What is HFE haemochromatosis?

HFE-associated haemochromatosis is the most common inherited genetic disorder in Caucasian populations. It is an autosomal recessive disorder of iron regulation which is characterized by:

1. Biochemical changes reflecting abnormal iron haemostasis
2. Clinical signs and symptoms of high iron burden
3. Pathological changes in organs which may ultimately lead to disease (termed 'iron overload').

Multiple organ systems can be affected by excess systemic iron but with disease progression liver damage predominates. Although several, rarer genetic polymorphisms can manifest as haemochromatosis, variants in the HFE gene on chromosome 6 underpin the vast majority of cases, and so *HFE*-associated haemochromatosis forms the basis of this review.

Table 1. Stages of haemochromatosis

Stage 1	Patients with 'genetic susceptibility' but with no increase in iron stores
Stage 2	Patients with 'genetic susceptibility' and with asymptomatic evidence of iron overload (increased ferritin and transferrin saturations) without organ damage
Stage 3	Patients with 'genetic susceptibility' and with symptoms (lethargy, arthralgia) but without organ damage
Stage 4	Patients with 'genetic susceptibility' with iron overload and organ iron deposition to the degree that causes tissue damage especially cirrhosis

From Adams et al (2000)

Genotype

Linkage studies performed in 1975 first localized the genes responsible for hereditary haemochromatosis to the major histocompatibility complex on chromosome 6. Twenty years later the haemochromatosis gene *HFE* (*High Fe*) was cloned. In most cases (90%) the mutation responsible is a single base change resulting in the substitution of tyrosine for cysteine at position 282 of the HFE protein (C282Y) (McCune et al, 2006). C282Y is likely to have originated in Celtic and northern European populations over 2000 years ago and has managed to survive evolution, potentially by once conferring protection against dietary iron deficiency. C282Y homozygosity is found in 1:250 people and heterozygosity in 1:10 people of northern European descent (European Association for The Study of The Liver, 2010). This prevalence of homozygosity is 10x greater than the genotypes conferring cystic fibrosis.

Other mutations in the HFE gene have been described, with the H63D aspartate for histidine substitution being the most common but of little clinical significance. Occasionally the C282Y and H63D mutations can exist together as a so-called compound heterozygote. *HFE* C282Y mutations are far rarer in black and Asian populations and therefore hereditary haemochromatosis can be considered a predominantly Caucasian disease. Multiple gene variants outside of *HFE* in important iron-regulatory proteins (e.g. HJV, TfR2, ferroportin and HAMP) have been discovered in iron storage diseases, particularly in juvenile-onset haemochromatosis, but none of these have the population-wide significance of *HFE* haemochromatosis.

Clinical penetrance

All patients who are homozygous for C282Y are genetically predisposed to the harmful accumulation of iron; however, the proportion of patients who go on to develop clinically significant disease may be as few as 2% (Beutler et al, 2002). Clinical penetrance of compound heterozygotes (C282Y/H63D) is even lower at 0.5–2% and lower still in H63D homozygotes. Predicting which patients with an at-risk genotype will develop clinically significant disease is extremely difficult.

In recognition of the spectrum of pathology caused by *HFE* mutations the European Association for the Study of the Liver Consensus Group defined four stages of disease (European Association for The Study of The Liver, 2010) (*Table 1*).

This classification demonstrates that genotype is only the first step in a cascade towards organ damage. Haemochromatosis is best viewed as a multifactorial iron overload disorder with host factors (menses, diet, blood loss), modifying genes (such as hepcidin, matriptase 2, transferrin receptor 2, haem oxygenase 1) and superimposed liver disease (alcohol, non-alcoholic fatty liver, viral hepatitis) all playing their part in tipping genetically susceptible individuals towards overt disease (Pietrangelo, 2004).

Iron haemostasis and pathophysiology

Because there are no in-built physiological mechanisms for iron removal other than menstrual blood loss, once iron enters the body through the small intestine it must be used or stored. Iron which is used in the production of haemoglobin is continually recycled back into plasma from senescent red cells by macrophages. In hereditary

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haemochromatosis the rate of iron absorption from the gut and the rate of macrophage iron recycling is accelerated. This leads to the gradual accumulation of iron first in blood and then in organs which ultimately causes damage via the production of reactive oxygen species.

