Haemochromatosis Diagnosis and Management

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<thead>
<tr>
<th>CATEGORY:</th>
<th>Clinical Guidelines</th>
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<tr>
<td>CLASSIFICATION:</td>
<td>Clinical</td>
</tr>
<tr>
<td>Controlled Document Number:</td>
<td>CG098</td>
</tr>
<tr>
<td>Version Number:</td>
<td>Version 2</td>
</tr>
<tr>
<td>Controlled Document Sponsor:</td>
<td>Clinical Guidelines Group</td>
</tr>
<tr>
<td>Controlled Document Lead (Author):</td>
<td>Dennis Freshwater, Consultant Hepatologist</td>
</tr>
<tr>
<td>Approved By:</td>
<td>Clinical Guidelines Group</td>
</tr>
<tr>
<td>On:</td>
<td>January 2018</td>
</tr>
<tr>
<td>Review Date:</td>
<td>January 2021</td>
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# Haemochromatosis Diagnosis and Management

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**IMPORTANT NOTE:**

This document should be used to guide patient care and should only be used in the correct clinical context. Always confirm medication doses with the BNF and when uncertain discuss with the liver unit consultants.
INTRODUCTION

The purpose of this Guideline is to provide information and guidance to all clinical staff on the investigation and management of Haemochromatosis within the Trust. It is particularly aimed at general physicians.

DEFINITION

Haemochromatosis (HC) is the clinical condition of iron overload\(^1\).

Genetic haemochromatosis\(^1\) refers predominantly to iron accumulation in the body due to the inheritance of mutations in the HFE gene on both copies of chromosome 6. This leads to excessive absorption of iron from food. In the UK over 90% of patients with genetic haemochromatosis are homozygous for the C282Y mutation of the HFE gene and another 4% are compound heterozygotes (C282Y/H63D). This is the condition previously known as HLA-linked haemochromatosis. There are other rarer forms of inherited haemochromatosis where patients have ‘classical’ clinical features of haemochromatosis but lack mutations in the HFE gene (see transferrin receptor 2, ferroportin disease and juvenile haemochromatosis, below). In such families there may be no association with HLA haplotypes or other markers for chromosome 6.

Transferrin receptor 2 (TfR2)-associated haemochromatosis was the second form of haemochromatosis characterised at the genetic level. It is also called “type 3 haemochromatosis” and is similar to HFE-related disease in terms of abnormalities of iron parameters, clinical complications and type of liver iron storage but may present early in life.

Ferroportin Disease is due to mutations of SLC40A1 that encodes the iron exporter ferroportin, is inherited in a dominant fashion and is phenotypically heterogeneous. Two main forms have been defined: the more frequent is distinct from haemochromatosis in that patients show normal/reduced transferrin saturation and preferential iron accumulation in macrophages (these cases indeed represent the true “ferroportin disease”). A rarer form has clinical and pathological features of classic haemochromatosis.

Juvenile haemochromatosis\(^1\) is an inherited condition in which there is clinical onset in the second or third decade. Mutations in the hemojuvelin gene are responsible for the vast majority of juvenile hemochromatosis patients. A small number of patients have mutations in the hepcidin (HAMP) gene. African iron overload describes a syndrome originally thought to be related to the drinking of large quantities of beer brewed in iron containers, although a genetic influence has been detected.

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Secondary iron overload\(^1\) (secondary haemochromatosis, haemosiderosis) describes iron overload following chronic blood transfusion for haematological conditions, including thalassaemia major and aplastic anaemia. This also includes conditions in which enhanced iron absorption is secondary to ineffective erythopoiesis with marrow hyperplasia. Thalassaemia intermedia and inherited sideroblastic anaemias are examples. Neonatal haemochromatosis is a condition of acute liver damage with iron accumulation. This encompasses severe iron overload in neonates of undefined pathogenesis.

**PREVALENCE**

The prevalence of C282Y homozygosity in clinically recognized individuals with iron overload was assessed in a meta-analysis including 32 studies with a total of 2802 hemochromatosis patients of European ancestry\(^2\). This analysis of pooled data shows that 80.6% (2260 of 2802) of HC patients are homozygous for the C282Y polymorphism in the HFE gene. Compound heterozygosity for C282Y and H63D was found in 5.3% of patients. Hence, 19.4% of clinically characterized HC patients have the disease in the absence of C282Y homozygosity. Although compound heterozygosity (H63D/C282Y) appears to be disease associated, in such individuals with suspected iron overload, cofactors should be considered as a cause.

