Hyperferritinemia: causes and significance in a general hospital

Hajime Senjo\textsuperscript{a}, Takakazu Higuchi\textsuperscript{b}, Sadamu Okada\textsuperscript{b} and Osamu Takahashi\textsuperscript{c}

\textsuperscript{a}Internal Medicine, St. Luke’s International Hospital, Tokyo, Japan; \textsuperscript{b}Division of Hematology, St. Luke’s International Hospital, Tokyo, Japan; \textsuperscript{c}Center for Clinical Epidemiology, St. Luke’s International Hospital, Tokyo, Japan

\textbf{ABSTRACT}

\textbf{Objective:} To elucidate conditions which cause elevation of the serum ferritin, extent of the elevation in each condition, and clinical relevance of hyperferritinemia in general practice.

\textbf{Methods:} We retrospectively studied medical records of all patients who had at least one serum ferritin measurement above 500 \(\mu\)g L\(^{-1}\). Patients who had a marked elevation of the serum ferritin over 10,000 \(\mu\)g L\(^{-1}\) were studied separately.

\textbf{Results:} We studied 1394 patients to identify the etiologies of hyperferritinemia. Median serum ferritin level was 1024 \(\mu\)g L\(^{-1}\) and 49.2\% had ferritin levels of 501–1000 \(\mu\)g L\(^{-1}\). The most frequent cause of hyperferritinemia was non-human immunodeficiency virus infection followed by solid tumor, liver dysfunction, renal failure, and hematological malignancy. The distributions of the causes were different among groups stratified by the ferritin level. Forty-one percent had multiple causes and there was a tendency that the more underlying causes a patient had, the higher the ferritin level. Each condition led to a wide range of the ferritin level, and some patients could present with marked hyperferritinemia. Seventy percent of 111 patients with marked hyperferritinemia had multiple etiologies and a variety of diseases could lead to marked hyperferritinemia by themselves.

\textbf{Discussion:} Patients with hyperferritinemia frequently had multiple conditions. The level of the serum ferritin was determined by the underlying conditions to a certain extent; however, the variation was significant. While patients with marked hyperferritinemia mostly had multiple underlying causes, various diseases could cause hyperferritinemia by themselves.

\textbf{Conclusion:} Hyperferritinemia is associated with both etiology and the number of underlying causes.

\textbf{Introduction}

Ferritin is a 24-subunit protein composed of H- and L-subunits and mainly functions as an iron storage protein \cite{1}. The amount of ferritin is regulated in response to intracellular iron pool, and the serum level of ferritin has been used most prevalently as an indicator of iron deficiency or overload. In addition to its role in the regulation of the iron pool, serum ferritin level is elevated in various conditions and used as a nonspecific marker of various diseases, such as infection, rheumatologic and inflammatory disease, and malignant tumor \cite{1–3}. However, conditions which cause elevation of the serum ferritin level and the extent of the elevation in each condition remain unclear and, thus, the clinical relevance of the serum ferritin level in such conditions has not been established yet. It is conceivable that the pattern of elevation of the serum ferritin may differ among various conditions; however, the degree of the elevation in any specific conditions has rarely been reported, except as diagnostic criteria of hemophagocytic lymphohistiocytosis (HLH) and iron overload and as the indication of iron chelation for the latter \cite{4,5}.

In the setting of primary care, it is reported that more than half of patients with hyperferritinemia with serum ferritin levels above 1000 \(\mu\)g L\(^{-1}\) appeared to be left without evaluation, suggesting that the guidance to manage patients with hyperferritinemia in general practice is needed \cite{6}. For this purpose, it would be necessary to elucidate the causes and pattern of hyperferritinemia in a cohort of unselected patients seen in general practice. In addition, as a primary care-based screening study in North America revealed that Asians had higher mean serum ferritin level than whites, it would be interesting and meaningful to study the profile of hyperferritinemia in Asians, which, to the best of our knowledge, has not been studied in a large patient population \cite{7}. Therefore, we studied causes and profile of hyperferritinemia of the patients in a general hospital in Tokyo, Japan, which accepts both primary care patients and those referred to receive secondary and tertiary medical care. In addition, we also studied conditions which caused marked hyperferritinemia with serum ferritin levels above 10,000 \(\mu\)g L\(^{-1}\) because we considered that, as hyperferritinemia encompasses a very wide range of serum ferritin levels and the upper limit is...
Subjects and methods

This study is a retrospective observational cohort study approved by the Ethics Committee of St. Luke’s International Hospital, Tokyo, Japan.

