Haemochromatosis: a time for guidelines?

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Hereditary haemochromatosis is an autosomal recessive metabolic abnormality which causes excessive absorption of dietary iron. Iron accumulation leads to potentially fatal damage to organs such as the heart, liver and pancreas. Normal life expectancy can be restored simply by therapeutic venesection. Discovery of the gene, HFE, has rekindled interest in pathogenesis, management and screening strategies.

Because iron overload affects many organ systems, patients with hereditary haemochromatosis (HH) can present at many different specialist clinics and diagnosis is commonly delayed. There is good evidence that non-diabetic and non-cirrhotic patients treated by venesection have normal life expectancy. The availability of a test for the recently described HFE gene mutations is changing the approach to the diagnosis of HH and the development of screening strategies. It is hoped that this article will encourage wider debate as patients will clearly benefit from a more unified and systematic approach to the management of the disease.

DEFINITION

HH is a common disorder of iron metabolism caused by homozygosity for the haemochromatosis gene mutation. This is a genetically-based definition and does not therefore require proof of iron overload.

HISTORY

For centuries iron has been thought to have medicinal properties. In ancient Greece, iron filings dissolved in vinegar were taken in the belief that the strength of the iron would be acquired by the recipient. Sixteenth century alchemists and physicians commonly prescribed iron, especially for chlorosis (anaemia) in young women. However, it was not until the early 18th century that iron was found to be a constituent of animal liver and blood. In 1872 Boussingault showed that iron was an essential nutrient.

The first report of HH probably occurred in 1865 following the death of a 28-year-old newspaper seller in Paris. He died of a febrile complication of diabetes, but was noted to have bronzed skin and an enlarged cirrhotic liver. In 1871, a second autopsy case was reported describing a 51-year-old Parisian with skin and visceral pigmentation and an enlarged, pigmented liver. In 1882 and 1886, the terms 'pigmentation cirrhosis' and 'bronzed diabetes' were coined. In 1889, Von Recklinghausen described 12 patients with iron pigmentation of body organs. Assuming that haemoglobin was the origin of the pigment, he applied the term 'hamochromatose'. Sheldon (1935) recognized the inherited nature of the problem but it was not until 1975 that further advances in understanding were achieved. The frequency of the HLA-A3 antigen was found to be higher in HH patients than in the general population and further studies provided evidence for autosomal recessive transmission with expression limited by sex.

The next 20 years saw hectic activity in the search for an HH gene in the vicinity of the HLA gene complex on chromosome 6. In 1996, a paper in *Nature Genetics* by Feder et al described the gene HLA-H, thought to be the haemochromatosis gene. Since then the Nomenclature Committee of the Genome Database has renamed the gene HFE and a polymerase chain reaction kit has become available for routine testing.

PATHOGENESIS

Iron metabolism

Iron is the second most abundant metal in the earth's crust and the core itself is thought to consist of solid iron or iron nickel. Iron compounds were probably responsible for the catalytic generation of some of the atmospheric oxygen on which life depends (de Duve, 1990). It is not surprising, therefore, that iron plays an essential role in human metabolism, being a component of, or a cofactor for, many proteins and enzymes.

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However, iron is extremely toxic in excess, so a tight homeostatic mechanism ensures that excretion and absorption are balanced. As there is no specific excretion pathway, total body iron levels are maintained within narrow limits by regulation of absorption alone (*Figure 1*). Nevertheless, iron deficiency and iron excess remain common clinical problems.

Iron toxicity: Iron is thought to catalyse the conversion of hydrogen peroxide and superoxide anions to free radicals (McCord, 1998). The hydroxyl radical probably has a direct toxic action on DNA and hyaluronic acid, and causes the peroxidation of lipid membranes. Lysosomal damage causes the release of powerful hydrolytic enzymes and resultant cellular damage. It is therefore of crucial importance that iron is kept in a soluble and non-toxic state. Physiological forms of fully coordinated iron include haemoglobin, myoglobin, cytochromes, ferritin, transferrin and lactoferrin.

