Haemochromatosis

WJH Griffiths

Abstract

The discovery of the principal gene associated with hereditary haemochromatosis (*HFE*) in 1996 led to the complete revision of our understanding of this condition. The impact of homozygosity for the C282Y mutation, accounting for the majority of cases, cannot be underestimated. Early accurate diagnosis is now possible and the disease entirely preventable through phlebotomy. Liver biopsy is mainly reserved to identify cases for hepatoma surveillance. Presentation with classical signs relating to end-organ damage is less typical, though joint symptoms are common and impair quality of life in patients with haemochromatosis. Penetrance is much lower in females and immediate treatment is not always required in the presymptomatic state. A low clinical index of suspicion avoids delay in diagnosis and family screening is fundamental. Venesection is effective in removing liver iron, though new oral iron chelators are showing promise.

Although environmental factors, such as alcohol, are important for expression of HFE-related haemochromatosis, genetic modifiers are likely. Novel genes underpinning less common types of haemochromatosis interact in a common molecular pathway involving HFE and the regulatory hormone 'hepcidin', which via the iron export protein ferroportin maintains body iron balance. Improving our understanding of the mechanisms of iron regulation may lead to novel strategies for the treatment of iron overload.

Keywords ferroportin; haemochromatosis; hepcidin; *HFE*; iron; liver

What's new?

- Blood diagnosis of hereditary haemochromatosis by C282Y mutation testing in individuals with evidence of biochemical iron loading
- Liver biopsy in homozygotes is unnecessary if ferritin <1000 μg/litre, no hepatomegaly and normal transaminase (low risk of significant fibrosis)
- Magnetic resonance imaging can be used to quantify hepatic iron
- Asymptomatic patients with modest ferritin elevation (400—800 μg/litre) may be observed but with low threshold for venesection
- Patients minimally iron loaded or undergoing maintenance phlebotomy can donate every 12 weeks via the National Blood Service if otherwise eligible
- Instead of directly screening children, the spouse can be excluded as a carrier on 90% of occasions
- Patients with unexplained iron overload but without typical *HFE* mutations may be suitable for non-*HFE* gene testing
- Hyperferritinaemia with normal transferrin saturation should raise suspicion of classical ferroportin iron overload
- The new daily oral iron chelator, deferasirox, shows preliminary efficacy and safety profile at 10 mg/kg in patients with hereditary haemochromatosis

Hereditary haemochromatosis (HH) is an autosomal recessive disorder characterized by toxic accumulation of iron. The disease occurs more commonly in males than in females, in whom natural iron losses are greater. Gradual deposition of iron occurs in the liver and in a number of other tissues, including the pancreas, joints, skin, heart and the gonadotrophin-secreting cells of the anterior pituitary. Disease manifestations respectively include hepatic fibrosis, diabetes mellitus, arthropathy, pigmentation, cardiomyopathy and hypogonadotropic hypogonadism. Fatigue and arthralgia are common early symptoms and painful arthropathy is a considerable cause of morbidity. Cirrhosis is associated with significantly reduced survival and a 100-fold increased risk of hepatocellular carcinoma (HCC), the commonest cause of death in this condition.[1] Phlebotomy either weekly or fortnightly remains the primary treatment to remove iron, typically until the serum ferritin falls below 50 μg/litre followed by maintenance every 2—6 months. Venesection before the onset of cirrhosis or diabetes ensures normal survival, and has been associated with regression of hepatic fibrosis.[2] Notably, HCC can occur in non-cirrhotic patients and despite iron depletion.[3] The outcome following liver transplantation has improved for patients with hereditary haemochromatosis (often associated with HCC and additional liver disease, due for example to alcohol).[4]

Under normal circumstances, gastrointestinal iron absorption is homeostatically controlled according to body iron, though excretion of iron, via desquamation of intestinal epithelia and in women through menstruation, is not.[5] In HH the homeostatic mechanism is disrupted and increased iron absorption continues despite iron excess (Figure 1). Once plasma transferrin has been saturated, tissue iron deposition occurs associated with elevated serum ferritin. Total body iron, approximately 4 g in a normal adult, can exceed 20 g in severely affected individuals.

Identification of the *HFE* gene in 1996 significantly revised our understanding and management of HH.[6] Homozygosity for the C282Y mutation accounts for the vast majority of HH presentations in Caucasians; thus, a specific tool has emerged for non-invasive diagnosis and screening, estimating prevalence, understanding the natural history and expression of HH, and for evaluating liver diseases where siderosis is a secondary feature. The HFE protein, in keeping with major histocompatibility complex (MHC) class I molecules, requires β_2-microglobulin binding for cell surface expression.[7] The common missense mutation C282Y abrogates this association and disables the protein within the cell, preventing interaction with surface transferrin receptors.[8]

The diagnosis of HH can be established in most cases without recourse to liver biopsy: a compatible genotype combined with biochemical evidence of iron loading is sufficient.[9] A high serum ferritin and transferrin saturation is highly suggestive and

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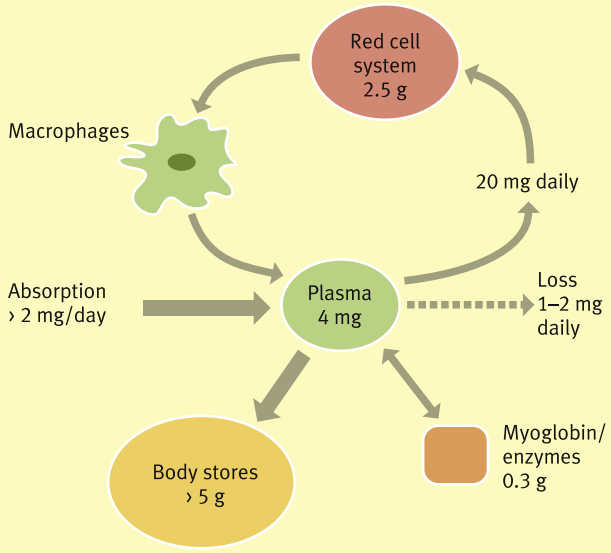
Conflicts of interest: none declared.