The prevalence of the C282Y allele in European countries is shown in Figure 1. As can be seen, C282Y homozygosity is more frequent in Northern than Southern Europe.

The prevalence of C282Y homozygosity among patients with porphyria cutanea tarda (PCT) was found to be increased significantly compared with control populations, ranging from 9% to 17% in several studies (See EASL Clinical Practice Guideline). The association between PCT and the common HFE gene polymorphisms C282Y and H63D was illustrated by a meta-analysis, where the odds ratios for PCT were 48 (24–95) in C282Y homozygotes, and 8.1 (3.9–17) in C282Y/H63D compound heterozygotes [126]. Thus screening with ferritin and transferrin saturation should be considered in all PCT patients.

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However, clinical penetrance appears to be somewhat variable. Olynyk et al\(^4\) conducted a population-based study of 3011 unrelated, white adults in Busselton, Australia and found that 0.5% were homozygous for HFE C282Y. The serum transferrin saturation was 55% or more in a fasting sample in 15 of these 16 subjects, but only half of these had clinical features of haemochromatosis, and in 25% serum ferritin levels remained normal over a 4-year period. The subjects homozygous for C282Y were from 26 to 70 years old at the start of the study. A recent meta-analysis concluded that 10 - 33% of C282Y homozygotes eventually would develop haemochromatosis-associated morbidity\(^5\). There is no information about the proportion of relatives who will show clinical manifestations of haemochromatosis.

\(^3\) European Association for the Study of the Liver. EASL Clinical Practice Guidelines for HFE Hemochromatosis. J Hepatol (2010).


SYMPTOMS AND SIGNS

Various symptoms and signs have been found in haemochromatosis patients\(^6\) as in the table below.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
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<tr>
<td>Weakness or fatigue</td>
<td>52-82</td>
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<tr>
<td>Pigmentation</td>
<td>47-72</td>
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<tr>
<td>Arthralgia</td>
<td>32-44</td>
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<tr>
<td>Impotence</td>
<td>36-40</td>
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<tr>
<td>Cirrhosis</td>
<td>27-57</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>14-48</td>
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<tr>
<td>Cardiac disease</td>
<td>10-12</td>
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DIAGNOSIS

The persistent presence of symptoms listed in the table above should lead to screening for genetic haemochromatosis. In addition, patients with abnormal liver function tests on repeat testing after a 6 week interval should be screened for genetic haemochromatosis, as should any patients who have a sibling with haemochromatosis.

To screen patients, measure transferrin saturation and measure ferritin. In normal subjects, ferritin concentrations of \(> 300\, \text{mcg/l}\) for men and post-menopausal women and \(> 150\, \text{mcg/l}\) for pre-menopausal women may indicate elevated iron stores\(^6\).

If transferrin saturation is less than 50% then the individual is unlikely to have genetic haemochromatosis. If transferrin saturation is greater than 50% repeat the measurement on a fasting sample.

A fasting transferrin saturation of greater than 55% (men and post-menopausal women) or 50% (pre-menopausal women) indicates iron accumulation\(^6\). Under this circumstance refer to a Consultant Hepatologist and request HFE gene test to confirm whether genetic haemochromatosis is present.

MANAGEMENT

All patients who are identified as C282Y homozygous on HFE gene testing should be referred to the Molecular Genetics Unit at Birmingham Women’s Hospital to perform screening of siblings and offspring. The Molecular Genetics Unit will then liaise with the patients to arrange the screening.

All patients who have confirmed haemochromatosis should be referred to a hepatologist for staging, venesection and monitoring. The most important prognostic factor at the time of diagnosis is the presence or absence of hepatic fibrosis or

cirrhosis, or diabetes mellitus. Patients without these conditions may be expected to have a normal life expectancy with phlebotomy therapy. Adequate phlebotomy treatment is the major determinant of survival, and it markedly improves prognosis. Early diagnosis and therapeutic phlebotomy to maintain low normal body stores is crucial and can prevent all known complications of haemochromatosis. If untreated, haemochromatosis may lead to death from cirrhosis, diabetes, malignant hepatoma, or cardiac disease. Thus, all patients with haemochromatosis should be referred to a Hepatologist for ongoing monitoring and treatment.

Patients with hereditary haemochromatosis and ferritin >300 mcg/l for men and post-menopausal women and > 150 mcg/l for pre-menopausal women
Refer to a consultant Hepatologist for consideration of fibroscan or liver biopsy and establishment of a venesection programme aiming for ferritin <100 mcg/l and transferrin saturation <50%. Such patients will also be followed up in a hepatology clinic to monitor liver tests and liver fibrosis.

