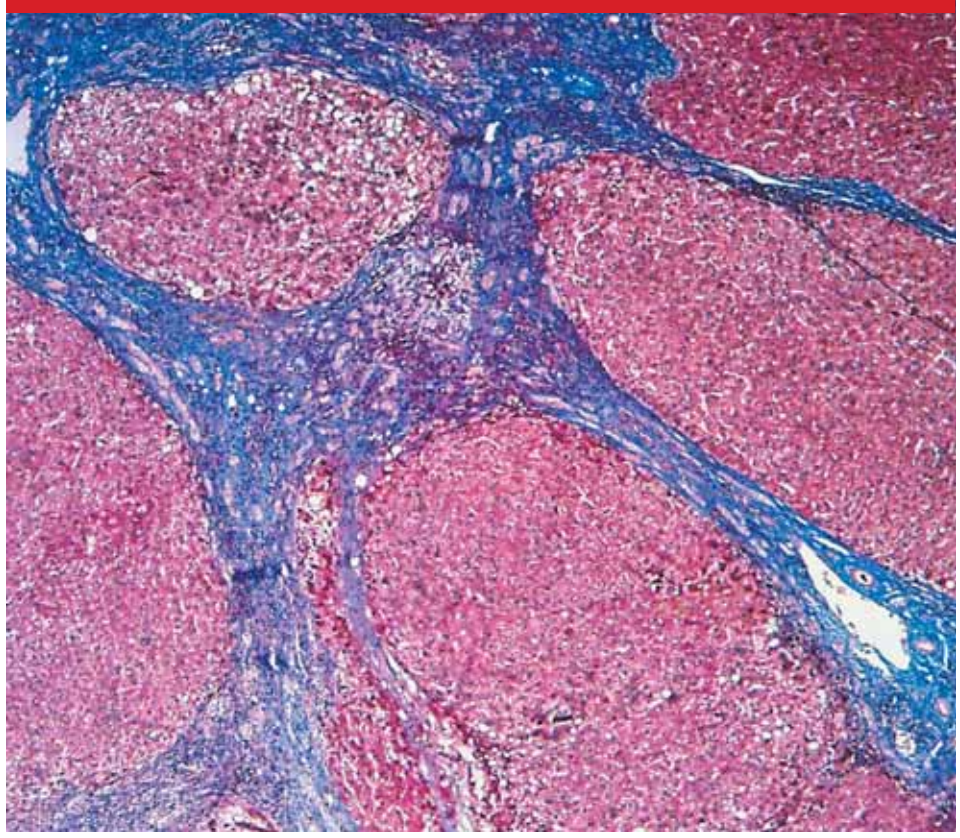
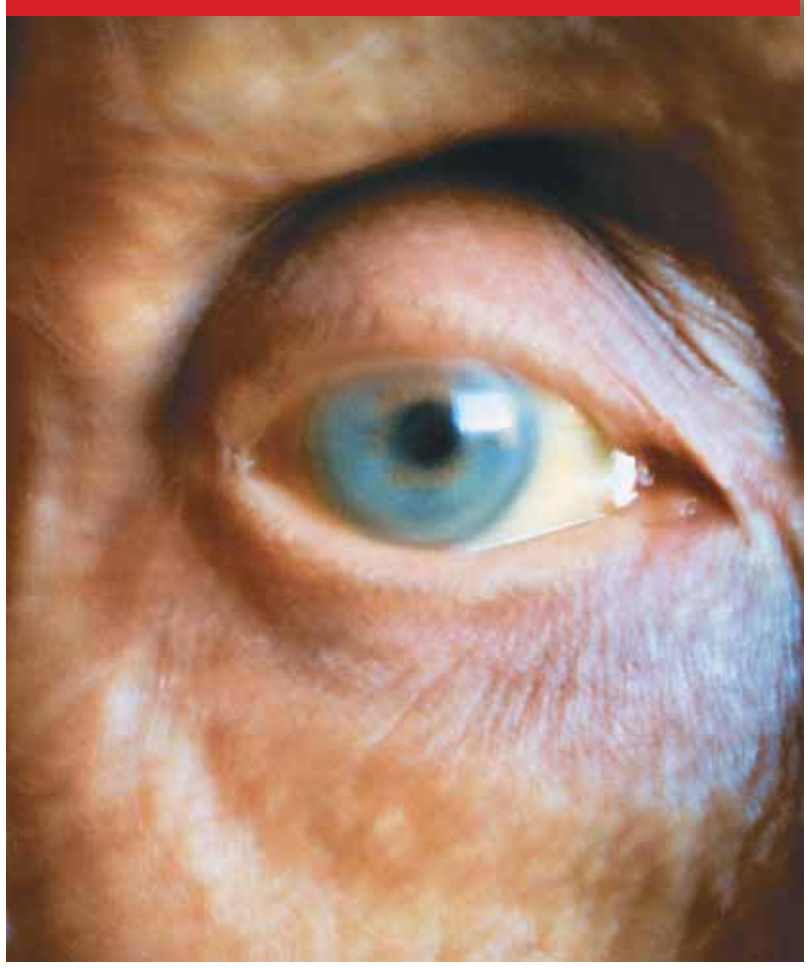


Figure 2: Scleral icterus. Chronic liver disease is a late complication of hereditary haemochromatosis.



from page 33

dysfunctions may occur in the presence of iron overload. Diabetes mellitus may be present in up to 50% of patients at the time of diagnosis of iron overload. Typically, these patients have reduced C-peptide levels and may require insulin. Patients' insulin requirements may dimish with reducing iron levels.

