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Retrospective Experience of Hyperferritinemia in a Single-center

Tek Merkezde Retrospektif Hiperferritinemi Deneyimi

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ABSTRACT

Aim: Malignancy, infection, inflammation, liver and renal diseases, hematological disorders, iron overload, metabolic syndrome, and alcohol consumption can cause hyperferritinemia. This study aimed to identify the underlying causes of hyperferritinemia in patients at a tertiary care medical center.

Materials and Methods: We retrospectively evaluated the patients with serum ferritin (SF) levels higher than 1000 µg/L between 2014 and 2016. Among these patients (n=94), 89 patients with hematological disorders (n=69) or oncological diseases (n=20) were included in the study. For patients with multiple SF measurements, the highest level was considered. The association between SF levels and patients' demographics, clinical characteristics, laboratory parameters, and the total number of red blood cell transfusions received were evaluated using the median SF value as a comparison point.

Results: The patients' median (min-max) age was 61 (20-94) years, and 49 (55.1%) patients were female. The median (min-max) SF level of the patients' was 1739 µg/L. Serum aspartate aminotransferase and gamma-glutamyl transferase levels were higher in patients with SF levels above the median value than those with SF below the median (p=0.001, p=0.003, respectively). No significant difference was found in erythrocyte sedimentation rate and C-reactive protein levels between patients with SF levels above the median and those below the median (p=0.689, 0.230, respectively). Patients with SF levels above the median received a higher total number of red blood cell transfusions compared to those with levels below the median (p<0.001).

Conclusion: In this study, hematological disorders were the predominant underlying cause of hyperferritinemia potentially due to chronic red blood cell transfusions and inflammation.

Keywords: Hematological disorder, hyperferritinemia, inflammation, iron overload

ÖZ

Amaç: Malignite, enfeksiyon, enflamasyon, karaciğer ve böbrek hastalıkları, hematolojik hastalıklar, aşırı demir yüklenmesi, metabolik sendrom ve alkol tüketimi hiperferritinemiye neden olabilir. Bu çalışmanın amacı, üçüncü basamak bir tıp merkezindeki hastalarda hiperferritineminin altında yatan nedenleri belirlemektir.

Gereç ve Yöntem: 2014-2016 yılları arasında serum ferritin (SF) düzeyi 1000 µg/L'den yüksek olan hastalar retrospektif olarak değerlendirildi. Bu hastalar arasından (n=94), hematolojik (n=69) veya onkolojik hastalık (n=20) tanıları olan 89 hasta çalışmaya dahil edildi. Birden fazla SF ölçümü olan hastalarda en yüksek düzey dikkate alındı. SF düzeyleri ile hastaların demografik özellikleri, klinik özellikleri, laboratuvar parametreleri ve aldıkları toplam eritrosit transfüzyonu sayıları arasındaki ilişki, karşılaştırma noktası olarak medyan SF değeri kullanılarak değerlendirildi.

Bulgular: Hastaların medyan (min-maks) yaşı 61 (20-94) yıldı ve 49 (%55,1) kadındı. Hastaların medyan SF düzeyi 1739 µg/L idi. Serum aspartat aminotransferaz ve gama-glutamil transferaz düzeyleri, SF düzeyi medyan değerin üzerinde olan hastalarda, SF düzeyi medyan değerin altında olanlara kıyasla daha yüksekti (sırasıyla p=0,001, p=0,003). SF düzeyleri medyanın üzerinde olan hastalar ile medyanın altında olan hastalar arasında eritrosit sedimantasyon hızı ve C-reaktif protein değerleri açısından anlamlı bir fark bulunmadı (sırasıyla p=0,689, 0,230). SF düzeyleri medyan değerin üzerinde olan hastalar, medyan değerin altında olanlara kıyasla daha fazla sayıda eritrosit transfüzyonu almıştır (p<0.001).

Sonuç: Bu çalışmada hematolojik bozukluklar, muhtemelen kronik eritrosit transfüzyonlarına ve enflamasyona bağlı olarak, hiperferritineminin temel nedeniydi.

