Original Research Paper

Volume - 15 | Issue - 10 | October - 2025 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Biochemistry

EXTREME HYPERFERRITINEMIA : A CASE SERIES

Mauchumi Saikia Pathak	MD, Professor and Head, Department of Biochemistry, Gauhati Medical College and Hospital, Guwahati, Assam 781032
Syed Washbir Hussain*	Post Graduate Trainee,Department of Biochemistry, Gauhati Medical College and Hospital, Guwahati, Assam 781032 *Corresponding Author
Elteza T. Jahir	Assistant Professor, Department of Biochemistry, Gauhati Medical College and Hospital, Guwahati, Assam 781032
Alakesh Choudhury	Assistant Professor, Department of Biochemistry, Nagaon Medical College and Hospital, Nagaon, Assam

ABSTRACT Extreme hyperferritinemia, defined as ferritin levels exceeding 10,000 ng/mL, can result from various conditions such as sepsis, iron overload, and hemophagocytic lymphohistiocytosis (HLH). This study presents three cases with ferritin levels ranging from 32,200 to 85,800 ng/mL, each stemming from different causes: HLH, transfusion-related iron overload in beta-thalassemia, and Macrophage Activation Syndrome (MAS) associated with Systemic Juvenile Idiopathic Arthritis (SJIA). Despite elevated ferritin and severe anemia, these conditions differed in underlying pathologies and clinical management. All patients ultimately succumbed to complications. This highlights that extreme hyperferritinemia is a non-specific acute-phase response marker, necessitating comprehensive clinical evaluation and a multidisciplinary approach for accurate diagnosis and management. Further research is needed to refine ferritin's role as a biomarker.

KEYWORDS : Ferritin, Hemophagocytic Lymphohistiocytosis, Hyperferritinemia

INTRODUCTION

Ferritin is a multifunctional molecule that aids in inflammation, cell communication, immunological function, and binding and storage of iron [1]. Serum ferritin levels have been found to rise in several common illnesses, such as sepsis brought on by bacteria, fungi, or viruses, iron overload from hemochromatosis or long-term transfusions, or as a general indicator of inflammation [2-4]. A higher serum ferritin level has been associated with a worse prognosis [5]. Serum ferritin levels can occasionally reach extremes of more than 10,000 ng/mL [6]. Patients with such severe hyperferritinemia have traditionally been evaluated for a relatively narrow differential diagnosis, which includes sepsis, infection (particularly fungal), iron overload, and uncommon causes such as hemophagocytic lymphohistocytosis (HLH) [7-9].

Acquired Hyperferritinaemia can be caused by autoimmune illnesses, malignancies, hemolysis, liver diseases, and chronic inflammatory states (i.e, anaemia of chronic disease, with shift of iron from circulation to storage sites [10-12]. Hereditary disorders, the well-known of which is hereditary hemochromatosis, can also result in elevated ferritin levels [13].

There are two kinds of hemophagocytic lymphohistiocytosis: secondary (sHLH) and familial (fHLH) [14]. If left untreated, fHLH, an autosomal recessive disorder, can be deadly and usually manifests in early infancy [15]. Strong immune system activation, frequently brought on by infection, is assumed to be the etiology of sHLH [16].

Fever, splenomegaly, bicytopenia, elevated triglycerides and /or decreased fibrinogen, hemophagocytosis (usually in a bone marrow, liver or lymph node specimen), decreased or absent natural killer (NK) cell function, increased soluble interleukin 2 (IL 2) receptor and hyperferritinemia are the eight findings that must be included in the diagnosis of HLH [17-18].

Doctors still link HLH to extreme hyperferritinemia (levels >10,000 ng/ml) in their diagnostic thinking, even though HLH is rare, and numerous studies have shown that extreme hyperferritinemia has a low positive predictive value. [19-20].

Since ferritin is an easily accessible assay that is frequently acquired as part of the fundamental laboratory evaluation of anemia, its use in hospitalized patients is growing. Numerous medical diseases that reflect various comorbidities and frequently an acute and severe clinical presentation might have an impact on ferritin levels in hospitalized patients. Consequently, several illnesses and medical disorders may be linked to high ferritin levels. It is frequently unclear what the clinical relevance of significantly high ferritin levels in hospitalized patients is.