At present it is not routine practice to screen all people newly diagnosed with diabetes for haemochromatosis unless other features are present such as skin pigmentation or liver disease. Skin pigmentation is an important sign (the so-called bronzed diabetic), and when present should prompt testing for hereditary haemochromatosis.

The most serious hepatic complication of haemochromatosis is the development of hepatocellular carcinoma.

Iron deposition in the pituitary gland most commonly results in secondary hypogonadism, with low serum testosterone, follicle stimulating hormone (FSH) and luteinising hormone (LH) levels in men. Clinical features include impotence and reduced libido. Impotence in males due to haemochromatosis diagnosed after age 50 is unlikely to improve with phlebotomy.

Other endocrine disease may be present, including hypothyroidism, amenorrhoea and osteoporosis.

Investigation and diagnostic methods

A 62-year-old man presents with fatigue and right upper-quadrant pain. You find hepatomegaly on examination. He has elevated aminotransferase and bilirubin levels. Iron studies reveal a transferrin saturation of 65% and ferritin level of 875µg/L. You refer him for further assessment.

When the diagnosis of iron overload and haemochromatosis is suspected, investigation should start with the screening of iron stores and LFTs. Iron studies should be requested after an overnight fast.

A transferrin saturation in excess of 60% predicts a homozygous genotype in more than two-thirds of patients with hereditary haemochromatosis, although a normal level may occur in rare cases of iron overload such as dysmetabolic hepatosiderosis and hereditary acaeruloplasminaemia.
Transferrin saturation may also be increased in other conditions, including iron-loading anaemias and hepatitis.

Serum ferritin level is a good indicator of excess total body iron stores, although it can also be raised in many conditions, including inflammation, malignancy and other causes of liver disease. In haemochromatosis the serum iron level is usually >36mmol/L.

A combination of the above is strong evidence of iron overload.

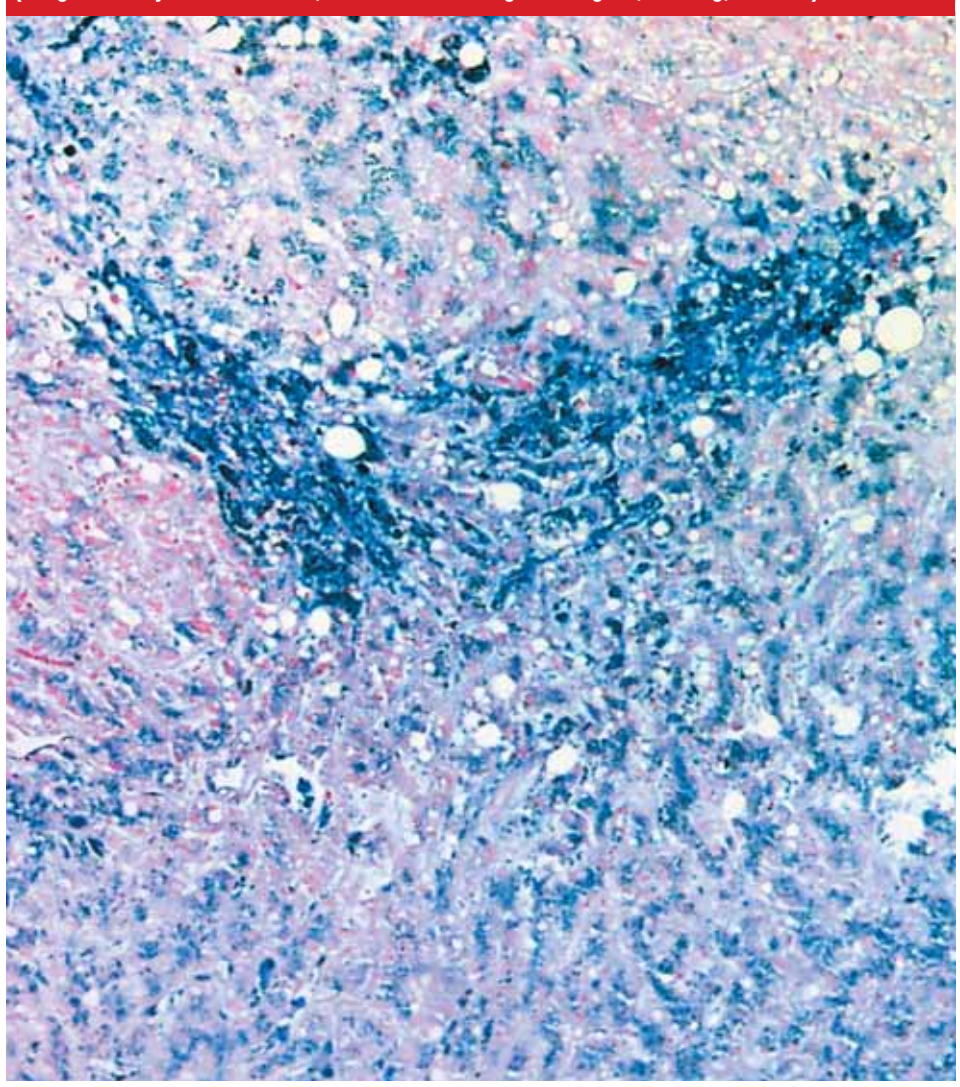
Parents and children of index cases should be screened by gene analysis; occasionally a parent will be an undiagnosed homozygote with minimal disease expression.