Iron absorption: Iron absorption occurs principally in the proximal small intestine. An average Western diet contains around 20 mg of elemental iron per day. Its bioavailability is influenced by several factors including the chemical form and the presence of foods which promote or inhibit absorption (*Table 1*).

Absorption is also altered by intestinal factors, by the rate of red blood cell production and the amount of storage iron.

Role of the enterocyte in iron absorption: The process of iron absorption incorporates three phases:

1. Iron uptake by the enterocyte
2. Intra-enterocyte transport and storage
3. Extra-enterocyte transfer.

Iron binds to specific mucosal membrane sites (*Figure 2*), is internalized by the enterocyte and then either retained as mucosal ferritin or transported to the basolateral membrane. Duodenal levels of ferritin mRNA are decreased in iron deficiency and HH but increased in secondary iron overload (*Table 2*). This supports the putative role of mucosal ferritin as a regulator of iron absorption (Pietrangelo et al, 1992).

In the plasma pool, iron is bound to transferrin. Transferrin receptors (TfR) are found at the basolateral surface of enterocytes. In iron deficiency and HH, levels of TfR mRNA increase (*Table 2*). It has been suggested that internalized plasma ferro-transferrin may allow the enterocyte to monitor body iron status and thus regulate iron absorption (Beard et al, 1996).

Transferrin: Transferrin, a glycoprotein synthesized in the liver, is the major iron transport protein. It binds iron in its ferric form, keeping it in a soluble, non-toxic state. Plasma transferrin is normally present in excess and about 30% saturated with iron. Of plasma iron turnover, 80% is accounted for by plasma to erythroid precursor transport. This is mediated by TfRs on reticulocytes. The number of receptors present on the cell surface is a function of intracellular iron content, rate of erythroid cell proliferation and metabolic demand for iron. Indeed, measurement of soluble TfRs in plasma may be a useful marker of iron status. Mature erythrocytes no longer express TfRs.

Iron storage: Iron stores are present in the liver, muscles and reticuloendothelial system in the form of ferritin and haemosiderin. Ferritin, a soluble protein, is found in all human cells and in

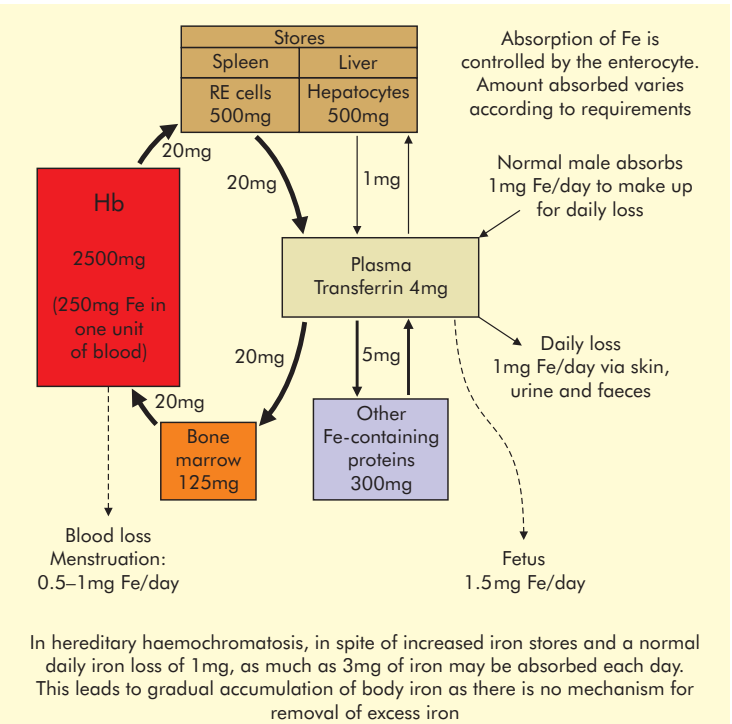

Figure 1. Iron distribution and daily iron turnover in normal adult. FE = iron; Hb = haemoglobin.

