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ASSOCIATION OF SERUM FERRITIN LEVEL WITH SYMPTOMS OF WEAKNESS AND DIZZINESS IN PATIENTS WITH NORMAL HEMOGLOBIN

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Abstract

Introduction. Latent iron deficiency (LID), characterized by depletion of tissue iron stores with preserved hemoglobin levels, remains an underappreciated clinical problem. Patients with LID frequently present with complaints of reduced work capacity, asthenia, and neurological symptoms, which are often erroneously interpreted by primary care physicians as manifestations of chronic fatigue syndrome or psychosomatic disorders.

Aim of the study. To examine the prevalence and severity of clinical symptoms in the anemic spectrum (primarily weakness and dizziness) in individuals with normal hemoglobin levels and reduced serum ferritin values.

Materials and methods. This single-center comparative study enrolled patients who presented to internal medicine and general practice outpatient clinics between December 2022 and July 2023. Hematological parameters were measured by flow cytofluorometry; serum ferritin was assessed by immunochemical assay. Patients were divided into two groups: the Study Group (normal hemoglobin, ferritin < 30 ng/mL) and the Control Group (normal hemoglobin, ferritin ≥ 30 ng/mL). Subjective fatigue was assessed using the Fatigue Severity Scale (FSS); a structured questionnaire recorded the presence of dizziness and restless legs syndrome (RLS).

Results. The mean age of participants was 30.3 ± 9.5 years. Statistically significant between-group differences were found for sex ($p < 0.001$) and body mass index ($p = 0.007$). In the study group (low ferritin), the frequency of dizziness complaints was significantly higher ($p = 0.001$). The mean FSS score was also significantly higher than in the control group ($p = 0.039$), confirming the high prevalence of true tissue fatigue in iron deficiency without anemia.

Conclusion. Low serum ferritin is associated with clinically significant weakness, dyspnea, and dizziness even with normal hemoglobin values. Timely screening of ferritin levels in asthenic patients enables detection of latent iron deficiency before systemic anemia becomes manifest.

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Keywords

latent iron deficiency, iron deficiency without anemia, serum ferritin, weakness, dizziness, Fatigue Severity Scale (FSS).

Introduction

Iron is an indispensable micronutrient that ensures the functioning of numerous biological systems in the body. Traditionally, iron deficiency has been viewed by clinicians through the lens of iron-deficiency anemia (IDA). However, the pathophysiological process of iron depletion follows a staged course, and a decrease in hemoglobin synthesis represents only its terminal, manifest stage. The state in which iron stores are depleted (low serum ferritin) but tissue hypoxic syndrome has not yet caused hemoglobin to fall below threshold values is classified as latent iron deficiency (LID), or Iron Deficiency Without Anemia (IDWA).

The biological role of iron extends far beyond oxygen transport by hemoglobin. It is a component of myoglobin, mitochondrial respiratory chain cytochromes (which support ATP synthesis), and a cofactor for key CNS enzymes such as tyrosine hydroxylase, which participates in dopamine synthesis.

At the cellular level, iron deficiency leads to mitochondrial dysfunction and reduced cellular respiration in skeletal muscle and neurons, which can manifest clinically long before changes appear in erythrocyte indices.

Despite pathophysiological justification, patients with isolated low ferritin frequently encounter underdiagnosis. Their complaints of marked fatigue, unmotivated weakness, and episodic dizziness are often attributed to autonomic dysfunction or psycho-emotional stress, since routine complete blood count reveals no pathology. In this regard, studying and systematizing the clinical features of LID—particularly asthenic and neurological manifestations—represents an urgent task for modern practical healthcare.

Literature Review

The clinical manifestation of iron deficiency with normal hemoglobin levels has been actively discussed in the international literature. Several authors emphasize that fatigue and reduced exercise tolerance in LID are directly related to decreased activity of iron-containing enzymes in muscle tissue. Foundational studies have established that tissue iron depletion limits the rate of oxidative phosphorylation, leading to early anaerobic glycolysis and lactate accumulation.