A liver biopsy is recommended, but is not an essential investigation unless the diagnosis is in doubt. It carries a mortality of 1:1000 to 1:10,000. It confirms the diagnosis of hereditary haemochromatosis and the presence of liver fibrosis (figure 3).

The absence of fibrosis can be predicted in patients who lack certain high-risk factors, including:
- Ferritin level >1000µg/L
- Hepatomegaly
- Abnormal aminotransferase levels
- Age >40.

If these indicators are absent and the diagnosis is not in doubt, referral for liver biopsy can be deferred.

Figure 3: Perls' stain (blue) of liver cirrhosis revealing heavy iron deposition. (Image courtesy of Dr S Wallace, Pathcare Consulting Pathologists, Geelong, Victoria.)



HFE gene analysis is funded by Medicare for:
- First-degree relatives of patients with hereditary haemochromatosis.
- For patients with first-degree relatives who are C282Y homozygous or C282Y/H63D heterozygotes.
- Patients with high suspicion (elevated transferrin saturation or raised serum ferritin level).

Haemochromatosis genetics

C282Y/C282Y
- The most common form of hereditary haemochromatosis (>90% of cases).
- Clinical iron overload may range from no disease to multi-organ involvement.
- Up to 50% of homozygotes do not have clinical iron overload. Consider serial screening of serum ferritin and transferring saturation every 1-10 years.

C282Y/H63D
- These patients may have normal iron studies or mild to moderate iron overload.
- It is more common to develop severe iron overload in the setting of other causes of liver disease such as alcohol.

C282Y alone
- Most of these patients have normal iron studies.
- Rarely the ferritin level is raised and in these cases it is commonly due to another cause (see Causes of a raised ferritin level, page 36). Occasionally a liver biopsy may be needed to quantify hepatic iron and determine the need for treatment.

H63D/H63D
- Iron studies are usually normal. Rarely mild to moderate iron overload is seen.
- Occasionally a liver biopsy may be needed to quantify hepatic iron and determine the need for treatment.

H63D alone
- Iron studies are normal. If iron studies are abnormal, the changes are most likely to be due to another cause (see

Screening for complications

After the diagnosis is confirmed, possible complications of iron overload should be screened for. A fasting

cont'd next page

from previous page
blood glucose level, transthoracic echocardiocardiography, joint X-ray and tests of pituitary function, including FSH and LH levels, are useful screening investigations.

Raised ferritin level — so what?

Ferritin is responsible for the intracellular storage of iron. A raised ferritin level is commonly interpreted as an indication of increased iron storage or iron overload. However, this is not always the case because elevations in ferritin may be the result of acute and chronic inflammatory conditions, as well as some malignancies.

Before accepting that a patient with a raised ferritin level has hereditary iron overload and proceeding to genetic testing, it is important to consider other causes of elevated ferritin. Most of these will be easily obtained from the history and examination, but some causes are not as clear, such as non-alcoholic steatohepatitis or asymptomatic chronic viral hepatitis.

Is there a cut-off ferritin level above which the diagnosis of haemochromatosis is most likely?

We often see highly elevated ferritin levels (eg, 2000-5000µg/L) in the setting of acute hepatitis of any cause, and moderately elevated ferritin levels (300-600µg/L) in the setting of non-hepatic acute infection. In most of these cases acute or chronic inflammation is the cause of the increased level.

Elevations in ferritin may be the result of acute and chronic inflammatory conditions, as well as some malignancies.

Nevertheless, it is our practice, particularly in patients presenting with liver-related disorders, to perform genetic analysis for haemochromatosis. If the patient is neither a C282Y/C282Y homozygote nor a C282Y/H63D compound heterozygote, the diagnosis of hereditary haemochromatosis is unlikely.

