Interpretation of an elevated serum ferritin

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The interpretation of an elevated serum ferritin requires consideration of several separate disease categories. These come under the broad headings of:

- Iron overload
- Acute inflammatory conditions
- Liver disease
- Alcohol excess

Causes of iron overload

Primary

- Hereditary haemochromatosis
- Hereditary aceruloplasminemia (Wilson's disease)

Secondary

- Transfusion overload
- Excess dietary iron
- Porphyria cutanea tarda
- Ineffective erythropoiesis (Sideroblastic anaemia, Thalassemia)

Causes of high serum ferritin without iron overload

- Liver disease – non-alcoholic hepatitic steatosis (NASH)* or viral hepatitis (B/C?G)
- Alcohol excess*
- Chronic inflammatory conditions
  - Rheumatoid arthritis, inflammatory bowel disease
  - Bacterial infections
- Malignancy especially haematological
- Thyrotoxicosis
- Familial hyperferritinemia and cataract syndrome

* *Can have iron overload in certain settings*

The most sensitive method for predicting whether the elevated serum ferritin represents iron overload due to haemochromatosis is the transferrin saturation. A transferrin saturation of >60% in males and >50% in females has a sensitivity of >90% for iron overload.[1,2] If the transferrin saturation is elevated on more than one occasion then testing for the common mutations of the HFE gene is indicated in Caucasian patients.

Try to test patients when they are otherwise well and avoid screening tests for haemochromatosis if a patient is acutely unwell. If the patient is sick, the serum ferritin may be *misleadingly high* as it is an acute phase reactant. Conversely the serum transferrin saturation *falls* during acute illness and therefore may mask the presence of iron overload. If a high transferrin saturation is unexplained a fasting sample may be useful as iron saturation can be affected by a high iron meal.

Hereditary haemochromatosis

The most common cause of iron overload is mutation of the HFE gene, by the substitution of tyrosine for cysteine at amino acid 282. Homozygosity for the C282Y mutation is found in 85–90% of patients of Northern European origin who have typical hereditary haemochromatosis and results in absence of the HFE gene on the cell surface.

There is high prevalence of this mutation with 10–14% C282Y heterozygosity rates and 0.5% homozygosity amongst Caucasians. Homozygous patients have a 50–75% chance of developing iron overload. Heterozygotes are unlikely to develop the disease in the absence of other risk factors for iron overload but can transmit the gene mutation to their children. Fifteen to 20 per cent of the patient population is heterozygous for a different mutation resulting in the substitution of aspartate for histidine at amino acid 63 termed H63D. This mutation alters the binding affinity for the transferrin receptor and does not usually contribute to increased iron overload in the absence of the C282Y mutation. Patients heterozygous for both C282Y and H63D mutations are termed heterozygotes and can develop haemochromatosis.

Patients heterozygous for either C282Y or H63D mutations can develop iron overload in the setting of alcohol excess, non-alcoholic hepatic steatosis or porphyria cutanea tarda. Other mutations involving the transferrin 2 receptor and ferroportin are termed HFE 3 and HFE 4 respectively. Juvenile haemochromatosis (HFE2) is an autosomal recessive disorder also and involves mutation of chromosome 1q. Affected children have a profound defect in regulation of intestinal iron absorption, and develop symptomatic haemochromatosis in their early 20s.

Clinical manifestations of hereditary haemochromatosis can be grouped as early or late.

Early

- Asthenia
- Arthralgia
- Elevation of serum transaminses

Late

- Hepatomegaly
- Cirrhosis and hepatoma
- Diabetes
- Arthritis of the 2nd and 3rd MC P joints 'painful handshake'
- Cardiomyopathy
- Pigmentation
- Impotence

Patients with a diagnosis of hereditary haemochromatosis genotype must therefore have serum glucose and liver enzymes checked on a regular basis. If there is hepatomegaly, elevation of the liver enzymes or the serum ferritin is greater than 1 000 ug/L then a liver biopsy to exclude liver cirrhosis is indicated.[3] If cirrhosis is present the patient requires screening for hepatocellular carcinoma at regular intervals.

