fact file 37

Genetic haemochromatosis (iron overload disorder) and diabetes

Haemochromatosis is a genetic condition which may lead to diabetes. It tends to be underdiagnosed, so it is worthwhile healthcare professionals being aware of the connection between the two conditions, says **David Head**, Chief Executive, Haemochromatosis UK

Haemochromatosis diabetes is a secondary diabetes, caused by damage to the pancreas as a result of the presence of toxic levels of iron. Diabetes is one of many results of haemochromatosis, therefore, healthcare professionals should be looking for symptoms of diabetes in known haemochromatosis patients, and for other symptoms of haemochromatosis in known diabetes patients, especially where there are question marks about whether lifestyle is wholly to blame for that condition.

Historically, haemochromatosis diabetes has sometimes been referred to as bronze diabetes because, in the advanced stages of haemochromatosis, patients would present with diabetes, bronzed/yellowed complexions and liver damage.

What is genetic haemochromatosis?

Genetic haemochromatosis (GH) is caused by one of the most, if not the most, common genetic mutations in people of White northern European, particularly Irish, heritage. Higher prevalence of the condition in certain geographical areas around the world strongly correlate to the Irish diaspora.

Mutations of the HFE gene are responsible for the vast majority of GH cases. Mutation C282Y is the most prevalent, followed by H63D. The condition is described as autosomal recessive, although many cases of heterozygotes and of compound (C282Y/H63D) heterozygotes loading iron are known, suggesting that there are also other genes at play, which have not yet been identified. This is further borne out by the fact of low and variable penetrance, with many homozygotes not loading iron at all.

The mutations disrupt the production of the hormone hepcidin, which regulates the absorption of iron in the duodenum. As a result, the body's usually finely balanced process for controlling iron absorption from the diet fails, and iron continues to be absorbed when this would normally be switched off.

The iron cycle within the body is to all intents and purposes a closed system, so continual absorption leads to a build up, initially in the liver and then more widely. At high concentrations, this iron is toxic and causes damage to many systems, of which the pancreas is one.

Typically, a person with haemochromatosis develops symptoms in the fifth and sixth decades, although this is very variable. It is worth noting that, although both sexes are equally likely to be predisposed to load iron, for women the process tends to be slower prior to menopause as some protection is offered by natural menstrual blood loss.

In a survey of haemochromatosis patients by Haemochromatosis UK in 2017, reported in 2018, over 80% of respondents reported chronic fatigue and over 80% of respondents reported joint pains and arthritis, both now recognised as the most common early indicators of iron overload.

Symptom	% reporting experience
Joint pain and arthritis	86
Chronic fatigue	81
Psychological or cognitive difficulties	73
Skin conditions	70
Menstrual problems	62 (F)
Sexual health issues	57
Heart and breathing difficulties	49
Liver problems	29
Diabetes	8

How is GH identified?

Genetic haemochromatosis can be diagnosed by two straightforward blood tests, namely serum ferritin and transferrin saturation. Both should be performed. Serum ferritin (SF) is a proxy measure for stored iron, notably in the liver, and transferrin saturation (TSat) is a direct measure of how loaded the body's iron transport system has become.

Raised SF can, however, be caused by other conditions and can fluctuate significantly. Transferrin saturation above normal, if the test is duplicated, is a more certain indicator, although this may not rise significantly until late in many patients.

Clinical guidelines from The British Society for Haematology say that: 'All adult patients of north European ancestry with unexplained raised SF and Tsat (>300µ/l and >50% males; >200µ/l and >40% females) and normal FBC should have molecular (genetic) testing for HFE GH.'; ie diagnosis can be confirmed (or supplemented) by testing for the major known mutations of the HFE gene noted above. On the rare occasions that these flaws are not present, testing for mutations on rarer haemochromatosis genes is also possible.