Diagnostic workup of haemochromatosis

Iron studies
- Iron level >36µmol/L (9-31µmol/L)
- Transferrin saturation >45% (16-60%)
- Ferritin level >250µg/L (30-300µg/L)

Genetic testing — possible results
- C282Y/C282Y — diagnosis made
- C282Y/H63D — compound heterozygote
- C282Y +/– : carrier and not the cause of raised transferrin saturation
- C282Y -/-: another cause of iron overload is present (including rare inherited)

LFTs and ultrasound
- Raised aminotransferase levels
- Possibly raised bilirubin level if cirrhosis present
- If clinical suspicion of cirrhosis, arrange an ultrasound

Liver biopsy
- A liver biopsy is useful to establish the presence of fibrosis and to exclude other comorbid diseases. Fibrosis is likely in the setting of age >40, a ferritin level >1000µg/L, abnormal LFTs or hepatomegaly

Other tests
- Fasting blood glucose level
- Sex hormones and thyroid function tests
- ECG +/– transthoracic echocardiography
- Joint X-ray

Causes of a raised ferritin level
- Any acute inflammatory process (eg, infection or inflammation)
- Chronic viral hepatitis, alcoholic hepatitis and non-alcoholic steatohepatitis
- Chronic inflammatory diseases, including rheumatoid arthritis
- Malignancies

Management

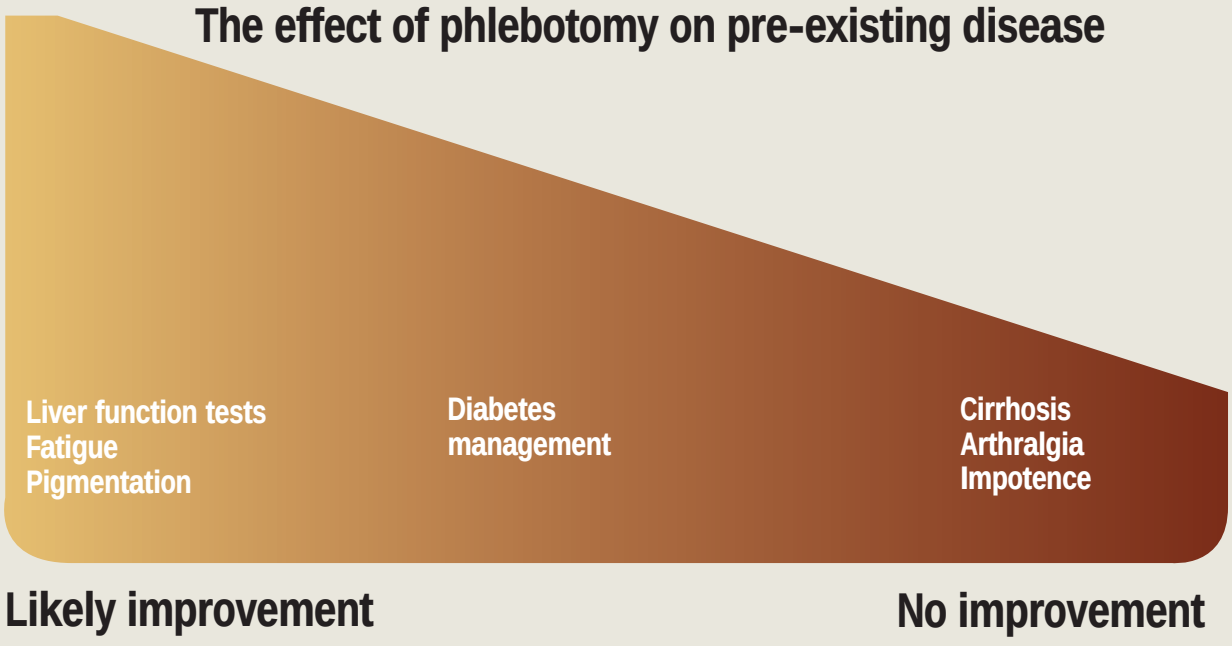
A 43-year-old man presents requesting testing for haemochromatosis. His father has been recently diagnosed with haemochromatosis. He is asymptomatic. You request iron studies, LFTs and HFE-gene studies, which reveal a ferritin level of 1350µg/L, a transferrin saturation of 55% and a raised aspartate aminotransferase (73I U/L). His gene study reveals a C282Y/H63D genotype. He consumes 50g of alcohol a day, has a BMI of 28 and a random blood sugar level of 10.4mmol/L. What management would you advise?

This man has hereditary haemochromatosis with iron overload. Without treatment he may develop severe complications, including chronic liver disease and ultimately cirrhosis, hepatocellular carcinoma, diabetes mellitus, gonadal failure, arthritis, cardiac failure and arrhythmias.

In the presence of cirrhosis a patient with haemochromatosis has a fivefold increased mortality. Therefore, after the diagnosis of haemochromatosis is confirmed by gene testing, initial management includes reducing iron stores and establishing the presence of complications such as liver fibrosis and diabetes.

