University Hospitals of Derby and Burton NHS Foundation Trust

Haemochromatosis – Full clinical guideline

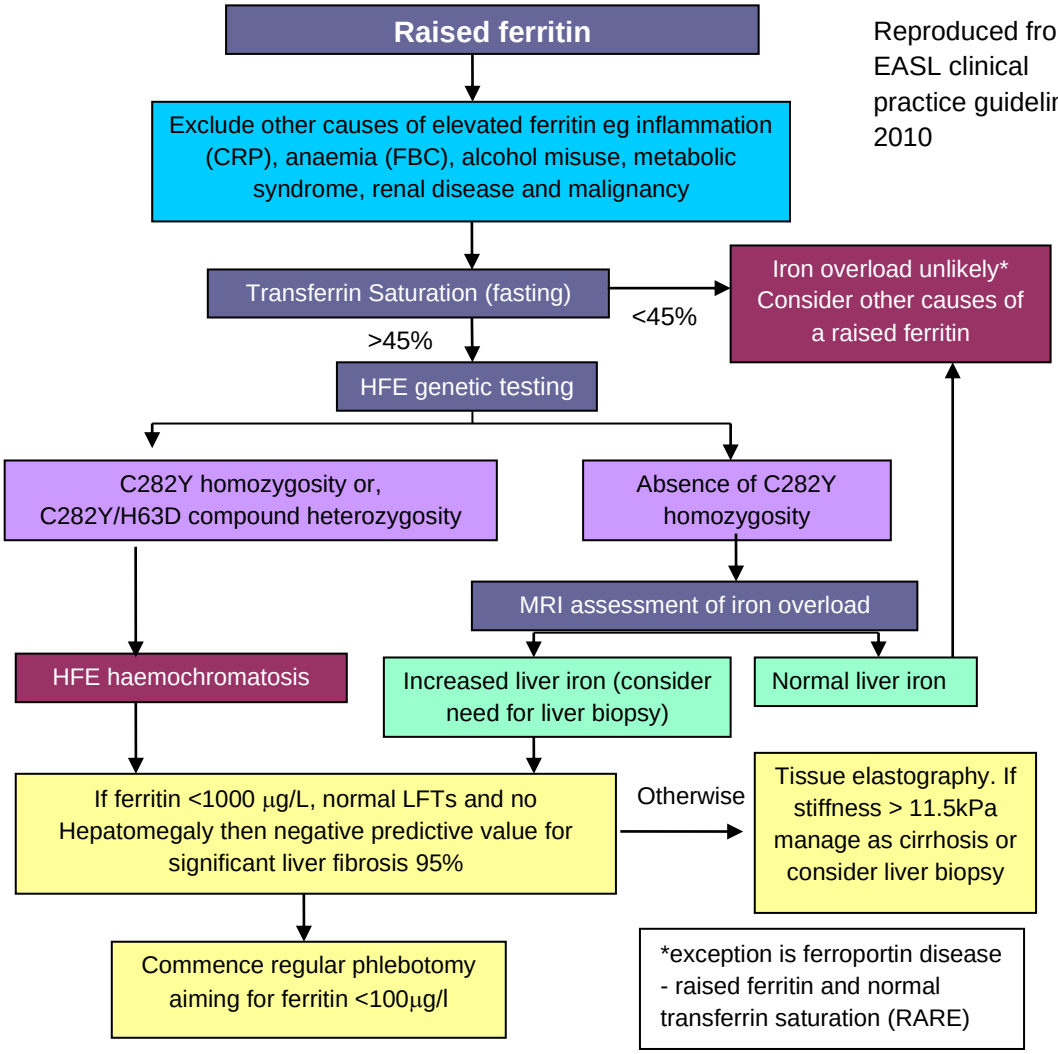
Reference no:CG-HEP/1144/23

Iron overload is associated with a variety of genetic and acquired conditions. HFE haemochromatosis is the most frequent and remains the most commonly identified genetic disorder in Caucasians. Patients may be referred directly to the liver clinic with hyperferritinaemia, an abnormal HFE gene following family screening, or alternatively a raised ferritin may be noted on a NIL screen.

Patient with hyperferritinaemia (>400 µg/L in men/ post menopausal women, >150 µg/L in pre-menopausal women)

The likelihood of a patient > 30 years referred from primary care with a raised ferritin and transferrin saturation having HFE haemochromatosis (C282Y homozygote) is 20%

A normal ferritin excludes iron overload, but a raised ferritin has low specificity and in the majority of cases it will be elevated as a result of inflammatory, metabolic or neoplastic conditions.



Reproduced from EASL clinical practice guidelines 2010

Patient with abnormal HFE gene

C282Y homozygosity is seen in 1 in 260 Caucasians but disease penetrance is variable with end-organ manifestations only seen in 10-33%. Approximately 80% of haemochromatosis patients are C282Y homozygote and 5% C282Y/ H63D compound heterozygotes. H63D homozygosity is not a sufficient genetic cause of iron overload.

