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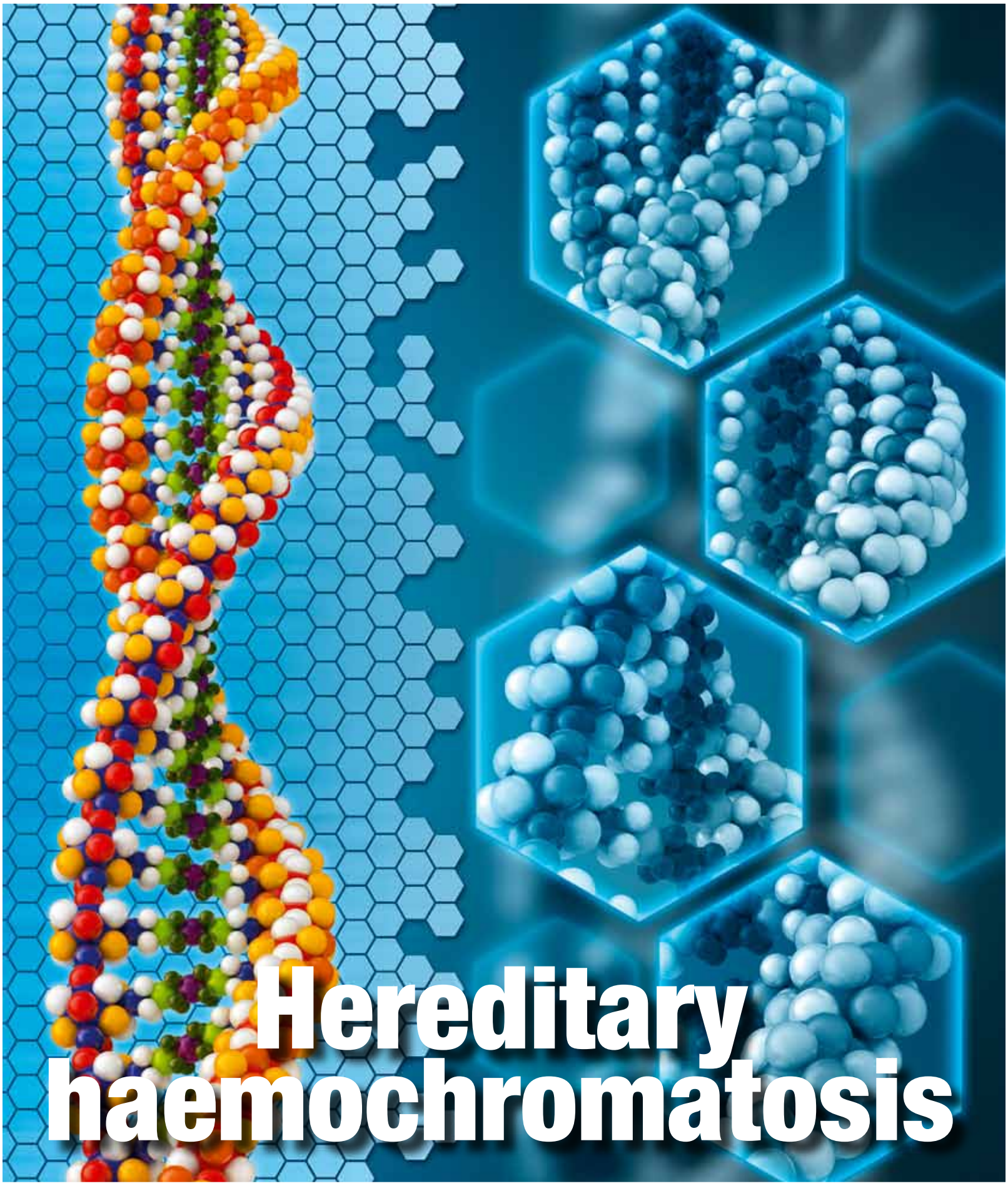

Hereditary haemochromatosis

Introduction

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.

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INSIDE

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With the rise in genetic screening, more affected individuals are likely to be diagnosed either asymptomatically through family screening or during the early stages of iron overload.

Individuals may also be diagnosed after the discovery of elevated iron studies while investigating fatigue to rule out suspected iron deficiency. It is important to be aware of the other potential aetiologies of abnormal iron studies associated with iron overload, which are shown in table 1.