Study population and data collection

We recruited all outpatients and hospitalized patients who had at least one serum ferritin measurement above 500 μg L\(^{-1}\) between 1 April 2010 and 30 September 2016 at St. Luke’s International Hospital, Tokyo. The medical records of these patients were reviewed to determine the diagnoses and etiologies which could cause elevation of the serum ferritin level at the time when hyperferritinemia was present as well as the demographic data. If serum ferritin levels above 500 μg L\(^{-1}\) were measured on multiple occasions, the highest value was adopted. Patients who were not Japanese and those who were younger than 18 years old at the time of ferritin measurement, on iron-supplementation therapy, and had received temporal red cell transfusion for operation and/or hemorrhage were excluded.

To study the characteristics of patients who presented with marked hyperferritinemia, we recruited additional adult patients with serum ferritin level above 10,000 μg L\(^{-1}\) between 1 April 2006 and 30 September 2016 with the same inclusion criteria.

Data analyses

Patients were categorized according to the diagnoses and/or etiologies of elevated serum ferritin as having HLH, rheumatologic/inflammatory disease, hematologic malignancy, solid tumor, non-HIV infection, liver dysfunction, renal failure, HIV infection, iron overload, hemolytic anemia, and others. HLH was diagnosed according to the HLH-2004 criteria by the Histiocyte Society [4]. Diagnoses of rheumatologic/inflammatory disease, hematologic malignancy, solid tumor, non-HIV infection, and hemolytic anemia were based on the established diagnoses. Liver dysfunction was defined as an established diagnosis of chronic liver disease and/or having aspartate aminotransferase and alanine aminotransferase levels higher than 500 U L\(^{-1}\). Renal failure was defined as receiving renal replacement therapy or having a glomerular filtration rate lower than 20 mL min\(^{-1}\) 1.73 m\(^{-2}\). HIV infection was defined as having a positive polymerase chain reaction result. Iron overload was defined as having been diagnosed by an attending physician or received regular red blood cell transfusions more than once a month for longer than the last six months. The underlying etiologies were not considered mutually exclusive and, if a patient had multiple underlying diagnoses and/or etiologies, all etiologies were adopted. In addition, patients who had single detectable etiology were separately studied to determine the level of hyperferritinemia associated with each etiology. Patients were categorized into five groups according to the serum ferritin level: >500 μg L\(^{-1}\) and ≤1000 μg L\(^{-1}\), >1000 μg L\(^{-1}\) and ≤3000 μg L\(^{-1}\), >3000 μg L\(^{-1}\) and ≤5000 μg L\(^{-1}\), >5000 μg L\(^{-1}\) and ≤7000 μg L\(^{-1}\), and >7000 μg L\(^{-1}\), and the etiologies of each category were studied. Furthermore, patients whose highest serum ferritin value exceeded 10,000 μg L\(^{-1}\) were analyzed separately to determine the conditions that could lead to marked hyperferritinemia, recruiting additional patients as described above. The diagnoses and etiologies of markedly elevated serum ferritin were investigated by the same methods used for patients with serum ferritin levels above 500 μg L\(^{-1}\).

Statistical analyses

All statistical analyses, including average, median, and trend-test, were carried out by IBM SPSS ver.22 (Tokyo, Japan).

Results

One thousand six hundred and seventy patients who had at least one ferritin measurement above 500 μg L\(^{-1}\) were identified. According to the exclusion criteria, 276 patients were excluded and 1394 patients were included in the studies to identify the etiologies of hyperferritinemia. The characteristics of these patients are presented in Table 1. The average age of the patients was 66.0 years and 62.7% were male. Median serum ferritin level was 1024 μg L\(^{-1}\) (interquartile range: 715–2102). The distribution of the serum ferritin values stratified as described in the methods is presented in Figure 1. Nearly half (49.2%) of the patients had a modest increase of serum ferritin with serum ferritin levels 501–1000 μg L\(^{-1}\) and 78% had serum ferritin levels below 3000 μg L\(^{-1}\).

