

Please read this section first

The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will **not** issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.

The Thistle QA CEU No is: **MT-2014/004**.

Each attendee should claim **THREE** CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

CHEMISTRY LEGEND

JANUARY 2014

HYPERFERRITINEMIA

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 and Alcohol excess.

Causes of iron overload

Primary

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

Secondary

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

Hereditary hemochromatosis (HH)

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 hemochromatosis 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. Clinical manifestations of HH can be grouped as:

- **Early** - Arthralgia, Asthenia, Elevation of serum transaminases
- **Late** - Hepatomegaly, Cirrhosis and hepatoma, Diabetes, Arthritis of the 2nd and 3rd MC Points 'painful handshake', Cardiomyopathy, Pigmentation, Impotence

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 is usually self-evident and does not present a diagnostic problem. Management includes venesection and avoidance of alcohol, exogenous oestrogen and certain drugs. 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.

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 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.

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.

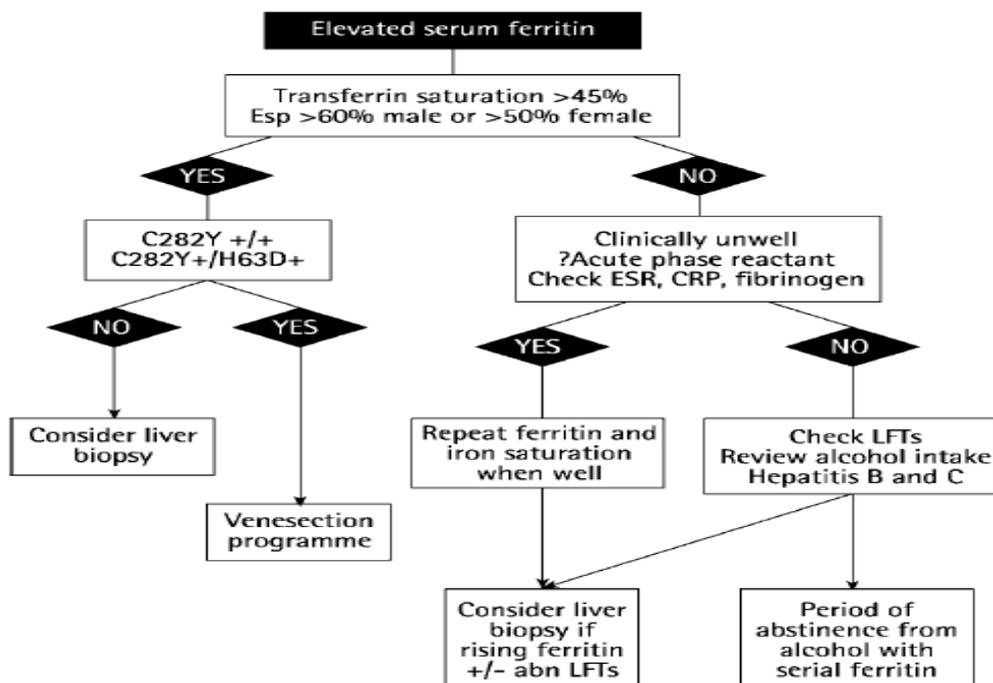
Inflammatory conditions

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. 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 ultra-marathon running can cause an elevated serum ferritin amongst other acute phase reactants. 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 abnormalities. The serum ferritin is elevated in thyrotoxicosis. 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.

Guideline for the investigation and management of hyperferritinemia



References

1. Continuing Medical Education Interpretation of an elevated serum ferritin-Leanne Berkhan Diagnostic Medlab in Auckland

Questions

1. Discuss the causes of a high serum ferritin with iron overload.
2. Discuss the causes of an increased serum ferritin without iron overload.
3. Discuss the investigation and management of hypoferritinemia.