Mutations in four other genes, hemojuvelin (HJV; type 2A juvenile HH), hepcidin (HAMP; type 2B juvenile HH), transferrin receptor 2 (TR2; type 3 HH) and ferroportin (SLC40A1; type 4 HH) are rare genetic causes of iron overload. Mutations in HJV and HAMP result in juvenile haemochromatosis, which is a very severe disorder where very high levels of iron accumulate during childhood and, if left untreated, almost invariably results in liver cirrhosis and cardiomyopathy.

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

There are several secondary causes of iron overload (see box, right). In addition, as ferritin is an acute phase reactant, serum ferritin (SF) can be elevated in the absence of iron overload in conditions such as neoplasia, inflammation, metabolic syndrome, infection and autoimmune disease.

The remainder of this article will focus on HFE-related HH.

Primary (genetic) and secondary causes of iron overload

Primary iron overload*	Secondary iron overload
Type 1 HH — due to mutations in HFE	Chronic anaemia (eg, thalassaemia, sideroblastic anaemia)
Type 2a HH — due to mutations in HJV	Excess ingestion/infusion of iron
Type 2b HH — due to mutations in HAMP	Liver disease (eg, alcoholic liver disease, hepatitis B and C, non-alcoholic fatty liver disease)
Type 3 HH — due to mutations in TR2	Porphyria cutanea tarda
Type 4 HH — due to mutations in SLC40A1 (also called ferroportin disease)	Neonatal HH (an autoimmune disorder)
African iron overload (gene yet to be identified)	Multiple blood transfusions (eg, for the treatment of chronic anaemia such as thalassaemia)

* types 1, 2a, 2b and 3 HH are autosomal recessive while type 4 HH is autosomal dominant

Presentation

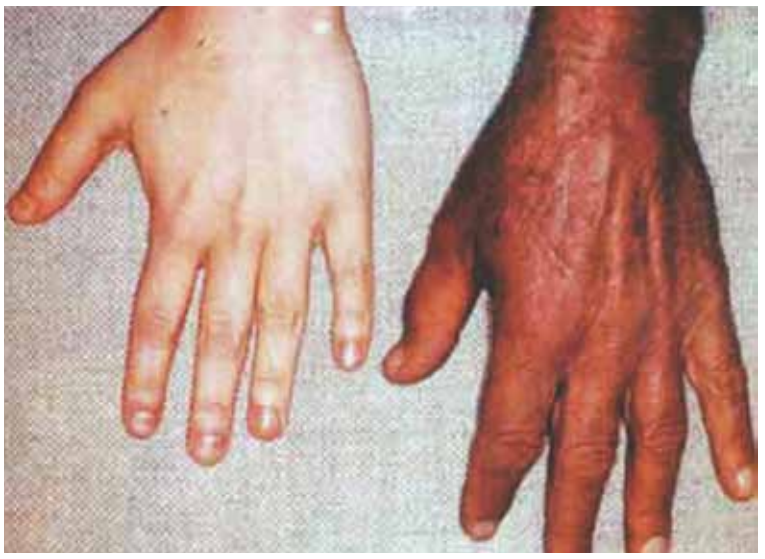
AFTER the discovery of the HFE gene in 1996, it was initially believed that every individual with a mutation in each copy of the gene would develop iron-overload-related disease consistent with HH. However, more recently it has been shown that only 60-80% of C282Y homozygotes develop abnormal iron indices in their life, with only one third of men and one in 100 women developing significant iron-overload-related disease, that is, HH.[1]

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 without abnormality of iron indices (C282Y homozygous).
Stage 2. Raised transferrin saturation (TS) with normal SF.
Stage 3. Iron overload (raised SF in the presence of a raised fasting TS) without symptoms.
Stage 4. Iron overload with HH-associated symptoms (such as arthritis and fatigue).
Stage 5. Iron overload with organ damage, in particular cirrhosis.[2]

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.



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.[2]

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.

'Bronzed diabetes' ... is now rarely seen owing to more aggressive testing for genetic predisposition.

Diagnosis

INDIVIDUALS who are homozygous for the C282Y substitution can be categorised into five disease stages (0-4), depending on iron indices, symptoms and evidence of end organ damage (table 1).[2]

Although genetic testing can diagnose those who have a genetic predisposition to HH, an individual who is homozygous for C282Y might only have a genetic predisposition — homozygous state is not sufficient to make a diagnosis of HH. The presence of the combination of raised SF (normal range generally up to 200µg/L for females and 300µg/L for males) and TS (normal range <45% for females and <50% for males) generally indicates systemic iron overload, and, in the context of C282Y homozygosity, indicates that individual is at risk of iron-overload progression.