TABLE 1.
Bioavailability of iron

Bioavailability ↑	Haem iron (10% of dietary iron, but 30% of total absorbed iron)
	Acidic pH
	Vitamin C
	Fe^{2+}
Bioavailability ↓	Non-haem iron (100% of iron in vegetable material, 60% of iron in animal sources)
	Tannins
	Phytates
	Fe^{3+} (reduced to Fe^{2+} by hydrochloric acid in stomach)

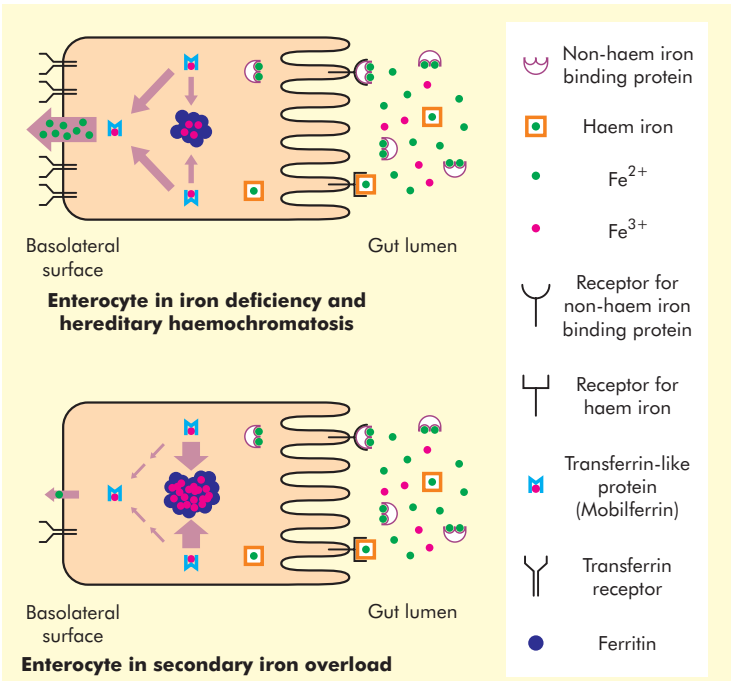

Figure 2. Schematic diagram of enterocyte in iron deficiency, hereditary haemochromatosis and secondary iron overload. FE = iron.

TABLE 2.
Levels of mRNA in duodenal enterocyte

mRNA	Iron deficiency	HH	Secondary iron overload
Ferritin	↓	↓	↑
Transferrin receptors	↑	↑	↓

HH = hereditary haemochromatosis

small amounts in plasma. It is able to accumulate and release iron rapidly and plasma ferritin is closely correlated with body iron stores.

Ferritin is degraded to form haemosiderin, an insoluble iron storage protein, found in secondary lysosomes especially in the liver. In states of iron overload, haemosiderin accumulates in the liver at up to 10 times the normal rate and is thought to be of importance in cellular toxicity.

Defect in HH: The biochemical problem in HH appears to be an inability to downregulate intestinal iron absorption even when iron stores are high. McLaren et al's kinetic studies (1991) of iron absorption in HH suggest that the primary defect in the disease results from the unregulated transfer of iron from the basolateral membrane of enterocytes.

Recently two separate groups, using different approaches, have identified an intestinal transmembrane iron transporter, Nramp2 (DCT1) (Fleming et al, 1997; Gunshin et al, 1997) which is thought to have a role in iron uptake at the brush border. It is speculated that Nramp2 function could be increased in HH patients (Andrews and Levy, 1998).

Genetic background

In people of Northern European descent, the prevalence of HH is said to be about 1 in 300–400, with a carrier frequency of 1 in 10. The gene is particularly common in Brittany, Wales, Scotland and Ireland and therefore may be of Celtic or Viking origin. Feder et al (1996) described a newly discovered gene, HLA-H, related to the major histocompatibility complex (MHC) class 1 family (approximately 4.5 Mb from HLA-A on the short arm of chromosome 6), which may have one of two mis-sense mutations. Of HH patients, 83% were homozygous for the Cys282Tyr (C282Y) alteration. More recent British studies have shown that more than 90% of HH patients were homozygous for the C282Y mutation. A second mutation, His63Asp (H63D), is relatively common in the general population but may be of clinical importance only in patients heterozygous for both mutations. It is not known how many homozygotes for the C282Y mutation will eventually develop iron overload.

