

## Update on hereditary haemochromatosis

Dr John Ryan and Prof John Crowe look at recent developments in the understanding and management of hereditary haemochromatosis

Hereditary haemochromatosis (HH) is Ireland's most common inherited disease and affects thousands of Irish adults. It is an autosomal recessive disorder of iron metabolism, and the most common genetic disease in Europe. In fact, Ireland has the highest reported prevalence of HH in the world.

When the 'haemochromatosis gene', or HFE, was revealed by Feder and colleagues in 1996, it appeared the pathogenesis of this common disorder had been unravelled. As it has since emerged, this was just one piece of a complex puzzle that is still being assembled.

Once the HFE gene was identified and individuals screened for pathogenic mutations, it transpired that not all those with mutations came to harm or developed HH, indicating that the disease has incomplete penetrance. The vast majority of HH patients carry mutations in the HFE gene, the C282Y substitution of cysteine for tyrosine the commonest, followed by the H63D aspartate for histidine substitution.

Homozygosity for the C282Y mutation (i.e. having two copies) confers the greatest risk of developing HH, while some 'compound heterozygotes' with shared C282Y and H63D mutations, and, rarely, H63D homozygotes may develop clinical disease. To be diagnosed with HH, an individual requires both an at-risk HFE genotype and objective clinical manifestations of iron overload.

Irish studies estimate a prevalence of C282Y homozygosity of approximately one in 83 persons, indicating that over 25,000 Irish adults are at risk for developing HH.

Despite this high prevalence, large population studies from North America and Australia suggest that approximately 30 per cent of males and 1-5 per cent of females who are C282Y homozygous will actually develop clinically-significant complications related to iron overload. However, Irish studies indicate that these figures could be higher in a homogeneous Irish population.

### Pathophysiology

Several major advances in our understanding of HH and iron metabolism have surfaced in the past decade. The greatest breakthrough was in 2001, with the discovery of the hormone hepcidin, which controls systemic iron balance. When iron stores are sufficient, the liver secretes hepcidin, which prevents further iron absorption by inhibiting a plasma-membrane iron exporter on duodenal enterocytes and macrophages.

HH is characterised by a deficiency of hepcidin. Despite replete iron stores, the body continues to absorb excessive amounts of iron, as not enough hepcidin is produced to switch off this process. This discovery has drawn contrasts between HH and type I diabetes mellitus, with the liver as the endocrine organ controlling iron homeostasis through hepcidin, while the pancreas controls glycaemia via insulin, and deficient hormone manifests as hyperferritinaemia in HH, as compared with hyperglycaemia in diabetes.

## Clinical features

The classic triad described by Trousseau in 1865 of cirrhosis, diabetes and bronze skin-pigmentation is now exceptionally rare, as most individuals are discovered incidentally at health checks or through family screening. Typically, iron overload-related disease does not manifest until adulthood, with women protected by menstruation and pregnancy through physiological blood loss and therefore presenting later. Female C282Y homozygotes with normal iron profiles at 60 years of age have almost no risk of developing iron overload.

The hepcidin deficiency of HH means that iron absorption continues unchecked, despite iron excess, as evidenced by elevated serum ferritin, transferrin saturation and serum iron levels. As serum ferritin levels can be elevated for non-HH reasons (alcohol, fatty liver disease, viral hepatitis or inflammation), the best screening test for HH is transferrin saturation. A fasting transferrin saturation >45 per cent in females and >55 per cent in males should be further evaluated with HFE genotyping, liver function testing and referral to a hepatologist, if abnormal.

The portal vein carries dietary iron directly to the liver, the main site of storage and therefore the organ most affected by its excess. Hepatic iron deposition may culminate in fibrosis, cirrhosis and hepatocellular carcinoma (HCC), if untreated. The risk of HCC is greatest in patients with cirrhosis (up to 50 per cent of cirrhotic patients), who require twice-yearly alpha feto-protein levels and yearly liver ultrasound.