The main goal of haemochromatosis management is to re-establish normal body iron stores. This is achieved in most patients through venesection and avoiding excess oral iron intake and alcohol. The latter recommendation applies to all patients, that is, symptomatic and asymptomatic homozygotes and compound heterozygotes.

Figure 4: While LFT results, fatigue and pigmentation may improve with a reduction in the total body iron store, it is unlikely that there is any significant benefit in cirrhosis, arthralgia and impotence. In the setting of diabetes mellitus, phlebotomy may lead to reduced requirements for insulin.



Asymptomatic homozygotes

Many homozygous patients may remain asymptomatic throughout life. Current recommendations for the management of asymptomatic homozygotes with normal ferritin levels include annual iron studies and LFTs and a physical examination to screen skin, liver, heart, joints and endocrine systems.

Other authors have recommended less intensive follow-up (ie, 2-10 yearly) based on the observation that only a small proportion of these patients will develop significant complications in the long term.

Dietary recommendations

Many patients are concerned about consuming red meats and other products with presumed high iron content. While no dietary changes are necessary, patients should avoid iron supplements, particularly in association with vitamin C. Vitamin C facilitates iron absorption, and excessive doses have been associated with fatal arrhythmias in patients with iron overload.

A balanced diet that contains a component of fruit and vegetable is recommended. The diet should minimise alcohol intake. Heavy alcohol intake is associated with an increased rate of development of cirrhosis and hepatocellular carcinoma in homozygotes for the C282Y mutation.

Phlebotomy

The main treatment of symptomatic haemochromatosis is phlebotomy. Phlebotomy of 500mL of whole blood removes 250mg of iron. Iron is mobilised from tissues to replenish the bone marrow to enable it to replace removed erythrocytes, thus reducing stored iron levels.

While the absolute regimen of phlebotomy is not well established, it is generally recommended that phlebotomy initially be performed weekly. At the time of initial diagnosis total body iron stores can range between 10g and 40g; therefore, weekly venesection may take up to three years to re-establish normal iron stores.

There may be subtle individual variation in response to phlebotomy, and tolerance of phlebotomy; the elderly and patients with cardiac or other end-organ disease may not tolerate weekly phlebotomy, while young males may tolerate removal of up to two units of blood a week.

When normal iron stores have been achieved (and in the absence of cirrhosis and diabetes mellitus), life expectancy is no different to that of the normal population. Further venesection at

Treatment
- Weekly phlebotomy to remove 500mL of blood (250mg of iron)
- Monitoring of haematocrit pre-phlebotomy
- Measurement of serum ferritin level initially weekly and then 2-3-monthly until it reaches <50µg/L
- When iron stores have been depleted, initiate 3-6-monthly phlebotomy to maintain transferrin saturation <35% and serum ferritin level <50µg/L
- Avoid consuming excessive alcohol and vitamin-C-containing multivitamins
- Recommend a balanced diet, including red meat and fruits

When to refer

- Any patient suspected of chronic liver disease, or patients with high risk features for liver fibrosis.
- Complicated comorbidites, including haemolytic anaemia or thalassaemia, when phlebotomy may be challenging.
- When the diagnosis is in doubt, in particular, if genotype does not explain raised serum ferritin levels or transferrin saturation.

regular intervals (eg, 3-6 monthly) will help maintain normal iron stores in the long term. Blood removed at phlebotomy is currently approved for re-use in transfusion recipients.

