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ORIGINAL ARTICLE

Elevated serum ferritin is not specific for hemophagocytic lymphohistiocytosis

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Abstract Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal, syndrome of excessive and ineffective activation of the immune system. The majority of the reported data on HLH is from pediatric patients and lacks specificity. This makes HLH diagnosis challenging especially in adults where HLH is triggered by many conditions and can resemble many disease entities. Elevated ferritin is one of the diagnostic criteria for HLH. We determined the conditions associated with elevated ferritin at our medical center to assess how specific ferritin is for predicting HLH. We retrospectively reviewed all ferritin results >10,000 μg/L in pediatric and adult patients. The most common condition associated with elevated ferritin was hematologic malignancy in adults (25.7%) and HLH in pediatric patients (48.9%). HLH was diagnosed in 14.2% of adults and 48.9% of children with ferritin >10,000 μg/L. Hyperferritinemia occurs in a variety of conditions and is not specific for adult or pediatric HLH. Common causes of elevated ferritin should be considered before entertaining the possibility of HLH, especially in adult patients.

Keywords Hemophagocytic lymphohistiocytosis · Ferritin · Specific · Diagnosis · Adults · Pediatrics

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal, syndrome of excessive and ineffective activation of the immune system resulting in overproduction of inflammatory cytokines [1]. Although initially described and commonly reported in children, HLH is being increasingly diagnosed in all age groups. Common presenting features include fever, cytopenias, elevated serum ferritin, and splenomegaly [2]. Evidence of hemophagocytosis in bone marrow and other organs of the reticuloendothelial system is common (hence the name "hemophagocytic lymphohistiocytosis"); however, it is not essential for the diagnosis of HLH and might not be present in the initial stages of disease [3, 4].

In the most recent revised classification, the Histiocyte Society categorized histiocytic disorders into five groups designated L (Langerhans), C (cutaneous and mucocutaneous), M (malignant), R (Rosai-Dorfman), and H (hemophagocytic) [5]. Entities included in the H group include hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), and they share the clinical features of uncontrolled immune activation. Primary HLH, which occurs mostly in children and young adolescents, is related to known immune disorders with underlying mutations affecting the function of cytotoxic T cells [6]. On the other hand, secondary HLH typically occurs in adults and is often triggered by infections, hematologic malignancies, or rheumatologic diseases [7]. In some cases, the underlying trigger is undetermined.

Serum ferritin ≥500 μg/L is one of the diagnostic parameters for HLH [8]. It is common to see high ferritin levels in HLH patients, and ferritin concentrations greater than 10,000 μg/L were observed in 25% of pediatric patients [9]. Different ferritin cut-offs with varying specificities for HLH have been proposed in different age groups [10–12]. In one case series, a ferritin cut-off of >10,000 μg/L was 90%

sensitive and 96% specific for HLH in children [10]. In our experience, serum ferritin >10,000 μg/L occurred in 54/73 (74%) of adult HLH patients [13]. Thus far, studies on ferritin specificity in HLH have been inconsistent in their findings [10–12]. In this retrospective study, we determined the conditions associated with ferritin >10,000 μg/L in adult and pediatric patients to evaluate how specific an elevated ferritin is for predicting HLH.

Methods

This is a single-institution, retrospective chart review of patients with markedly elevated ferritin (defined as serum ferritin value >10,000 μg/L) results at Washington University Medical Center in St. Louis, Missouri. Institutional Review Board (IRB) approvals were obtained from the Washington University Human Research Protection Office to review the charts of patients with markedly elevated ferritin concentrations. Ferritin values were collected over the periods from October 1, 2003 through March 31, 2016 and from January 31, 2009 through December 31, 2016 at Barnes-Jewish Hospital (BJH) and Saint Louis Children's Hospital (SLCH), respectively. The decision to choose these specific study periods in both hospitals was based on the availability of the same ferritin assay (Siemens ADVIA Centaur for BJH and Roche Cobas for SLCH) during the assigned study periods. Patients were categorized as adults if their age was ≥18 years on the date of ferritin measurement.