Patients with hereditary haemochromatosis and ferritin < 300 mcg/l for men and post-menopausal women and < 150 mcg/l for pre-menopausal women
Are unlikely to have clinical iron overload and venesection will not be needed. However, the patient should be screened with transferrin saturation and serum ferritin every 12 months and referred to a Hepatologist if the ferritin rises above these figures.

Patients without evidence of hereditary haemochromatosis but evidence of raised transferrin saturation or raised ferritin
Consider referral to a Hepatologist to enable a search for other causes of elevated transferrin saturation or serum ferritin concentration, e.g. NAFLD, alcoholic liver disease, cirrhosis of other cause or myelodysplasia. If the diagnosis of HFE-haemochromatosis is not confirmed by finding a susceptible HFE genotype, it is advisable to demonstrate increased total body iron, before starting expensive and time-consuming search for mutations in other genes. Liver iron concentration (LIC) is considered a measure of total body iron and liver biopsy remains the gold standard for defining LIC. Therefore liver biopsy should be performed and secondary causes of raised ferritin excluded before embarking on any referrals for genetic analysis for non-HFE haemochromatosis.

Patients with C282Y/H63D compound heterozygosity
Studies have demonstrated that patients who are C282Y/H63D compound heterozygotes are at low risk of haemochromatosis-related morbidity in the absence of other factors. Thus, patients who are C282Y/H63D compound heterozygotes presenting with increased serum ferritin (>150 mcg/l in post-menopausal females, >300 mcg/l in males and pre-menopausal women), increased transferrin saturation (>45% in females, >50% in males) should first be investigated for other causes of hyperferritinaemia (NAFLD, alcoholic liver disease, cirrhosis of other cause or myelodysplasia). If no other cause for hyperferritinaemia is found, these patients should have an assessment of iron overload via liver biopsy, or MRI of liver if liver
biopsy is declined or not possible. If iron overload is confirmed, such patients should proceed to venesection.

**Venesection**
There is the facility for venesection within UHB for haemochromatosis patients who live within the local catchment area. This venesection clinic is run within Liver Outpatients and the point of contact is SN Carmel Maguire (Extension 15667). However, patients must be under the care of the Liver Unit and only that team will be able to arrange venesection. There is not sufficient capacity to be able to venesection patients who are not within our local area. Such patients should be referred to their local hospital for venesection.

Venesection of 1 unit of blood will usually be performed once a week, depending on the degree of iron overload. Treatment may need to be continued at this frequency for up to 2 years, occasionally longer. During the course of treatment, the serum ferritin and transferrin saturation levels are monitored, indicating the size of the remaining iron stores. Treatment should usually continue until the serum ferritin level reaches 20µg/l, and thereafter the patient will be monitored with maintenance venesection as needed, aiming for ferritin <100 mcg/l and transferrin saturation <50%.

**Chelation**
In patients with hemochromatosis and heart disease, anaemia, or poor venous access, treatment with iron chelation agents is only recommended if venesection is not possible.

Deferasirox (Exjade) is an oral iron chelator that should be taken as 20mg/kg once daily instead of phlebotomy in patients in whom these procedures are poorly tolerated. Deferasirox is very efficacious in liver iron removal, but has not been shown to be effective in the pancreas. However, this medication is not licenced for haemochromatosis, so should only be prescribed by a consultant hepatologist after discussion in a multi-disciplinary meeting. During treatment with deferasirox, kidney function should be monitored. Treatment will be required long-term.

**Proton Pump Inhibitors**
PPIs have been shown in a small study to reduce phlebotomy requirements and to reduce the absorption of non-heme iron⁷. However, large scale studies have not yet been performed. Whilst the evidence base is insufficient to suggest that all patients with haemochromatosis should be prescribed a PPI, the use of PPIs if otherwise indicated may be helpful for haemochromatosis patients.

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The Haemochromatosis Society www.haemochromatosis.org.uk
Haemochromatosis Algorithm

Measure Transferrin saturation and Ferritin

If Transferrin saturation > 50%
repeat with fasting sample.

If fasting Transferrin saturation >55% in men or 50% in women
perform HFE gene test

If C282Y homozygous (or
C282Y/H63D heterozygous) and
ferritin >300 mcg/l for men and post-
menopausal women and > 150
mcg/l for pre-menopausal women
refer to hepatology for investigation
and venesection

Patients without evidence of
hereditary haemochromatosis but
fasting Transferrin saturation >55%
should be referred to hepatology

If C282Y homozygous and ferritin
normal, screen with Ferritin and
Transferrin saturation annually