The clinical management of hereditary haemochromatosis

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Received 13 June 2017
Revised 4 August 2017
Accepted 19 August 2017
Published Online First
23 September 2017

ABSTRACT

Hereditary haemochromatosis is an autosomal recessive disorder with variable penetrance. Most patients are C282Y homozygotes while heterozygotes or patients who are homozygous with other mutations are uncommonly affected. The true genotype to phenotype expression remains unclear. Treatment with phlebotomy is highly effective and cost-efficient while liver transplantation confers a curative option.

SPECIALITY CERTIFICATE EXAM-STYLE QUESTIONS

Hereditary haemochromatosis (HH) (OMIM # 235200) is one of the most common inherited genetic diseases with high prevalence in populations from Northern European descent.¹ In 1996, the principal HFE (HFE for High Iron Fe) gene defect was identified on chromosome 6, and is a G-to-A missense mutation leading to the substitution of tyrosine for cysteine at amino acid position 282 of the protein product (C282Y). The majority of patients with HH are homozygotes for the C282Y polymorphism (80%).^{2,3} There are two other identified mutations: the substitution of aspartate for histidine at amino acid position 63 (H63D) and the substitution of Serine for Cysteine at position 65 (S65C). Individuals predisposed may develop iron overload which can lead to life-threatening complications.

QUESTION 1

A 63-year-old male patient presents with arthralgia and loss of libido. On routine blood tests, he is found to have ferritin levels of 1020 µg/L. Further iron studies reveal an iron saturation percentage of 56%. Genetic screening shows that he is homozygous for C282Y mutation. What is the most appropriate next step?

1. Start chelating therapy with desferrioxamine
2. Request hepcidin levels before considering treatment

3. Arrange for urgent phlebotomy at the medical day unit
4. Arrange for a liver biopsy
5. Encourage the patient to start a diet heavy in oxalate and tannins. If the diet fails, start treatment with phlebotomy.

Correct answer 4

QUESTION 2

Phlebotomy remains the mainstay of treatment for patients with HFE-related hereditary haemochromatosis. How much iron is actually removed during each phlebotomy session?

1. 250 mg
2. 600 mg
3. 100 mg
4. 400 µg
5. 1 g

Correct answer 1

EPIDEMIOLOGY

In the general population, the allelic frequency of C282Y mutation was found to be 6.2% in a pooled cohort of 127 613 individuals included in a meta-analysis of 36 studies.^{3,4} The estimated homozygosity for the mutation was 0.38% (1:260).⁴ The carrier frequency for H63D was much higher (14%) with less geographic variation.⁴ The S65C mutation was identified in approximately 0.5% of the population.⁴

Among patients with confirmed HH, C282Y/C282Y homozygosity is the most common mutation with a reported prevalence of 80.6% in a meta-analysis including 2802 patients from 32 studies.^{1,3,4} Moreover, 5.3% of patients with confirmed HH, were heterozygous for the C282Y/H63D mutation.⁴ The frequency of H63D homozygosity has been reported to be in the range of 0%–1.5%.^{2,5–9} Heterozygosity to C282Y, H63D or S65C can explain the iron-overload status of the

To cite: Pericleous M, Kelly C. *Frontline Gastroenterology* 2018;**9**:110–114.

Table 1 Non-HFE conditions of abnormal iron metabolism which may lead to states of iron overload**Non-HFE causes of iron overload**

Genetic	Secondary iron overload
Juvenile haemochromatosis or type 2 hereditary haemochromatosis	Multiple blood transfusions, for example, haemoglobinopathies, myelodysplasia
Type 3 hereditary haemochromatosis (transferrin receptor 2 mutations)	Excessive iron replacement therapy
Type 4 hereditary haemochromatosis or ferroportin disease	Chronic liver disease
Hereditary hyperferritinaemia-cataract syndrome	Haemolysis
H-ferritin disorder	

remaining patients and so can other hereditary conditions associated with iron metabolism. These are listed in [table 1](#).

Men present earlier and are more symptomatic than female patients, possibly due to the lack of 'physiological protection' conferred by menstruation, the effect of oestrogens and other gender-specific genetic modifiers.¹ Allen *et al* analysed data from 31 192 Australian patients of northern European ancestry and found 29.2% of patients with phenotypic HH, out of which 28% were male.¹⁰ Similar findings were also reported by Aguilar-Martinez *et al* for C282Y/C282Y homozygous French patients.¹¹

The heterogeneous research methodology employed and the variable disease penetrance make elucidation of the genotype-to-phenotype association in HH rather challenging. Moreover, the definition used by various authors for confirming the diagnosis is varied and inconsistent. Beutler *et al* identified 152 C282Y/C282Y homozygous patients from a large US cohort of 41 000 individuals. Only one patient met the clinical criteria for a robust diagnosis HH (penetrance 0.67%).¹² A meta-analysis of 19 studies, reported a penetrance of C282Y/C282Y homozygous disease of 13.5%.⁴ C282Y/H63D compound heterozygotes have a much lower disease penetrance which has been estimated to be 0.5%–1.5%.^{6 13} These patients will only develop clinical disease when there is an additional compound insult to the liver.¹³

