Low ferritin with normal hemoglobin, a common neglected and hidden hematological disorder

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Abstract;
To highlight the clinical significance of low ferritin with normal hemoglobin in young adult women and to raise awareness about this disorder among physicians and general practitioners. This pathology is easy to be missed since normal CBC or hemoglobin will give false feeling of assurance about iron store in patients with long-standing generalized weakness of unknown etiology. A descriptive study of 120 female patients who were consulting the outpatient Internal medicine clinics at Al-Ramadi Teaching Hospital, peripheral blood samples were obtained for analysis of complete blood count and serum iron status. Fifty (41.7%) of all patients had ferritin less than 10 ng/mL indicating severe iron deficiency. Of the 120 patients with iron deficiency, fatigue is the commonest symptom that present in ninety-five patients (79.2%), followed by hair loss 88(73.3%) and dizziness 84(70.0%), headache 79 (65.8%), poor concentration 74 (61.7%), palpitation 72 (60.0%), chest pain 67 (55.8%), and legs pain (47.5%). Heavy menstrual bleeding is significantly associated with low ferritin level in younger age group (≤25 years) p=0.001. While poor nutrition is a significant risk factor among older age group (>25 years) p= 0.000. In conclusion, low ferritin with normal hemoglobin is a hidden disorder which
needs to be addressed by general practitioners and physicians when diagnosis and treatment is considered. It is accepted that individuals with low serum ferritin with normal hemoglobin or CBC will develop iron-deficiency anemia in the weeks or months following diagnosis, thus, evaluation of iron storage in at-risk patients should prompt early initiation of iron therapy and relief of symptoms.

**Keywords:** serum ferritin, normal hemoglobin, iron deficiency anemia


**Introduction:**
Globally, iron deficiency is the most prevalent nutritional insufficiency that results in anemia. World Health Organization (WHO) has defined anemia level according to sex as lower than 130 g/L for men and below 120 g/L for women. There are several forms of anemia and these cannot be differentiated from each other by the hemoglobin concentration alone. Iron deficiency per se markedly higher in prevalence than iron deficiency anemia. In Western countries there are many studies that have shown that 11–33% of young women have iron deficiency after menarche. Among menstruating women, the prevalence of iron deficiency is constantly high 9–22%, but after menopause the prevalence settles to around 1.4–4%. Gender is a risk for iron deficiency anemia and 25–40% of females are expected to develop it during life time. Iron deficiency may be severe despite a normal hemoglobin concentration and with normal complete blood count (CBC) parameters.

There is a misunderstanding not in the community alone, but even in many practicing doctors that iron deficiency is only clinically significant if the patient is anemic. In reality these claims are scientifically baseless, because many studies in females, adolescents and youth have proven that a person who is iron deficient may have one or more symptoms of anemia such as chronic fatigue, hair loss, headache, dizziness, palpitations, shortness of breath by doing simple tasks (walking short distances, climbing stairs, doing housework), sleep disturbances restless legs, pica (desire to chew ice or non-food items,) and loss of interest in work, relationships, and intimacy. In addition, it is accepted that individuals with low ferritin will develop iron-deficiency anemia in weeks or months following diagnosis if they are not treated with iron supplementation. Two factors encourage early management of iron deficiency; simplicity of treatment and deleterious effect of the deficiency on life quality, screening for iron deficiency in at-risk populations (women with heavy menstruation, pregnancy, frequent or excessive blood donation, fibroids, digestive tract disease (including infections), patient on certain medications, such as pain relievers with aspirin, and also as a result of poisoning from lead, toxic chemicals or alcohol abuse) is an important aspect of health maintenance.

The serum ferritin concentration (cut off <30 ng/L) is the most sensitive and specific indicator used for identification of iron deficiency. Because of the anticipated high rate of iron deficiency among menstruating women, neither hemoglobin level nor the complete blood count (CBC), can identify iron deficiency without
anemia. Our study aims to highlight the importance of low serum ferritin level without anemia and to make it familiar observation among physicians and general practitioners because it is easy to be missed while the patient has long-standing suffering of obscure general weakness.