Liver biopsy

A liver biopsy should be considered if the patient has an unexplained high ferritin especially in the setting of high transferrin saturation. The pattern of iron distribution in HH is periportal and hepatocytic rather than predominantly in the Kuppfer cells. Liver biopsy provides the hepatic iron concentration – a semiquantitative evaluation of iron excess. A value greater than 1.9 is very suggestive of HH. Liver biopsy frequently detects associated lesions such as steatosis.

Management of haemochromatosis

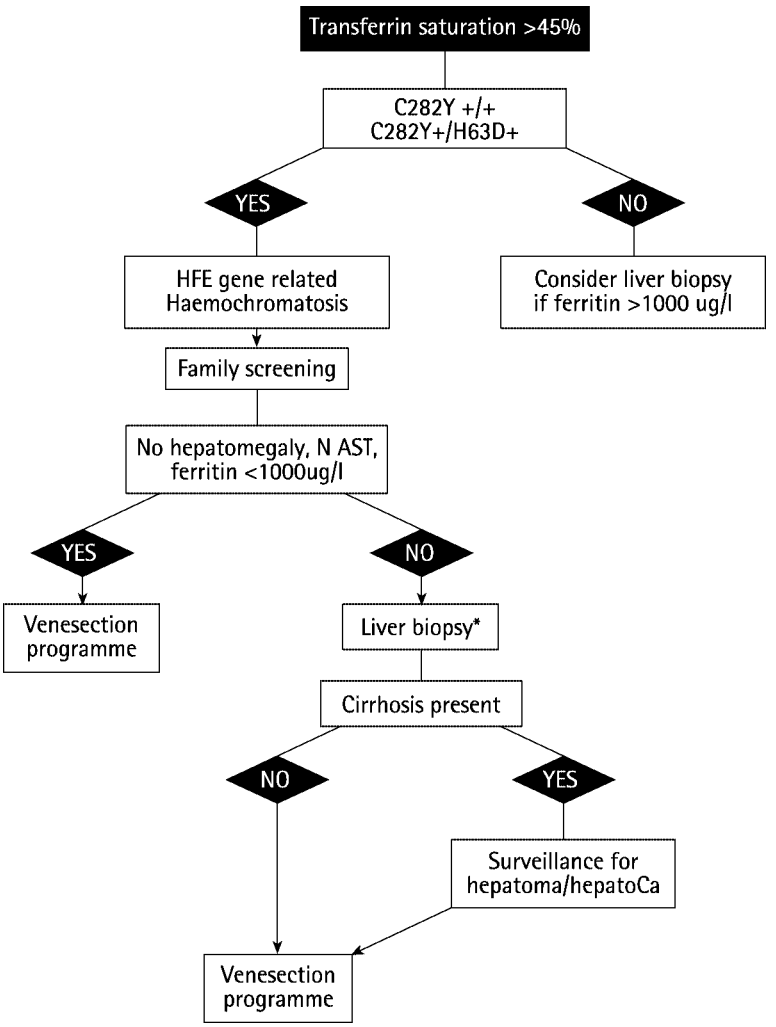
Venesection

Patients with elevated serum ferritin and HFE mutations C282Y +/+ or C282Y+/H63D+ should be referred for venesection. The goal of venesection is to reach and then maintain a serum ferritin at the lower end of the normal range, usually 50 ug/l. This is achieved by initiating 400–500 mL venesections on a weekly basis and continuing until the goal ferritin is reached. The frequency or volume of venesections are reduced if the patient does not maintain a normal haemoglobin or has difficulty tolerating the procedure. Once the patient has achieved the desired ferritin level then maintenance (3–6 monthly) venesections are scheduled.