The most frequent underlying cause of hyperferritinemia was non-HIV infection which was present in 44.8% of the patients, followed by solid tumor (26.3%), liver dysfunction (20.3%), renal failure (20.2%),

| Table 1. Characteristic of the patients with serum ferritin level above 500 μg L\(^{-1}\) (n = 1394). |
|-------------------------------------------------------------|
| **Characteristics** |
| **Age, mean (SD), years** | 66.0 (16.0) |
| **Gender, n (%)** |  |
| Male | 879 (62.7) |
| Female | 520 (37.3) |
| **Serum ferritin level, median (interquartile), mg L\(^{-1}\)** | 1024 (715–2102) |
| **SD:** standard deviation. |
Infectious disease 88 (6.3)
Non-HIV infection 1133 (6701)
Liver dysfunction 283 (20.3)
Renal failure 321 (20.2)
Hemolytic anemia 3 (0.2)
HIV infection 11 (0.8)
Iron overload 94 (6.7)
Others 150 (10.8)

As the underlying causes of these studies were not considered mutually exclusive, it was apparent that the majority of the patients had multiple causes, and we studied the number of the underlying causes each patient had and the level of the serum ferritin according to the number (Table 3). Fifty-nine percent of the patients had one detectable cause of hyperferritinemia, and there was a tendency that the more underlying causes a patient had, the higher the serum ferritin level was, although it was not statistically significant ($p = 0.08$). Table 3 also indicates that 41% of the patients had multiple underlying causes and their ferritin levels appeared to reflect the combined effect of the coexisting causes. Accordingly, as the degree of the elevation of the serum ferritin associated with each etiology could not be determined, we next analyzed the serum ferritin level of 823 patients in whom only one etiology was detected to elucidate the degree of the elevation of the serum ferritin associated with each etiology (Table 4). In this analysis, HLH patients without confirmed etiology were judged to have a single cause, although we considered it was likely that undetermined virus was involved. While the range of serum ferritin level associated with each etiology was wide, the degree of the serum ferritin elevation was relatively modest and seldom exceeded 2000 μg L$^{-1}$ in patients with renal failure, non-HIV infection, and solid tumor. In contrast, despite the small number of the patients, patients with HLH and HIV infection tended to have higher serum ferritin level, and some patients showed marked hyperferritinemia with serum ferritin levels of tens of thousands micrograms per liter. Patients with rheumatic/inflammatory disease, hematologic malignancy, and liver disease had a wide range of the serum ferritin levels and some patients had marked hyperferritinemia. Table 4 also shows that even diseases that caused a relatively modest increase of the serum ferritin level could also cause marked hyperferritinemia over 10,000 μg L$^{-1}$ in some patients. Considering the results in Table 3 which showed that coexisting diseases may cause further elevation of the ferritin level and the very wide range of the serum ferritin level without upper limit that ‘hyperferritinemia’ encompasses, it appeared important and valuable to study the conditions which caused marked hyperferritinemia. We, thus, investigated the distribution and prevalence of the conditions which caused marked hyperferritinemia over 10,000 μg L$^{-1}$. For this purpose, we extending the recruitment period and recruited a total of 111

| Disorder                     | Number (%) |
|-----------------------------|------------|
| HLH                         | 20 (1.4)   |
| Rheumatologic/Inflammatory disease | 88 (6.3)   |
| Hematologic malignancy      | 167 (12.0) |
| Solid tumor                 | 366 (26.3) |
| Non-HIV infection           | 625 (44.8) |
| Liver dysfunction           | 283 (20.3) |
| Renal failure               | 251 (20.2) |
| Hemolytic anemia            | 3 (0.2)    |
| HIV infection               | 11 (0.8)   |
| Iron overload               | 94 (6.7)   |
| Others                      | 150 (10.8) |

SD: standard deviation.

**Figure 1.** Serum ferritin levels of 1394 patients with hyperferritinemia. Patients were stratified into five groups according to the serum ferritin level, and the number of patients in each group are presented at the top of the bars.