Case 1

The first patient is a 5-year-old girl who presented to the paediatric outpatient department with chief complaints of generalised weakness for 2 months. Multiple episodes of on and off fever for 2 months (undocumented).No history of recent blood transfusion. One episode of bleeding per rectum was also noted.

Examination

The patient was pale, and the tip of the spleen was palpable.

Investigations

Hemoglobin- 5.8 g/dl, Red Blood Cell Count-2.3 × 10^6/microlitre, Serum Triglyceride -220 mg/dl, Serum Ferritin-77800 ng/ml, Bone marrow Aspiration- Hemophagocytosis.

Diagnosis

The patient was provisionally diagnosed to be a case of Hemophagocytic Lymphohistiocytosis.

Treatment

She was treated aggressively with help from the Department of Haematology. She was treated with standard protocol, which included Etoposide and Dexamethasone. She was planned for bone marrow transplantation.

Follow up

She finally succumbed due to Multi-Organ Dysfunction Syndrome.

Case 2

The second patient is a 16-year-old boy, a known case of beta thalassemia with hemophilia on regular blood transfusion since 2011. The patient had an episode of nasal bleeding last year, which stopped upon receiving an injection of tranexamic acid. After about 2 months, the patient had pain in the right elbow, followed by the right hip, right foot, left hip, and knee.

Examination

A swelling was also noted around the left knee, hepatosplenomegaly

Investigations

- Hemoglobin- 5.4 g/dl, low white blood cell count, low platelet count, Serum Ferritin-85800 ng/dl.
- Contrast-enhanced computed tomography LEFT KNEE- Joint Effusion with multiloculated peripherally enhancing suggestive of hemarthrosis.

Diagnosis

Known case of beta thalassemia with hemophilia.

Treatment

The patient was on regular blood transfusion, iron chelation therapy,

folic acid supplementation, and factor IX concentrate for hemophilia.

Follow up

The patient finally succumbed due to heart failure.

Case 3

The third patient is a 5-year-old girl, a referred case of severe anaemia with polyarthralgia from another peripheral tertiary care hospital. The patient presented with chief complaints of intermittent low-grade fever on medication, generalised weakness for 3 months, bleeding during micturition, and a history of multiple joint pains for 2 to 3 months (Metacarpals, ankle joint, wrist joint).

Examination

Hepatomegaly and Splenomegaly were found.

Investigations

Hemoglobin - 4.6 g/dl, Serum ferritin- 32200 ng/ml, serum Triglyceride-258 mg/dl, bone marrow aspiration- Hemophagocytosis.

Diagnosis

The patient was provisionally diagnosed to be a case of Systemic Juvenile Idiopathic Arthritis with Macrophage Activating System.

Treatment

The patient was started on high-dose corticosteroids, cyclosporin A, and supportive care.

Follow up

The patient is alive on treatment.

DISCUSSION

Despite HLH being an uncommon condition, it remains a prominent diagnostic consideration in cases of extreme hyperferritinemia. However, recent literature cautions against over-reliance on ferritin levels alone for diagnosing HLH, noting a low positive predictive value of extreme ferritin elevation, especially in adults. HLH diagnosis requires a combination of clinical and laboratory criteria, with at least five of eight diagnostic features—such as fever, splenomegaly, cytopenias, hypertriglyceridemia, hemophagocytosis, and others—being essential for confirmation.

The three cases presented illustrate the diagnostic and prognostic complexity of hyperferritinemia:

- Case 1, a pediatric patient, presented with a classic HLH picture: prolonged fever, splenomegaly, cytopenia, hypertriglyceridemia, extreme hyperferritinemia (77,800 ng/mL), and confirmed hemophagocytosis on bone marrow examination. Despite aggressive management, the patient succumbed to multi-organ dysfunction, highlighting the fulminant nature of HLH in children and the critical need for early recognition and intervention.
- Case 2 featured a patient with beta-thalassemia and hemophilia, undergoing chronic transfusions. This patient developed ferritin levels of 85,800 ng/mL, likely reflecting iron overload, complicated by hemarthrosis and cardiac failure. This case underscores the need for careful monitoring of iron burden in transfusion-dependent patients and the importance of distinguishing iron overload from other hyperinflammatory conditions like HLH.
- Case 3 presented diagnostic overlap with Systemic Juvenile Idiopathic Arthritis (SJIA) and Macrophage Activation Syndrome (MAS)—a form of secondary HLH. The patient's symptoms (fever, cytopenia, splenomegaly, arthralgia), lab findings (serum ferritin 32,200 ng/mL, elevated triglycerides, hemophagocytosis), and chronic inflammatory background were consistent with this rare but life-threatening SJIA complication. MAS often mimics HLH, reinforcing the importance of comprehensive clinical correlation.

These cases collectively reflect the diagnostic ambiguity of hyperferritinemia in clinical settings. Elevated ferritin is often a marker of disease severity rather than a specific diagnosis, and its interpretation must always be contextualized within the patient's clinical presentation, history, and supporting laboratory/imaging data.

Furthermore, in hospitalized patients, especially those with multiple comorbidities or chronic inflammatory states, ferritin can be markedly elevated without the presence of HLH. Conditions such as autoimmune diseases, malignancy, chronic liver disease, and repeated transfusions are common contributors. Hence, indiscriminate pursuit of an HLH diagnosis based solely on ferritin levels can lead to misdiagnosis, unnecessary treatment, or delayed diagnosis of other causes.

CONCLUSION

In conclusion, while extreme hyperferritinemia should alert clinicians to potentially serious conditions such as HLH, it should not be viewed in isolation. A multidimensional diagnostic approach that integrates clinical features, lab parameters, imaging, and bone marrow findings is critical. Future research should focus on refining the diagnostic utility of ferritin in different clinical contexts and developing more specific biomarkers to aid in differentiating between various causes of elevated ferritin.

Conflict of Interest: None

Consent /Ethical Issue: The data has been obtained from our day-to-day routine diagnostic work in a large Central Clinical Laboratory of a tertiary care hospital. The samples are received as per the clinician's need for patient management. Prior to collecting a sample, they obtain verbal consent from every patient or their guardian. Patient identifying details have not been disclosed in the manuscript.

REFERENCES

[1] Sandnes, M., Ulvik, R. J., Vorland, M., & Reikvam, H. (2021). Hyperferritinemia—A clinical overview. Journal of Clinical Medicine, 10(9), 2008. https://doi.org/10.3390/jcm10092008

[2] Serra, M., Longo, F., Roetto, A., Sandri, A., & Piga, A. (2011). A child with hyperferritinemia: Case report. Italian Journal of Pediatrics, 37, 20. https://doi.org/10.1186/1824-7288-37-20

[3] Sackett, K., Cunderlik, M., Sahni, N., Killeen, A. A., & Olson, A. P. J. (2016). Extreme hyperferritinemia: Causes and impact on diagnostic reasoning. American Journal of Clinical Pathology, 145(5), 646–650. [https://doi.org/10.1093/ajcp/aqw053] (https://doi.org/10.1093/ajcp/aqw053)

[4] Israel, A., Bornstein, G., Gilad, L., Shechtman, L., Furie, N., Ben-Zvi, I., et al. (2022). Clinical and prognostic significance of elevated ferritin levels in hospitalised adults. Postgraduate Medical Journal, 98(1162), 622–625.https://doi.org/10.1136/postgradmedj-2021-139832

[5] Knovich, M. A., Storey, J. A., Coffman, L. G., Torti, S. V., & Torti, F. M. (2009). Ferritin for the clinician. Blood Reviews, 23(3), 95–104. https://doi.org/10.1016/j.blre.2008.08.001

[6] Crook, M. A., & Walker, P. L. C. (2013). Extreme hyperferritinaemia: Clinical causes. Journal of Clinical Pathology, 66(5), 438–440. https://doi.org/10.1136/jclinpath-2012-201298

[7] Rosario, C., Zandman-Goddard, G., Meyron-Holtz, E. G., D'Cruz, D. P., & Shoenfeld, Y. (2013). The hyperferritinemic syndrome: Macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Medicine, 11, 185. https://doi.org/10.1186/1741-7015-11-185