Other than in the patient with juvenile haemochromatosis venesections are not recommended to commence before 18 years of age in view of the importance of iron in childhood and adolescence

Blood from haemochromatosis patients can be used by the New Zealand Blood Service for transfusion provided the patient fulfils all their usual criteria for safe blood donation. A study of patients with haemochromatosis undergoing venesection at a hospital clinic found 40% fulfilled criteria for blood donation.[4]

Figure 1. Guidelines for management of hereditary haemochromatosis[5]



Expectations of the venesection programme

Life expectancy returns to normal provided neither diabetes nor cirrhosis were present at the time of diagnosis. Specific symptoms respond variably.

Improvement likely: asthenia, skin pigmentation, liver enzymes

Improvement possible: diabetes, non-cirrhotic fibrosis, arthralgias

No improvement: cirrhosis is irreversible. Hepatocellular carcinoma can still develop in cirrhotic patients

despite iron overload reversal by venesection.

There is a national support group for haemochromatosis, IRONZ, which is supported by the Leukemia and Blood Foundation.

Family screening is indicated of C282Y positive proband.

Homozygous C282Y are at high risk of developing disease.

Heterozygotes will likely not develop the disease but can transmit to their children.

Due to the high prevalence of the mutation of the HFE gene, the probability of a heterozygote marrying another heterozygote is 10%.

Phenotypic screening should precede or accompany gene testing.

Dietary issues

Alcohol (>60 g/day) has been shown to exacerbate liver damage due to iron overload.

Avoid taking vitamin C when eating foods high in iron such as red meat. Tea with meals is felt to be beneficial as the phytates in tea bind iron.

Hereditary aceruloplasminemia

Hereditary aceruloplasminemia (Wilson's disease) is a rare disorder due to a mutation in chromosome 3 which causes marked hyperferritinemia as well as copper overload. Aceruloplasminemia mimics HH as it is familial and can cause hepatic iron overload and diabetes. It is, however, associated with neurologic abnormalities such as dementia, cerebellar ataxia which are not seen in HH. It can be distinguished from HH by a low serum transferrin saturation and an undetectable serum ceruloplasmin concentration.

Secondary iron overload

Iron overload secondary to multiple blood transfusions or haematological conditions such as sideroblastic anaemia are usually self-evident and do not present a diagnostic problem. Management is more difficult as venesection is not appropriate. Desferroxamine is given as a subcutaneous infusion 8–12 hours/day to remove excess iron particularly in transfusion dependent thalassemic patients.

Porphyria cutanea tarda is usually manifest as cutaneous photosensitivity and hepatic iron overload and is diagnosed by an increased urinary and faecal porphyrin excretion. Management includes venesection and avoidance of alcohol, exogenous eostrogen and certain drugs.