Recently, two interesting observations have been made. A significant proportion of patients with porphyria cutanea tarda, an iron dependent condition which often responds to phlebotomy, possess the C282Y mutation (Roberts et al, 1997). There may also be an association between the C282Y mutation and the factor V Leiden allele in a Canadian population with thrombosis (Xie et al, 1998). The authors speculate that disregulation of iron metabolism may contribute to the enhanced risk of clinical thrombosis in these patients.

Gene product: A proposed effect of the C282Y mutation is the failure of the HFE protein to bind β2 microglobulin (β2M) and achieve cell surface expression (*Figure 3*). β2M is well known for its role of stabilizing HLA class I molecules. Of interest, mice lacking β2M expression exhibit spontaneous iron storage.

Recent evidence suggests that the C282Y mutation prevents the association of HFE protein with the TfR, thereby increasing the affinity of the receptor for transferrin (Feder et al, 1998). This may result in increased uptake of iron by certain tissues (*Figure 4*). However, the actual mechanism by which HFE regulates iron transport remains unknown.

CLINICAL PICTURE

Organ injury usually begins by the age of 50 years. The male:female ratio of clinical HH is 2:1, as premenopausal women are protected from the development of iron overload by menstruation, pregnancy and lactation. There may also be a sex difference in intestinal iron absorption.

The classical triad of bronzed skin, diabetes and cirrhosis occurs much later than the non-specific symptoms which herald the disease. These include lethargy, weight loss, impotence, arthralgia and abdominal pain. Later, the patient may develop bronzed skin as a result of melanin deposition, with skin biopsy showing iron pigmentation in eccrine sweat glands. Paradoxically, patients may look very well because of their tanned appearance. Joint pain and swelling characteristically involves the index and middle metacarpophalangeal joints, but sometimes progresses to a severe polyarthritis. Chondrocalcinosis on X-ray may alert the clinician to the diagnosis.

Endocrine damage includes testicular atrophy, which is caused by iron deposition in the anterior pituitary. Clinical or laboratory features of hypothyroidism may also be apparent. Because of earlier diagnosis, insulin-dependent diabetes is much less common than mild abnormalities of glucose metabolism. Clinical or electrocardiographic signs of dilated cardiomyopathy and arrhythmias occur in about a third of HH patients. Hepatomegaly is one of the commonest physical findings and 50% of patients have raised aminotransferases. At presentation, up to 70% of symptomatic patients may already have cirrhosis on liver biopsy (Niederau et al, 1996).

It is often quoted that, before diagnosis, the HH sufferer has seen 5 physicians over a period of 5 years. He/she may present at any clinic and with non-specific symptoms which may delay diagnosis.

PROTOCOL FOR MANAGEMENT OF HH

The authors have become interested in producing a locally agreed protocol with the following aims: to increase awareness of this important medical condition within the region, to improve the quality of care and to provide a basis for audit. The protocol was derived from literature review and dialogue both with experts in the field and with colleagues from related specialties. A multidisciplinary regional meeting was held and the following management scheme constructed.

It is expected that this will be a dynamic document. Our knowledge and understanding of HH is developing rapidly and definitive guidelines will ultimately emerge from the evidence base and from consensus among national and international experts.

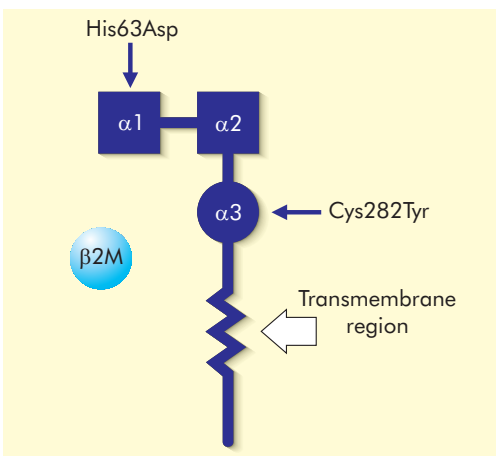

Figure 3. Hypothetical model of HFE gene product showing positions of mutations associated with hereditary haemochromatosis.

