Clinical Update

Genetic Haemochromatosis: A Clinical Update

Authors:

Martin JOHNSON
PhD, MSc, RN, RNT
Emeritus Professor in Nursing
University of Salford

GERRI MORTIMORE
PhD; MSc Advanced Practice; PgCert (IPPE); Ba(Hons) Health Studies; iLM.
RGN; NMP; FHEA

Lecturer in Advanced Practice
University of Derby

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Contact:
Martin Johnson, martinjohnson1953@gmail.com
Twitter: @martinjohnson33

University of Salford
School of Health and Society
Mary Seacole Building
Frederick Road
Salford M5 4WT

Genetic Haemochromatosis: Diagnosis and Treatment of an Iron Overload Disorder

Summary

Genetic haemochromatosis is a potentially lethal iron overload disorder which is more common than most health professionals and the public realise. In the UK 1 in 8 people are carriers and up to 1 in 150 have the condition, often undiagnosed. Serious disease of the liver, heart and other systems can be prevented by early diagnosis and treatment in which nurses can play a big part. In the majority of patients effective management is straightforward and can lead to a normal lifespan and a minimisation of symptoms.

Keywords

Iron overload
Genetic (hereditary) haemochromatosis
Evolution
Venesection
Liver Cancer

Learning Outcomes

- Explain the probable evolution of genetic haemochromatosis
- List the common symptoms?
- Describe how haemochromatosis is managed

Ten times the risk of liver cancer.

Genetic (hereditary) haemochromatosis (GH, sometimes called HH) is a potentially fatal metabolic disorder caused by an excessive retention of iron by people with a particular genetic mutation (1). An article published in Nursing Standard by Sheahan and O'Connell in 2009 (2) highlighted key aspects of this condition. Our

paper aims to update this further. There are five types of GH and the most common (Type 1 or HFE Haemochromatosis) which leads to iron overload is a mutation of the HFE gene at C282Y. About 1 in 8 people are carriers of the mutation and 1 in 150 have two mutations meaning that they are at risk of developing iron overload (3). According to www.nurses.co.uk there are over 650,000 nurses registered in the UK which means that over 4,300 British nurses may have the genetic mutations which predispose the condition and most of them will not yet know! Indeed, awareness of the condition is not as universal as it could be among the public nor, importantly, among health professionals. Its importance has been brought into focus by recent research showing that men who have this disorder may be ten times more likely to develop and potentially die of liver cancer by the age of 75 (4). The research draws on a database of high quality data produced by the UK Biobank Study, which uses medical and genetic data from half a million volunteer participants to improve understanding of the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses (5). The same team has previously reported that people having the double faulty gene quadruples the risk of liver disease and doubles the risk of arthritis and frailty in older age groups compared to the population at large.

