

Elevated serum ferritin

Identifying iron overload

FEI WEN CHEN BMedSc, MB BS(Hons)

AMANY ZEKRY MB BS, FRACP, PhD

It is important to determine whether elevated ferritin levels are associated with iron overload conditions, such as hereditary haemochromatosis, or other causes, such as liver or inflammation-related conditions.

Remember

- Ferritin, an iron storage protein, is critical to iron haemostasis. Its serum concentration closely reflects the body iron stores in the absence of inflammation.
- Alterations in ferritin level are seen commonly in clinical practice, often reflecting perturbations in iron homeostasis or metabolism.

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Dr Chen is a Gastroenterology Advanced Trainee in the Department of Gastroenterology and Hepatology at St George Hospital, Sydney. Associate Professor Zekry is a Clinical Academic at St George and Sutherland Clinical School; and a Gastroenterologist and Hepatologist at St George Hospital, Sydney, NSW.

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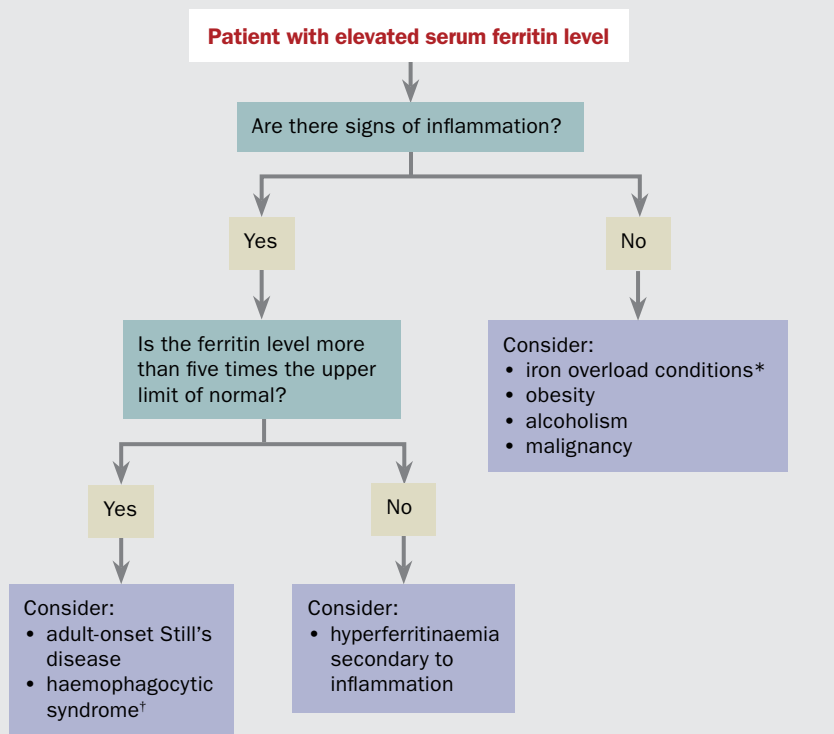


- Ferritin is an acute-phase reactant that can become elevated in several conditions related to inflammation or infections, without concurrent elevations in transferrin saturation. In addition, hyperferritinaemia is seen in patients who misuse alcohol and patients with fatty liver disease associated with obesity, certain haematological conditions and autoimmune diseases. Raised ferritin levels are also caused by overexpression of tissue ferritin in a large number of cancers, including hepatocellular carcinoma, haematological malignancies, and breast and pancreatic cancers.
- Patients with iron overload conditions such as autosomal recessive hereditary haemochromatosis and transfusional iron overload have elevated ferritin levels.
- An elevated ferritin level is associated with a number of autoimmune conditions. These include adult-onset Still's disease, haemophagocytic syndrome and sideroblastic anaemia.

Assessment

- The most common iron overload condition is hereditary haemochromatosis. The likelihood of having this condition depends on the degree of ferritin elevation and is affected by sex and weight.
- A ferritin level of more than 200 µg/mL in women or 300 µg/mL in men has a sensitivity of 66% and specificity of 85% to detect hereditary haemochromatosis, whereas a ferritin level of 400 µg/mL or higher in women and 500 µg/mL or higher in men has a sensitivity of 45% and specificity of 97%.

AN APPROACH TO INVESTIGATING ELEVATED SERUM FERRITIN LEVELS AND POTENTIAL CAUSES



* Associated with elevated liver enzymes, transferrin saturation >60% in men and >50% in women, confirmed with gene analysis or liver biopsy.

† Serum ferritin is classically >10,000 µg/mL with hypertriglyceridaemia, pancytopenia and multiple organ failure.

- Transferrin saturation is the ratio of serum iron to total iron binding capacity. A transferrin saturation of greater than 50% in women or greater than 60% in men has sensitivity of greater than 90% to detect iron overload conditions, with or without elevated liver enzymes.
- In younger patients, a ferritin level lower than 200 µg/mL and transferrin saturation lower than 45% has a negative predictive value of around 97%. However, the positive predictive value of these thresholds is only 20%; hence, confirmatory testing using gene analysis for *HFE* gene mutations or a liver biopsy with hepatic iron index may be needed.
- Elevated serum ferritin levels are seen in 89% of patients with adult-onset Still's disease, which typically affects young women and is characterised by fever, arthritis and rash. Ferritin levels greater than five times the upper limit of normal and high ferritin to C-reactive protein ratios are useful in distinguishing between adult-onset Still's disease and rheumatoid arthritis (flowchart).
- Haemophagocytic syndrome is a heterogeneous group of disorders with a final common pathway consisting of hyperferritinaemia, pancytopenia, splenomegaly and multiple organ failure. In patients with haemophagocytic syndrome, serum ferritin levels are classically

elevated above 10,000 µg/mL. It is strongly associated with viral illness, most prominently Epstein-Barr virus infection, and should be considered as a differential diagnosis in any critically ill patient with evidence of systemic inflammation or multiple organ involvement with associated cytopenias.

Management

- Provided other causes of elevated ferritin levels such as fatty liver disease and alcohol misuse have been excluded, hereditary haemochromatosis and other iron overload conditions are treated with therapeutic phlebotomy, typically removing one unit of blood (equivalent to approximately 250 µg of iron) weekly or twice weekly until a goal ferritin level of 50 to 100 µg/mL is maintained.
- In patients with transfusional iron overload, iron chelation therapy with desferrioxamine, deferiprone or the iron chelator deferasirox is the preferred treatment.

Conclusion

- Hyperferritinaemia is often encountered in clinical practice and the results must be interpreted in relation to the results of the remaining iron studies, the patient's general condition and their liver enzyme levels.
- Concurrently elevated ferritin and fasting transferrin levels are suggestive of hereditary haemochromatosis, and this should prompt testing for *HFE* gene mutations.
- An elevated ferritin level can result from fatty liver disease or excess alcohol intake.
- Further, hyperferritinaemia is commonly associated with inflammatory, neoplastic or autoimmune diseases.

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COMPETING INTERESTS: None.