**Figure 2.** Distribution of the causes of hyperferritinemia according to the serum ferritin level. Patients were stratified into five groups according to the serum ferritin level, and the underlying causes of hyperferritinemia in each group are presented. Numbers at the top of the bars indicate the number of the patients in each group.
patients with serum ferritin levels over 10,000 μg L⁻¹.

The most frequent underlying disease of patients with marked hyperferritinemia was non-HIV infection (47.3%), followed by liver dysfunction (35.5%), hematologic malignancy (30.9%), renal failure (23.6%), and iron overload (21.8%) (Table 5). Although non-HIV infection, liver dysfunction, and renal failure generally did not cause marked hyperferritinemia by themselves as described previously (Table 4), these diseases frequently contribute to the development of marked hyperferritinemia when combined with other etiologies (Figure 3). Distribution of the etiologies presented in Figure 3 also showed that while most of the patients with serum ferritin level above 10,000 μg L⁻¹ had multiple causes of hyperferritinemia, 33 patients (30%) had a single detectable etiology. Among them, eight patients had rheumatologic/inflammatory disease, seven hematological malignancy, five solid tumor, three non-HIV infection, and three liver dysfunction. These results indicated that while patients with marked hyperferritinemia mostly had multiple underlying causes which might contribute cooperatively to the marked elevation of the serum ferritin, various diseases could cause hyperferritinemia by themselves.

**Table 4.** Serum ferritin level of each disorder of 823 patients who had a single etiology

| Disorder                        | Number (%) | Ferritin (μg L⁻¹), range | Ferritin (μg L⁻¹), median (SD) |
|---------------------------------|------------|--------------------------|--------------------------------|
| HLH                             | 2 (0.3)    | 6603–83,200              | 44,901 (54,163)                |
| Rheumatologic/Inflammatory disease | 29 (3.5)  | 510–72,948               | 1142 (14,438)                 |
| Hematologic malignancy          | 63 (7.7)   | 508–49,218               | 1330 (9308)                   |
| Solid tumor                     | 145 (17.6) | 528–11,800               | 1165 (1707)                   |
| Non-HIV infection               | 250 (30.3) | 512–23,200               | 872 (1969)                    |
| Liver dysfunction               | 95 (11.5)  | 562–306,000              | 1080 (33,202)                 |
| Renal failure                   | 80 (10.7)  | 503–19,400               | 720 (2109)                    |
| Hemolytic anemia                | 0 (0.5)    | NA                       | NA                            |
| HIV infection                   | 4 (0.5)    | 1300–112,831             | 2551 (55,355)                 |
| Iron overload                   | 0 (0.5)    | NA                       | NA                            |
| Others                          | 147 (17.9) | 501–202,200              | 828 (16,681)                  |

SD: standard deviation; NA: not available.

**Table 5.** Distribution of causes of hyperferritinemia of 111 patients with markedly elevated serum ferritin level above 10,000 μg L⁻¹

| Disorder                        | Number (%) |
|---------------------------------|------------|
| HLH                             | 15 (13.6)  |
| Rheumatologic/Inflammatory disease | 16 (14.5)  |
| Hematologic malignancy          | 34 (30.9)  |
| Solid tumor                     | 23 (20.9)  |
| Non-HIV infection               | 52 (47.3)  |
| Liver dysfunction               | 39 (35.5)  |
| Renal failure                   | 26 (23.6)  |
| Hemolytic anemia                | 2 (1.8)    |
| HIV infection                   | 3 (2.7)    |
| Iron overload                   | 24 (21.8)  |
| Others                          | 4 (3.6)    |

**Discussion**

While the amount of ferritin is mainly regulated by the intracellular iron pool, it is also regulated by various stimuli, such as cytokines, growth factors, hormones, oxidative stress, and hypoxia, and ferritin is involved not only in the storage of iron but also in inflammation, immunity, and cancer [1–3]. Accordingly, serum ferritin
is elevated in various conditions and a variety of diseases are known to cause hyperferritinemia and, in general, serum ferritin levels greater than 1000 μg L⁻¹ are regarded to be a nonspecific marker of such diseases [1]. However, profiles and degrees of the elevation of the serum ferritin in patients with hyperferritinemia have not been sufficiently elucidated to be used as a marker of specific diseases in general practice, and it is necessary to clarify the characteristics of hyperferritinemia to provide a reference for general practitioners.