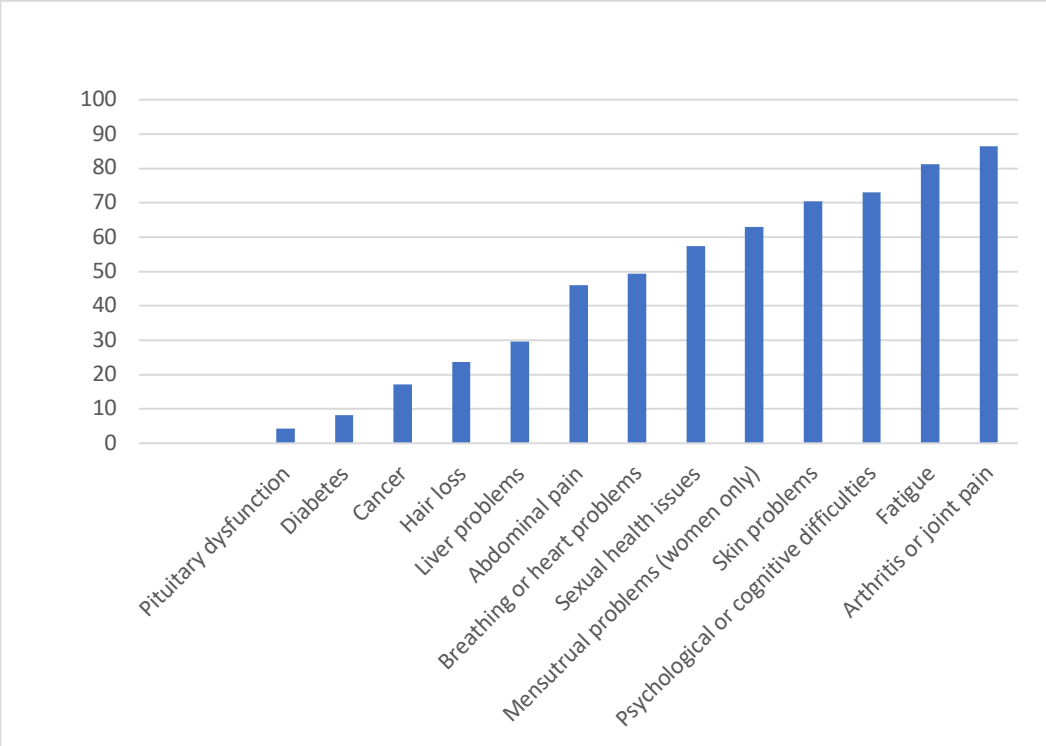
The other four types are all very much more rare but should be investigated for in people with iron overload not explained by repeated blood transfusions, excessive intake of iron (such as in tonics and multivitamin preparations) or the gene mutations present in type 1. Unlike Type 1, Type 2 or juvenile haemochromatosis is caused by mutations in the different HFE 2 gene and usually presents under the age of 30 with symptoms like abdominal pain and cramps. These mutations are not so restricted to European populations and so could easily be missed in patients with Asian heritage, for example (3). Also very rare and caused by mutation of the TFR2 gene, Type 3 haemochromatosis is intermediate in its age of onset and severity between types 1 and 2. Type 4 haemochromatosis is also called ‘ferroportin disease’. Its management can be more complex as the gene mutations affect SLC40A1. The condition is inherited in an autosomal dominant mode, so 50% of children of an affected parent will also have the condition, and being 100% penetrant it means that those affected will certainly need careful management (3). These mutations can of course co-exist with the more common Type 1 genetic haemochromatosis this being

called ‘digenic’. Type 5 haemochromatosis is caused by changes to the heavy ferritin chain 1 (FTH1) gene. This disease is so rare it has only been discovered in one family in Japan (6).

What patients experience

A large survey of patient experience (7) revealed that people with GH endure a wide range of symptoms and since many of these can be attributed to other causes such as anaemia or depression, for example, being diagnosed with haemochromatosis can be a rather hit and miss affair. As can be seen from Table 1, a wide range of medical issues are reported by patients, and some research is now being done to tease out which of those are indeed likely to be caused by iron overload, by other related genetic interactions, and which could just be age-related or coincidental comorbidities.

Table 1. Percentage of respondents that had ever experienced symptoms (n = 1,689). Patients could report multiple symptoms (after Smith et al 2018, P 21)



The problems most commonly reported by patients in the survey were arthritis and joint pain, fatigue, psychological or cognitive difficulties, skin problems and sexual health issues, mainly loss of libido. Arthritis was found typically to affect knuckles, hips, hands and wrists, with ‘cognitive difficulties’ amounting to ‘brain fog’, forgetfulness or depression.

These problems contrast somewhat with the life-threatening illness which can be found in newly diagnosed patients whose body iron levels have reached high levels with iron deposits in important organs. In undiagnosed patients iron overload can cause serious damage to the heart resulting in cardiac failure, the liver causing cirrhosis and cancer, the pancreas leading to diabetes mellitus and the pituitary gland leading to pan-hypopituitarism (widespread failure of the endocrine system). Indeed, the term ‘haemochromatosis’ is derived from the dark grey-brown skin experienced by patients in very serious iron overload whose endocrine system is failing and resulting in adrenal cortical insufficiency (Addison’s Disease) (1, 7, 8).