The discovery of hepcidin in 2001 provided an elegant explanation for the disordered iron handling by enterocytes and macrophages in haemochromatosis. Hepcidin binds to and internalizes ferroportin, the body's main cellular iron exporter, and therefore reduces a cell's ability to move iron into the plasma compartment (Nemeth et al, 2004). In conditions of hypoxia or anaemia the liver responds by reducing hepcidin production to allow liberation of iron for erythropoiesis. Haemochromatosis is characterized by hepcidin deficiency leading to unchecked liberation of iron from macrophages and duodenal enterocytes (Pietrangelo, 2004). This discovery has drawn comparisons between haemochromatosis and type I diabetes mellitus, with the liver as the endocrine organ controlling iron homeostasis through hepcidin while the pancreas controls glycaemia via insulin. Deficient hormones manifest as hyperferritinaemia in haemochromatosis, as compared with hyperglycaemia in diabetes.

Clinical features: signs and symptoms

Owing to earlier diagnosis of haemochromatosis in many patients, the classic triad of cirrhosis, bronze skin and diabetes described by Trousseau in 1865 is now extremely rare. Haemochromatosis is now more commonly identified incidentally from abnormal iron studies, as part of family screening or is suspected from more subtle clinical signs. Most patients will be asymptomatic, but those who do have symptoms will often present non-specifically with fatigue, malaise and joint pain. Organ involvement predominantly involves the liver and ranges from mildly elevated aminotransferase levels, occasionally with hepatomegaly, to cirrhosis and hepatocellular carcinoma. Extra-hepatic manifestations include endocrine disorders (diabetes, hypogonadotrophic hypogonadism, impotence, hypothyroidism), cardiac disorders (cardiomyopathy, arrhythmias, heart failure), joint disease (arthralgia, chondrocalcinosis) and skin changes (hyperpigmentation, porphyria cutanea tarda).

Despite aberrant iron metabolism erythropoiesis is not affected with haemoglobin levels usually within normal range. Women are relatively more protected against iron overload through menstrual and pregnancy-associated blood loss, and in older series where haemochromatosis was identified solely with clinical findings women tended to present 10 years later than men. Furthermore, contemporary series demonstrate that the proportion of C282Y homozygous patients with definite clinical manifestations is 1% in women and 25% in men (Allen et al, 2008).

Diagnosis: elevated iron stores and genotyping

The definitive diagnosis of haemochromatosis relies on finding both an at-risk genotype and biochemical evidence of iron accumulation. This biochemical evidence is most commonly derived from transferrin-iron saturation and serum ferritin levels. Elevations in transferrin-iron saturation are the earliest marker of plasma iron accumulation and can occur within the first decade of life.

Over the years several different transferrin-iron saturation cut-off values have been trialled to try and identify patients who would benefit from further testing for haemochromatosis with HFE genotyping. Currently a transferrin-iron saturation of >45% is proposed in most guidelines owing to its high sensitivity for detecting C282Y homozygotes, although higher cut-off values would boost specificity and positive predictive value. The combination of elevated transferrin-iron saturation with an elevated serum ferritin level offers the most sensitive and specific initial approach to diagnosis.

Ferritin levels correlate with total iron body stores and better reflect hepatic iron concentration in patients with haemochromatosis. However, it must be remembered that the commonest cause of raised ferritin levels in the general population is not iron overload and is instead accounted for by chronic inflammatory states, which include liver diseases such as alcoholic liver disease, chronic viral hepatitis and non-alcoholic fatty liver disease. Ferritin levels must therefore be interpreted with caution in the diagnosis of haemochromatosis. When used together, however, a normal ferritin level and a transferrin-iron saturation of <45% has a 97% negative predictive value for excluding iron overload.

Where ferritin is particularly useful is as a marker of hepatic fibrosis. Ferritin levels of >1000 μg/litre should increase suspicion for underlying cirrhosis in those homozygous for C282Y irrespective of age or aminotransferase levels and should prompt liver biopsy. Transient elastography (FibroScan) may be useful but has not been fully validated in this cohort. Once cirrhosis has developed, patients with haemochromatosis have a 100-fold increased risk of hepatocellular carcinoma (Niederau et al, 1996) at a rate of 9% per year (Yang et al, 1998), which is at least twice as frequent as other causes of cirrhosis. A proposed diagnostic algorithm is outlined in *Figure 1*.