Neither serum iron levels nor haemoglobin levels can be used to diagnose iron overload since serum iron levels usually represent recent dietary intake and haemoglobin is not usually affected significantly until the later stages of disease (such as if varices develop in association with liver disease).

Table 1: Stages of disease in HFE C282Y homozygotes[2]

Stage	Features
0	C282Y homozygous with normal TS and SF and no symptoms
1	C282Y homozygous with raised TS and normal SF and no symptoms
2	C282Y homozygous with raised TS and SF and no symptoms
3	C282Y homozygous with raised TS and SF with symptoms such as fatigue and/or arthritis but no evidence of end-organ damage
4	C282Y homozygous with raised TS and SF with symptoms such as fatigue and/or arthritis and evidence of end-organ damage associated with reduced life span such as liver cirrhosis, cardiomyopathy and/or diabetes

TS = transferrin saturation SF =serum ferritin

Neither serum iron levels nor haemoglobin levels can be used to diagnose iron overload.

Iron studies

In individuals presenting with signs or symptoms suspicious of HH, a fasting TS ratio and SF should be undertaken. In early disease, TS may be elevated before a rise in SF.

An increased TS reflects increased absorption of iron — the underlying biological defect of this condition. SF reflects body iron stores but, as an acute phase reactant, can be elevated non-specifically on occasions (eg, through alcohol consumption, chronic inflammation and other liver diseases). HH is unlikely if the SF is very high but the TS is normal. In such cases, testing the HFE gene may be helpful to exclude HH.

A diagnostic algorithm for the approach to individuals with raised SF is presented in figure 1, page 28. If an individual is found to have raised SF and fasting TS and has two HFE mutations then the diagnosis of HH is confirmed. If an individual has raised SF and TS and has one or no mutations in the HFE gene then there are four ways to confirm whether or not HH is present:

- Sequencing of HFE and the other known genes may reveal the causative mutation(s).
- The presence of a hepatic iron index (calculated as micromoles of iron per gram dry weight of liver divided by age in years) of ≥1.9 on liver biopsy is diagnostic of HH.
- Liver MRI can quantify hepatic iron levels and can therefore aid in the diagnosis of HH. This technique requires considerable expertise and therefore is only available in relatively few centres in Australia.
- The most common way to clinically ascertain iron overload is to undertake "therapeutic phlebotomy". If >4g of iron are removed to normalise SF then again the diagnosis of HH is confirmed. This amount of iron equates to the removal of about 16 units (450mL) of whole blood.

The SF level is correlated with the degree of iron overload. That is, the higher the SF, in general, the greater the degree of iron overload that is present.

An SF of greater than 1000µg/L places the individual at increased risk of severe HH-related morbidity such as liver cirrhosis. Such morbidity is very rare when the SF is below 1000µg/L.

Cirrhosis is present in 20-45% of those with SF greater than 1000µg/L but fewer than 2% of those with SF below that cut-off. Therefore if an individual has an SF level above 1000µg/L, a liver biopsy should be performed to assess whether there is liver fibrosis and/or cirrhosis and also to quantify the degree of iron overload by measurement of the hepatic iron index.

Because most complications

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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 rebatable 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; or
- 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 with compound heterozygosity for recognised genetic mutations for haemochromatosis.

When an individual is diagnosed with HH and has elevated SF, they should have an LFT and fasting blood glucose. If there is evidence of hepatic dysfunction such as abnormalities on LFT or