- **NORMAL** ferritin - discharge to GP, repeat ferritin annually and refer back when raised
- **ELEVATED** ferritin - Check LFTs and HbA1c
  - If indicated by symptoms: ECHO; testosterone, FSH/LH and sex hormone binding globulin; joint x-ray
  - Consider need for liver biopsy (see below)
  - Commence venesection

It is possible to request genetic testing for non-HFE mutations via the national Genomic laboratories. The R96.2 panel includes additional tests for SLC40A1 (Type 4 haemochromatosis- Ferroportin mutation), TFR2 (Type 3), HFE2 (Juvenile Type 2A), HAMP (Juvenile Type 2B) and ATP7B (Wilsons disease gene). Additional genetic testing should only be requested in patients with proven iron overload and once secondary causes (e.g metabolic syndrome, viral hepatitis, alcohol, inflammatory disorders, malignancy) have been excluded.

Need for biopsy

An elevated ferritin in a C282Y homozygote patient is sufficient for a diagnosis of haemochromatosis. The role of liver biopsy has, therefore, traditionally been in assessing liver fibrosis. The negative predictive value of a ferritin < 1000 µg/L and normal transaminases in the absence of hepatomegaly for the presence of severe fibrosis/ cirrhosis is 95%. All other patients require an assessment of liver fibrosis. There is no study comparing liver biopsy with tissue elastography in haemochromatosis, but it is still appropriate to first assess fibrosis using Fibroscan and reserving liver biopsy for those cases where the result is in grey zone (7.5-11.5 KPa) or does not correlate with clinical findings.

Alternative methods for assessing iron overload

- **MRI:** Useful in the investigation of hyperferritinaemia in the absence of abnormal LFTs or C282Y homozygosity, or alternatively where liver biopsy contraindicated. Mark requests for the attention of Dr Singh/ Thurley and specify for the estimation of hepatic iron
- **Venesection:** If a substantial amount of iron (5g for men, 3g for women - assuming 225 mg/iron per unit) can be removed by venesection without inducing iron deficiency anaemia then it is likely that iron overload was present.

Family screening

Siblings (25% chance of homozygosity) and children of patients with C282Y homozygosity should have serum ferritin and HFE genotype assessed. There is a standard letter which is sent to the patient to distribute to relevant family members - *please request this to be sent in your clinic letter dictation*. Where there are children younger than the age of consent, HFE genotype testing of the

unaffected spouse to assess the likelihood of genetic susceptibility can be recommended or testing can wait until the child reaches the age of consent. If C282Y homozygote but normal ferritin then annual monitoring of ferritin recommended and encourage to become blood donor.

Management (refer to EPU for venesection using admission form)

All changes in clinical condition or treatment plan will be recorded in eCasenote (CITO) by the venesection team by completing a Gastroenterology Continuation sheet which will include the reasons for referral back to the Consultant clinic

PLEASE NOTE: PATIENTS WITHOUT SEVERE FIBROSIS/ CIRRHOSIS DO NOT REQUIRE FOLLOW-UP IN THE LIVER CLINIC ONCE VENESECTION COMMENCED and should be given an RTT outcome in clinic – Discharged to GP.

- INDUCTION PHASE - Weekly venesection until ferritin <100 µg/L
- MAINTENANCE PHASE
    - Patients will routinely be booked for 3 monthly venesection
    - FBC/ferritin will be checked at every visit
    - Alterations to the interval between venesection will be based upon the last three readings, either increasing or decreasing the interval by 1 month to achieve a stable trajectory (range 50-100µg/L)
    - EPU team will refer patients back to liver clinic for Consultant review when:
        - Patients have a fall in ferritin and haemoglobin, or a fall in haemoglobin after a period of stability on regular venesection *(Require investigations for GI blood loss)*
        - Patients who have not had a venesection for one year due to stable ferritin levels under 100 *(Require decision whether to discharge back to GP)*
        - All patients over 75 years (*Require review by the consultant with a view to discontinuing venesection).*

- Young patients (age 17 -60) without significant co-morbidity, diagnosed prior to the onset of end-organ damage and entering the maintenance phase should be encouraged to become regular blood donors (haemachromatosis patients can donate every 6 weeks) but may still choose to continue venesection at Derby Hospitals. Monitoring of ferritin in blood donors should pass to the GP.

- Patients with severe fibrosis/ cirrhosis (compensated) require annual review in the stable cirrhosis clinic and HCC surveillance. Assuming a recent USS/AFP has been completed, it is the responsibility of the referring clinician to request the next 6/12 surveillance USS/AFP, book a DM clinic in order to review the results and request HEPSC definite 12/12 OPA at which appointment the Liver CNS will assume responsibility for on-going surveillance.

Further reading

AASLD guidelines, Hepatology, July 2011 AASLD guideline
EASL guidelines, J Hepatol, April 2010 EASL guidelines
British Society of Haematology (BSG endorsed) guidelines on diagnosis and therapy of haemochromatosis 2018

Documentation Controls (these go at the end of the document but before any appendices)

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<tr><td>Reference Number

CG-HEP/1144/23</td><td colspan="2">Version:

4</td><td>Status

Final</td><td>Final</td></tr>
<tr><td rowspan="3">Version / Amendment History</td><td>Version</td><td>Date</td><td>Author</td><td colspan="2">Reason</td></tr>
<tr><td>4</td><td>2022</td><td>Liver Management Group</td><td colspan="2">Previous version of guideline expired</td></tr>
<tr><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td colspan="5">Intended Recipients: All clinicians managing patients with liver disease</td></tr>
<tr><td colspan="5">Training and Dissemination: Forms part of liver handbook which is disseminated to all clinicians rotating through Hepatology</td></tr>
<tr><td colspan="5">Development of Guideline:
Job Title: Dr A Austin and A Lawson (Consultant Hepatologist)</td></tr>
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