Ferritin measurements were collected from the hospital laboratory information system (Cerner Corporation, Kansas City, MO, USA). Patients' demographic and clinical data were collected from the hospital electronic medical record (Clinical Desktop 2). We identified patients with ferritin values >10,000 μg/L and reviewed their medical charts to determine the primary diagnosis and potential cause(s) of elevated ferritin. If patients had multiple ferritin measurements, we used the highest ferritin value during the same visit or hospital admission for the analysis. We extracted demographic, clinical, and laboratory data from medical charts. Included patients were categorized based on our review as having the following primary diagnoses: HLH, MAS, hematologic malignancy, solid tumor, renal failure, liver failure, infection, iron overload, hemoglobinopathy, graft versus host disease (GVHD), rheumatologic disorder, hemolysis, and hemochromatosis. To capture undiagnosed cases of HLH, all records were reviewed for all clinical and laboratory findings that constitute the current diagnostic criteria for HLH [8].

We established a diagnosis of HLH if patients met the 2004 Histiocyte Society Criteria for HLH diagnosis (HLH-2004) [8] which requires one of the following: A molecular diagnosis consistent with HLH, or meeting five of the following eight criteria: (1) fever ≥38.5 °C; (2) splenomegaly; (3) cytopenia of two or three lines: absolute neutrophil count (ANC) $<1 \times 10^9$/L, hemoglobin <9 g/dL, platelet count $<100 \times 10^9$/L; (4) serum triglycerides ≥265 mg/dL or serum fibrinogen ≤150 mg/dL; (5) serum ferritin ≥500 μg/L; (6) soluble IL-2 receptor (i.e., soluble CD25) ≥2400 U/mL; (7) low or absent NK cell activity; and (8) pathology showing hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver. Patients who were diagnosed with HLH based on clinical and laboratory findings, but did not meet the HLH diagnostic criteria, were not categorized as having HLH as a primary cause of elevated ferritin. We followed the recent classification of histiocytic disorders in subgrouping HLH cases into primary, secondary, or idiopathic [5]. The most likely trigger of secondary HLH (malignancy, infection, and rheumatologic disorders) was assigned for each patient based on treating physician's assessment. We also analyzed data from our ongoing adult HLH database to evaluate sensitivity of elevated ferritin.

All data analysis was performed in Microsoft Excel (version 10, Microsoft, Seattle, WA, USA). Results were presented as median +/- range or percentages as indicated.

Results

Patients' characteristics

There were 153,619 ferritin assays performed at Barnes-Jewish Hospital and Saint Louis Children's Hospital during the study periods. A total of 1064 (0.7%) ferritin results (196 pediatric and 868 adult ferritin results) were above 10,000 μg/L for 628 unique patients (45 pediatric and 583 adult patients). Table 1 summarizes the patients' demographics of both age groups. Table 2 details the distribution of patients with ferritin >10,000 μg/L by disorders associated with hyperferritinemia; the most common condition was hematologic malignancy (25.7%) and HLH (48.9%) in adult and pediatric patients, respectively.

Ferritin in HLH

In adult patients, HLH comprised only 14.2% of cases of hyperferritinemia; prevalence of HLH increased with increasing ferritin reaching 61% of cases at a ferritin cut-off of 100,000 μg/L (Table 3). On the other hand, ferritin was more specific in pediatric HLH predicting 50% of cases with ferritin levels >10,000 μg/L. HLH was the primary diagnosis with the highest median ferritin levels (35,515 μg/L) and the widest range of ferritin levels (10,002–684,000 μg/L) in adults compared to other diagnoses. Pediatric patients with HLH also displayed the widest range of ferritin levels (12,614–350,098 μg/L). Table 3 summarizes the prevalence of HLH at different ferritin cut-offs for adults and pediatrics.