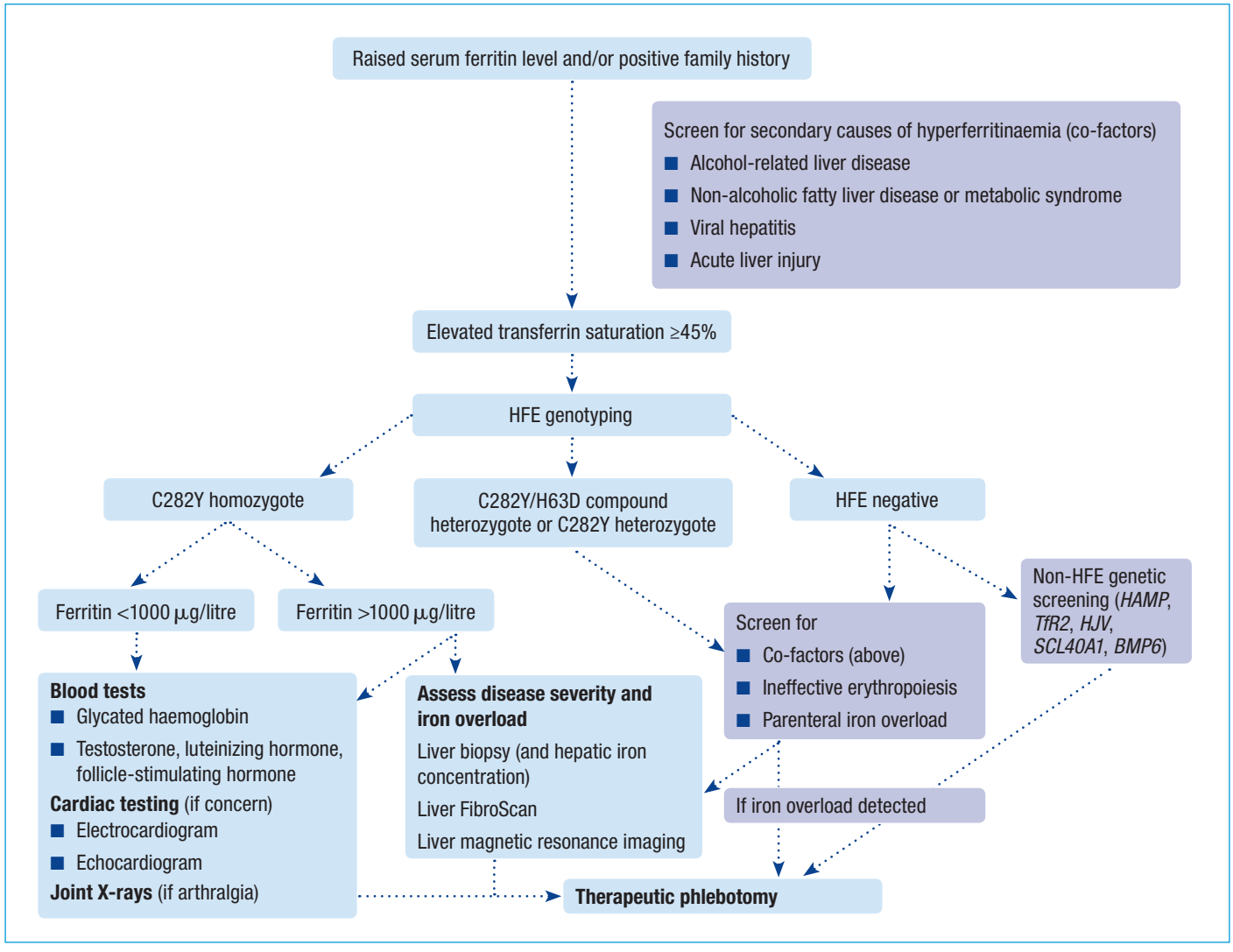
HFE genotyping

Molecular genetic testing of the common mutations in the *HFE* gene (C282Y and H63D) is now widely available and should be considered if there is clinical suspicion of hereditary haemochromatosis with raised transferrin-iron saturation and/or ferritin levels. Occasionally patients will have raised transferrin-iron saturation and ferritin levels and/or deranged liver function tests but will not demonstrate mutations in C282Y or H63D on molecular genetic testing. At this point clarification can be provided by either second-line genetic testing for rarer gene variants or liver biopsy and iron staining. Some patients may have non-haemochromatosis liver disease such as non-alcoholic fatty liver disease where raised serum ferritin level is an independent predictor of histological severity and advanced fibrosis (Kowdley et al, 2012). Extremely high serum ferritin levels, often with elevated transferrin-iron saturation, may be also seen in acute liver injury and should be kept in mind in the acute setting.

Screening

Population screening for *HFE* haemochromatosis remains controversial. Proponents for screening will cite the disease's high prevalence, potentially fatal outcomes and its relatively simple treatment. Thankfully concerns regarding potential psychosocial implications of labelling asymptomatic individuals with haemochromatosis, many of whom will not go on to iron overload-related disease, have been unfounded. Indeed, specific statutes exist in many western European countries to protect individuals from insurance or health-care discrimination

Figure 1. Proposed diagnostic algorithm in suspected haemochromatosis.



based on their genetic diagnosis. Currently population screening is not performed. However, once a patient with hereditary haemochromatosis has been identified, family screening with *HFE* genotyping and iron studies should be recommended for all adult first degree relatives. If C282Y homozygosity or compound heterozygosity is found in a first degree relative and serum ferritin level is increased then treatment can be commenced. If there is an at-risk genotype with a normal ferritin level (stage 1 disease) then these patients can have annual surveillance with measurement of ferritin levels. Heterozygotes can be reassured that they are not at risk for developing progressive iron overload, but it must be recognized that this genotype may act as a cofactor with non-alcoholic fatty liver disease, viral hepatitis and alcohol in driving fibrosis and hepatocellular carcinoma.

Treatment