Family genetics

The genetic haemochromatosis mutation affects women and men equally as it is inherited as an autosomal recessive condition. This means that for the condition to be present in an individual two copies of the mutated gene need to be inherited, one from each of biological parent. If only one copy is present the person may be a ‘carrier’ but is unlikely to develop iron overload (see Figure 1). Women are said to be protected to some extent from iron overload by menstruation and pregnancy at which points iron is lost from the body naturally. This means that generally women are more likely to develop symptoms of the condition later in life. It must be said that not everyone whose HFE gene test is positive for the most common and potentially harmful mutations (2 x C282Y mutations) develops iron overload. If 1000 people were diagnosed with the same two variant genes, they would all store iron at different rates. This is termed penetrance and other factors are at play; environmental, genetic and modifiable factors such as alcohol consumption.

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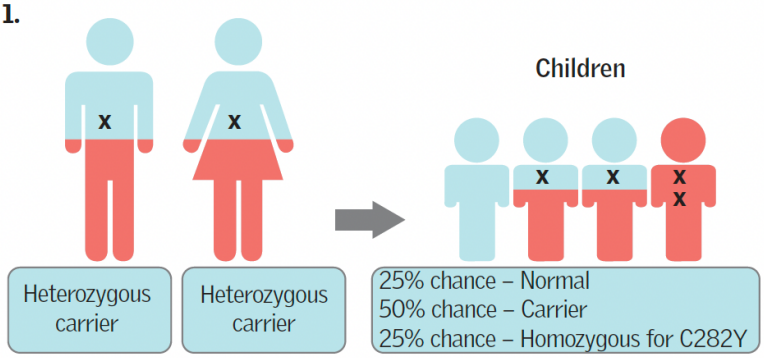
From Sheahan and O'Connell (2009) Page 51: Inheritance of Haemochromatosis

FIGURE 1

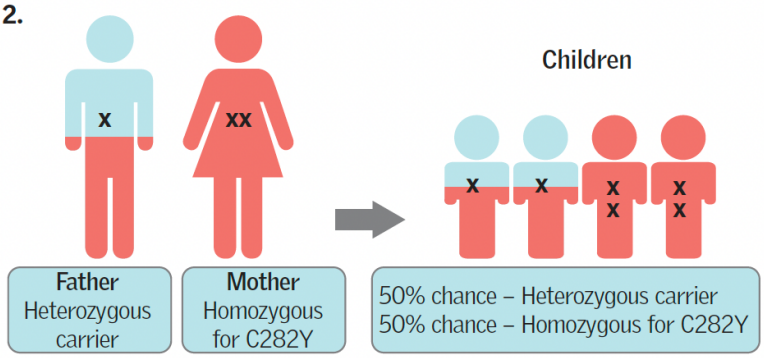
Inheritance of haemochromatosis

1.



Where both parents are carriers, on average one quarter of their children will be normal, a further quarter will develop haemochromatosis and approximately 50% will be carriers.

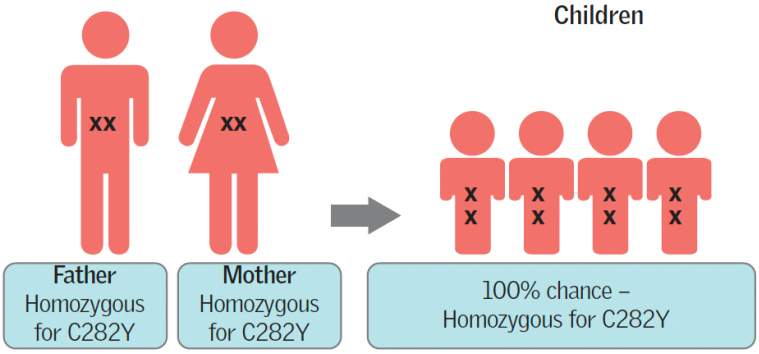
2.



