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Comparative Characteristics Of Ferrokinetic Parameters And Their Relationship With Inflammation In Patients With CHF In Advanced And Senile Age

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ABSTRACT

To perform a comparative analysis of anemia of chronic disease (ACD) and iron-deficiency anemia (IDA) in late middle-aged and elderly patients with chronic heart failure (CHF) by ferrokinetic parameters, inflammation indexes, and their associations. Materials and methods. 65 patients with ischemic heart disease were evaluated, including 35 patients with CHF and ACD, 10 patients with CHF and IDA, and 20 patients without CHF, ACD, and IDA (control group, CG). Results. Patients with CHF and IDA had true iron deficiency whereas 54% of patients with CHF and ACD had functional iron deficiency, and 46% of patients had no iron deficiency. Levels of acute phase proteins, ferritin and hepcidin, C-reactive protein (CRP), and interleukin-6 (IL-6) were highly significantly different in patients with CHF and ACD and patients with CHF and IDA; positive and significant correlations were found for levels of IL-6 and ferritin, IL-6 and CRP, and CRP and hepcidin. In patients with CHF and IDA, levels of acute phase proteins, ferritin and hepcidin, CRP, and IL-6 were low and correlations of IL-6 with ferritin, IL-6 with CRP, and CRP with hepcidin were non-significant. Concentrations of erythropoietin were significantly higher in patients with CHF and ACD and patients with CHF and IDA compared to the control group; however, significant differences between them were absent.

KEYWORDS

Chronic heart failure, anemia of chronic disease, iron deficiency anemia, hepcidin, ferritin, erythropoietin, interleukin-6 (IL-6)

INTRODUCTION

Anemia in patients with CHF occurs in 4–53% of cases [1], which depends on the severity of the underlying disease and the criteria used for anemia [2]. Especially often (up to 80%) it develops in patients with FC IV CHF [3]. In a large systematic review of several studies, which included 153180 patients with CHF, 48% mortality was noted within six months in patients with anemia compared with 29.5% without anemia [4]. In the RENAISSANCE study [5], it was found that an increase in hemoglobin level by 1 g / dL in CHF patients reduces the risk of death by 15.8%. A particularly unfavorable effect of anemia on the course of CHF and an increase in the risks of cardiovascular events was shown in the TIME study [6] in patients over 75 years of age. In this age group of patients, a decrease in hemoglobin by 1 g / dl led to an increase in the risk of death from cardiac causes by 28%, the risk of developing acute myocardial infarction, ACS, and the need for percutaneous coronary interventions by 23% [6].

In CHF, the 2 most common forms of anemia most often develop: iron deficiency (IDA), which occurs in up to 21% of cases [7], and anemia of chronic diseases (ACD), the frequency of which is up to 58% of cases [8].

Unlike IDA, in which the diagnosis, as a rule, is not difficult, ACD is often not diagnosed [9], primarily due to the fact that in the early stages it proceeds as normocytic and normochromic [10], and a moderate decrease in values hemoglobin is explained by an alimentary factor, while its manifestations such as shortness of breath, weakness and tachycardia fit the doctors entirely within the framework of CHF. It is known that a clinical blood test cannot objectively indicate iron deficiency in patients with anemia [10]. Meanwhile, it was found that in patients with ACD and IDA, iron deficiency is different in severity: with IDA - true, and with ACD - functional or "redistribution" and for its detection there are

not enough hemogram indicators, but it is necessary to study ferrokinetic indices, first of all, ferritin [11, 12], which, unlike IDA in ACD, remains normal or, more often, elevated, since, like C-reactive protein (CRP), it is an acute phase of inflammation protein synthesized in the liver in response to inflammatory stimuli [13]. It is also important to study other indicators of ferrokinetics: hepcidin, which also has properties characteristic of acute phase proteins, increases in inflammatory processes and which in the pathogenesis of ACD acts as a direct mediator that has a significant effect on iron homeostasis [14]; erythropoietin (EPO), which, according to the literature, increases during IDA, which is stimulated by chronic blood loss [15]. At the same time, the data on the level of EPO in patients with ACD against the background of CHF are contradictory, since some researchers point to an increased level of it [16, 17], and others - to a lower one, attributing this to the action of proinflammatory cytokines that negatively affect the production of EPO [18, 19]. All these issues have not been sufficiently studied in elderly and senile patients with CHF, in whom the identification of the cause of anemia due to high comorbidity is especially difficult, and the management strategy of these patients is fundamentally different. All of the above determines the relevance of this work.