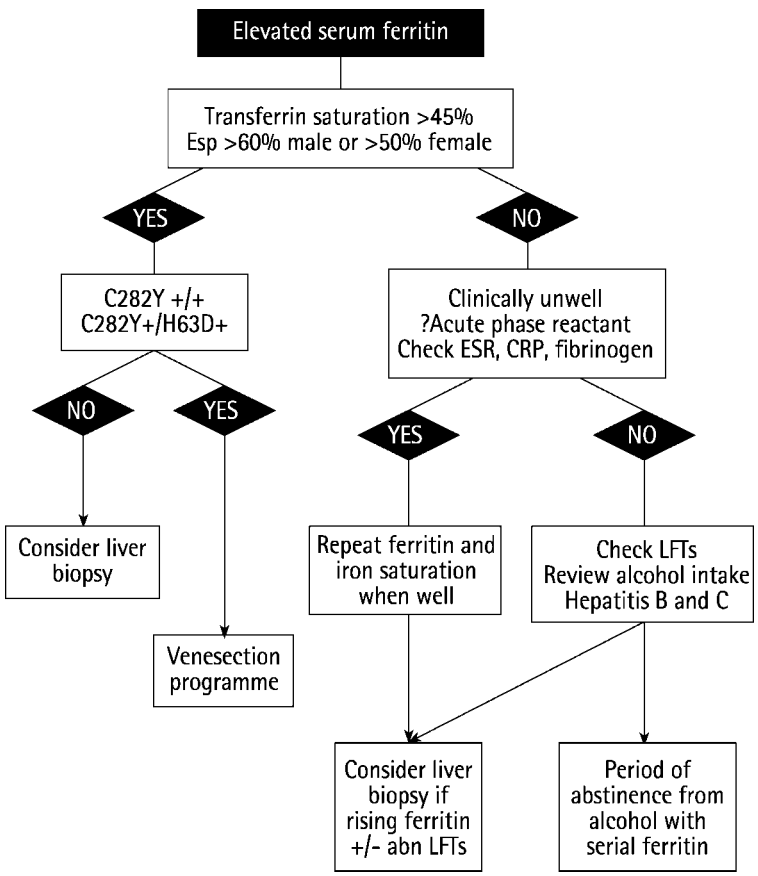
Due to the high prevalence of the mutation of the HFE gene, the probability of a heterozygote marrying another heterozygote is 10%

Excess dietary iron as a cause of secondary iron overload classically refers to inhabitants of sub-Saharan Africa who consume a traditional fermented beverage brewed in iron cans that is rich in iron. This condition is distinctive on histological grounds from alcoholic iron overload and HH.

Alcohol

It is known that the regular consumption of alcohol is responsible for the disruption of normal iron metabolism in humans, resulting in the excess deposition of iron in the liver in approximately one-third of alcoholic subjects. The mechanisms involved are largely unknown; however, it is likely that the two major proteins of iron metabolism, ferritin and transferrin are intimately involved in the process. The elevation of serum ferritin caused by alcohol excess can occur without elevation of other liver enzymes often

Figure 2. Guideline for the investigation and management of hyperferritinemia



falls dramatically with abstinence from alcohol.

Increased ferritin without iron overload

Steatohepatitis

Increased ferritin with normal transferrin saturation is frequently found in patients with hepatic steatosis. The elevated ferritin is thought to be due to the combination of disrupted glucose, lipid and iron metabolism. The elevated ferritin reflects iron overload only in those patients in whom it persists despite an appropriate (diabetic) diet.[6]

Viral hepatitis

Acute hepatitis secondary to viral infection with hepatitis A, B, C, EBV, and CMV will cause an elevation in serum ferritin indicative of the liver inflammation but not iron overload. Chronic infection with hepatitis C or B may be less obvious clinically and serologies should be checked even if there is only minimal disturbance of liver enzymes in cases of unexplained hyperferritinemia.

Inflammatory conditions

Patients with autoimmune inflammatory diseases, such as SLE and rheumatoid arthritis commonly have an elevated serum ferritin which more likely reflects disease activity, especially in the case of SLE, than iron status.[7] Where the patient is anaemic the serum ferritin is an unreliable guide to the patient's iron status. The soluble transferrin receptor is a more reliable guide to the presence of iron deficiency than the serum ferritin because of its dual role as acute phase reactant. Unfortunately the soluble transferrin receptor is not available as a routine test.

Active infection will also be associated with an elevated serum ferritin in the absence of iron overload. An elevated CRP or ESR should alert you to these possibilities in patients with occult inflammation.

Heavy exercise as in ultramarathon running can cause an elevated serum ferritin amongst other acute phase reactants.[8]

Malignancy is also an important cause of an acute phase reaction but is unlikely to manifest as an isolated elevation of serum ferritin in the absence of other clinical signs or laboratory abnormalitites.

The serum ferritin is elevated in thyrotoxicosois.

Familial hyperferritinemia and cataract syndrome is a rare disorder which is not associated with iron overload. Affected family members do require ophthalmology assessment and cataract removal.

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