46) A 45 year old Caucasian man is referred because of abnormal liver function tests. He complains of the recent onset of lethargy. Examination reveals a 15cm smooth edged liver and some spider naevi.

Blood investigations show:

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count</td>
<td>7.5 x 10⁹/L</td>
<td>4.0 – 11.0</td>
</tr>
<tr>
<td>Normal differential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>124 g/L</td>
<td>120-160</td>
</tr>
<tr>
<td>Platelet count</td>
<td>120 x 10⁶</td>
<td>150 –400</td>
</tr>
<tr>
<td>Sodium</td>
<td>140 mmol/L</td>
<td>135-150</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.5 mmol/L</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td>Urea</td>
<td>6.5 mmol/L</td>
<td>3.6-9.3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.09 mmol/L</td>
<td>0.06 -0.12</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>28 microm/L</td>
<td>3-21</td>
</tr>
<tr>
<td>ALP</td>
<td>95 U/L</td>
<td>30-115</td>
</tr>
<tr>
<td>GGT</td>
<td>120 U/L</td>
<td>&lt;65</td>
</tr>
<tr>
<td>AST</td>
<td>135 U/L</td>
<td>5-40</td>
</tr>
<tr>
<td>ALT</td>
<td>148 U/L</td>
<td>5-40</td>
</tr>
<tr>
<td>Albumin</td>
<td>35 g/L</td>
<td>38-50</td>
</tr>
<tr>
<td>PT-INR</td>
<td>1.2</td>
<td>0.9 -1.1</td>
</tr>
<tr>
<td>Ferritin</td>
<td>2360 microg/L</td>
<td>20-235</td>
</tr>
<tr>
<td>Iron</td>
<td>240 micromol/L</td>
<td>50-150</td>
</tr>
<tr>
<td>Transferrin</td>
<td>200 g/L</td>
<td>250-370</td>
</tr>
</tbody>
</table>

The next most appropriate blood test in the investigation of this patient is:

A. Hepatitis serology
B. Autoimmune serology
C. Testing for the haemachromatosis gene (HFE)
D. Alpha-1-antitrypsin phenotyping
E. Haemolysis screen

Answer:

Young man with smooth hepatomegaly and:
- Evidence of liver dysfunction
  - Decreased hepatic synthetic function (↓ albumin and ↑ INR)
  - Spider naevi (secondary altered oestrogen metabolism)
- Hepatocellular pattern
  - AST and ALT elevated > 3x normal
  - Associated GGT elevation 2x normal
  - Normal ALP suggesting no biliary obstruction
- ↑ ferritin levels (even if it is an acute phase reactant, still ↑ if divided by 3)
  → suggests haemachromatosis

Haemachromatosis
- Autosomal recessive disorder of excessive Fe absorption
- Very common in Caucasian population
- Commonest mutations:
  - C282Y
  - H63D
  - S65C (rare)
Can be C282Y homozygote, C282Y heterozygote, H63D homozygote which rarely develops Fe overload, H63D heterozygote, compound heterozygote (eg C282Y/H63D)

- Heterozygotes may have ↑ Fe storage but do not develop disease – Fe may act as co-factor to worsen other liver diseases eg viral hepatitis, ETOH
- Clinical features develop after **20g accumulation** (normal person absorbs and loses 1mg daily, in haemachromatosis 2-4mg is absorbed)

**Pathophysiology:**
- **HFE mutations** lead to impaired binding of **transferrin-Fe complex** to **transferrin receptor** of intestinal **crypt cells** thus there is a false signal that Fe stores are ↓
- If body Fe stores are ↑, there would be ↑ transferrin-Fe complexes -> ↑ binding to crypt cells -> ↑ intracellular Fe -> ↓ regulate production of **DMT-1** (Fe transporter) -> ↓ absorption of dietary Fe
- Fe deposition in parenchymal cells then reticuloendothelial cells later in disease (the other way round in transfusional Fe overload)

**Clinical features:**
**Early dx and Rx can improve/ reverse end organ damage**

- **Liver disease (75%)**
  - Hepatomegaly, abnormal LFTS, fibrosis and cirrhosis with its complications
  - Potentiates liver failure from other causes eg viral hepatitis
- **Diabetes (50%)**
  - Progressive pancreatic deposition but selective for beta cells
- **Heart failure**
  - Dilated cardiomyopathy with characteristic low signal on MRI
  - Conduction defects and sick sinus
  - Controversial if accelerates atherosclerosis
- **Arthropathy (45%)**
  - Similar to pseudogout
- **Skin pigmentation (70%)**
- **Hypogonadism (45%)**
  - Fe deposition in pituitary but tends to affect gonadal axis more (↓ FSH/ LH/ testosterone/ oestrogen – but females < affected)
  - Primary testicular failure also occurs but less common
- **Hypothyroidism**
  - May be related to pituitary deposition
  - Often ↑ anti-thyroid Ab -? Thyroid deposition and damage
- **Cancer**
  - Mainly **hepatocellular cancer** and +/- extrahepatic cancers
- **Susceptibility to certain infections**
  - Fe loving organisms (siderophoric) eg Listeria, Yersinia enterocolita and vibrio vulnificus (uncooked seafood)
  - Fe laden macrophages also less effective
- **Weakness and lethargy (75%)**
- In heterozygotes
  - Some studies suggest ↑ risk of diabetes, colorectal cancer and haematological malignancies

**Diagnosis:**
Test: relatives of index case and symptomatic (eg liver disease, diabetes, heart failure)

- **Serum ferritin**
- **Fasting** Transferrin saturation (TS) > 45% (>90% sensitive)
- TS = (serum Fe/2) / (serum TF x 100)
- HFE gene testing (specific)
- Liver biopsy if older, ferritin > 1000 +/- abnormal LFTs or HFE testing non-diagnostic
  - Hepatic iron index (HII) = hepatic iron concentration (HIC)/ age
  - Usually HII > 1.9 and HIC > 80 microm/g

**Treatment:**
- Lifelong venesection (monthly till aim ferritin 20 then 3 monthly)
  - 1 unit of blood contains 250mg Fe (normal man has 1g Fe stores thus 4 venesections will render them anaemic)
  - Need to take off > 20 units in haemochromatosis
- Moderate red meat intake
- Avoid Fe supplements and Vitamin C (aids Fe absorption)
- Avoid hepatotoxics and moderate ETOH intake
- Similar treatment for other overload syndromes except transfusional Fe overload:
  - Chelation
    - Principle is that Fe has 6 binding sites to allow binding of chelating molecules (previously S/C infusions, now oral available)
    - Complications: siderophoric infections, ototoxicity, visual changes, hepatotoxicity

**Other iron overload syndromes:**
1) Massive Fe intake
2) Normal Fe intake but ↑ absorption
   - Hereditary haemachromatosis
   - Inelegant erythropoiesis (eg sideroblastic anaemia or porphyria cutanea tarda)
   - African iron overload (not HFE gene, ?ferriforlin protein)
   - Juvenile haemochromatosis (autosomal recessive, mostly in Italy)
3) Parenteral administration of Fe +/- transfusional Fe overload
   - Each unit of blood 250mg Fe (normal dietary intake 1mg daily)
   - Eg child with beta thalassaemia major