Iron balance in hereditary haemochromatosis (HH)



Normally iron absorption is regulated to match insensible losses and total adult body iron equates to 4 g. In HH the iron storage compartment greatly increases due to unopposed intestinal uptake as normal feedback mechanisms are disrupted. Note the size of the transferrin iron pool, approximately 0.1% of total body iron, and that transferrin saturates early during the natural history of HH.

Figure 1

magnetic resonance imaging an effective non-invasive method to demonstrate hepatic iron deposition. As well as the common genotype C282Y/C282Y, which accounts for 90–95% of cases in Northern Europe, the compound heterozygous form C282Y/H63D is seen in approximately 4% of cases with usually a mild iron burden.[10] Liver biopsy is reserved for those cases without a recognizable genotype or in those where there is a risk of significant liver fibrosis. In homozygotes, in whom serum aminotransferase values are normal, hepatomegaly absent and serum ferritin below 1000 μg/litre, the risk of significant fibrosis is negligible.[11] Furthermore, a serum hyaluronic acid concentration over 46.5 ng/ml is associated with 100% sensitivity and specificity for cirrhosis.[12] Cirrhosis has become less common at presentation during recent years, in part due to greater clinical awareness and access to HFE testing.[13]

Approximately 1 in 200 Caucasians are homozygous for the C282Y mutation and therefore genetically 'predisposed'.[14] Only a proportion will have evident morbidity as many, particularly premenopausal females, will have either presymptomatic or no iron loading. The penetrance of C282Y homozygosity varies according to the definition and study population: for 'iron-related disease' in males it is approximately 28%, whereas for biopsy-proven cirrhosis across both sexes it is as low as 1%.[15,16] Longitudinal studies have shown that progressive iron loading does not always occur.[17] Population screening in general has therefore not been advocated, though screening of first-degree relatives has been proven to be effective in uncovering morbidity and is universally accepted.[18] Environmental factors that modify iron loading and hence expression of the disease include excess alcohol, iron-rich diet and blood donation. Genetic modifiers are likely to be important determinants of disease expression in C282Y homozygotes and this is an area of current research interest.[19]

The contribution of *HFE* mutations to liver diseases where lesser degrees of siderosis are relatively common has been evaluated. In chronic hepatitis C infection, *HFE* mutations have been associated with iron deposition and accelerated fibrosis.[20] Phlebotomy had been shown to improve responses to standard interferon treatment, to reduce fibrosis progression and the risk of hepatocellular carcinoma.[21–23] *HFE* mutations have not been associated with the siderosis observed in alcohol-related liver disease, in which the deposition of excess iron may be mediated via a reduction in hepcidin, a circulating peptide that inhibits intestinal iron uptake.[24,25] In non-alcoholic steatohepatitis (NASH), an association between hepatic iron and *HFE* mutations has been observed although data conflict regarding effects on fibrogenesis.[26,27] Abnormal iron parameters in patients with NASH may reflect the metabolic syndrome rather than true iron overload, in which case they improve with dietary restriction.[28] Phlebotomy has been shown to improve insulin sensitivity and liver function in patients with NASH-associated iron overload, suggesting that iron may facilitate hepatocellular damage indirectly via effects on insulin resistance.[29,30] A clear link between *HFE* mutations and iron is seen in the context of porphyria cutanea tarda (PCT), where iron overload is associated with a high prevalence of *HFE* mutations and where phlebotomy typically induces regression of skin lesions.[31]

Inherited iron overload without *HFE* mutations has been termed 'non-HFE haemochromatosis'. In addition to HFE-related or 'type 1' haemochromatosis, several newly-identified gene defects are associated with primary iron overload (Table 1). Apart from the distinct phenotype associated with classical ferroportin iron overload, these syndromes resemble HFE-related disease in a more severe form, particularly the juvenile variants. Interrogation of this heterogeneous group at a molecular level has revealed novel key proteins involved in iron metabolism and has considerably advanced our understanding of the molecular control of iron homeostasis.

A specific phenotype is seen in patients with ferroportin haemochromatosis. The ferroportin protein controls iron release from cells involved in iron turnover, in particular enterocytes and macrophages.[32] Mutations in the ferroportin (*SLC40A1*) gene

Online Mendelian inheritance in man (OMIM) classification of inherited haemochromatosis disorders

Name	Type	Gene	OMIM	Example mutation
HFE	1	*HFE*	235200	C282Y
Juvenile	2A	*HJV*	608374	G320V
	2B	*HAMP*	606464	93delG
TfR2	3	*TfR2*	604250	Y250X
Ferroportin	4	*SLC40A1*	606069	V162del

All are autosomal recessive apart from ferroportin iron overload, which is dominantly transmitted. Additional rare disorders include neonatal haemochromatosis, acaeruloplasminaemia and atransferrinaemia.

Table 1