Although previous studies of hyperferritinemia adopted different cutoff levels of serum ferritin among studies, we adopted the cutoff level of 1000 μg L⁻¹ for hyperferritinemia [8,9]. As for marked or extreme hyperferritinemia, most studies used the cutoff level of 10,000 μg L⁻¹ and we used this value in our study [9–12].

Most of the previous studies either defined primary diagnosis as a single cause or allowed multiple diseases as causes of hyperferritinemia [8–11,13–16]. Our observation that 41% of the patients with hyperferritinemia had multiple underlying causes indicated that, together with reports showing that 16.8–46% of patients with hyperferritinemia had more than one etiology, either approach was not satisfactory to elucidate the etiologies of hyperferritinemia encountered in the clinical setting [8,13,17]. Therefore, we studied both the actual distribution of the etiologies allowing multiple diseases as possible etiologies to elucidate the characteristics of hyperferritinemia encountered in general practice and the profiles of hyperferritinemia caused by single etiology to elucidate the degree of hyperferritinemia associated with each etiology. To the best of our knowledge, only one study reported results of a similar approach; however, the study was performed in a department of gastroenterology and their results cannot be applied to general practice [17].

In nearly half of the patients, the serum ferritin level was 501–1000 μg L⁻¹, showing that hyperferritinemia of modest degree is most frequently encountered. Although the distribution of the underlying causes of hyperferritinemia differed depending on the degree of the elevation of serum ferritin, non-HIV infection was the most common etiology of hyperferritinemia both in the whole patient population and in the patients with single etiology. Three studies of the causes of hyperferritinemia not restricted to the marked hyperferritinemia in which the causes were not mutually exclusive reported conflicting results [8,13,17]. They reported that the most common cause of hyperferritinemia was liver disease, non-HIV infection, and renal failure, respectively. Two studies in which single diagnosis was determined reported malignancy or liver disease to be the most common cause; however, the presence of other causes was not considered in either of them [9,14]. In addition, these reports were from university hospitals [8,9,13], a department of gastroenterology [17], or a teaching hospital [14], and significant selection bias could exist and we consider that our results represent the distribution and profile of the causes of hyperferritinemia close to those actually encountered in general practice.

While non-HIV infection was the most common etiology of hyperferritinemia, the median ferritin level of the patient with non-HIV infection alone was 872 μg L⁻¹, indicating that it seldom caused significant elevation of the ferritin level unless other causes of hyperferritinemia were complicated, although the serum ferritin level of patients with non-HIV infection alone could occasionally be as high as 23,200 μg L⁻¹. Overall, the degree of the elevation of the serum ferritin level differed among underlying diseases and, thus, it would be useful to know the degree of hyperferritinemia to which each disease might lead when considering a differential diagnosis. Moreover, the degree of the elevation of the serum ferritin level tended to be higher as more etiologies were present, suggesting that, when a patient presents an unexpectedly high serum ferritin level for the diagnosis, it would raise the possibility that other diseases are present and prompt further evaluation.

As the range of the serum ferritin level is wide without upper limit but the ferritin elevation was mild or modest in many patients, it appeared clinically important and useful to study the characteristics of marked hyperferritinemia. Previous studies of a relatively small number of patients which determined a primary cause as the etiology reported that either chronic transfusion or malignancy was the most frequent cause of marked hyperferritinemia [9–11,15]. One large study which similarly determined a primary cause reported hematological malignancy to be the most common cause followed by liver failure, HLH, and infection [12]. However, these studies do not appear to properly represent the picture of marked hyperferritinemia in general practice. We attempted to elucidate the actual picture of marked hyperferritinemia by studying the distribution of the causes in each patient according to the method used in a previous study [16]. As expected, 70% of the patients had multiple diagnoses. While non-HIV infection was the most common cause and diagnosed in 52 patients (47%), 49 of them also had other etiologies, indicating that non-HIV infection plus other causes was the most common cause of marked hyperferritinemia. Overall, 70% of patients with marked hyperferritinemia had multiple etiologies and 33 patients (30%) with a single underlying etiology. The etiologies of the 33 patients were diverse and the most frequent etiology was rheumatic/inflammatory disease followed by hematological malignancy, but other diseases also caused marked hyperferritinemia. These findings support the notion that HLH is not a specific disease which causes marked hyperferritinemia in adults and a diagnosis of
HLH cannot be made by serum ferritin level alone [11,12,16,18].