Despite the paucity of randomized controlled trials, therapeutic phlebotomy remains the cornerstone of treatment in haemochromatosis with cohort studies demonstrating clear mortality benefits (Adams et al, 1991). As a result there has been a drive for pre-emptive therapy in at-risk individuals (*Table 2*). This includes fully asymptomatic homozygotes with ferritin level >1000 μg/litre. Whether to treat patients who are homozygous for C282Y with a raised ferritin level but not >1000 μg/litre (stage 2/3 disease) has remained a grey area as many of these patients will never go on to develop problems. However, given that phlebotomy is simple to perform, inexpensive and safe many advocate initiation of treatment. Data have demonstrated a reduction in cardiovascular and extrahepatic cancer mortality by venesection in these patients (Bardou-Jacquet et al, 2015). Furthermore a significant societal benefit is gained with those patients undergoing maintenance venesection (ferritin levels within reference range) able to contribute their blood to national blood banks.

The aim of therapeutic phlebotomy is to reduce accumulated iron stores to safe levels reflected by a serum ferritin level of <50–100 μg/litre. The intensity of venesection needed to achieve this target value is highly variable with some individuals with late diagnosis requiring years of treatment before achieving favourable ferritin levels.

Once safe iron levels have been restored the rate of re-accumulation is also variable with maintenance venesection requirements ranging from once a month to once a year. During maintenance therapy attempts should be made to keep ferritin levels within the low–normal range. Iron deficiency states

Table 2. Management of hereditary haemochromatosis depending on stage at presentation. Management stage recommendations are summative

Stage 1 (Patients with the genetic disorder with 'genetic susceptibility' but with no increase in iron stores)	■ Yearly ferritin and iron studies in primary care ■ Family screening of adults
Stage 2 (Patients with the genetic disorder and with asymptomatic evidence of iron overload (increased ferritin and transferrin saturations) without organ damage)	■ Avoid vitamin C or iron supplements, avoid excess alcohol consumption and uncooked shellfish (otherwise no role for dietary restriction) ■ Consider tertiary referral to hepatologist or haematologist ■ Consider treatment with venesection (no formal guidelines) ■ Monitor yearly in primary care for progression to stage 3–4
Stage 3 (Patients with the genetic disorder and with symptomatic evidence of iron overload (lethargy, arthralgia) but without organ damage)	■ Initiate treatment with venesection ■ Assess for organ damage (liver ultrasound and/or biopsy, magnetic resonance imaging of the liver or FibroScan where available, glycated haemoglobin, cardiac and hormonal investigations if suspected)
Stage 4 (Patients with the genetic disorder with iron overload and who have organ iron deposition to the degree that causes organ damage especially cirrhosis)	■ Ensure serum ferritin 50–100 μg/litre achieved with venesection if tolerated ■ 6-monthly ultrasound and alpha fetoprotein levels if cirrhotic