PROTOCOL FOR CASE FINDING AND DIAGNOSIS OF HH

Patients will fall into two categories: those with suggestive clinical features of HH and those discovered through family studies (*Figure 5*). There follow some specific points relating to *Figure 5*.

Transferrin saturation

In the Utah Red Cross study of over 11 000 blood donors (Edwards et al, 1988), TS had a positive predictive value of 66%. When ferritin alone was used 60% of homozygotes were missed. The threshold value for TS should vary according to sex. Milman (1991) has confirmed that a TS of 60% or more identifies nearly all homozygotes with iron loading, whereas a value

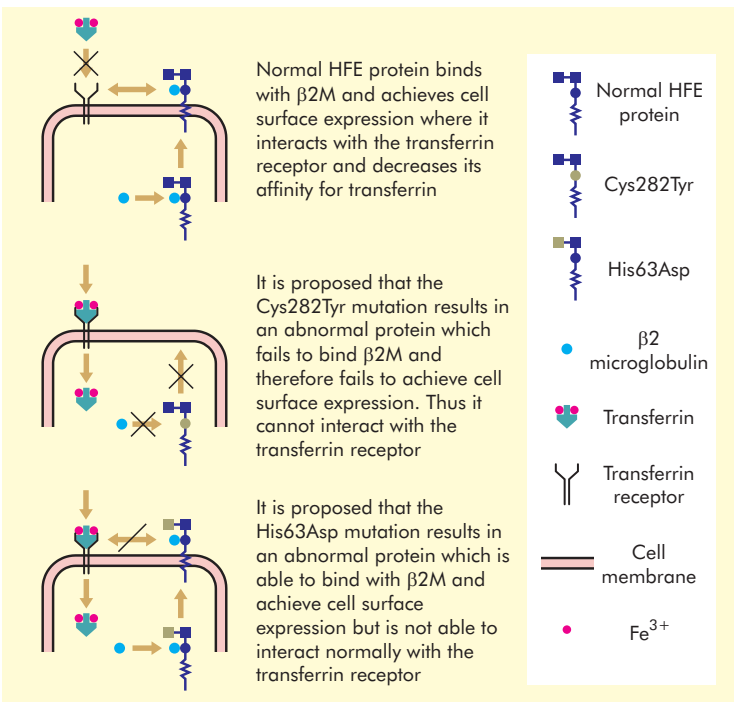

Figure 4. Schematic diagrams showing proposed effects of HFE mutations. FE = iron.

of 50% identifies nearly all homozygotes regardless of sex or iron burden. To make screening practical, a consensus suggests threshold values of 60% for men and 50% for women (Edwards and Kushner, 1993).

Ferritin

Ferritin concentrations correlate well with hepatic iron stores and define those patients with iron overload. In a study by Bassett et al (1986), hepatic fibrosis was not seen in HH subjects with ferritin < 700μg/litre. Spurious increase may occur in liver disease, infection, inflammatory disease and malignancy.

Causes of secondary iron overload

- Ineffective erythropoiesis, e.g. thalassaemia major and sideroblastic anaemia
- Increased erythropoiesis, e.g. congenital spherocytosis or other chronic haemolytic anaemias
- Increased iron intake, e.g. repeated blood transfusions or dietary — 'Bantu siderosis'
- Others, including alcoholic liver cirrhosis, portocaval shunt, porphyria cutanea tarda (associated with C282Y mutation), atransferrinaemia (rare).