There are several limitations of this study. First, this is a retrospective study and the decision to study the serum ferritin level was at the discretion of the attending physicians, and a considerable number of patients with hyperferritinemia could have been left without being recognized. Next, although we attempted a thorough review of the medical records, it is possible that some conditions had not been diagnosed or the diagnoses were incorrect. Finally, we could not fully check oral iron supplements prescribed by other institutions or obtained commercially, and the influence of such supplements was not considered. However, in spite of these limitations, we believe that our results represent the characteristic of hyperferritinemia in the general clinical setting.

Knowing the etiologies and profiles of hyperferritinemia, effective approach to patients with hyperferritinemia would be feasible guided by the degree of hyperferritinemia. When patients have higher serum ferritin levels for the diagnoses, the presence of other conditions should be considered. Moreover, sequential observation of the serum ferritin level may provide a chance and rationale to consider possible complication of new diseases.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**References**

[1] Wang W, Knovich MA, Coffman LG, et al. Serum ferritin: past, present and future. Biochem Biophys Acta. 2010;1800(8):760–769.

[2] Crook MA. Hyperferritinaemia: laboratory implications. Ann Clin Biochem. 2012;49(Pt 3):211–213.

[3] Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immumol. 2017;29(9):401–409.

[4] Henter II, Horne AC, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124–131.

[5] Bennett JM. Consensus statement on iron overload in myelodysplastic syndromes. Am J Hematol. 2008;83(11):858–861.

[6] Ogilvie C, Fitzsimons K, Fitzsimons EJ. Serum ferritin values in primary care: are high values overlooked? J Clin Pathol. 2010;63(12):1124–1126.

[7] Harris EL, McLaren CE, Reboussin DM, et al. Serum ferritin and transferrin saturation in Asians and Pacific Islanders. Arch Intern Med. 2007;167(7):722–726.

[8] Lee MH, Means RT. Extremely elevated serum ferritin levels in a university hospital: associated diseases and clinical significance. Am J Med. 1995;98(6):566–571.

[9] Moore C, Ormseth M, Fuchs H. Causes and significance of markedly elevated serum ferritin levels in an academic medical center. J Clin Rheumatol. 2013;19(6):324–328.

[10] Crook MA, Walker PLC. Extreme hyperferritinaemia: clinical causes. J Clin Pathol. 2013;66(5):438–440.

[11] Sackett K, Cunderlik M, Sahni N, et al. Extreme hyperferritinemia. Causes and impact on diagnostic reasoning. Am J Clin Pathol. 2016;145(5):646–650.

[12] Otrock ZK, Hock KG, Riley SB, et al. Elevated serum ferritin is not specific for hemophagocytic lymphohistiocytosis. Ann Hematol. 2017;96(10):1667–1672.

[13] Le Page L, Leflon P, Mahévas M, et al. Spectre étiologique des hyperferritinémies. Rev Méd Interne. 2005;26(5):368–373.

[14] Narayanan D, Waise A. Causes of hyperferritinaemia. Ann Clin Biochem. 2013;50(4):381–382.

[15] Marshall GA, Pretorius CJ, Ungerer JP. Extreme hyperferritinaemia: further considerations. Ann Clin Biochem. 2012;49(Pt 3):306.

[16] Schram AM, Campigotto F, Mullally A, et al. Marked hyperferritinemia does not predict for HLH in the adult population. Blood. 2015;125(10):1548–1552.

[17] Hearnshaw S, Thompson NP, McGill A. The epidemiology of hyperferritinaemia. World J Gastroenterol. 2006;12(36):5866–5869.

[18] Allen CE, Yu X, Kozinetz CA, et al. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008;50(6):1227–1235.