Anahtar Kelimeler: Hematolojik bozukluklar, hiperferritinemi, enflamasyon, aşırı demir yükü

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INTRODUCTION

Ferritin, mainly a cytosolic protein, regulates iron homeostasis by storing and buffering intracellular iron to prevent free iron toxicity and releasing iron as needed for essential processes. Serum ferritin (SF) measurement is the primary non-invasive method for assessing body iron storage, though levels generally represent iron-poor extracellular ferritin in clinical practice[1]. Hyperferritinemia is generally defined as SF levels above 200 µg/L in adult females and 300 µg/L in adult males[2]. Hyperferritinemia can result from various conditions, including malignancy, infection, inflammation, liver disease, hematological disorders, renal disease, metabolic syndrome, chronic alcohol intake, and iron overload[2-8]. The pattern of SF elevation varies among these conditions; however, the degree of this elevation is infrequently quantified, except when applied as a diagnostic criterion for hemophagocytic lymphohistiocytosis or as an indication for iron chelation therapy in patients with iron overload[9,10]. It was demonstrated that individuals with moderately elevated SF levels ≥200 µg/L have an increased risk of total, cancer-related, endocrinological, and cardiovascular mortality compared to those with SF levels <200 µg/L[11]. SF levels exceeding 1000 µg/L warrant a thorough evaluation, regardless of transferrin saturation, as they reliably indicate an underlying pathology[1]. Considering the clinical importance of such elevated SF levels, we aimed to investigate the underlying causes in patients managed at a tertiary care medical center.

MATERIALS AND METHODS

Selection and Description of the Cases

We conducted a retrospective, descriptive study at a single center. We retrieved the medical records of patients who were 18 years and older with SF levels higher than 1000 µg/L at Dokuz Eylül University Hospital, between January 2014 and February 2016. Among these patients (n=94), 5 patients (chronic kidney disease, n=2; hereditary hemochromatosis, n=1; still's disease, n=1; and pectus excavatum, n=1) were excluded from the study to simplify the grouping of the patient population. The remaining 89 patients all had hematological (n=69) disorders or oncological (n=20) disease diagnoses and were included in the study.

Our study was based on the 2013 amendment of the Helsinki Declaration, and ethical approval was obtained from the Dokuz Eylül University Institutional Review Board (protocol number: 2584-GOA, decision no: 271, date: 24.03.2016).

Study Design

Demographic and clinical data of the patients were obtained from medical and/or electronic hospital records. The highest value was considered for patients with multiple ferritin measurements exceeding 1000 µg/L. The patients' ages, genders, laboratory parameters (transferrin saturation, alanine aminotransferase (normal range: 0-35 U/L), aspartate aminotransferase (AST) (normal range: 0-35 U/L), gamma-glutamyl transferase (GGT) (normal range: 0-38 U/L), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) (normal range: 0-5 mg/L) at the time of the highest ferritin levels and total number of erythrocyte transfusions they received in 25 months at Dokuz Eylül University Hospital were noted. Underlying disorders were classified as either hematological disorders or oncological diseases. Hematological disorders encompass benign and malignant conditions affecting the blood, blood cells, and organs involved in hematopoiesis. Oncological diseases, on the other hand, refer to malignant conditions characterized by the uncontrolled proliferation of cells, resulting in the formation of solid tumors. The association between SF levels and patients' demographics, clinical characteristics, laboratory parameters, and the total number of erythrocyte transfusions received was evaluated using the median SF value as a comparison point. Additionally, patients who received iron chelation therapy were documented, and ferritin levels of these patients were evaluated in the 3rd-6th and 10th months of iron chelation therapy.

Technical Information

SF levels were measured by a chemiluminescent method in the Beckman Coulter DxI-800 autoanalyzer and measurements were recorded as µg/L.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics for Windows, Version 15.0. Descriptive findings were presented as percentage distributions for categorical variables and mean ± standard deviation for continuous variables. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. As the distributions were not normal, the non-parametric Mann-Whitney U test was used to compare the two independent groups. The chi-square test was used to analyze categorical variables when comparing groups based on the median ferritin value.