Pathophysiology and clinical presentation

The normal iron body content is approximately 3–4 g with the majority found in circulating haemoglobin and myoglobin (~3 g). Iron is stored in the liver, spleen and bone marrow in the form of ferritin and haemosiderin (~1 g). There are no physiological mechanisms to regulate iron loss; therefore, iron homeostasis depends on controlled duodenal absorption and iron recycling. Before iron can be absorbed by the enterocytes, it needs to be reduced from ferric (Fe²⁺) to ferrous (Fe³⁺) state by the enzyme ferric reductase. Iron within enterocytes can be stored as ferritin (lost as enterocytes are shed) or transferred through the basal lateral membrane via ferroportin (the iron export protein) to plasma. Iron is transported in the plasma bound to transferrin.

Iron is absorbed in the duodenum and is regulated according to body requirements. Hepcidin, a liver-derived peptide, has been reported as pivotal in iron homeostasis by coordinating duodenal iron absorption, mobilisation and storage.^{14 15} Hepcidin acts as a negative regulator of iron load by its interaction with ferroportin by altering the amount of available ferroportin channels. Hepcidin expression is regulated by total body iron, erythropoiesis, hypoxia and inflammation.^{14 15}

Even though we do not routinely measure hepcidin levels in clinical practice, other parameters are normally used to assess iron metabolism (iron studies). These include measurement of ferritin, serum iron, total iron-binding capacity (also known as transferrin) and transferrin saturation (TS) levels. TS is a ratio of $\frac{\text{Serum Iron}}{\text{TIBC}} \times 100$ expressed as a percentage. The higher the percentage, the more saturated the iron transporters are and this reflects the extent of iron overload in the body.^{14 15}

The pathophysiology of HH involves excessive iron absorption from the gut and intracellular iron accumulation, especially in the hepatocytes. Mechanisms involved in HFE-related haemochromatosis may include increase basal lateral transfer of iron from the enterocytes to plasma or increased absorption into enterocytes.

Liver disease, diabetes mellitus and skin pigmentation are the most common presenting features of the diseases. Patients may present with a plethora of symptoms such as arthritis and arthralgia and these are summarised in [table 2](#).

Diagnosis

HH is often considered in patients with hyperferritinaemia; however, other causes of high ferritin levels should be considered, such as infection and inflammation ([table 3](#)). The evaluation of patients with hyperferritinaemia should include formal iron studies and thorough clinical assessment. If TS >45% then HH should be suspected prompting HFE gene testing. For patients who are found to be homozygous for the C282Y mutation, ferritin levels should be used to guide further management. A liver biopsy may be required if ferritin levels are >1000 µg/L in order to

Table 2 Conditions and symptoms associated with hereditary haemochromatosis

Complication	Clinical manifestation	% of patients with complication
Diabetes mellitus	Polydipsia, polyuria, hyperglycaemia, weight loss	48% ²⁰
Liver function abnormalities	Abnormal liver function tests or symptoms of hepatic decompensation such as encephalopathy, ascites, gastrointestinal bleeding and infections	75% ²⁰
Arthropathy	Arthralgia and arthritis	44% ²⁰
Dilated cardiomyopathy	Dyspnoea, reduced exercise tolerance, coughing, haemoptysis, ascites, peripheral oedema, pulmonary oedema, valvular incompetency	31% ²⁰ (electrocardiographic abnormalities)
Hypopituitarism including hypogonadism	Anorexia, nausea, vomiting, polydipsia, polyuria, fatigue, lethargy, weight fluctuations, sensitivity to cold, hair loss, loss of libido, amenorrhoea, infertility	45% male impotence ²⁰ 26% loss of libido ²⁰
Hepatocellular carcinoma	Abdominal pain, weight loss, death	45% of all deaths in hereditary haemochromatosis ²⁰
Elevated levels of melanin	Skin hyperpigmentation if combined with high iron levels	70% ²⁰
Iron-driven susceptibility to infection	<i>Listeria monocytogenes</i> , <i>Yersinia enterocolitica</i> and <i>Vibrio vulnificus</i> ¹⁴	Percentage not available
Extrahepatic malignancy	Colorectal cancer ¹⁴ Female breast cancer ¹⁴	Percentage not available

stage the degree of liver disease. **Figure 1** summarises the diagnostic and management approach for patients with iron overload.

Family screening

Family screening should be offered to all first-degree relatives of a newly diagnosed patient (proband). This should include iron studies and genetic testing for HFE mutations (**figure 1**). In probands who have or wish to have children and wish to know the hereditary risk to the offsprings, screening of the unaffected spouse should be considered. Screened family members or partners should be reassured if they are found to be heterozygotes (C282Y, H63D, S65C) as the risk of becoming iron-overloaded is only minor and not clinically significant unless they sustain a compounded liver injury due to other insults, for example, alcohol and

viral hepatitis. Similar reassurance should be provided to patients who are found to be H63D homozygous, who may have minor identifiable abnormalities during biochemical testing of iron profile.