Monitoring during and after phlebotomy

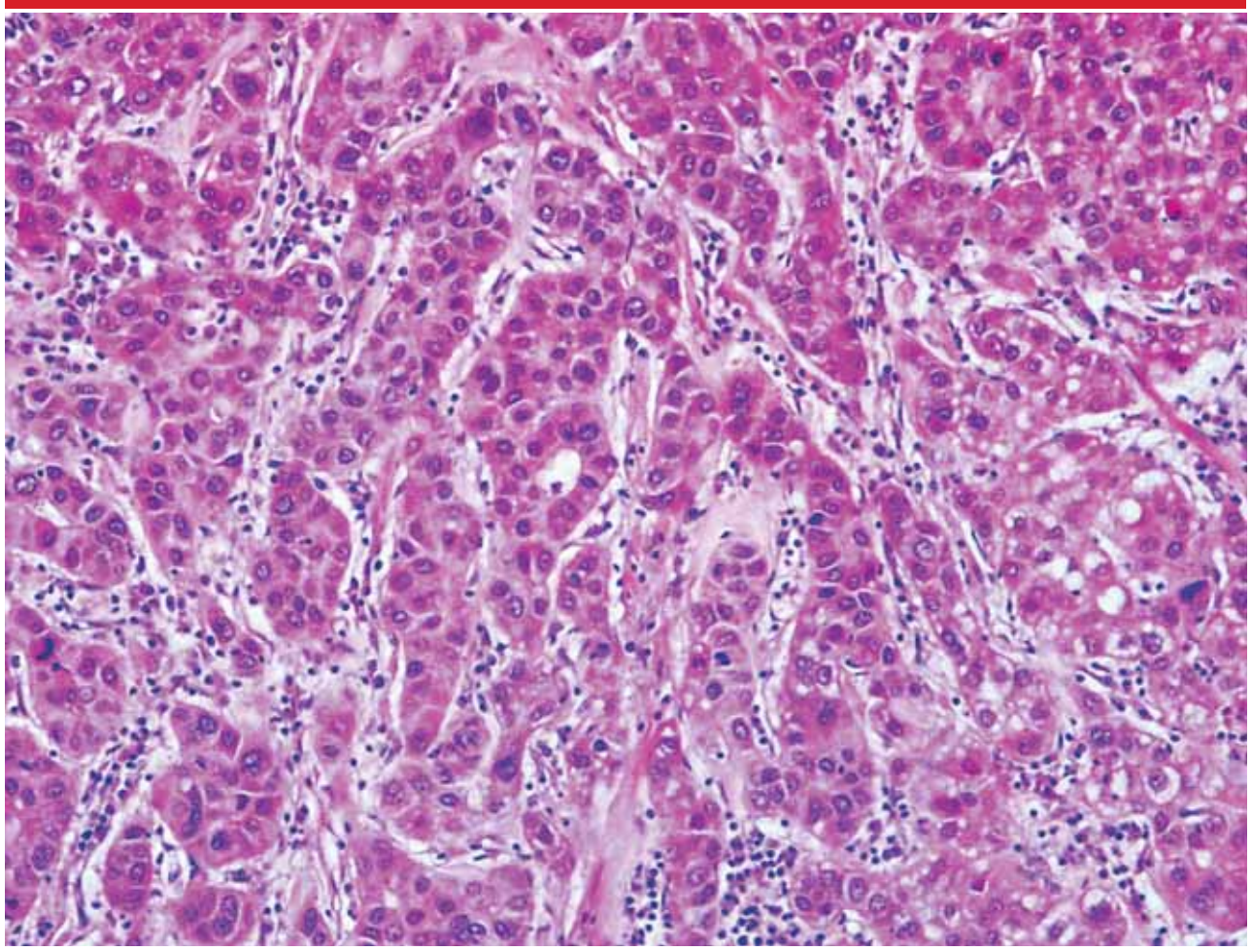
Monitoring of haemoglobin and ferritin should be undertaken at regular intervals during weekly phlebotomy. Most patients will maintain haemoglobin in a normal range during phlebotomy; however, the frequency of phlebotomy may need to be reduced if the haemoglobin level falls below 10g/L, or the haematocrit level falls below 20% of previous levels.

The serum ferritin level should be checked every 10-20 phlebotomies and the fasting ferritin levels should return to <50µg/L after successful therapy with phlebotomy. A serum ferritin <20µg/L is indicative of iron deficiency, and should prompt the clinician to withhold phlebotomy until the ferritin has risen.

The transferrin saturation should also fall to <35% in this setting, although other authors recommend ranges between 35% and 50%. Transferrin saturation <35% and ferritin level <50µg/L can be maintained with further phlebotomy at regular intervals.

In general, 3-6-monthly phlebotomies will be required, although there is significant individual variation in the re-accumulation of iron. Therefore the interval may need to be adjusted on an individual basis in response to the transferrin saturation and serum ferritin levels.

Figure 5. Hepatocellular carcinoma arising in a cirrhotic liver due to hereditary haemochromatosis. (Courtesy of Dr. S Wallace, Pathcare Consulting Pathologists, Geelong, Victoria)



Blood removed at phlebotomy is currently approved for re-use in transfusion recipients.

What can phlebotomy achieve?

Phlebotomy is useful for improving aesthenia, pigmentation and improving LFT results. It may reduce insulin requirements in the setting of diabetes mellitus. Unfortunately it appears to offer lesser improvement of arthralgia and gonadal failure. Normalising iron stores does not benefit cirrhosis or hepatocellular carcinoma (figure 4), although there may be some reversal of fibrosis in up to 30% of patients.

The patient with cirrhosis — complications of chronic liver disease and cancer risk

The patient with suspected or confirmed cirrhosis should be referred to a gastroenterologist for further management. The long-term management of the cirrhotic patient includes optimising health, preventing infection and further hepatic insults, preventing complications and screening for hepatocellular carcinoma.

If complications of cirrhosis occur, the patient has decompensated chronic liver disease. In the setting of cirrhosis and advanced fibrosis related to haemochromatosis, there is an increased risk of future development of hepatocellular carcinoma (figure 5).

Complications of cirrhosis

- Hepatic encephalopathy
- Hepatocellular carcinoma
- Hepatorenal and hepatopulmonary syndromes
- Spontaneous bacterial peritonitis
- Variceal haemorrhage

Earlier literature reported that the proportion of deaths due to hepatocellular carcinoma in the setting of hereditary haemochromatosis was about 30%. With advances in therapy for hepatocellular carcinoma and liver transplantation, the modern mortality rate in this setting may be less; nevertheless, the complication is significant and the clinician should adopt a suitable screening strategy to allow early detection.