Neurological symptoms, including dizziness and restless legs syndrome (RLS), are pathogenetically explained by the concept of central (cerebral) iron deficiency. Iron is critically important for myelination of nerve fibers and modulation of dopaminergic transmission in the basal ganglia. A decrease in serum

ferritin closely correlates with a reduction in its concentration in cerebrospinal fluid, which provokes dysfunction of the dopamine system. This manifests clinically as motor restlessness in the lower extremities and cognitive fatigue.

Current clinical guidelines are gradually revising diagnostic algorithms, expanding indications for ferritin measurement. Nevertheless, the threshold values for initiating therapy in the absence of anemia remain a subject of debate: values ranging from < 15 ng/mL to < 30 ng/mL (and even < 50 ng/mL in the presence of concomitant inflammatory processes) are cited as criteria for store depletion. The present study uses a cutoff of 30 ng/mL as the most sensitive marker of latent deficiency.

Materials and Methods

This is an observational comparative study conducted at outpatient departments of internal medicine and general practice.

Inclusion criteria: age 18 to 65 years; normal hemoglobin level (HGB ≥ 120 g/L for women, ≥ 130 g/L for men).

Exclusion criteria: confirmed anemia of any etiology; acute or exacerbated chronic inflammatory diseases (which can falsely elevate ferritin as an acute-phase protein); oncological pathologies; pregnancy and lactation; use of iron supplements or blood transfusions within the preceding 3 months.

Group formation. A total of 141 patients were enrolled and divided into two groups:

Study Group (Group 1, n = 78): patients with normal hemoglobin but reduced serum ferritin (< 30 ng/mL).

Control Group (Group 2, n = 63): patients with normal hemoglobin and target ferritin level (≥ 30 ng/mL).

Clinical and laboratory assessment. Venous blood was collected strictly under fasting conditions. The hematological profile (including HGB, MCV, MCH, RDW) was analyzed on an automated analyzer. Serum ferritin was determined by electrochemiluminescence immunoassay.

The validated Russian-language version of the Fatigue Severity Scale (FSS), consisting of 9 statements rated on a 7-point scale (minimum 9, maximum 63 points), was used for standardized assessment of asthenic syndrome severity. The presence of dizziness, dyspnea, restless legs syndrome, and other somatic complaints (pica, alopecia, cheilitis) was recorded using a specialized structured questionnaire during in-person interviews.

Statistical analysis. Data were processed using SPSS Statistics. Normality of distribution was tested by the Kolmogorov–Smirnov criterion. Continuous variables are presented as mean ± standard deviation (M ± SD). Comparison of

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continuous variables was performed using Student's t-test or the Mann–Whitney U test. Categorical variables were compared using Pearson's chi-squared (χ^2) test. Differences were considered statistically significant at $p < 0.05$.

Results

The final analysis included 141 participants. The mean age of the total sample was 30.3 ± 9.5 years. Analysis of anthropometric and demographic data revealed substantial between-group differences, reflecting the epidemiological features of iron deficiency distribution (Table 1).

Table 1. Comparative Demographic and Anthropometric Characteristics of the Study Groups

Parameter	Study Group (Low Ferritin) (n=78)	Control Group (Normal Ferritin) (n=63)	p-value
Age (M ± SD)	28.9 ± 8.1	32.1 ± 10.8	0.044
Sex (female), n(%)	72 (92.3%)	31 (49.2%)	< 0.001
Smoking, n(%)	14 (17.9%)	23 (36.5%)	0.025
Height, cm (M ± SD)	164.2 ± 6.4	171.8 ± 8.9	< 0.001
Weight, kg (M ± SD)	60.4 ± 11.2	74.5 ± 14.3	< 0.001
BMI, kg/m² (M ± SD)	22.4 ± 3.8	25.1 ± 4.2	0.007

** statistically significant differences ($p < 0.05$)*

The study group with latent iron deficiency was predominantly composed of women of reproductive age (92.3%), which is explained by regular menstrual blood losses. Patients in this group also had significantly lower body weight and BMI compared to the control group.