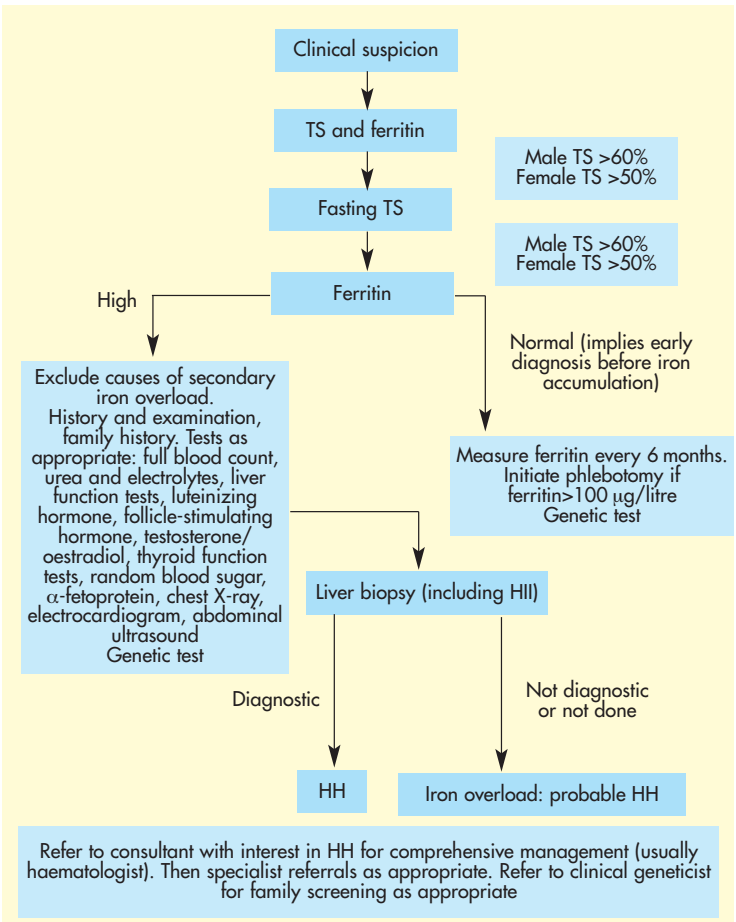

Figure 5. Protocol for case finding and diagnosis of hereditary haemochromatosis (HH). TS = transferrin saturation, calculated as TS = (iron concentration/total iron binding capacity) x 100%.

Genetic test

Mutation screening is positive in over 90% of patients, with few false positives (The UK Haemochromatosis Consortium, 1997).

Liver biopsy

Before the introduction of genetic testing, liver biopsy was the gold standard diagnostic test for HH (Bassett et al, 1986; Ludwig et al, 1993). In HH, as opposed to other iron overload states, iron deposition occurs primarily in periportal hepatocytes with sparing of the centrilobular areas and Kupffer cells (*Figure 6*). The hepatic iron index (HII) — μmolFe/g dry weight divided by age — if ≥1.9, is indicative of HH. Although the value of this invasive test may have diminished since the discovery of HFE, it may still provide useful information about cirrhosis and therefore about prognosis.

TREATMENT

Venesection remains the simplest and best means of iron reduction (*Table 3*). Each unit of blood removes 250 mg of iron. The iron chelating agent, desferrioxamine, works more slowly and it may have significant toxicity.

TESTING OF FAMILY MEMBERS

Genetic testing should be offered to children (and/or partner) as well as siblings of the index case, because of the high frequency of heterozygosity in the population. A C282Y homozygote, whose partner is negative for the HFE mutations at both alleles, will have heterozygous children. However, if the partner is found on testing to be a C282Y heterozygote (1:10 chance), a child has a 50% chance of being either a carrier or a homozygote at risk of developing the disease.

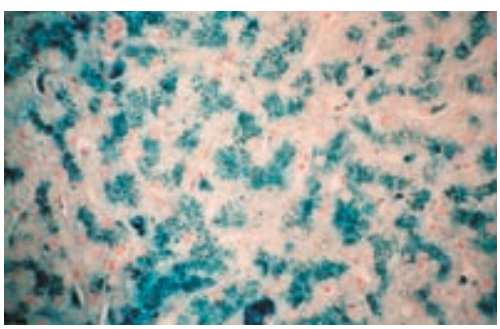

Figure 6. Liver biopsy (Perl's stain) showing iron deposition in periportal hepatocytes with sparing of the centrilobular areas and Kupffer cells.