Liver function tests may be run to identify whether the

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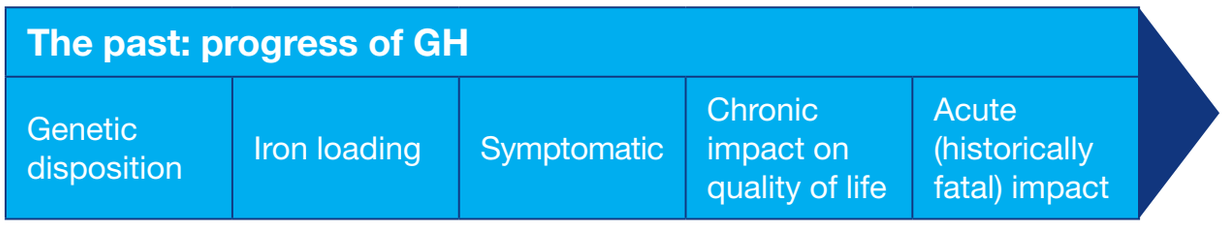

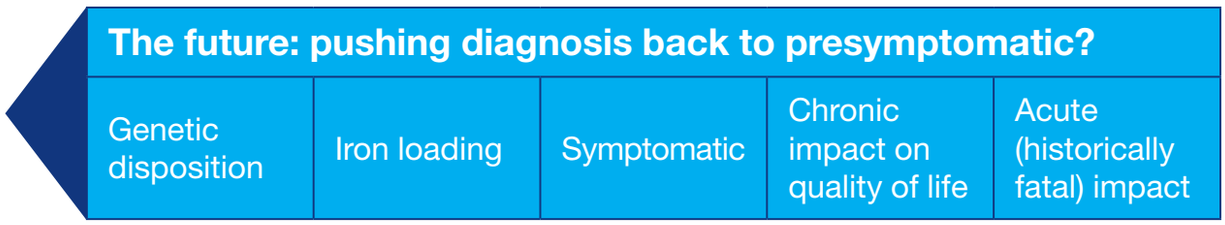

liver is damaged in any way and, increasingly, liver iron concentration is also measured using MRI scanning technology, the adoption of which is replacing the use of painful and often inefficient liver biopsies.

How is GH treated?

The treatment of choice is venesection therapy. For most patients, this is a straightforward process that involves the removal of 400–500ml of blood at each session. In the early phase of treatment (known as de-ironing), this can be as frequently as weekly, and for as long as a couple of years, but more usually is fortnightly for a period of months. In the UK, this blood is currently discarded.

Once storage iron levels are returned to normal or below normal, venesection (or possibly blood donation) a few times a year is usually enough to maintain the status quo; this is known as the maintenance phase of treatment.

Each unit of blood taken removes about 250mg of iron from iron stores as the body manufactures red blood cells to replace those removed during the venesection.

Venesection itself, although a simple concept and usually straightforward, does bring its own issues. It can be traumatic, painful and exhausting for some patients and, if not managed carefully, can lead to anaemia.

Chemical de-ironing, through the use of chelators, can be used on the rare occasions where venesection is not possible for a particular patient.

The link with diabetes

In a survey of haemochromatosis patients in 2004 by Haemochromatosis UK (which was known at the time as The Haemochromatosis Society), 18% of respondents reported diabetes. In 2017, in a similar, but much larger survey, this has been reported at 8%.

It is feasible that this is a result of improved identification and earlier treatment of GH in the years since the mutations were identified, and understanding and awareness of the condition took a corresponding leap forward in 1996. This speculation is also borne out in a fall in the number of respondents reporting liver complications.

The identification and treatment of GH in diabetes patients does result in significant improvement, with 84% of respondents in the maintenance phase in the 2017 survey reporting that symptoms of diabetes were alleviated by de-ironing. This strengthens the case for healthcare professionals treating and advising people with diabetes to be aware of iron overload and the other complications it can cause.

Symptom as diagnosis

Genetic haemochromatosis is generally accepted to be very underdiagnosed, and one of the key reasons for this is an understandable tendency to diagnose and treat the complication as presented, rather than delve further to identify an underlying cause. For example, mental health issues and fatigue are often attributed to workload and to stress, liver problems to diet and alcohol, and joint disease to ageing and injury.

Diabetes is generally attributed to lifestyle factors and, in most cases, this is quite appropriate. However, it is our belief, at Haemochromatosis UK, that a significant number of people with diabetes will be experiencing some of the other symptoms listed above and should be tested for iron overload.

Early diagnosis and treatment meaningfully reduces the impact of chronic symptoms on people with haemochromatosis. This also tells us that there is significant potential to reduce the burden on our highly pressured healthcare services.

The future

With the advent of cheaper, more accessible genetic testing for suspected patients and family screening, the diligent use of simple blood tests, and increased use of MRI technologies, the average age and average time taken for diagnosis of GH should continue to fall. Pushing back diagnosis to the earliest stages could mean that no patient with GH has to experience the related diabetes, liver disease and cardiomyopathy we have seen in the past. And, fewer will experience the chronic conditions associated with delayed intervention (see chart above).

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