Materials and Methods
This observational study was conducted during the period from November 2018 to February 2020. Five milliliter of peripheral blood sample was collected from 120 patients who visited the internal medicine outpatient clinic of Al-Ramadi Teaching hospital in Anbar Governorate, west of Iraq. The cases were females aged between 13-45 years. The study inclusion conditions were; symptomatic patients with different complains such as fatigue, hair loss, dizziness, headache, palpitation and chest pain, associated with low serum ferritin <30 ng/L and Hemoglobin $\leq$ 12 g/dL. Exclusion criteria: Abnormal CBC, Family history of hemoglobinopathy disorders, patients on iron treatment, patient with chronic kidney disease, heart diseases, liver disease, and malignancy are excluded from this study. Full medical history with clinical examination was done for all patients.

Blood samples obtained for following laboratory tests: complete blood count done by Swelab Alfa® auto analyzer (Sweden), reticulocyte count, serum iron, Total Iron Binding Capacity(TIBC) done by spectrophotometry using a kit supplied by BIOLABO® Company(France) and serum ferritin done MiniVidas® machine (BioMérieux, France) using its costume kit, other tests like ECG, TFT, Hb-electrophoresis and testing for fecal occult blood whenever indicated. Documented agreement was requested from all patients.

Statistical analysis:
The statistical analysis was performed with SPSS Statistics software (version 24.0, Chicago, USA). Normality of datadistribution was evaluated. Variables displaying a normal distribution were expressed as mean ± SD. Frequency distribution Tables and Chi squared test were performed to compare between the groups for the whole study. The level of Statistical significance was set when the p-value was less than 0.05

Results
The demographic, clinical and laboratory (age, marital status, parity, Hb level and serum ferritin) characteristics of the one hundred twenty patients, are shown in Table 1.

Table 1: Characteristics of the study sample including age, marital status, parity, Hb level and serum ferritin

<table>
<thead>
<tr>
<th>variables</th>
<th>No. (120)</th>
<th>% (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups(years):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$25</td>
<td>25</td>
<td>20.8</td>
</tr>
<tr>
<td>26-35</td>
<td>41</td>
<td>34.2</td>
</tr>
</tbody>
</table>
The age group of the study sample ranged between 13 and 45 years, most of them (45.0%) 36 years and older. Hemoglobin levels ranged between 12.0 and 14.8 gm/dl, however, 72.5% of the patients had Hb level of 12.0-12.9 gm/dl. While the patients' ferritin levels ranged (2.1-26 ng/L) and more than 50% of the patients had a level of 10-19.9 ng/L. (Table 1).

Table 2 illustrates the different symptoms among 120 patients with low serum ferritin and normal hemoglobin. Fatigue is the commonest symptom that present in ninety-five patients (79.2%), followed by hair loss 88(73.3%), dizziness 84(70.0%), headache 79 (65.8% ), poor concentration 74 (61.7% ), palpitation72(60.0%), chest pain 67 (55.8% ) and legs pain (47.5%).

Table 2: Symptoms complained by non-anemic patients with low ferritin (n=120).
Table 3 shows the risk factors among the symptomatic subjects according to age groups. It was found that low serum ferritin in 120 females is positively correlated with heavy menstrual bleeding (65%), poor nutrition (81.7%), too much Tea and Coffee intake (67.5%) and low economic status (49.2%). Heavy menstrual bleeding is significantly associated with low ferritin level in younger age group (<=25 years) p=0.001. While poor nutrition is a significant risk factor among older age group (>25 years) p= 0.000. Low economic status is also significantly associated with low ferritin level.