[8] Bennett, T. D., Hayward, K. N., Farris, R. W. D., Ringold, S., Wallace, C. A., & Brogan, T. V. (2011). Very high serum ferritin levels are associated with increased mortality and critical care in pediatric patients. Pediatric Critical Care Medicine, 12(3), 233–236. https://doi.org/10.1097/PCC.0b013e3181e2a951

[9] Schram, A. M., Campigotto, F., Mullally, A., Fogerty, A. E., Massarweh, N. N., Perkins, J., et al. (2015). Marked hyperferritinemia does not predict for HLH in the adult population. Blood, 125(10), 1548–1552. https://doi.org/10.1182/blood-2014-10-605071

[10] Allen, C. E., Yu, X., Kozinetz, C. A., & McClain, K. L. (2008). Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatric Blood & Cancer, 50(6), 1227–1235. [https://doi.org/10.1002/pbc.21423] (https://doi.org/10.1002/pbc.21423)

[11] Henter, J. I., Horne, A. C., Aricò, M., Egeler, R. M., Filipovich, A. H., Imashuku, S., et al. (2007). HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatric Blood & Cancer, 48(2), 124–131. https://doi.org/10.1002/pbc.21039

[12] Olson, A. P. J., Sahni, N., Kim, B., Sackett, K., & Killeen, A. A. (2015). Not a textbook case. Journal of Hospital Medicine, 10(4), 266–270. [https://doi.org/10.1002/jhm.2337] (https://doi.org/10.1002/jhm.2337)

[13] Croskerry, P. (2003). Cognitive forcing strategies in clinical decision making. Annals of Emergency Medicine, 4(1), 110–120. [https://doi.org/10.1067/mem.2003.22] (https://doi.org/10.1067/mem.2003.22)

[14] Henter, J. I., Elinder, G., Söder, O., & Ost, A. (1991). Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatrica, 80(4), 428–434. [https://doi.org/10.1111/j.1651-2227.1991.tb11999.x] (https://doi.org/10.1111/j.1651-2227.1991.tb11999.x)

[15] Moore, C., Ormseth, M., & Fuchs, H. (2013). Causes and significance of markedly elevated serum ferritin levels in an academic medical center. Journal of Clinical Rheumatology, 19(6), 324–328. [https://doi.org/10.1097/RHU.0000000000000019] (https://doi.org/10.1097/RHU.0000000000000019)

[16] Jordan, M. B., Allen, C. E., Weitzman, S., Filipovich, A. H., & McClain, K. L. (2011). How I treat hemophagocytic lymphohistiocytosis. Blood, 118(15), 4041–4052. https://doi.org/10.1182/blood-2011-03-278127

[17] Henter, J. I., Samuelsson-Horne, A., Aricò, M., Egeler, R. M., Elinder, G., Filipovich, A. H., et al. (2002). Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood, 100(7), 2367–2373. https://doi.org/10.1182/blood-2002-01-0172

[18] Arosio, P., & Levi, S. (2010). Cytosolic and mitochondrial ferritins in the regulation of cellular iron homeostasis and oxidative damage. Biochimica et Biophysica Acta (BBA) - General Subjects, 1800(8), 783–792. [https://doi.org/10.1016/j.bbagen.2010.02.005] (https://doi.org/10.1016/j.bbagen.2010.02.005)

[19] Henter, J. I., Elinder, G., & Ost, A. (1991). Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. Seminars in Oncology, 18(1), 29–33.

[20] Wang, W., Knovich, M. A., Coffman, L. G., Torti, F. M., & Torti, S. V. (2010). Serum ferritin: Past, present and future. Biochimica et Biophysica Acta (BBA) - General Subjects, 1800(8), 760–769. [https://doi.org/10.1016/j.bbagen.2010.03.011] (https://doi.org/10.1016/j.bbagen.2010.03.011)

[21] Burtis, C. A., Bruns, D. E., & Sawyer, B. G. (Eds.). (2015). Tietz fundamentals of clinical chemistry and molecular diagnostics (7th ed., p. 964). Elsevier.