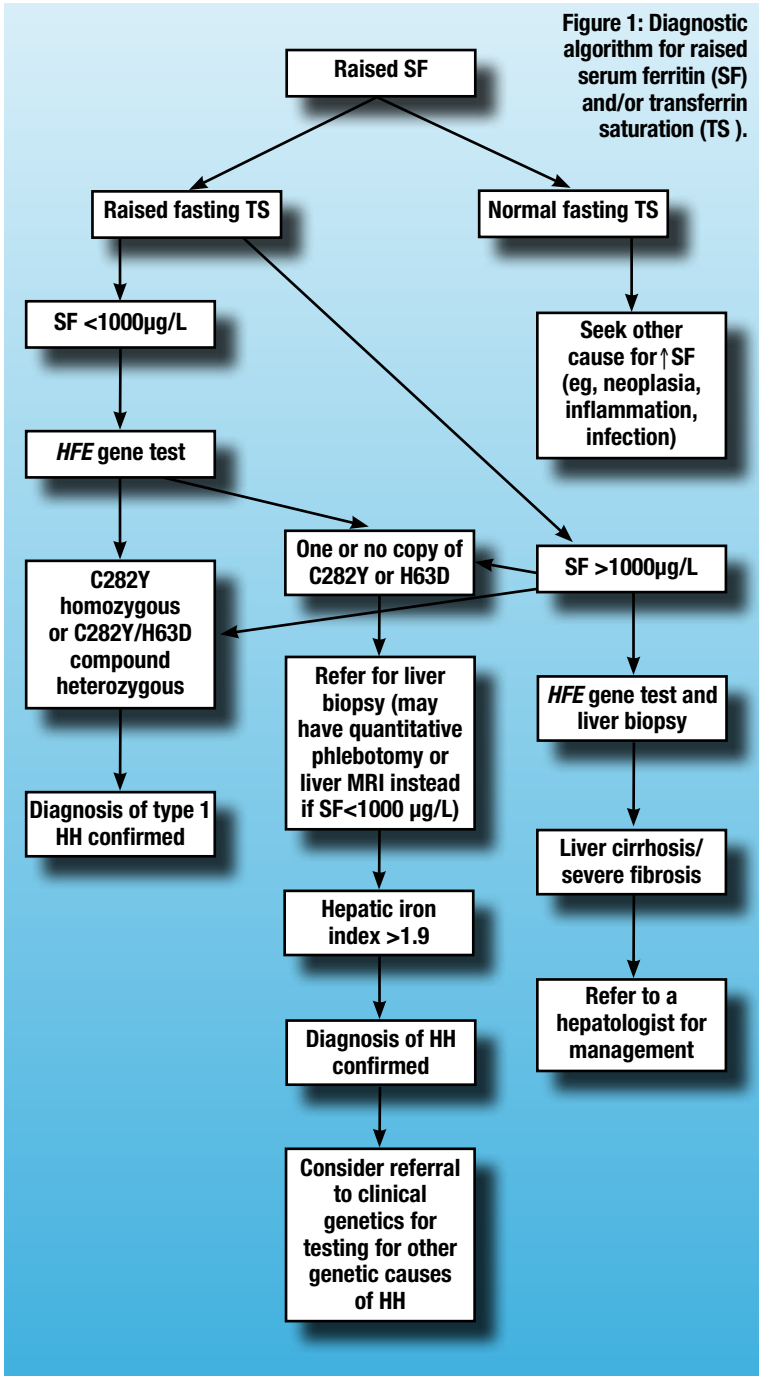

Figure 1: Diagnostic algorithm for raised serum ferritin (SF) and/or transferrin saturation (TS).

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 or 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.

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.

Signs of chronic hepatic failure, including spider naevi and palmar erythema, may be seen if liver cirrhosis is present. Signs of end-stage hepatic failure such as reduced conscious state, hepatic flap and signs of coagulopathy are fortunately rare.

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 Hepascore 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 measures 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.

Endocrine manifestations

Diabetes occurs more frequently in HH, with 20-50% 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 is >1000µg/L. This can result in decreased libido, impotence and testicular atrophy. This can be diagnosed by appropriate endocrine investigations, including serum-free testosterone, FSH and LH.

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

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

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.

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).[1,3] 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.

Simple C282Y heterozygotes may have mildly elevated iron indices but are not at increased risk of iron-overload-related disease. Individuals with significant iron overload who are simple C282Y heterozygotes should be investigated for other genetic causes. 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.

There is strong evidence that if an individual has a genetic predisposition to HH and has other liver morbidity, then the combination is synergistic. That is, the individual is at higher risk of liver cirrhosis than if they have one of the conditions alone. Therefore individuals with severely elevated iron with morbidity such as high alcohol intake or hepatitis B or C, for example, are much more likely to have severe liver disease than those with HH and increased iron indices alone.

Prevention and treatment

MOST morbidity in HH can be prevented by reversion or maintenance of total body iron in the normal range.[4-6] Treatment guidelines recommend that any individual with HFE-related HH and SF above the upper limit of normal with raised TS should have treatment to normalise iron indices. If there is raised TS but normal SF, treatment is not required as it is only with raised SF that 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. Venesections 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/or 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 fainting. In these individuals erythrocytapheresis 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 agent.

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 hepatocellular 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 moderately increased iron overload 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 hepatocellular 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 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*.

This is thought to be due to this bacterium, most prevalent in raw shellfish and in particular oysters, proliferating at a far greater rate in a high-iron environment.