KEY POINTS

- *HFE* haemochromatosis is the commonest genetic disorder in Europe.
- The majority of individuals with HFE mutations will not develop clinical disease.
- Women tend to have milder disease and present 10 years later than men.
- Patients present non-specifically with fatigue and arthralgia.
- Elevated serum ferritin levels and transferrin saturation >45% should lead to *HFE* testing and specialist referral.
- Individuals with serum ferritin levels >1000 μg/litre, abnormal liver function tests and/or >50 years of age should have a liver biopsy.
- Cirrhotics have a higher risk of hepatocellular carcinoma development and should be closely screened.
- Treatment is with regular venesection to a target ferritin level of 50–100 μg/litre.
- Patients who have finished intensive venesection and are in the maintenance stage of their treatment can be accepted as blood donors.

do not confer any additional therapeutic benefit and should be avoided. Occasionally phlebotomy is contraindicated in the context of severe anaemia, heart failure or is poorly tolerated and in these circumstances iron chelators have been proven to be safe and effective in reducing ferritin levels in C282Y homozygotes.

In haemochromatosis patients with overt disease certain clinical features respond to phlebotomy and others do not. Typically malaise, fatigue, skin pigmentation and insulin requirements are favourably affected by treatment whereas arthropathy and hypogonadism commonly persist. There is some evidence that phlebotomy may reverse hepatic fibrosis (Falize et al, 2006) but not advanced cirrhosis in patients with haemochromatosis. There are no studies which prove a further benefit of dietary iron restriction in addition to venesection although iron supplements, fortified foods and uncooked shellfish (because of the increased risk of rare infections such as *Vibrio vulnificus*) should be avoided.

Established cirrhosis in patients with haemochromatosis confers a significant risk of developing hepatocellular carcinoma and surveillance should be along standard lines with regular ultrasound scanning and measurement of alpha fetoprotein levels. Patients who have cirrhosis with decompensated liver disease (ascites, encephalopathy) should be considered for orthotopic liver transplantation. Early studies reported a mildly reduced post-transplant survival of haemochromatosis patients compared with those with other liver diseases (Brandhagen et al, 2000) but outcomes have improved with more aggressive pre-transplant phlebotomy. Indeed there is emerging evidence that orthotopic liver transplantation for haemochromatosis normalizes serum hepcidin levels and ameliorates abnormal iron metabolism (Bardou-Jacquet et al, 2014).

Extra-hepatic manifestations tend to be more difficult to treat, with variable response to venesection therapy. Arthropathy can be progressive and is not typically ameliorated by phlebotomy, although cardiomyopathy, while rare and typically associated with juvenile haemochromatosis, may improve following iron reduction therapy. Venesection may prove beneficial for endocrinopathies such as diabetes but not for hypogonadism or osteoporosis (Valenti et al, 2007; European Association for The Study of The Liver, 2010; Bacon et al, 2011).

Conclusions

This review provides a reference for *HFE*-associated haemochromatosis, a relatively common condition that is often overlooked in clinical practice as a result of its non-specific presentation. It particularly affects Caucasians of northern European descent, and can lead to significant clinical sequelae if left untreated, albeit in a minority of those with the main at-risk HFE genotype (C282Y homozygosity). Important recent advances have been made in understanding the pathogenesis of the condition and identifying rarer contributory genetic mutations. Despite this, treatment with iron reduction by repetitive venesection has remained unchanged for decades, owing to its low cost, high efficacy and safety. Identifying those at risk of progressive disease in order to initiate preventative therapy represents a challenge for the future. **BJHM**

Conflict of interest: none.

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