Table 1 Patient demographics

		Adult patients ($N = 583$)	Pediatric patients ($N = 45$)
Age	Median	52 years	6 years
	Range	18–91 years	1 day–17 years
Gender, number (%)	Male	362 (62.1)	28 (62.2)
	Female	221 (37.9)	17 (37.8)

Ferritin sensitivity

We calculated the sensitivity of ferritin in HLH patients included in an ongoing database of adult HLH cases which included 110 patients who were diagnosed over the same period of the ferritin study (October 1, 2003 through March 31, 2016). Eighty-three had peak ferritin >10,000 μg/L for a sensitivity of 75.5% (83/110).

HLH patients' characteristics

Eighty-three adult patients were diagnosed with HLH; only one patient was diagnosed with primary HLH and was heterozygous for *Munc13–4* gene mutation. This was the only patient with positive genetic testing among a total of eight patients who underwent genetic testing for primary HLH. Disease triggers in patients with secondary HLH ($N = 82$) were attributed to infections ($N = 33$, 40.2%), hematologic malignancies ($N = 26$, 31.7%), rheumatologic disorders ($N = 5$, 6.1%), primary immunodeficiency ($N = 1$, 1.2%), post transplantation ($N = 3$, 3.7%; one allogeneic hematopoietic stem cell transplantation, one liver transplantation, and one kidney and pancreas transplantation), and idiopathic ($N = 14$, 17.1%). Among the infections triggering HLH, viral infections were the most common cause in 21 patients followed by bacterial ($N = 7$) and fungal ($N = 5$) infections. Twenty-two pediatric patients were diagnosed with HLH; 3/19 patients had primary HLH (double heterozygous mutations in *PRF1* gene, double heterozygous mutations in *SH2D1A* gene, and heterozygous mutation in *STXBP2* gene in the three patients, respectively). Disease triggers in the remaining patients ($N = 19$) were infections ($N = 5$, 26.3%), hematologic malignancies ($N = 1$, 5.3%), rheumatologic disorder ($N = 1$, 5.3%), primary immunodeficiency ($N = 1$, 5.3%), post kidney

Table 2 Conditions associated with elevated ferritin (>10,000 μg/L)

Primary diagnosis	Adult patients ($N = 583$)		Pediatric patients ($N = 45$)	
	Number (%)	Ferritin (μg/L), median (range)	Number (%)	Ferritin (μg/L), median (range)
Hematologic malignancy	150 (25.7)	14,141 (10,001–204,420)	8 (17.8)	31,716 (14,798–134,970)
Liver failure	93 (16)	19,396 (10,049–668,400)	2 (4.4)	47,703 (13,250–82,157)
HLH	83 (14.2)	35,515 (10,002–684,000)	22 (48.9)	36,091 (12,614–350,098)
Infection	81 (13.9)	17,004 (10,031–162,815)	6 (13.3)	21,136 (10,298–98,540)
Renal failure	59 (10.1)	16,510 (10,363–342,095)	0 (0)	–
Hemoglobinopathy	43 (7.4)	14,542 (10,220–48,721)	1 (2.2)	14,684
Iron overload–- transfusion	28 (4.8)	15,311 (10,384–96,453)	2 (4.4)	23,751 (13,159–34,343)
Solid tumor	16 (2.7)	14,706 (10,445–29,618)	0 (0)	–
GVHD	9 (1.5)	13,577 (10,999–23,259)	0 (0)	–
Rheumatologic disorder	9 (1.5)	15,534 (11,995–48,306)	1 (2.2)	51,885
Hemolysis	7 (1.2)	29,875 (14,713–85,870)	1 (2.2)	79,545
Hemochromatosis	3 (0.5)	23,976 (13,213–43,090)	0 (0)	–
MAS	1 (0.2)	63,063	0 (0)	–
Metabolic disorder	0 (0)	–	1 (2.2)	36,954
Unknown	1 (0.2)	12,845	1 (2.2)	23,045
Total	583 (100)	16,998 (10,001–684,000)	45 (100)	34,343 (10,298–350,098)

