

Extreme hyperferritinemia does not equal to HLH

Short communication

Ferritin is a protein that provides intracellular storage for iron in the body. It is found in high concentrations in the cells of specific organs; bone marrow, liver, and the spleen. Although the concentration of intracellular ferritin represents the accurate measure of iron storage, it cannot be readily available for measuring. Instead, we utilize serum ferritin (the secreted version of intracellular ferritin) to assess the iron stores, which can be measured with laboratory techniques.

Hyperferritinemia, a condition that denotes a higher than normal level of serum ferritin, is frequently encountered in clinical practice. In one study, hyperferritinemia was encountered in as much as 7% of all hospitalized patients [1]. There are a number of causes for elevated levels of serum ferritin, which can be classified under three broad categories based on the underlying mechanism. The three categories are as follows; total body iron storage overload, presence of inflammation (which causes hypersecretion of ferritin into the serum from storage cells without total body iron overload) and spillover of intracellular ferritin into the serum from cellular injury. Some common of etiologies hyperferritinemia include; hemochromatosis (iron overload mechanism), autoimmune diseases such as rheumatoid arthritis (inflammatory mechanism) and alcoholism (cellular injury mechanism). Occasionally, rare causes of hyperferritinemia, such as Hemophagocytic Lymphohistiocytosis (HLH) can also be encountered in specific clinical situations.

In most instances, the levels of the serum ferritin are modestly elevated (less than 1000 ng/ml). Sometimes however, extreme elevations can be seen. Although there is no standard definition of 'extreme hyperferritinemia'; the term is often used when the serum ferritin levels cross 10,000 ng/ml.

There is concern among physicians when extreme hyperferritinemia is encountered, as many studies have clearly demonstrated its

association with high mortality rates [1-3]. When extreme hyperferritinemia is encountered in the outpatient setting, physicians (rightly so) try to rule out malignancy (because of its association with very high serum ferritin levels), while working up other causes. But when extreme hyperferritinemia is found in patients admitted to the hospital, physicians usually overlook common causes before testing for rare conditions such as HLH. This practice is likely driven by the fear of missing a potentially devastating diagnosis such as HLH. But should HLH testing be done for all patients that have extreme hyperferritinemia? We attempt to answer this question with this review, in light of scientific evidence.

In a large done study by Sackett et al. (which enrolled more than 65,000 patients admitted to the hospital), showed that HLH accounted for only 9% of all cases of hyperferritinemia; much less common than conditions with iron overload (34%) and liver disease (31%) [4]. Moreover, HLH was ranked 4th in terms of the highest mean values of ferritin observed, behind viral infections, hematologic malignancies, and liver disease in the Sackett study. Thorne et al. showed that HLH accounted for only 5% of 155 hyperferritinemia cases with their study [1]. Similarly, another study by Schram et al., which was conducted at a large academic hospital, revealed that HLH was diagnosed in only 17% of hyperferritinemia cases [5]. On the contrary, Allen et al. in their study, showed that serum ferritin levels above 10,000 ng/ml were 90% sensitive and 96% sensitive for HLH; but the authors of that study concluded that these numbers applied to only to those patients who did not have other significant medical conditions [6]. Overall, in light of the evidence from the studies quoted above, we can conclude that HLH is a rare cause of hyperferritinemia and other causes such as liver disease, iron overload conditions, and inflammatory disorders account for the vast majority of the cases of extremely high serum ferritin levels. Hence, there is a need for a stepwise diagnostic approach for dealing with hyperferritinemia.

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Lorcerie et al. and Cullis et al. in their articles have proposed an algorithmic approach for efficient diagnosis of hyperferritinemia [7,8]. Both methods have significant overlap, and from them, we can derive a standard diagnostic sequence. So when a high serum ferritin level has been confirmed, we proceed to step 1.

Step 1: Rule out common etiologies such as alcohol excess, inflammatory disorders, and tissue damage (hepatitis or malignancy, etc.). If none of the common etiologies are present, we move to step 2.

Step 2: Rule out iron overload conditions by checking transferrin saturation. If a normal value of transferrin saturation is found, conditions associated with iron overload are excluded, we move to step 3.

Step 3: Investigate for rare conditions such as HLH and obtain a detailed assessment of the liver iron stores with a liver MRI (or liver biopsy).

Conclusion

HLH is a rare cause of extreme hyperferritinemia; other causes such as liver disease, malignancies, and iron overload conditions are more commonly implicated in increasing serum ferritin to extreme levels. HLH testing, although being important (because it carries significant morbidity and mortality); should be done with a systematic approach after other common causes are excluded in patients with hyperferritinemia.

References

1. Thorne I, Stroud J, Penn H. A retrospective series of conditions and mortality associated with extreme hyperferritinaemia in adults. *Int. J. Clin. Pract.* 72(9), e13215 (2018).
2. Hasuike Y, Nonoguchi H, Tokuyama M *et al.* Serum ferritin predicts prognosis in hemodialysis patients: the Nishinomiya study. *Clin. Exp. Nephrol.* 14(4), 349–355 (2010).
3. Meyer SC, O'Meara A, Buser AS *et al.* Prognostic impact of post transplantation iron overload after allogeneic stem cell transplantation. *Biology of blood and marrow transplantation. J. American Society. Blood. Marrow. Transplant.* 19(3), 440–444 (2013).
4. Sackett K, Cunderlik M, Sahni N *et al.* Extreme Hyperferritinemia: Causes and Impact on Diagnostic Reasoning. *Am. J. Clin. Pathol.* 145(5), 646–650 (2016).
5. Schram AM, Campigotto F, Mullally A *et al.* Marked hyperferritinemia does not predict for HLH in the adult population. *Blood.* 125(10), 1548–1552 (2015).
6. Allen CE, Yu X, Kozinetz CA *et al.* Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr. Blood. Cancer.* 50(6), 1227–1235 (2008).
7. Lorcerie B, Audia S, Samson M *et al.* Diagnosis of hyperferritinemia in routine clinical practice. *Presse. med.* 46(12), e329–e338 (2017).
8. Cullis JO, Fitzsimons EJ, Griffiths WJ *et al.* Investigation and management of a raised serum ferritin. *Br. J. Haematol.* 181(3), 331–340 (2018).