RESULTS

Demographic and General Clinical Features

The patients' median (min-max) age was 61 (20-94) years, and 49 (55.1%) patients were female. Sixty-nine (77.5%) patients had a hematological disorder diagnosis, and 20 (22.5%) patients had an oncological disease diagnosis. The association between SF level and gender and clinical diagnoses is shown in Table 1.

Laboratory Parameters of the Patients

The median (min-max) SF level of the patients was 1739 µg/L (1005-10,475). The patients' (n=66) mean transferrin saturation was 51.2±26.6%. When patients were divided into two groups according to median SF level (SF level <1739 µg/L and SF level ≥1739 µg/L), a statistically significant difference was found between these two groups in terms of AST and GGT levels (p=0.001, p=0.003 respectively) (Table 2). However, no significant difference was found in ESR and CRP values between patients with SF levels above the median value and patients with SF levels below the median value (p=0.689, p=0.230 respectively) (Table 2).

Red Blood Cell Transfusions

The mean total number of red blood cell transfusions received by the patients was 21.8±26.5. The total number of red blood cell transfusions received was higher in patients with SF levels above the median value compared to those with SF levels below the median (p<0.001) (Table 3).

Iron Chelation Therapy

Twenty (22.5%) of the patients received iron chelation therapy. Among the 20 patients, 18 had hematological disorders,

while 2 were diagnosed with oncological diseases. During the first assessment, 3 to 6 months after initiation of iron chelation therapy, two patients were lost to follow-up. Among the remaining 18 patients, 15 (83.3%) exhibited a ≥10% reduction in SF levels compared with baseline. During the second assessment at the 10th month of iron chelation therapy, six patients were lost to follow-up. Among the remaining 14 pateints, 10 (71.4%) showed a≥10% reduction in SF levels compared with baseline.

DISCUSSION

In this study, hematological disorders (77.5%) were identified as the most common underlying cause of hyperferritinemia, followed by oncological diseases (22.5%). Hyperferritinemia observed in these patients may be attributed to iron overload resulting from chronic red blood cell transfusions and chronic inflammation associated with malignancy[2]. On the other hand, red blood cell disorders characterized by ineffective

Table 1. Comparison of demographic and clinical features of the patients according to median serum ferritin levels

Patients (n=89)	Ferritin level <1739.0 µg/L		Ferritin level ≥1739.0 µg/L		p-value*
	n	%	n	%	
Gender					
Male	19	47.5	21	52.5	0.741
Female	25	51.0	24	49.0	
Diagnoses					
Hematological disorder	33	47.8	36	52.2	0.572
Oncological disease	11	55.0	9	45.0	

*: Chi-square test

Table 2. Comparison of laboratory parameters of the patients according to median serum ferritin levels

		Ferritin level<1739.0 µg/L	Ferritin level≥1739.0 µg/L	
Laboratory parameters	**n**	**Median (IQR)**	**Mean ± SD**	**p-value***
AST (U/L)	78	21 (18)	34 (30)	**0.001**
ALT (U/L)	85	18 (33)	24 (63)	0.07
GGT (U/L)	78	38 (53)	64 (132)	**0.003**
ESR (mm/h)	78	65.8±8.2	57.1±9.7	0.689
CRP (mg/L)	85	25.8±6.5	75.6±20.5	0.230

*: Mann-Whitney U test, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, SD: Standard deviation, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, IQR: Interquartile range

Table 3. Comparison of red blood cell transfusions received by patients based on median serum ferritin levels

	Ferritin level <1739.0 µg/L		Ferritin level ≥1739.0 µg/L		
Total number	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**p-value***
Red blood cell transfusions	44	14.7±20.0	45	28.7±30.3	<0.001

*: Mann-Whitney U test, SD: Standard deviation

erythropoiesis or hemolysis can result in increased iron absorption and elevated SF levels even in the absence of red blood cell transfusions[12], representing an additional mechanism in patients with hematological disorders.