HLH hemophagocytic lymphohistiocytosis, *GVHD* graft versus host disease, *MAS* macrophage activation syndrome

Table 3 Prevalence of HLH at different ferritin cut-offs for adult and pediatric patients

Ferritin (μg/L)	Adult patients (≥18 years)		Pediatric patients (<18 years)	
	HLH diagnosis	Prevalence	HLH diagnosis	Prevalence
>10,000	83/583	14.24%	22/45	48.89%
>20,000	57/245	23.26%	18/31	58.06%
>30,000	45/150	30%	12/23	52.17%
>40,000	32/110	29.1%	10/19	52.63%
>50,000	26/80	32.5%	8/16	50%
>100,000	11/18	61.1%	3/4	75%

transplantation ($N = 1$, 5.3%), and idiopathic ($N = 10$, 52.6%). The clinical and laboratory findings of adult and pediatric patients with HLH are presented in Table 4.

Discussion

HLH is a heterogeneous group of disorders characterized by overproduction of inflammatory cytokines. In the secondary ("acquired") form which occurs mostly in adults, the disease is most often triggered by underlying infections, hematologic malignancies, or autoimmune conditions [14]. The primary ("familial") form of HLH occurs in children and is associated with mutations particularly in the perforin gene [6].

HLH diagnosis is often challenging for physicians since most of the clinical and laboratory features of HLH are non-specific. This challenge is pronounced with patients admitted to the intensive care unit where physicians need to differentiate HLH from other similar presentations like sepsis or systemic inflammatory response syndrome [15, 16]. The widely used diagnostic criteria for HLH were developed from observations in children, and they have not been validated for adult HLH diagnosis. In addition, two of the diagnostic parameters, soluble IL-2 receptor and NK cell activity, are send-out tests at most hospitals which might delay diagnosis and subsequently the initiation of treatment. So there is a need for finding a test that is readily available to diagnose HLH with certainty.

Ferritin is predominantly a cellular protein that regulates iron homeostasis and storage [17]. Elevated serum ferritin is a clinical parameter for iron overload, inflammation, tumor load, and liver disease [18]. The expression of ferritin is regulated by a variety of factors including iron, cytokines, and oxidative stress [19]. In vivo studies have shown that serum ferritin is primarily secreted by splenic macrophages and proximal tubule cells of the kidney [20, 21].

Serum ferritin with a cut-off of ≥500 μg/L was added to the revised HLH-2004 criteria based on serum ferritin values from 31 children with familial HLH [8]. The authors reported a ferritin sensitivity of 84% with no information on specificity at this cut-off [8]. Subsequently, investigators have proposed different ferritin cut-offs with varying specificities for pediatric HLH patients which are being applied to diagnose adult HLH. For example, a cut-off of >10,000 μg/L was suggested to be 96% specific for pediatric HLH in a retrospective study

Table 4 Clinical and laboratory findings of adult ($N = 83$) and pediatric ($N = 22$) HLH patients with elevated ferritin (>10,000 μg/L)

Characteristic	Adult patients No. (%)	Pediatric patients No. (%)
Age (years), median (range)	46 (18–79)	6.5 (1 day–17 years)
Gender (male/female)	54/29	14/8
Fever ($t \geq 38.5$ °C)	80/83 (96.4)	21/22 (95.4)
Splenomegaly	60/83 (72.3)	14/22 (63.6)
Bicytopenia or pancytopenia (ANC <1 × 10^9/L, hemoglobin <9 g/dL, platelet count <100 × 10^9/L)	75/83 (90.4)	20/22 (90.9)
Hypertriglyceridemia (≥265 mg/dL)	51/77 (66.2)	13/21 (61.9)
Hypofibrinogenemia (≤150 mg/dL)	31/71 (43.7)	14/22 (63.6)
Hemophagocytosis	51/74 (68.9)	16/19 (84.2)
Ferritin (μg/L), median (range)	35,515 (10,002–684,000)	34,612 (12,614–350,098)
Elevated soluble IL-2 receptor (≥2400 U/mL)	25/30 (83.3)	12/13 (92.3)
Absent or decreased NK cell activity	4/8 (50)	12/14 (85.7)
Genetic mutations consistent with HLH	1/8 (12.5)	3/19 (15.8)

