**Hyperferritinaemia**

High Serum Ferritin results are a common finding in primary care. Because ferritin is an acute phase reactant this is usually due to inflammation, malignancy or liver disease. It can less commonly be associated with iron overload. This guide is designed to aid primary care physicians investigating hyperferritinaemia, the main causes of which are listed in Table 1 overleaf.

The ferritin range in the Central Manchester University Hospital laboratory are 30 - 400 μg/l for a male and 13 - 150 μg/l for a female. However Serum Ferritin levels can vary with age.

Hyperferritinaemia should not automatically generate a HFE gene mutation test or a referral to a Consultant Haematologist and general investigation should proceed as per the algorithm below. The patient should be questioned about alcohol intake and other risk factors for liver disease, transfusion history, family history of iron overload, and signs/symptoms of malignancy and inflammatory disorders.

**Algorithm for investigating hyperferritinaemia in patients without known secondary iron overload**

1. **Raised ferritin**
   - > 400 μg/L male
   - >200 μg/L female
   (Central Manchester Trust range)

2. **Check**
   - Repeat serum ferritin
   - Full Blood Count,
   - Liver Function Test,
   - Transferrin Saturation

3. **If FBC abnormal & Tsat raised (>50% male, 40% female)**
   - Consider iron loading anaemia
     (Table 1)

4. **ONLY if FBC is NORMAL & Tsat is RAISED (>50% male, 40% female)**
   - Proceed to HFE genotyping*

5. **If Tsat is NORMAL consider:**
   - Alcohol excess
   - Inflammatory disorders
   - Metabolic syndrome
   - Malignancy

6. **If YES then manage as per diagnosis**

7. **If NO is patient well with ferritin <1000 μg/L ?**
   - Consider repeat serum ferritin and Tsat in 3-6 months

8. **Consider assessment of liver iron stores (MRI or biopsy) & rare causes**
   (Consult with Specialist)

*Note: it is recommended to screen ADULT first degree relatives (siblings) of known C282Y HOMOZYGOTES ONLY for genetic haemochromatosis due to their increased risk for C282Y homozygosity. Screening should be performed by iron studies and ferritin, with genetic testing reserved for those with abnormal results. HFE testing can be performed in primary care and does not require referral to haematology or clinical genetics (see text).

HFE testing in children is inappropriate as this is an adult onset condition.
Considerations when investigating hyperferritinaemia

- Transferrin saturations do not need to be performed on fasting samples but this may be required if there is a borderline reading.
- In addition to the above algorithm and table 1 below, if investigating other causes, consider a viral hepatitis screen and abdominal ultrasound if liver function abnormal and blood glucose and lipid studies.
- If both Serum Ferritin and Transferrin Saturation are raised then HFE genotyping is indicated.
- HFE screening can be requested and performed in primary care and does not require a referral to the clinical genetics team, 7mls of blood in a EDTA is required and is sent to the local hospital laboratory who will then forward on. Please note that the mutations screened for are those common to the Caucasian population and are unlikely to be relevant to other ethnic groups, however the prevalence of haemochromatosis in the non-Caucasian population is very low.
- If the patient is found to be homozygous for the C282Y mutation or compound heterozygous for C282Y/H63D then referral (to the patient’s local hospital) for venesections is indicated. This should be in conjunction with managing other contributing risk factors such as alcohol consumption, fatty liver disease and metabolic syndrome. Carrier status for the HFE gene is 1 in 9 in the population and is not normally associated with health problems.
- If the Transferrin Satuations are normal and the Serum Ferritin is >1000µg/L, referral to a Hepatologist is required.
- If TS and ferritin high and HFE genotyping is negative or shows heterozygous states for the common haemachromatosis mutations, referral to a Hepatologist is advised for in depth quantification of liver iron. In patients with a severe iron overload phenotype, other rare forms of hereditary haemochromatosis cannot be excluded.

<table>
<thead>
<tr>
<th>Increased Ferritin synthesis due to iron accumulation</th>
<th>Increase in Ferritin synthesis not associated with significant iron accumulation</th>
<th>Increased Ferritin as a result of cellular damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary iron overload from blood transfusion or excessive iron intake/administration</td>
<td>Malignancies</td>
<td>Liver diseases including: Liver necrosis, Chronic viral hepatitis, Alcoholic and non-alcoholic steatohepatitis*</td>
</tr>
<tr>
<td>Hereditary (Genetic) Haemochromatosis</td>
<td>Malignant or reactive histiocytosis</td>
<td>Chronic alcohol consumption</td>
</tr>
<tr>
<td>Hereditary aceruloplasminaemia</td>
<td>Hereditary hyperferritinaemia with and without cataracts</td>
<td></td>
</tr>
<tr>
<td>Ineffective erythropoiesis: sideroblastic anaemia, some myelodysplasias (e.g. refractory anaemia with ring sideroblasts)</td>
<td>Gaucher’s disease</td>
<td></td>
</tr>
<tr>
<td>Thalassaemias</td>
<td>Acute and chronic infections</td>
<td></td>
</tr>
<tr>
<td>Atransferrinaemia</td>
<td>Chronic inflammatory disorders</td>
<td></td>
</tr>
<tr>
<td>FPN1 haemochromatosis</td>
<td>Autoimmune disorders</td>
<td></td>
</tr>
</tbody>
</table>

* May also have iron overloading