In the assessment of clinical symptomatology, the focus was on identifying subjective signs of tissue hypoxia and sideropenia. Convincing evidence was obtained of an association between low ferritin and several specific complaints (Table 2).

Table 2. Frequency of Symptoms and Asthenia Scores in the Study Groups

Symptom / Scale	Study Group (Low Ferritin) (n=78)	Control Group (Normal Ferritin) (n=63)	p-value
Dizziness, n (%)	38 (48.7%)	11 (17.5%)	0.001
Dyspnea on exertion, n (%)	29 (37.2%)	10 (15.9%)	0.006
Restless Legs	18 (23.1%)	4 (6.3%)	0.012

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Symptom / Scale	Study Group (Low Ferritin) (n=78)	Control Group (Normal Ferritin) (n=63)	p-value
Syndrome, n (%)			
Fatigue severity (FSS)	36.8 ± 11.4	32.1 ± 10.9	0.039
Clinically significant fatigue (FSS ≥ 36), %	53.8%	34.9%	0.029
Hair loss (alopecia), n (%)	41 (52.6%)	25 (39.7%)	0.106
Palpitations, n (%)	22 (28.2%)	10 (15.9%)	0.064
Pica (taste/smell perversion), n (%)	5 (6.4%)	1 (1.6%)	0.142
Angular cheilitis, n (%)	6 (7.7%)	3 (4.8%)	0.482

Dizziness was reported by almost half of the study group patients (48.7%), whereas in the control group this figure was only 17.5% (p = 0.001). The frequency of **dyspnea** with habitual physical activity was also substantially higher in patients with ferritin deficiency (37.2% vs. 15.9%, p = 0.006).

Of particular note is the integral assessment of fatigue. The mean FSS score in patients with sideropenia was 36.8 ± 11.4, significantly higher than in the group with a normal iron pool (32.1 ± 10.9, p = 0.039).

Accordingly, the proportion of individuals whose fatigue level was classified on the scale as clinically manifest (score ≥ 36) exceeded half of the study group sample (53.8%), vividly demonstrating the phenomenon of "fatigue without anemia."

Discussion

The data obtained in this study confirm the concept of the pathological impact of latent iron deficiency on the general somatic and neurological condition of patients. The high frequency of dizziness detected (48.7%) is consistent with contemporary neurobiological models postulating the high sensitivity of brain structures (in particular, the vestibular apparatus and cortex) to even a minor reduction in the activity of iron-containing mitochondrial enzymes. Since hemoglobin levels in all subjects were within reference ranges, the genesis of dizziness and dyspnea in the study group cannot be explained by classical

circulatory-hemic hypoxia. Evidently, tissue (histotoxic) hypoxia plays the key role in this case.

The identified statistically significant association of low ferritin with an increased total FSS score ($p = 0.039$) and frequency of manifest weakness ($p = 0.029$) underscores the need to change the diagnostic paradigm in primary healthcare. In clinical practice, physicians often limit themselves to a complete blood count and, finding no hemoglobin decrease, discontinue the diagnostic search for iron-deficient states. As a result, such patients are treated at length—and unsuccessfully—by neurologists and internists for asthenovegetative syndrome.

Limitations of the study. This study was conducted at a single center with a relatively small sample size, which calls for caution when generalizing conclusions to the entire population. Furthermore, the study did not assess levels of soluble transferrin receptors (sTfR) or hepcidin.

Conclusion

1. Depletion of iron stores, manifested by a decrease in serum ferritin below 30 ng/mL with preserved hemoglobin, is reliably associated with the development of subjective symptoms: dizziness ($p = 0.001$) and dyspnea ($p = 0.006$).
2. Latent iron deficiency serves as an independent trigger for the development of severe fatigue syndrome (an FSS score ≥ 36 is detected in 53.8% of patients, $p = 0.029$), and also significantly increases the risk of developing restless legs syndrome.
3. Measurement of serum ferritin levels should be incorporated into the standard workup for patients presenting with complaints of chronic weakness and unsteadiness/dizziness, regardless of normal complete blood count results.

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