Although no literature exists regarding screening for early detection of hepatocellular carcinoma in this setting, most clinicians would recommend six-monthly liver ultrasound and serum alpha-fetoprotein monitoring based on suggested recommendations for other patients with chronic liver disease.

Decompensated liver disease

Decompensated liver disease as well as the development of hepatocellular carcinoma in the setting of haemochromatosis is an indication for liver transplantation. This offers a long-term survival benefit compared with the non-transplanted patient. However, compared with patients undergoing liver transplantation who do not have haemochromatosis, survival is reduced.

It appears that much of the reduced comparative survival is as a consequence of cardiac complications and a greater susceptibility to infections in the post-transplant setting; the mechanism of the latter problem remains unclear. Therefore, development of decompensated liver disease should prompt the clinician to refer for liver transplantation.

Summary

- Hereditary haemochromatosis is one of a number of iron loading conditions
- Functional organ failure may occur as a result of excess iron deposition in a number of organ systems
- HFE-gene-related haemochromatosis is the most common genetic defect in Australians, affecting about 1:200-300 Australians.
- Only a minority of C282Y homozygous persons develop iron overload
- Fatigue, lethargy, arthralgia and loss of libido are common presenting symptoms
- Treatment of hereditary haemochromatosis before the development of cirrhosis is associated with a normal life expectancy
- Regular phlebotomy will establish normal iron stores in the majority of patients

Online resources

- Haemochromatosis Society Australia Inc: www.haemochromatosis.org.au
- Gastroenterological Society of Australia: www.gesa.org.au
- Centre for Genetics Education. Hereditary haemochromatosis. In: *The Australian Genetics Resource Book*, 2007: www.genetics.com.au/pdf/factsheets/fs36.pdf

GP's contribution

DR ROSS WILSON
Bathurst, NSW

Case study

BT, 65, presented six months ago complaining of lethargy and little else. He had not seen a GP for years and was on no medication although he did "borrow" some of his wife's Di-gesic tablets for occasional joint pain.

Physical examination and blood tests revealed a serum iron level of 16.2µmol/L (7.0-29.0µmol/L) and a ferritin level of 557µg/L (30-300µg/L).

He tells you his brother has the "iron disease" and is having venesections. Gene analysis revealed he was heterozygous for the CY5282TYR mutation, and the H1563ASP mutation was not detected. Liver function was normal.

Further questioning revealed a history of relative impotence and shortness of breath on exertion.

Questions for the author

What further testing and advice is needed?

This man is heterozygous for C282Y mutation. Rarely, this accounts for a raised ferritin level. Usually there are other causes of raised ferritin level, such as chronic inflammatory conditions or infections. A careful workup for other causes of a raised ferritin level is required (including repeat ferritin and transferrin saturation).

If no other cause is identified, and in the setting of a sibling with likely haemochromatosis, it is possible that BT's symptoms may be due to iron overload. A referral for iron quantification might be useful (such as a liver biopsy).

Will his impotence respond to reassurance and an erectile dysfunction agent (eg, sildenafil)?

It is unlikely that haemochromatosis is present. Therefore it is unlikely that iron overload is the cause of his impotence. A full workup for usual causes of impotence is required, and a trial of an agent for erectile dysfunction might be beneficial.

How does one discuss whether his brother and he need venesection and under what circumstances?

Evaluating current iron storage (crudely, the ferritin and transferin saturation) is a useful starting point. In the setting of haemochromatosis with evidence of iron overload, both biochemically and clinically, venesection may be indicated.

Informed discussion should be provided regarding the benefits of reduced iron storage (such as improved liver function, insulin requirements and pigmentation). Counselling should include the risk of transmission to offspring, and that offspring could receive genetic testing.

How to Treat Quiz

Hereditary haemochromatosis
— 19 October 2007

INSTRUCTIONS

Complete this quiz to earn 2 CPD points and/or 1 PDP point by marking the correct answer(s) with an X on this form. Fill in your contact details and return to us by fax or free post.

FAX BACK	FREE POST	ONLINE
Photocopy form and fax to (02) 9422 2844	How to Treat quiz Reply Paid 60416 Chatswood DC NSW 2067	www.australiandoctor.com.au/cpd/ for immediate feedback

1. Frenchman Pièrre, 45, had abnormal LFTs at a recent health check. Further investigation revealed a ferritin level of 900µg/L. With respect to hereditary haemochromatosis, which THREE statements are true?
- ❑ a) Pièrre's northern European ancestry increases his risk of hereditary haemochromatosis
- ❑ b) A history of loss of libido supports a diagnosis of hereditary haemochromatosis
- ❑ c) Hereditary haemochromatosis is a very uncommon inherited disorder in our community and is very unlikely
- ❑ d) Pièrre's iron study results make him eligible for a Medicare-rebatable hereditary haemochromatosis genetic screen