In the case of the father being a carrier and the mother having heredietary haemochromatosis, approximately 50% of children will be carriers and 50% will develop haemochromatosis.

Examples 1 and 2, give percentages that are averages for the whole population. For example, where both patients are carriers, it is possible that all children are carriers, all are normal or all have haemochromatosis.

3.



Where both parents have haemochromatosis, all children will inherit two defective genes and all will have heredietary haemochromatosis.

(Irish Haemochromatosis Association 2008)

The Celts and the Vikings

How did the condition come about? The strongest arguments seem to suggest that the HFE C282Y mutation occurred in mainland (Central) Europe possibly before 4000 BC but other estimates suggest later than this (9). In 1980, Simon et al proposed that the mutation originated in a Central European Celtic population and spread across Europe by population movement (10). Eventually, first Roman and later Anglo-Saxon invasions caused Celtic peoples to migrate and be partly confined to the Western fringes of Europe in Ireland, Wales, Scotland, Northern Spain and Brittany leading to high frequencies of the mutation in this population.

However, the fact that there are also quite high frequencies of C282Y in some parts of Scandinavia causes Olsson and Ritter (11) and Milman and Sorenson (12) to suggest that Viking conquests may have had a role in the spread of the gene. Whether they already had it or took it back with them after raiding the West of the British Isles remains a little uncertain and it could be both. The Vikings were known both to settle in the lands they visited but also to take some of the population back to their homelands. One of the authors of this article (MJ) has a diagnosis of GH and is aware of Irish heritage on the maternal side of the family. However, as a variant gene is required from both sets of parents this suggests that on the paternal side their origins were also either Celtic or Nordic. Charles Darwin did not know about haemochromatosis but his evolutionary theory tends to support a view that long-lasting mutations such as C282Y may have some survival value for the species (13). It is therefore probable that the mutation protected these early peoples from iron deficiency whilst they depended on a largely vegetarian and cereal-based diet which in some areas lacked iron. In Europe iron-rich diets are now plentiful and often supplemented by iron in flour, breakfast foods, and with many people taking fashionable supplements which often contain iron. This means that iron overload is a much greater risk for those with the double mutation.

Diagnosis

A high serum ferritin (normal for females 15-200 micrograms per litre, 15-300 for males) is often the first indication that a person with vague but troubling symptoms should be investigated further. Levels above 1000 are regarded as potentially dangerous, and some patients have levels of several thousand which require urgent

treatment. Ferritin is a protein which is a crude but useful indicator of a person's total body iron stores. It is crude because it can be substantially raised for reasons other than iron overload such as chronic inflammation or infection. If raised it should be repeated along with other iron markers, notably the transferrin saturation. This is a measure of the amount of iron that can be transported in the serum. A saturation above 50% in men and 40% in women means that a large amount of iron is available for transport and that treatment may be required. Depending on the progression of the condition, for example if the serum ferritin and transferrin saturation have possibly been high for years, then further assessment may be required such as ultrasound scans of liver and heart, and other tests of iron retention in the liver. The relatively invasive procedure of liver biopsy is now only rarely used where liver damage is especially severe.

Iron overload has several potential causes other than genetics. For example, some people ingest excessive iron from 'health' products, or iron tonics and multivitamin preparations. Indeed, because a key symptom of iron overload is fatigue not unlike that experienced in iron deficiency anaemia, some people self-prescribe large amounts of iron making their situation worse. However, genetic haemochromatosis can be confirmed by an HFE Gene test which any UK general physician or advanced nurse practitioner should be able to order. The gene test may take several weeks to return but will be clear about the HFE genetic status of the patient. Most commonly a 'positive' result is 'homozygous' C282Y, which means one mutated gene of this type was inherited from each parent. Other gene mutations exist, such as H63D which is more common in some people of South European heritage. If a person has two copies of this, or one of each (heterozygous) the potential for serious iron overload is generally less, but some people do still experience problems (7).

It is important to note that a number of other rare genetic iron overload disorders exist, some of which affect younger people, and so there may need to be a wider range of genetic tests and follow up in these much rarer cases.