The clinical significance of compound heterozygosity for C282Y and H63D is currently unclear.

Screening may be more appropriately performed by a clinical geneticist in view of the many contentious issues surrounding the screening of 'normal' individuals. Life insurance could, for instance, become a problem if a clinically unaffected individual is found to be homozygous for the HFE mutation on genetic screening (*Figure 8*).

PROGNOSIS

There is good evidence from long-term survival analyses that non-cirrhotic and non-diabetic patients, treated by venesection, have normal life expectancy (Niederau et al, 1996). Heart failure can respond to vigorous phlebotomy, but secondary hypogonadism is not altered. It is said that for HH patients with arthritis, a third improve, a third remain unchanged and a third worsen in spite of treatment. Ten-year survival for patients with diabetes is 65% and with cirrhosis 72% (Niederau et al, 1985). Liver transplantation, in most reported series, is disappointing.

Improved management of diabetes means that the three most common causes of death are now heart failure, liver failure and hepatocellular carcinoma. This tumour (*Figure 9*) develops in up to one-third of cirrhotic patients, even after depletion of iron stores (Niederau et al, 1985). It remains rare in patients without cirrhosis.

CONCLUSIONS

The identification of the candidate gene for HH has increased our understanding and clinical awareness of this much under-diagnosed disease. The subsequent availability of a genetic test has improved disease definition and highlighted the potential benefits of family screening.

'The prognosis of primary haemochromatosis appears to depend directly on the amount (and probably also the duration) of iron excess' (Niederau et al, 1994). The goal must

TABLE 3.
Protocol for treatment of hereditary haemochromatosis

Stage	Comments		
Initial rapid iron removal	Objective: rapid iron depletion without production of clinical anaemia		
	Venesect one unit (volume adjusted according to weight and clinical condition) 1–2 times each week		
	Check full blood count monthly		May need more frequent monitoring as approach iron depletion
	Check ferritin every 3 months		
	Check transferrin saturation when ferritin <20 μg/litre		
	Usual response to venesection is progressive decline in ferritin and late normalization of transferrin saturation (*Figure 7*)		
Confirmation of iron depletion	Ferritin < 20 μg/litre		May at this stage consider repeating the liver biopsy in cirrhotic patients
	Transferrin saturation <16%		
	Iron chelating agents are reserved for those patients where rigorous phlebotomy may not be possible, e.g. cardiomyopathy		
Maintenance	Objective: to maintain normal levels of storage iron (keeping ferritin <100 μg/litre)		
	Initially, monthly review checking full blood count, ferritin and transferrin saturation		
	Restart venesection when TS > 60% in men and 50% in women and/or repeated ferritin >100 μg/litre in the absence of any other acute phase markers		
	Patients may require 4–12 venesections per year to maintain normal levels of storage iron		
	Ensure other disease manifestations are appropriately managed, e.g. 6-monthly α–fetoprotein and liver ultrasound scan in patients with cirrhosis		
Education and diet	Objective: to increase patient awareness of the condition and any appropriate lifestyle modifications		
	Education	Patient information sheet	
		Need to screen family members	
		Haemochromatosis Society*	
	Diet	Avoid iron and vitamin C supplements	
		Phytates and tannins reduce iron absorption	
		Need to avoid alcohol if evidence of cirrhosis	
Testing of family members	It is good practice to refer to a clinical geneticist for counselling and appropriate family studies		

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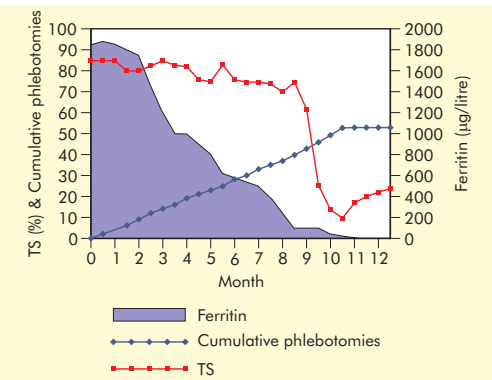

Figure 7. Typical response to venesection. TS = transferrin saturation.