Extra-hepatic manifestations include fatigue, arthralgia (classically the second and third metacarpo-phalangeal joints), hypogonadism and erectile dysfunction, osteoporosis (bone densitometry is worthwhile) and, less commonly, diabetes and cardiomyopathy. Established hypogonadism, arthritis and diabetes may not respond to venesection, which improves or reverses several other iron-related complications.

One recent Australian study involving Irish descendents reported a two fold increased risk of colorectal and breast cancer in C282Y homozygotes, although the cause of the association remains unclear and the study has yet to be replicated elsewhere. Overall, patients with HH who are detected and treated at a pre-cirrhotic stage enjoy a normal life expectancy.

## Management algorithm

The most recent HH management guidelines were published by the European Association for the Study of the Liver (EASL) in 2010. The diagnosis of HH relies on elevated iron indices accompanied by HFE mutational analysis. HFE testing has reduced the need for liver biopsy at diagnosis, which is reserved for those >40 years of age, with serum ferritin >1000µg/L, and elevated hepatic transaminases. Without these risk factors, the prevalence of cirrhosis is very low.

Furthermore, non-invasive methods of estimating hepatic fibrosis with serum biomarkers and quantifying iron accumulation using MRI techniques are becoming more common. Venesection remains the mainstay of treatment for HH and is acceptable, inexpensive and safe. Rarely are iron chelators such as desferrioxamine employed for those intolerant of phlebotomy. Regular venesection of approximately 500ml of blood every week until serum ferritin falls <50µg/L is standard. Venesection may be recommenced once ferritin rises above 200µg/L.

One important advance in HH therapy in Ireland is that HH patients may become blood donors in their maintenance phase of therapy, providing much-needed blood to the transfusion service.

## Management points

Other salient management points include avoiding excessive alcohol consumption, which has been shown to suppress hepcidin and therefore exacerbate excessive iron absorption. Vitamin C enhances intestinal iron absorption and so supplements should be avoided, along with iron-fortified foods and iron supplements. Once diagnosed with HH, an individual's family (siblings and parents) should be evaluated for HFE mutations. In the case of minors, HFE genotyping is inappropriate, unless iron overload is suspected.

Once children of a HH patient enter adulthood, the patient's spouse/partner should be tested first. As HH is an autosomal recessive condition, should he/she be negative for HFE mutations (i.e. normal HFE gene test), any offspring can only be carriers and do not require HFE gene testing. Concerns of significant psychological impact of HFE testing and insurance discrimination have not been borne out in international studies. In Australia, an agreement exists with the insurance industry to prevent discrimination following HFE testing.

## Future advances

Despite the importance of hepcidin in HH, serum or urine levels have been cumbersome to measure and are only performed for research purposes. Should a more facile method of hepcidin measurement become available, a potential role for assaying hepcidin would be in screening, as in conjunction with an 'at-risk' HFE genotype, low serum hepcidin levels may indicate an increased likelihood of iron overload and its complications.

One major question remains unanswered in HH, and that is why some C282Y homozygotes experience significant iron overload, while others do not. Alcohol and other environmental factors undoubtedly play a role, but the search for another gene mutation or single nucleotide polymorphism that modifies disease expression continues.

Finally, the issue of screening for HH lingers. Expert international reports have concluded that screening should only take place for high-risk groups. Considering that Irish adult males have the highest prevalence of C282Y homozygosity in the world – and therefore the highest risk of developing significant, potentially life-threatening complications related to iron overload – a strong case exists to initiate screening in this particular cohort.

Moreover, a 2006 working group commissioned by the Minister for Health recommended that "funding be prioritised to develop a HH screening programme". Unfortunately, this sensible recommendation has not been implemented. Nevertheless, significantly increased public and medical awareness of haemochromatosis in Ireland has undoubtedly led to earlier identification and treatment.

References available on request.

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