Being found to have a 'genetic disease' can be troubling for many people. The science of genetics is relatively new and the gene sequence mutations causing the condition were only discovered in 1996. On the other hand, early diagnosis,

treatment and maintenance can mean that a normal lifespan is to be expected (3). A recent paper in Gastrointestinal Nursing gives more detail on the biochemistry and nursing aspects (8).

Prevention and Screening

Ideally, since the gene mutations are present from birth but the risks of overload increase with later maturity it might seem logical to 'screen' individuals in some way by means of the genetic test before they reach later adulthood, perhaps around age 30. However, despite the potential risks to those who do progress to serious iron overload the UK Department of Health is reluctant to do this. It is argued that uncertainties as to the true likelihood of people screened genetically developing the iron overload disorder (14) might cause concern in the otherwise 'healthy' and their families. In 2020 a review was undertaken to see whether routine screening should be undertaken by blood tests, either for indicators such as the serum ferritin, or the HFE genetic test. The committee (15) found no strong evidence to support routine screening despite stating the following:

- "The chances of having the faulty gene are higher in people with raised levels of iron in their body than those with normal levels of iron
- Some people with hereditary haemochromatosis will have other health problems like extreme tiredness, liver cancer, and pneumonia. But most people will not" (Page 5)

The committee seem reluctant to accept that screening of some sort would reduce considerable ill health and a 10-times risk of liver cancer in men caused by the preventable condition of iron overload (4). Currently it is suggested that 'iron panel' (serum transferrin and transferrin saturation) tests ought to be sufficient if used when apparently clinically indicated by symptoms. However, many health professionals are not sufficiently aware of the condition and its potential for serious disease. We believe that adults aged over 30 and who could possibly have Celtic or Nordic heritage, which does not exclude people of colour since many also have European heritage, ought to have an iron panel test every three years as part of routine health screening, along with cholesterol, HbA1c (diabetes) and such other measures as may seem sensible.

Treatment

The first line treatment for iron overload is venesection, that is giving blood by means similar to routine altruistic blood donation, but in the early phase rather more frequently. Where iron overload is severe, venesections may be ordered on up to a weekly basis for many months with occasional breaks for holidays. Typically, the procedure removes 450 mls which, when performed in hospitals and clinics is discarded as clinical waste. Departments providing therapeutic venesection may have their own hospital approved venesection procedure, but brief best practice guidance is available from Haemochromatosis UK (16) by post or from the society's website https://www.haemochromatosis.org.uk/a-guide-for-nurses-healthcare-practitioners

Venesection is a routine procedure, but it needs to be undertaken with care and patients need to have eaten and be well hydrated before and after the procedure to reduce the risk of fainting. Regular patients become adept at managing their illness, but the newly diagnosed may find both the diagnosis and the procedure rather stressful. Award-winning evidence based guidance led by Francis and Mortimore contains resources on wider aspects of venesection (17) also available from the RCN or HUK
https://www.haemochromatosis.org.uk/Handlers/Download.ashx?IDMF=5b67c25e-e0eb-49a5-810b-6b37e14b7961

Once patients reach safer levels and are in sight of 'maintenance', provided they meet National Health Service Blood and Transplant criteria, many patients can give blood at blood donation centres. The centres are efficient, used to doing the procedure to a high standard, and the blood can of course usually be used for patients in need. Indeed, the service was extended with wider criteria during the Covid-19 lockdowns to free up NHS hospital clinics and staff for other priorities. However, routine follow-up by a consultant in the hospital or clinic setting is often also necessary to assess for the more dangerous conditions which can unfortunately arise from high iron overload levels. This may necessitate ultra-sound screening of liver and heart and regular blood tests. These sequelae include diabetes, cirrhosis of the liver and cardiomyopathy.