ANC absolute neutrophil count, *IL-2* interleukin 2, *NK* natural killer

from Texas Children's Hospital [10]. However, these statistics were based on a small cohort of pediatric HLH ($N = 10$). Data on ferritin specificity in adult HLH is sparse; at a cut-off of >10,000 μg/L ferritin was shown to be 9% specific for HLH in one study [12] and 17% in another study [11].

Our results show that hyperferritinemia occurs in a variety of conditions in adult and pediatric patients. In adults, the most common conditions associated with elevated ferritin were hematologic malignancies (25.7%) followed by liver failure (16%) and HLH (14.2%). Other common reasons for elevated ferritin included infections, renal failure, and hemoglobinopathies. In pediatric patients, HLH was the most common cause of elevated ferritin (48.9%) followed by hematologic malignancies (17.8%) and infections (13.3%). For the same ferritin cut-off that we have used, the study by Sackett et al. was the closest to ours in terms of methodology and patient population; the investigators found that conditions associated with elevated ferritin included chronic transfusion (34%), liver disease (31%), and hematologic malignancies (15%) in adults, and comprised chronic transfusion (37%), hematologic malignancies (21%), and liver disease (11%) in pediatrics [12]. HLH was the diagnosis associated with elevated ferritin in only 8% of adults (6/67 patients) and 11% of pediatrics (2/19 patients). These findings were different from ours, and they may reflect differences in clinical practice and patient population between the two institutions. In another study by Schram and colleagues, ferritin at 50,000 μg/L cut-off predicted 17% of adult HLH [11]. Although still not specific at this cut-off, ferritin was more specific in our study predicting 32.5% of adult HLH patients for that same ferritin cut-off.

We had a larger number of patients in both age groups over an extended study period which gives us confidence to support our conclusions. The suggested ferritin specificity of 96% in pediatrics as reported by Allen et al. [10], which is often used in the adult setting, had not been confirmed and we would recommend considering other causes for hyperferritinemia. We found that elevated ferritin levels higher than 10,000 μg/L could predict for HLH in around 14% of adults and 50% of pediatrics. However, ferritin became more specific for adult HLH with increasing ferritin levels predicting 61% of HLH patients at ferritin levels higher than 100,000 μg/L. Our results support previous reports that elevated ferritin is not specific for adult HLH [11, 12]. Other diagnoses such as hematologic malignancies and liver failure should be considered first in the clinical workup.

We calculated ferritin sensitivity at a cut-off of >10,000 μg/L in a subset of adult HLH patients based on our adult HLH database (partially reported in [13]). We have calculated a ferritin sensitivity of 75.5% (83/110) at a cut-off of >10,000 μg/L for diagnosing adult HLH.

The limitations to our study are inherent to its retrospective design and reliance on chart review. Although we performed a thorough review of the clinical and laboratory information of patients, we cannot exclude the possibility of undocumented information, inaccurate diagnoses, or coding errors. In addition, since our study was conducted at a large tertiary care medical center, our patient population may not be representative of the general hospital population.

In conclusion, our results show that hyperferritinemia occurs in a variety of conditions in adult and pediatric patients. This study adds valuable information regarding the value of ferritin in predicting HLH; elevated ferritin (>10,000 μg/L) is not specific for pediatric or adult HLH. In adults, other causes of elevated ferritin should be considered first before entertaining the possibility of HLH.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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