Treatment

Symptomatology and degree of iron overload will dictate the treatment strategy for patients with confirmed HH. Patients without iron overload or organ involvement do not normally require treatment and routine monitoring is recommended for these patients. Restricting dietary intake of iron is not normally required; however, it is important for patients to avoid taking any iron supplementation. Certain agents such as calcium, phosphate, oxalate and tannins have been found to reduce iron absorption but their consumption as a strategy to reduce iron overload is not routinely

Table 3 Other causes of hyperferritinaemia which need to be considered during the evaluation of the patient with suspected hereditary haemochromatosis

Name of condition	Examples	Comments
Inflammation	Diabetes mellitus Metabolic syndrome	TS is usually <45% CRP usually elevated
Infection	Urosepsis Pneumonia HIV	TS is usually <45% CRP and leucocytes elevated
Hepatic injury	Viral hepatitis Alcoholic hepatitis NASH/ASH Liver cirrhosis	Screen for viruses Take detailed clinical history Assess for risk factors and consider the need for histological assessment
Malignancy	Haematological cancers are much commoner than solid tumours	
Haemophagocytic lymphohistiocytosis	Ferritin usually elevated 'in the thousands'	
Macrophage activation syndrome	Ferritin usually elevated 'in the thousands'	

ASH, alcoholic steatohepatitis; HIV, human immunodeficiency virus; NASH; non-alcoholic steatohepatitis.

Figure 1 Diagnostic and management algorithm for patients with iron overload. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; LFT, liver function tests.

recommended. Supplementary vitamin C may be toxic for patients with iron overload as it can saturate transferrin and lead to accumulation of free radicals. Its pharmacological use is therefore not recommended for patients with HH.³

Therapeutic phlebotomy remains the mainstay of treatment for HH. Each phlebotomy session removes approximately 200–250 mg of iron through the removal of 400–500 mL of blood. Ferritin levels can be used to guide the frequency of phlebotomy and levels of less than 50–100 mg/L are regarded as therapeutic.^{3,4}

Erythrocytapheresis is another method of removing excess iron in symptomatic HH patients through the removal of red blood cells (RBCs) from patients' blood (apheresis) and the return of the erythropenic plasma to the body. The advantage of this method over traditional phlebotomy is that much larger amounts of RBC can be removed and processed during each session. In a phase III trial of phlebotomy versus erythrocytapheresis in 38 C282Y/C282Y homozygous HH patients, the two modalities were found to be equally cost-effective, although, patients undergoing erythrocytapheresis had a much lower mean number of sessions

required.¹⁶ However, the treatment remains expensive and the technique largely unavailable.

There is a group of patients who are unable to tolerate phlebotomy such as those patients with severe anaemia or with contraindications to the procedure, for example, poor intravenous access. These patients should be candidates for iron chelation therapy. Deferiprone and desferrioxamine have been in clinical practice for several years and confer good biochemical and clinical responses. Though available, these treatments are potentially toxic and costly. Deferasirox is a newer iron chelator which has been tried in phase 1 and 2 studies with mixed results. More studies with higher patient numbers are required to before the long-term clinical effectiveness of Deferasirox can be determined.

The prognosis of patients undergoing treatment who have not developed hepatic cirrhosis has been reported to be similar to the general population.^{17,18} In cirrhotic patients, the 1-year, 5-year and 20-year survival has been found to be 88%, 69% and 56%, respectively.¹⁹

Liver transplantation should be considered for all patients with end-stage liver disease due to HH. Transplantation for HH has comparable 1-year, 3–three and 5-year survival rates compared with other transplant indications. The transplantation trends have been unchanged over the last decade. Dual organ transplantation therapy such as liver/cardiac have also been considered for patients with HH and severe cardiomyopathy.

In summary, HH is an autosomal recessive disorder. Most patients are C282Y homozygotes while heterozygotes or patients who are homozygous with other mutations are uncommonly affected. The true genotype-to-phenotype expression remains unclear. Treatment with phlebotomy is highly effective and cost-efficient while liver transplantation confers a curative option. Patients with HH who develop cirrhosis appear to have a high preponderance of developing hepatocellular carcinoma and surveillance with ultrasonography and alpha fetoprotein levels are recommended.

Contributors MP: Involved in the conceptualisation of the work and designed the manuscript. He has carried out the literature review. He has drafted the work and revised it critically for important intellectual content. He has provided final approval of the version to be published and hereby agrees to be accountable for the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CK:MP: Involved in the conceptualisation of the work and designed the manuscript. She has carried out the literature review. She has drafted the work and revised it critically for important intellectual content. She has provided final approval of the version to be published and hereby agrees to be accountable for the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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