The aim of the study was to compare AChD and IDA in terms of ferrokinetics and to investigate their relationship with inflammation in elderly and senile CHF patients.

MATERIAL AND METHODS

We examined 65 elderly and senile patients of the Bukhara regional cardiological dispensary with coronary artery disease. Of these, 35 patients (19 women, 16 men) aged 76 to 97 years with CHF and ACD; 10 patients (6 women, 4 men) aged 76 to 92 years with CHF and IDA; 20 patients (11 women, 9 men) aged 77 to 91

years without CHF, ACD and IDA made up the control group (CG).

Since until now there are no official recommendations on the target level of hemoglobin in CHF, and most researchers agree on the value of 12 g / dL, and also due to the absence of physiological iron losses in women in old and old age, patients were included in the CHF group with ACD. with a hemoglobin level less than 12 g / dl, with a normal or increased ferritin level ($> 30 \mu\text{g} / \text{l}$), and in the CHF group with IDA - patients with a hemoglobin level less than 12 g / dl, a low ferritin level ($<30 \mu\text{g} / \text{l}$) and proven chronic blood loss (hemorrhoids, erosive gastroduodenitis, gastric ulcer). The control group (CG) included patients with a hemoglobin level of 12 g / dL or more, a normal ferritin level ($30\text{--}100 \mu\text{g} / \text{L}$) and no signs of chronic blood loss. The severity of CHF was assessed according to the CHF classification of the OASN, 2002. The severity of anemia was assessed by the WHO classification, 2008. The severity of chronic kidney disease (CKD) was assessed according to the Kidney Disease Outcome Quality Initiative classification (K / DOQI, 2009). Ferritin, transferrin, CRP were studied in blood serum by immunoturbidimetric method. Hcpidin, EPO and interleukin-6 (IL6) were investigated quantitatively in blood serum by enzyme-linked immunosorbent assay. The percentage of transferrin saturation with iron was calculated using the formula: $\text{serum iron } (\mu\text{mol} / \text{L}) \times 3.98 / \text{transferrin } (\text{g} / \text{L})$.

Exclusion criteria: megaloblastic, hemolytic, aplastic anemias, autoimmune, oncological diseases.

Statistical data processing was performed using the statistical software package "STATISTICA - 8". The probability of a random difference in mean p for 2 groups was determined by Student's t test (t), for a larger

number of groups using one-way ANOVA followed by post-hoc Newman-Kells and Duncan tests.

The probability of a random difference in the sums of the ranks of observations was determined for two groups using the Mann-Whitney test (U), for 3 or more - using the Kruscull-Wallis rank analysis of variance (H), followed by the multiple comparisons test. The significance of the difference in the frequency of occurrence of the traits was determined by Fisher's exact test (TCF) or the χ^2 test. Spearman's rank correlation coefficient (S) was used to assess the degree of monotone significant relationship. Differences were considered significant at $p < 0.05$.

RESULTS

It was revealed that patients with CHF with ACD did not significantly differ from patients with CHF with IDA in terms of age, sex, but significantly differed in the manifestations and course of IHD, the severity of CHF and CKD, since patients with IDA were selected purposefully without inflammatory diseases, without congestive CHF, with minimal comorbidity to exclude the influence of any inflammation on the formation of anemia, but with proven chronic blood loss.

Comparative characteristics of patients with CHF with ACD and CHF with IDA according to hemogram parameters

It was revealed that patients with CHF with ACD did not significantly differ from patients with CHF with IDA in terms of hemogram indicators: the level of decreased hemoglobin (Hb) - 10.11 ± 0.223 and $9.90 \pm 0.46 \text{ g} / \text{dL}$, respectively ($p = 0.582$) and the number of erythrocytes - 3.67 ± 0.085 and $3.77 \pm 0.097 * 10^{12} / \text{L}$, respectively ($p = 0.445$), but at the same time significantly differed in color index (CP) - 0.85 ± 0.014 and 0.76 ± 0.03 , respectively ($p < 0.0001$), the average erythrocyte volume

(MCV) - 83.86 ± 0.969 and 77.50 ± 1.92 fl, respectively ($p < 0.0001$) and the average hemoglobin content in one erythrocyte (MCH) - 28.76 ± 0.340 and 27.21 ± 1.43 pg, respectively ($p = 0.027$) (Table 2). In this regard, patients with normocytic anemia - 71% and normochromic anemia - 60% prevailed in the group of CHF with ACD, while in the group of CHF with IDA with microcytic anemia - 60% and hypochromic anemia - 80%.