Table 3: Risk factors of low ferritin in non-anemic patients according to age

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>&lt;=25 (n=25)</th>
<th>&gt;25 (n=95)</th>
<th>Total (n=120)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual bleeding:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>23 (92.0)</td>
<td>55 (57.9)</td>
<td>78 (65.0)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Normal</td>
<td>2 (8.0)</td>
<td>40 (42.1)</td>
<td>42 (35.0)</td>
<td></td>
</tr>
<tr>
<td>Nutritional status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>13 (52.0)</td>
<td>9 (9.5)</td>
<td>22 (18.3)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Poor</td>
<td>12 (48.0)</td>
<td>86 (90.5)</td>
<td>98 (81.7)</td>
<td></td>
</tr>
<tr>
<td>Tea consumption:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>17 (68.0)</td>
<td>64 (67.4)</td>
<td>81 (67.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mild</td>
<td>8 (32.0)</td>
<td>17 (17.9)</td>
<td>14 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>0 (0.0)</td>
<td>14 (14.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economic status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>14 (56.0)</td>
<td>6 (6.3)</td>
<td>20 (16.7)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (4.0)</td>
<td>40 (42.1)</td>
<td>41 (34.2)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>10 (40.0)</td>
<td>49 (51.6)</td>
<td>59 (49.2)</td>
<td></td>
</tr>
</tbody>
</table>
**Family history of low ferritin:**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>2 (8.0)</td>
<td>23 (92.0)</td>
</tr>
<tr>
<td></td>
<td>2 (2.1)</td>
<td>93 (97.9)</td>
</tr>
<tr>
<td></td>
<td>4 (3.3)</td>
<td>116 (96.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.144</td>
</tr>
</tbody>
</table>

**High income More than 1.5 Million ID/month, Moderate 0.5 -1.5 Million ID/month, Low income less than 0.5 Million ID/month**

**Discussion**

Anemia is a common syndrome which is easily identified by naked eye since it gives a pale appearance of skin and mucus membrane color. Anemia due to iron deficiency is the most prevalent form and results from iron inadequacy as the name suggests [9]. Iron deficiency passes into two stages; pre-latent, latent before leading to the final destiny which is anemia. At the pre-latent and latent stage, ferritin and serum iron are reduced respectively without change in hemoglobin level [10, 11]. The late development of anemia in the course of iron deficiency give false impression to the medical professional about adequacy of iron store. Iron is involved in many biological function other than its vital function in oxygen transport in red blood cellhemoglobin, such as deoxyribonucleic acid (DNA) synthesis, electron transport and function of many enzymes [12]. These function will be impaired upon deficiency of iron with subsequent symptoms development [13]. Iron level is very tightly regulated through regulation of its uptake and loss. Iron is stored in bone marrow as ferritin and the later level in blood is a reflection of the body store [14]. It is a fact the menstruating women have normally lower hemoglobin and ferritin level than men and non-menstruating women [15].

The USA Centers for Disease Control and Prevention (CDC) has defined heavy bleeding in a plain language that can be easily comprehend by female of all educational level and cultural background as “changing tampon or pad in less than every two hours or pass clots the size of a quarter or larger, that is heavy bleeding or if lasts more than 7 days” [16]. In our work we found a very strong inverse association between heavy menstrual bleeding and ferritin level.

The average amount of blood loss during each cycle is about 80 ml, though the range is wide from 30 to 180 ml, and this amount is much larger in heavy menstrual cycles [17], this is typically associated with a mean loss of iron of 3.2 mg for a loss of 80 ml [17]. Another factor, in our work, that has a positive correlation with ferritin level is economic status. It is well known that food of animal sources have more iron which is readily absorbable, however it is expensive when compared to vegetable sources [18].

It is not surprising to detect significant number of female with reduced ferritin as a measure of Iron store. The deleterious effect of forcible displacement over three years' period have two-fold Negative effect on ferritin. Firstly, displacement is associated with reduced income and consequent reduction in food quality, secondly, stress, caused by displacement, is known to cause ‘heavy menses’ that is poorly appreciated by the suffering females. What complicates Iron deficiency in our community is the tradition of drinking tea and coffee which impairs iron absorption from non hemesources [19, 20]. All the iron deficiency associated symptoms are
associated with serious physical social and mental grief complications such as heart failure. Previous studies have shown that iron deficiency is a common nutritional disorder all over the world specially in the developing countries [21]. Worldwide, iron deficiency is responsible for 841,000 fatalities and 35,057,000 disability-adjusted life years lost, almost two third of the iron deficiency burden occur Africa and deprived parts, while North America has just more than one percent of the global problem [22].

**Conclusion**

Iron deficiency is a common nutritional problem that has been overlooked since hemoglobin was used as surrogate marker which lacks sensitivity and specificity. Patients with vague symptoms such as tiredness and poor concentration should be screened for iron deficiency regardless of hemoglobin status.

**References**