Indications for specialist referral

All individuals with severely elevated SF (>1000µg/L) should be referred to a gastroenterologist and/or hepatologist for assessment for liver biopsy. Similarly, individuals with elevated SF who have abnormal liver function or hepatomegaly should be referred for consideration of liver biopsy. Individuals with cardiomyopathy, diabetes or hypogonadotrophic hypogonadism should be referred to relevant specialists.

Any individual with juvenile HH should be referred to a paediatric hepatologist or adult hepatologist depending on the individual's age. If an individual does not tolerate routine venesection therapy and may require erythrocytapheresis or iron chelation therapy, referral to a haematologist is indicated. Referral to a clinical geneticist or genetic counsellor should be considered for patients with HH not due to HFE mutations, in order to test for other genes.

Familial implications of HH

Because HFE-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.

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)

- >90% 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 establish or 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 to 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.

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 ± 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.[7,8] 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.

Table 2: Arguments for and against introducing population screening for HH

Arguments for screening	Arguments against screening
HH is common	Severe disease from HH is relatively rare
HH can result in severe morbidity and mortality	People who would never develop disease may be made worried by being diagnosed as being at risk of morbidity (so called "worried well")
Most complications of HH are preventable	Diagnosis of risk of HH may impact on obtaining life and disability insurance
HH can be diagnosed by a simple test	There is no definite data showing that population screening is cost effective
Blood from people with HH can generally be used for donation	Screening might uncover non-paternity

Genetic testing of an asymptomatic individual has no implications for health insurance.

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 also are having treatment to normalise their iron levels, will not be penalised when obtaining new life/disability insurance policies on the basis of their HFE genetic test result.

Online resources

Douglass Hanly Moir Pathology
Medicare Criteria for Rebates May 2012:
www.dhm.com.au/media/8601026/dhmpbsp_medicarerebate_web.pdf

Red Cross Blood Service
Therapeutic Venesection Policy
www.transfusion.com.au/high_ferritin

Murdoch Children's Research Institute
Mi-iron Study
www.mi-iron.com.au

Financial Services Council
Genetic Testing for Haemochromatosis — Will it Impact Your Life Insurance?
bit.ly/XEaOUy [PDF file]

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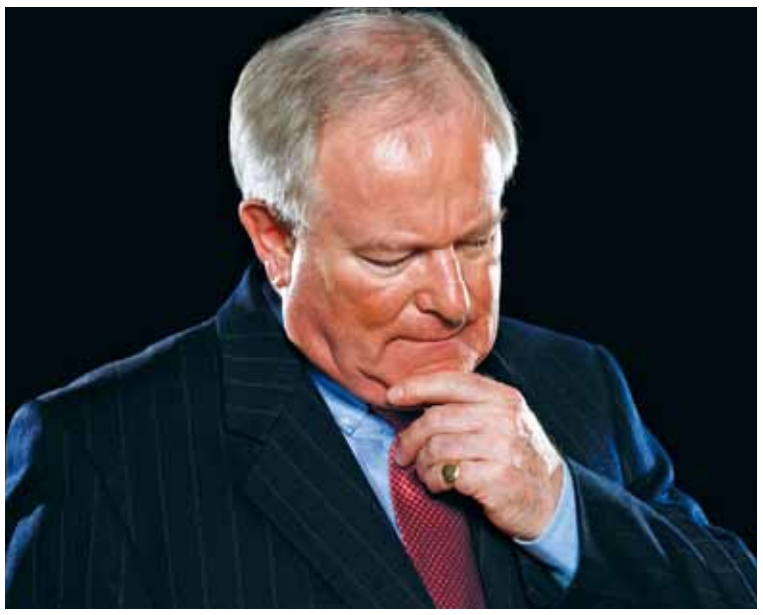
Author's case study

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.

Lawrie'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, TS 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 mutation 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 venesection 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 weekly 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 easily preventable disease.

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.
We no longer accept quizzes by post or fax.