Comparative characteristics of patients with CHF with ACD and CHF with IDA in terms of ferrokinetics

Significant differences in ferrokinetic parameters were revealed between CHF patients with ACD and CHF with IDA: ferritin level - 131.97 ± 17.993 versus 18.90 ± 3.59 $\mu\text{g} / \text{l}$ ($p < 0.0001$), while 54% of patients showed normal (30–100 $\mu\text{g} / \text{L}$) ferritin level, which indicates functional iron deficiency [20, 21], and in 46% of patients - increased ferritin level (100–505 $\mu\text{g} / \text{L}$), which indicates the absence of iron deficiency [20, 21], as well as serum iron - 7.30 ± 0.270 versus 4.86 ± 0.77 $\mu\text{mol} / \text{L}$ ($p = 0.045$), hepcidin - 23.81 ± 3.625 versus 6.31 ± 1.15 pg / ml ($p = 0.001$), transferrin - 2.44 ± 0.084 versus 2.96 ± 0.23 g / L ($p < 0.0001$) and the percentage of transferrin saturation with iron - 12.37 ± 0.674 versus $7.22 \pm 1.504\%$ ($p = 0.016$). Both in patients with CHF with ACD and in patients with CHF with IDA, increased levels of EPO were found without significant differences between them: 44.92 ± 5.367 versus 44.13 ± 6.23 mIU / ml ($p = 0.913$). However, the EPO level was significantly higher in CHF patients with ACD than in CG patients - 44.92 ± 5.367 versus 17.30 ± 3.302 mIU / ml ($p < 0.001$), as well as in CHF patients with IDA than in CG patients - 44.13 ± 6.23 versus 17.30 ± 3.302 mIU / ml ($p < 0.001$).

Comparative characteristics of patients with CHF with ACD and CHF with IDA in terms of inflammation

Significant differences in CRP level were revealed between CHF patients with ACD and CHF with IDA - 20.6 ± 5.3 versus 5.58 ± 1.25 mg / l ($p = 0.049$). Also, the CRP level was significantly higher in CHF patients with ACD than in CG patients - 20.6 ± 5.3 versus 2.9 ± 0.3 mg / l ($p = 0.044$). There were no significant differences in CRP levels between CHF patients with IDA and CG patients - 5.58 ± 1.25 versus 2.9 ± 0.3 mg / l ($p = 0.769$). In addition, significant differences in the level of IL-6 were revealed between patients with CHF with ACD and CHF with IDA - 5.51 ± 0.783 versus 2.23 ± 0.99 pg / ml ($p = 0.011$), as well as between patients with CHF with ACD and CG patients - 5.51 ± 0.783 versus 0.82 ± 0.13 pg / ml ($p = 0.001$), while there were no significant differences between CHF patients with IDA and CG patients - 2.23 ± 0.99 versus 0.82 ± 0.13 pg / ml ($p = 0.265$).

Correlation of ferrokinetic indices with inflammation indices in CHF patients with ACD, CHF with IDA and CG patients

During the Spearman correlation analysis in CHF patients with ACD, significant positive relationships of average strength were revealed: between IL-6 and ferritin ($r(S) = 0.404$, $p(r) = 0.016$), IL-6 and EPO ($r(S) = 0.424$, $p(r) = 0.011$), IL-6 and CRP ($r(S) = 0.427$, $p(r) = 0.010$), CRP and hepcidin ($r(S) = 0.561$, $p(r) < 0.0001$). On the contrary, insignificant relationships were found in CHF patients with IDA: between IL-6 and ferritin ($r(S) = 0.193$, $p(r) = 0.593$), IL-6 and EPO ($r(S) = -0.006$, $p(r) = 0.986$), IL-6 and CRP ($r(S) = 0.623$, $p(r) = 0.071$), CRP and hepcidin ($r(S) = -0.498$, $p(r) = 0.143$). CG patients also revealed insignificant relationships: between IL-6 and ferritin ($r(S) = 0.106$, $p(r) = 0.657$), IL-6 and EPO ($r(S) = 0.056$, $p(r) = 0.816$), IL-6 and CRP ($r(S) = 0.387$, $p(r) = 0.092$), CRP and hepcidin ($r(S) = 0.008$, $p(r) = 0.972$). (Fig. 1: A, B, C, D).