Because iron is absorbed more effectively in the presence of normal or heightened gastric acidity proton pump inhibitors (PPIs) like Omeprazole which reduce this acidity may inhibit iron absorption and so reduce the need for venesection. A small randomised controlled study of 30 people over 12 months (15 on the PPI pantoprazole and 15 on placebo) showed a reduced need for venesection in the PPI group by about half (18). The British Society for Haematology suggest that for people who do not tolerate venesection well this approach may offer some benefit but that venesection remains the mainstay of treatment (1).

In rare exceptions, patients who for good reasons cannot tolerate venesection may be offered chelation, which is the use of desferrioxamine and similar preparations which bind iron and lead to its excretion (7). It is expensive, can cause a lot of side-effects, sometimes not tolerated and compares unfavourably with venesection in most respects.

Diet

On first learning of the diagnosis it is natural to assume that a disorder of iron metabolism might be able to be controlled by diet and books are available based on that idea (19). However, unless the diet is unusually high in red meat which contains easily absorbed 'haem' iron such as steak, liver or black puddings, there is little need to modify the diet substantially. Vegetables contain iron in the form of non-haem iron, which is not readily absorbed so despite their reputation for iron content popularised by Popeye, such as spinach, they need not be avoided. We do know, however, that iron is more easily absorbed in the presence of high doses of vitamin C or alcohol. Provided these are moderated rather than taken to excess and avoided when eating iron rich foods patients ought to be able to eat a balanced diet and have their iron levels controlled by venesection. It is worth noting however that many foods, such as many popular breakfast cereals (Weetabix and Corn Flakes for example) have added iron which, if taken daily could slow progress of treatment or raise iron levels in maintenance. It is important for new patients to orientate to reading food and drink labels to look for added content like this. Sometimes products which may mimic popular brands may actually contain less or no added iron. Beverages containing anti-oxidants such as tea are said to slow iron absorption so are good with meals which might contain it (3). Many sufferers avoid shellfish such

as clams, scallops and oysters as there was thought to be risk of a serious gram negative infection of *vibrio vulnificus* presenting either as serious diarrhoea and vomiting or as a wound infection with septicaemia (20). In the laboratory iron seems to enhance the growth of this organism, and certainly it is a leading cause of death from shellfish when insufficiently cooked, but its association with iron overload remains disputed by clinicians.

Patient support

For historical reasons, patients are managed by more than one type of medical consultant. Some come to the attention of gastroenterologists or hepatologists because of the risk to the liver, and some are treated by haematologists. In the UK, many patients are treated in day units or have venesection in departments more oriented toward cancer chemotherapy. This can be quite alarming for the patient and reassurance from the nursing staff is required. Once patients' ferritin levels are brought down to normal levels (usually below 50mcgs) and provided they have minimal other health issues it ought to make sense in the future to enable patients to be venesected in more local facilities like the larger health centres. However, the NHS is some way from achieving this at present. Once patients are in maintenance many meet the criteria to have their venesections at Blood and Transplant Centres which are efficient and sensibly provide a litre of pre-procedure fluid and then a much-needed cup of tea or coffee and biscuits.

Haemochromatosis UK (HUK) an active charity with modest resources supports patients and provides up to date information through diagnosis, treatment and later management. It provides a telephone and email helpline, runs a Facebook patient support group and raises funds and lobbies government. It provides a members' service for a fee which includes subsidised genetic testing and other advisory functions. https://www.haemochromatosis.org.uk/

This group may not meet everyone's needs and other Facebook Groups are also currently available to both UK and the wider World community of people facing diagnosis and treatment.

Conclusion

In this article we have examined iron overload and how genetic haemochromatosis, its most common cause in the UK, is a very common double genetic mutation possessed by 1 in 150 people. Undiagnosed the condition can be fatal due to liver, heart or endocrine failure, but even when less serious results in substantial ill health and symptoms for many people. Nurses can have a significant role in helping to spot the condition, especially in GP surgeries and hospital clinics where, sadly, even surgeons, physicians and general practitioners are not as aware as they might be. A raised serum ferritin a common blood test, especially if it is flying really high (such as 1000 mcg per litre) can be a first sign that something is amiss, and iron overload should be excluded.

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