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

GO ONLINE TO COMPLETE THE QUIZ

www.australiandoctor.com.au/education/how-to-treat

1. Which TWO statements about the epidemiology and aetiology of hereditary haemochromatosis (HH) are correct?

a) Any individual who is homozygous for HFE 282Y will develop haemochromatosis if left untreated
b) HH is the most common genetic condition of Caucasian populations, with more than one in 200 such individuals at risk
c) HFE 282Y gene mutations are the only genetic anomalies associated with significant iron overload
d) Symptomatic iron overload due to HH usually emerges between the ages of 30 and 60, with women usually diagnosed at an older age

2. Which THREE statements about assessment of iron studies in suspected HH are correct?

a) Serum iron levels usually represent recent dietary intake, so are unreliable for the diagnosis of iron overload
b) HH may be suggested by an elevated transferrin saturation (TS) before serum ferritin (SF) rises
c) An elevated serum ferritin is highly sensitive and specific for underlying HH
d) If the diagnosis remains uncertain based on iron studies, HFE gene testing, liver biopsy, MRI or "therapeutic phlebotomy" may be of use

3. Liza, 57, attends for a check-up after a work medical showed elevated transaminases. She has a 12-month history of fatigue, palpitations and reduced libido. Which TWO statements about investigation for HH are correct?

a) Liza should have TS, SF and HFE genetic mutation testing first line to rule out HH
b) If HH is confirmed, and SF elevated, Liza should undergo repeat LFTs as well as BSL and hepatitis B/C serology
c) Liza only warrants cardiac assessment if she has a very elevated SF
d) Pituitary function tests should be considered, given Liza's reduced libido, if she has a very high SF

4. Liza is confirmed to have HH. You suspect she may have hepatic complications. Which TWO statements are correct?

a) Both fibrosis and cirrhosis due to HH are reversible through normalisation of body iron stores
b) While non-invasive methods can be used to diagnose fibrosis and cirrhosis, liver biopsy is the gold standard investigation
c) The risk of hepatocellular carcinoma is 20-100 times greater in patients with HH compared with the general population
d) Hepatocellular carcinoma occurs only in HH patients with associated cirrhosis

5. You are concerned that Liza may also have extra-hepatic complications of HH. Which THREE statements are correct?

a) Up to 50% of patients with symptomatic HH develop diabetes
b) All patients with symptomatic HH should be screened for hypothyroidism
c) Investigation for arrhythmia and congestive cardiac failure as a result of dilated or restrictive cardiomyopathy should be considered in patients with very high SF
d) Unlike other manifestations of HH, arthropathy is not directly related to SF levels

6. Simon, 52, has recently been diagnosed with C282Y homozygous HH. Which TWO statements are correct?

a) Up to 45% of males and 9% of females who are C282Y homozygotes develop iron-overload-related disease
b) Up to 45% of compound heterozygotes for C282Y/H63D develop iron overload, and 5% progress to cirrhosis
c) C282Y heterozygous state in isolation has a high risk of iron overload, deranged transaminases and liver disease
d) Alcohol use or viral hepatitis increase the likelihood of hepatic complications in patients with iron overload due to HH

7. Simon currently has an elevated TS and normal SF. Which THREE statements are correct about treatment considerations for Simon?

a) Simon does not currently require treatment for his HH
b) Simon should have three-monthly monitoring of his SF, with instigation of treatment should it become elevated
c) Should Simon need treatment, regular venesection will almost certainly be sufficient to normalise his SF
d) Proton-pump inhibitors can reduce iron absorption and if Simon is on a PPI, may help reduce the need for venesection

8. Jane, 65, has HH with associated cirrhosis and diabetes, which requires insulin. Which TWO statements are correct?

a) The guidelines state that Jane should have regular alpha-fetoprotein assessment, to monitor for development of hepatocellular carcinoma
b) Venesection, and normalisation of her iron indices, will have no impact on her diabetes or its management
c) If Jane developed decompensated liver failure, she would be a candidate for liver transplantation
d) Jane should be vaccinated against hepatitis A and B

9. Jim, 42, has recently started venesection treatment for HFE-related HH, which has been associated with elevated serum ferritin but no end-organ damage. Which TWO statements about dietary advice for Jim are correct?

a) Jim should avoid alcohol both now and in the future
b) Jim should adhere to a low-iron diet
c) Jim should not take vitamin C supplements when his iron indices are high
d) Jim should avoid raw shellfish when his iron indices are high

10. Jim is concerned about the implications of his diagnosis for his family and his insurance status. Which of the following THREE statements are correct?

a) Jim's brother and sisters should be encouraged to have iron studies and HFE gene mutation testing
b) The mother of Jim's three children aged under eight, who are all well, should be tested for HFE mutation to determine whether their children should be screened
c) This diagnosis and treatment will have no impact on Jim's health insurance cover and premiums
d) If Jim applies for life or disability insurance now, he can expect penalties to be applied due to his HH

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.

Australian Doctor Education

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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.