2. Although you suspect Pièrre has hereditary haemochromatosis, you consider other possible causes for his abnormal LFTs and ferritin level. These include which THREE of the following?
- ❑ a) Acaeruloplasminaemia
- ❑ b) Non-alcoholic fatty liver disease
- ❑ c) Dietary iron overload
- ❑ d) Coeliac disease

3. Pièrre is found to be homozygous for the C282Y HFE-gene mutation. Discussing the diagnosis of hereditary haemochromatosis with Pièrre, which TWO statements are true?
- ❑ a) Pièrre's mutation is the least common mutation associated with hereditary haemochromatosis
- ❑ b) All C282Y/C282Y homozygotes develop iron overload sooner or later
- ❑ c) About 10% of people with hereditary haemochromatosis have no as-yet detectible genetic abnormality
- ❑ d) Men are more at risk of early development of iron overload

4. Pièrre asks you about the risk in his family and the general community. Which TWO pieces of advice are correct?
- ❑ a) If his siblings have the mutations but do not have iron overload, it is impossible to predict which of them may go on to develop iron overload
- ❑ b) Incomplete penetrance means that mass genotype screening is unlikely to begin in the near future
- ❑ c) Pièrre's children, aged three and five, should have the genetic test now, as they may already be iron overloaded
- ❑ d) Unless they have iron overload, Pièrre's siblings will not qualify for a Medicare rebate for genetic screening

5. Guillame, Pièrre's brother, is also homozygous C282Y/C282Y. On clinical assessment, which features suggest he has iron overload (choose THREE)?
- ❑ a) He feels tired all the time
- ❑ b) His random blood sugar level is 13mmol/L
- ❑ c) He has generalised joint pain with sparing of the metacarpophalangeal joints of the hands
- ❑ d) He has gynaecomastia, hepatomegaly and palmar erythema

6. You diagnose Guillame as having iron overload and diabetes. Guillame tells you about his poor libido and excessive alcohol intake. When discussing his condition with him, which information is correct (choose TWO)?
- ❑ a) Excessive alcohol intake may speed up the progression of his liver disease
- ❑ b) Phlebotomy and reduced iron accumulation should improve his impotence
- ❑ c) An ECG and echocardiogram are useful investigations to screen for cardiomyopathy related to iron overload
- ❑ d) If he requires insulin, his requirements will increase with treatment of his iron overload

7. With respect to iron studies in haemochromatosis, which TWO statements are correct?
- ❑ a) A transferrin saturation >60% is strongly suggestive of hereditary haemochromatosis
- ❑ b) Elevated transferrin saturation is specific for hereditary haemochromatosis and seen in no other conditions
- ❑ c) Ferritin level can be raised in many conditions other than hereditary haemochromatosis, including inflammation and malignancy
- ❑ d) Serum iron level in hereditary haemochromatosis is usually <36mmol/L

8. Pièrre and Guillame both require treatment of their iron overload. Which TWO statements about their treatment are true?
- ❑ a) They will need weekly phlebotomy to remove 250mg of iron a week
- ❑ b) After iron stores have been depleted they will need 3-6-monthly phlebotomy
- ❑ c) Ferritin will be tested regularly, with a target of <25µg/L
- ❑ d) It is important they take vitamin C supplements

9. Which TWO outcomes can they expect from treatment with phlebotomy?
- ❑ a) Improved energy
- ❑ b) Reduced pigmentation
- ❑ c) A marked improvement in joint pain
- ❑ d) Reversal of cirrhosis

10. Their sister Sophie, 40, is also homozygous C282Y/C282Y but has normal iron studies. What further assessment and treatment does she require (choose TWO)?
- ❑ a) She should become a vegetarian
- ❑ b) A screening physical examination of skin, liver, heart, joints and endocrine system
- ❑ c) Regular iron studies and LFTs
- ❑ d) Avoidance of the contraceptive pill, as this will reduce the volume of bleeding with her periods

CONTACT DETAILS

Dr: ..... **Phone:** ..... **E-mail:** .....

RACGP QA & CPD No: .....**and /or ACRRM membership No:** .....

Address: ..... **Postcode:** .....

Australian Doctor Education.

HOW TO TREAT Editor: **Dr Martine Walker**
Co-ordinator: **Julian McAllan**
Quiz: **Dr Martine Walker**

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer. Your CPD activity will be updated on your RACGP records every January, April, July and October.

NEXT WEEK Musculoskeletal injuries in children are common, and fractures account for about 20% of presentations with injury. The paediatric musculoskeletal system differs from the adult in its anatomy, biomechanics and physiology, leading to injury patterns unique to the child. The next How to Treat discusses the role of the GP in managing fractures and dislocations, bony injuries commonly encountered in children. The author is **Dr Helen J Mead**, paediatrician and emergency physician, Princess Margaret Hospital for Children, Perth; and senior clinical lecturer for the school of paediatrics and child health, University of WA.