Thus, between elderly and senile CHF patients with ACD and CHF with IDA of elderly and senile

age, significant laboratory differences were revealed, consisting, first, in different severity of iron deficiency (true with IDA and functional or "redistributive" deficiency with ACD or its absence), at the same time, in comparable increased levels of EPO, however, with different mechanisms of its increase; secondly, the identification of high levels of ferrokinetic parameters (ferritin, hepcidin and EPO) in patients with CHF with ACD, as well as high levels of inflammation indicators: CRP and IL-6 and significant positive relationships between them, and, on the contrary, the identification of patients with CHF with IDA of low levels of ferrokinetic indices (ferritin and hepcidin), as well as low levels of inflammation indices: CRP and IL-6 and the absence of links between them.

DISCUSSION

It is known that hemogram indices make it possible to conclude that anemia is present, but it is not possible to determine its form and severity of iron deficiency [11]. At the same time, the study of the main indicators of ferrokinetics provides more comprehensive information: it allows one to judge the presence and severity of iron deficiency, to establish a connection between anemia and inflammation. According to the data obtained in CHF patients with IDA, a true iron deficiency was revealed: extremely low levels of serum iron, ferritin and the percentage of transferrin saturation with iron. Whereas in CHF patients with ACD moderately reduced levels of serum iron and the percentage of transferrin saturation with iron were revealed, while 54% of patients had a normal level of ferritin, which indicates a functional or "redistribution" iron deficiency [20, 21], and 46% patients - an increased level of ferritin, which indicates the absence of iron deficiency [20, 21].

Noteworthy is the significantly increased level of EPO both in patients with ACD and in

patients with IDA relative to patients in CG. It is known that chronic blood loss in IDA increases the synthesis of EPO [15], and in ACD many authors, when describing the mechanisms of its development, indicate a decrease in EPO production under the influence of proinflammatory cytokines [18, 19]. However, a number of authors believe that EPO synthesis increases in patients with CHF due to a decrease in renal blood flow caused by the vasoconstrictor effect of neurohormones on renal vessels and the development of hypoxia [22, 23]. In addition, in CHF, low renal blood flow stimulates the production of renin, and this, in turn, of angiotensin II (AII), and a high level of AII leads to an increase in sodium reabsorption, which is accompanied by an increase in the consumption of ATP and oxygen, which ultimately increases the production of EPO [24]. Therefore, in many patients with CHF and ACD, not decreased, but, on the contrary, normal or increased levels of EPO are determined [16, 17].

According to our data, in CHF patients with ACD, in contrast to CHF patients with IDA and CG patients, high levels of inflammation indicators were revealed: CRP, as well as other indicators, which, like CRP, are proteins of the acute phase of inflammation - rarely used to assess inflammatory syndrome - ferritin and practically not used yet - hepcidin, synthesized in the liver under the action of proinflammatory cytokines [13, 14]. It is known that hepcidin blocks the release of iron from macrophages and the absorption of iron in the intestine, which ultimately leads to a functional iron deficiency with a sufficient amount in the body, which is characteristic of ACD [25]. The opposite situation occurs in IDA, in which there is a decrease in the expression of hepcidin, which leads to an increase in the uptake of iron from both macrophages and the intestine [14]. Also, in patients with CHF with ACD, a highly significant level of cytokine, IL-6, was revealed,

which was previously shown by other authors in ACD [15].

In connection with the above, it is important to identify significant positive relationships in CHF patients with ACD between IL-6 and ferritin, IL-6 and EPO, IL-6 and CRP, CRP and hepcidin, that is, indicators of inflammation and indicators of ferrokinetics, which indicates inflammation as the reason for the formation of AHZ. In contrast, in patients with CHF with IDA, similar relationships between the parameters of ferrokinetics and indicators of inflammation are insignificant.

CONCLUSION. Thus, between elderly and senile CHF patients with ACD and CHF with IDA of elderly and senile age, significant differences in laboratory parameters were revealed, firstly, consisting in different severity of iron deficiency (true with IDA and functional or "redistributive" deficiency with ACD or its absence) and at the same time, the increased levels of EPO are comparable, but with different mechanisms of its increase. Secondly, high levels of ferrokinetic parameters (ferritin, hepcidin and EPO), as well as high levels of inflammation indicators: CRP and IL-6 and significant positive relationships between them, and, on the contrary, in CHF patients with IDA were revealed in patients with CHF with ACD. revealed low levels of ferrokinetic parameters (ferritin and hepcidin), as well as low levels of inflammation indicators (CRP and IL-6) and the absence of links between them.

All of the above must be taken into account in the differential diagnosis of these two most frequent anemias in elderly and senile CHF patients, since the management strategy of these patients and approaches to treatment are fundamentally different.

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