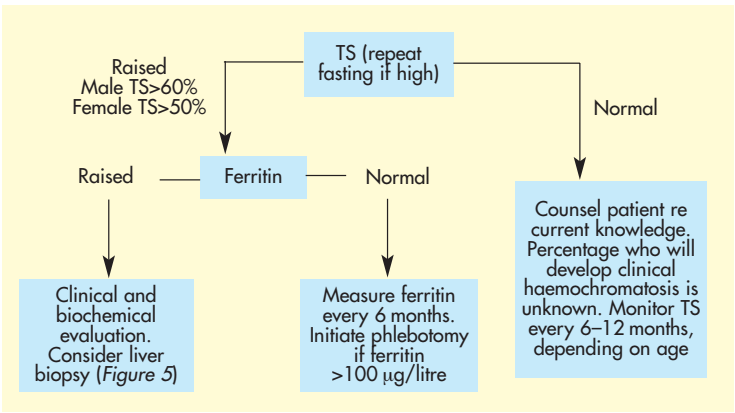

Figure 8. Management of asymptomatic family members with genetic predisposition to hereditary haemochromatosis (i.e. detected in family studies). TS = transferrin saturation.

therefore be to prevent iron damage in well, but genetically predisposed, subjects.

HH is a multi-organ disease requiring a multidisciplinary approach to management. Much evidence already exists on which to base management guidelines.

Future research is likely to focus on the genetic mutations and on the mechanism of action of the gene products. This may shed further light on the biology of iron metabolism.

Several studies have shown a discrepancy between the number of patients with clinical haemochromatosis and the number of C282Y homozygotes. Whether this represents variable penetrance of the gene or problems with diagnosis remains uncertain. More extensive studies are needed (Merryweather-Clarke et al, 1998) before the benefits and ethics of population screening can be explored. HM

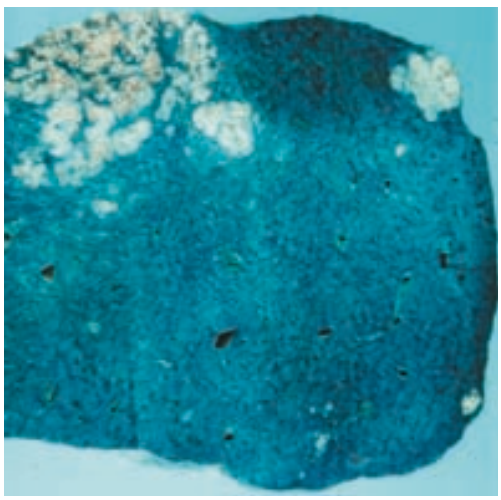

Figure 9. Liver (Perl's stain) showing multifocal hepatocellular carcinoma (pale areas) contrasting with heavy iron staining in surrounding tissue.

KEY POINTS

- The classical triad of bronzed skin, diabetes and cirrhosis occurs much later than the non-specific symptoms which herald the disease.
- More than 90% of hereditary haemochromatosis patients are homozygous for the Cys282Tyr mutation of the HFE gene.
- Transferrin saturation is the first-line screening test for hereditary haemochromatosis (positive predictive value of 66%).
- Ferritin correlates well with hepatic iron stores and defines those patients with iron overload.
- There is good evidence from long-term survival analyses that non-cirrhotic and non-diabetic patients treated by venesection have normal life expectancy.
- Hepatocellular carcinoma develops in up to one-third of cirrhotic patients and can occur many years after depletion of iron stores.
- Genetic testing should be offered to children (and/or partner) as well as siblings because of the high frequency of heterozygosity in the population.
- The hereditary haemochromatosis patient can present at many specialist clinics and clinical guidelines will improve screening, diagnosis and treatment.

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