In another study of 95 patients with SF levels above 1000 µg/L, the following conditions were identified: 20.0% had liver disease; 17.9% had renal disease; 17.9% had malignant conditions; 16.8% were infected with human immunodeficiency virus (HIV); 15.8% had non-HIV-related systemic infections; 10.5% required chronic blood transfusions; and 10.5% had sickle cell syndromes[5]. Variations in reported prevalence may be attributed to differences in demographic characteristics, geographic distribution, genetic predisposition, environmental exposures, healthcare infrastructure, and study design.

Inflammation stimulates ferritin synthesis through the action of pro-inflammatory cytokines and promotes its release via apoptosis and cellular damage[13]. Although mean CRP and ESR levels were elevated in this study, no significant association was found between acute-phase reactants and patients stratified by SF levels above or below the median. This lack of association may be attributed to several factors, including the presence of outliers, the timing of biomarker measurement, variability in individual inflammatory responses, and the multifactorial role of ferritin in inflammation. Interestingly, the mean ESR value was higher among patients with SF levels below the median, suggesting a greater inflammatory burden in this subgroup. However, it is essential to acknowledge that ESR is a non-specific marker and may be influenced by non-inflammatory factors, such as age, sex, and changes in plasma protein composition.

McKinnon et al.[14] showed a correlation between GGT and SF levels in Australian adult males and females ($p<0.0001$). This correlation was consistently evident across all age groups and was unaffected by body mass index adjustment. In the current study, patients with SF levels above the median level demonstrated significantly higher serum GGT levels than those with SF levels below the median ($p=0.003$). Our findings align with previous research, suggesting a link between metabolic dysfunction and an iron overload syndrome characterized by hyperferritinemia[15]. Non-alcoholic steatohepatitis may have contributed to these elevated GGT levels[2].

Chronic red blood cell transfusions can result in toxic iron accumulation in organs, leading to tissue damage and dysfunction. Excess iron presents ongoing toxicity risks; however, damage is often reversible with the prompt elimination of iron[16]. Iron chelators have been shown to effectively reduce tissue iron levels, mitigate complications associated with iron overload, and enhance event-free survival outcomes[17]. In the current study, only 22.5% of the patients received iron chelation therapy. This low percentage is likely due to varying opinions on the optimal timing for initiating treatment, challenges with patient adherence, and issues related to cost and accessibility[17]. In developed countries, the monitoring of iron load and the assessment of chelation therapy progress in regularly transfused patients are typically conducted through SF measurements every three months[16].

Study Limitations

Our study was retrospective, which constrained the availability of detailed information, including specific subgroups of the hematological disorders. The number of patients was small. Our patient population was derived from a tertiary care medical center; it may not represent the full spectrum of diseases or conditions commonly encountered in general practice. The number of red blood cell transfusions received by patients outside our medical center was not recorded, which may result in an underestimate of the iron burden. The study's strengths include the high ferritin cut-off value (>1000 µg/L), which allowed for the exclusion of numerous factors that could contribute to elevated SF levels.

CONCLUSION

This study examined the underlying causes of hyperferritinemia in patients at a tertiary care medical center. Our results suggest that hematological disorders were the primary underlying cause of hyperferritinemia, potentially as a result of ineffective erythropoiesis, hemolysis, chronic inflammation, and chronic red blood cell transfusions.

Ethics

Ethics Committee Approval: Our study was based on the 2013 amendment of the Helsinki Declaration, and ethical approval was obtained from the Dokuz Eylül University Institutional Review Board (protocol number: 2584-GOA, decision no: 271, date: 24.03.2016).

Informed Consent: A retrospective, descriptive study was conducted at a single center.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.A.G.D., A.O., M.A.Ö., Concept: Ş.A.G.D., A.O., M.A.Ö., Design: Ş.A.G.D., A.O., M.A.Ö., Data Collection or Processing: Ş.A.G.D., Analysis or Interpretation: Ş.A.G.D., A.O., M.A.Ö., Literature Search: Ş.A.G.D., A.O., M.A.Ö., Writing: Ş.A.G.D.

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