

Diagnosis and management of hereditary haemochromatosis

INTRODUCTION

Hereditary haemochromatosis is an autosomally recessive inherited genetic disorder associated with a defect in the iron regulating hormone hepcidin, causing increased intestinal absorption of iron and subsequent deposition in the liver, pancreas, heart, joints, skin, and gonads. Mutation in the human haemochromatosis protein (HFE) gene is the most common problem and was first described in 1996.¹ The majority of patients with HFE haemochromatosis express C282Y homozygosity, which accounts for 80%–85% of individuals with hereditary haemochromatosis. This mutation has a prevalence of 1 in 220–250 in the northern European population in which it is most commonly found.² The other commonly found mutation is H63D but this is not associated with iron overload unless with C282Y as the compound heterozygote, C282Y/H63D which accounts for approximately 5% of patients with hereditary haemochromatosis.² There are other mutations of non-HFE genes resulting in iron overload syndromes but these are rare.

A GP list of 2000 patients will have approximately four patients with hereditary haemochromatosis. Despite this, many GPs have never seen a case, although they are often best placed to make a diagnosis.³ The reasons for this are likely to be multifactorial and are discussed.

PRESENTATION

Although C282Y homozygosity is relatively common, many individuals remain asymptomatic throughout their lifetime, which is likely to contribute to underdiagnosis of the condition.² Phenotypic expression occurs in only 70% and women in particular have lower clinical penetrance, thought to be due to the protective effects of iron loss with menstruation and childbirth. When symptoms are present, they are often nonspecific and include lethargy, arthralgia, and vague abdominal complaints.^{2,4,5} GPs

should have a high index of suspicion and consider testing for hereditary haemochromatosis in patients presenting with these persistent, vague symptoms. Other presentations include arthropathy, chondrocalcinosis, heart failure, erectile dysfunction, and porphyria cutanea tarda.^{2,4} Abnormal liver function tests should result in testing for hereditary haemochromatosis and is the most common route of diagnosis in primary care.

The classical presentation of hereditary haemochromatosis is due to end organ damage including liver cirrhosis, diabetes, and skin pigmentation ('bronze diabetes'). This clinical manifestation is uncommon and occurs in less than 10% of cases.²

DIAGNOSIS

If hereditary haemochromatosis is suspected, serum ferritin and transferrin saturation levels should be requested. Ferritin levels are raised and transferrin saturation >45% in presence of the disease.^{2,4} However, a raised ferritin does not confirm the diagnosis of hereditary haemochromatosis and other causes of hyperferritinaemia should be excluded such as inflammatory conditions (infection, cancer), alcohol misuse, and metabolic syndrome. Transferrin saturation can also be raised in alcohol misuse.

The next step is to determine the HFE genotype in those patients with a suggestive clinical presentation and blood parameters, although in practice referral to a specialist, usually a gastroenterologist is indicated.

MANAGEMENT

All patients with C282Y homozygosity, even if asymptomatic, should be treated and have regular follow up by a gastroenterologist, as it is currently not possible to predict that patients will go on to express the full manifestations of the disease.^{2,4} Figure 1 shows an algorithm that can be used for the diagnosis and management of hereditary haemochromatosis.

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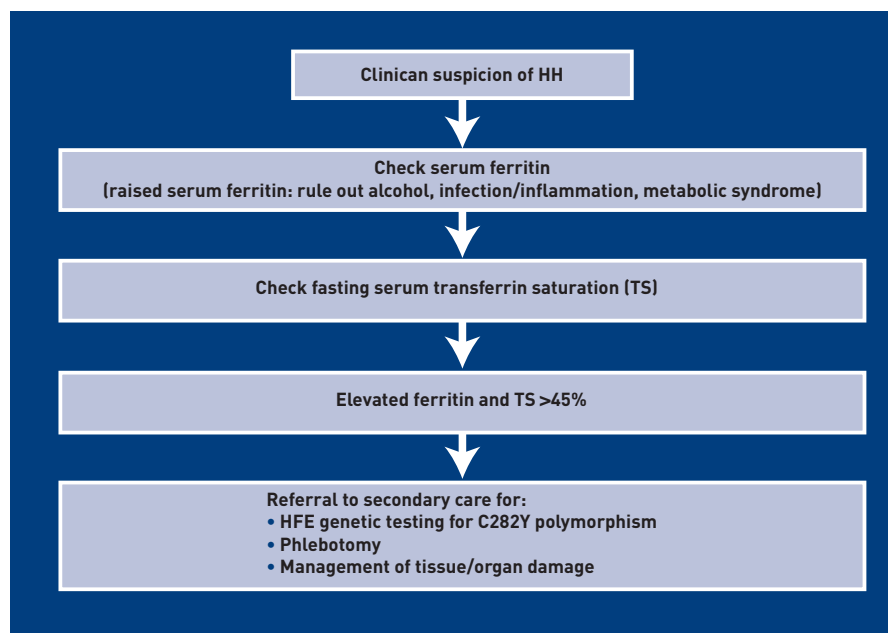
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Submitted: 12 June 2012; **final acceptance:** 26 September 2012.

©British Journal of General Practice 2013; 63: 331–332.

DOI: 10.3399/bjgp13X668410

Figure 1. Algorithm for the diagnosis and management of HFE hereditary haemochromatosis (HH).



The mainstay of treatment is phlebotomy, which may involve removal of one unit of blood once or twice per week aiming for a ferritin level of <50 ug/l. Once this is achieved, maintenance therapy should continue to keep ferritin levels between 50–100 ug/l.^{2,4} Evidence shows that initiating phlebotomy prior to the establishment of liver cirrhosis significantly reduces morbidity and mortality² and patients without cirrhosis can expect to have a normal life expectancy.

Patients who initially present with a ferritin level of >1000 ug/l have a greater risk of cirrhosis of the liver with a prevalence of 20%–45%.² Consideration should be given for these patients to undergo a liver biopsy, as patients with established cirrhosis have a relative risk for hepatocellular carcinoma of 20 and an annual incidence of 3%–4%.² These patients should therefore be enrolled in a hepatocellular carcinoma surveillance programme and also undergo surveillance for oesophageal varices. All patients with hereditary haemochromatosis are at an increased risk of osteoporosis and should have a dual energy X-ray absorptiometry scan.⁴

GENETIC TESTING OF FAMILY MEMBERS

Siblings of patients with HFE-haemochromatosis should be screened with serum ferritin and transferrin saturation and ideally these individuals should undergo HFE genotyping after appropriate counselling. A common question likely to be asked of a GP is whether or not children of an affected

individual, who may be under the age of consent, should be tested. As hereditary haemochromatosis exhibits autosomal recessive inheritance, HFE genotyping of the spouse is invaluable and can guide the need for testing of children in later life.⁴

RESOURCES FOR PATIENTS

Information and support is available for patients in the UK via The Haemochromatosis Society UK (www.haemochromatosis.org.uk) and through the British Liver Trust (<http://79.170.44.126/britishlivertrust.org.uk/home-2/liver-information/liver-conditions/haemochromatosis/>). NHS choices also provides an excellent interactive resource for patients (<http://www.nhs.uk/conditions/Haemochromatosis/Pages/Introduction.aspx>).

Provenance

Freely submitted; not externally peer reviewed.

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