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Serum concentrations of interleukin-6 and tumor necrosis factor alpha in patients with spondyloarthritis: a relationship between systemic inflammation and anemia

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ABSTRACT

Aim. To assess the relationship between the activity of systemic inflammation and the hemoglobin level in patients with spondyloarthritis (SpA).

Materials and methods. We examined 92 patients with SpA aged 42.9 ± 11.6 years (SpA duration – 14.8 ± 9.6 years, 55 (60%) men). We calculated the BASDAI and ASDAS-CRP scores, performed complete blood count, evaluated erythrocyte sedimentation rate (ESR), ferrokinetic parameters, C-reactive protein (CRP) level, and serum concentrations of tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6).

Results. Anemia was found in 52 (57%) patients: 13 (25%) patients were diagnosed with anemia of chronic disease (ACD), 39 (75%) individuals had a combination of ACD and iron deficiency anemia. A significant increase in CRP (17.8 vs. 9.0 mg / l, respectively; $p = 0.001$) and ESR (23 vs. 10 mm / h, $p < 0.001$), a tendency toward an increase in IL-6 levels (5.4 vs. 4.1 pg / ml, $p = 0.051$), and no difference in TNF-α levels (3.4 vs. 3.0 pg / ml, $p = 0.245$) were revealed in patients with anemia compared with patients without the disease. The hemoglobin concentration was negatively correlated with the CRP level ($r = –0.327$, $p = 0.001$) and ESR ($r = –0.527$, $p < 0.001$). IL-6 was positively correlated with the levels of TNF-a, CRP, and ESR ($r = 0.431$, $r = 0.361$, $r = 0.369$; all $p < 0.001$). With the IL-6 concentration >10 pg / ml, the odds for anemia were 5.3 times higher (95% confidence interval: 1.4–19.9, $p = 0.009$).

Conclusion. The relationship between the activity of systemic inflammation and anemia in patients with SpA was confirmed. Taking into account the pathogenesis of ACD, the aim of antianemic treatment is to achieve remission or minimal activity of SpA. Additional studies are required to determine the effect of backbone anti-inflammatory therapy on the development and course of anemia in patients with SpA.

Keywords: anemia, hemoglobin, inflammation, interleukin-6, tumor necrosis factor α, spondyloarthritis

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Сывороточная концентрация интерлейкина-6 и фактора некроза опухоли α у пациентов со спондилоартритами: связь между системным воспалением и анемией

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РЕЗЮМЕ

Цель – оценить взаимосвязи между лабораторной активностью системного воспаления и уровнем гемоглобина у пациентов со спондилоартритами (СпА).

Материалы и методы. Обследованы 92 пациента со СпА (возраст – 42,9 ± 11,6 года, длительность СпА – 14,8 ± 9,6 лет, 55 (60%) мужчин). Рассчитаны индексы BASDAI, ASDAS-CRP, исследованы клинический анализ крови, скорость оседания эритроцитов (СОЭ), параметры феррокинетики, уровень С-реактивного белка (СРБ), сывороточная концентрация фактора некроза опухоли α (ФНО-α) и интерлейкина-6 (ИЛ-6).

Результаты. У 52 (57%) пациентов выявлена анемия: у 13 (25%) диагностирована анемия хронического воспаления (АХВ), у 39 (75%) – комбинация АХВ и железодефицитной анемии. У пациентов с анемией по сравнению с больными без анемического синдрома отмечено статистически значимое увеличение уровня СРБ (17,8 и 9,0 мг/л соответственно, $p = 0,001$) и СОЭ (23 и 10 мм/ч соответственно, $p < 0,001$), установлена тенденция к повышению уровня ИЛ-6 (5,4 и 4,1 пг/мл соответственно, $p = 0,051$), концентрация ФНО-α статистически значимо не различалась (3,4 и 3,0 пг/мл, $p = 0,245$). Установлена обратная взаимосвязь между уровнем гемоглобина и уровнем СРБ ($r = –0,327$; $p = 0,001$), СОЭ ($r = –0,527$; $p < 0,001$). Концентрация ИЛ-6 статистически значимо взаимосвязана с уровнем ФНО-α, СРБ и СОЭ ($r = 0,431$; $r = 0,361$; $r = 0,369$; $p < 0,001$ для всех). При концентрации ИЛ-6 >10 пг/мл шансы развития анемии у пациентов со СпА увеличивались в 5,3 раза (95%-й доверительный интервал 1,4–19,9; $p = 0,009$).

Заключение. В ходе исследования подтверждена взаимосвязь между лабораторной активностью системного воспаления и анемией у больных СпА. Учитывая патогенез АХВ, основой антианемической терапии является достижение ремиссии, а при невозможности – минимальной активности СпА. Требуется проведение дополнительных исследований для определения влияния базисной противовоспалительной терапии на развитие и течение анемии у пациентов со СпА.

Ключевые слова: анемия, гемоглобин, воспаление, интерлейкин-6, фактор некроза опухоли α, спондилоартрит

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Проведение исследования одобрено этическим комитетом Саратовского ГМУ им. В.И. Разумовского (протокол № 3 от 07.11.2017).

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INTRODUCTION

Anemia of chronic disease (ACD) is the second most prevalent type of anemia after iron deficiency anemia (IDA) and is characterized by high prevalence among different groups of patients [1–3]. Anemia is a common comorbid pathology in patients with rheumatic diseases, which is associated with the pathogenesis of autoimmune diseases [4]. Overproduction of interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) plays a key role in the pathogenesis of ACD and leads to impaired iron homeostasis and erythropoiesis [4, 5].

Significant effects of IL-6 include stimulation of hepcidin production in the liver. Increased levels of circulating hepcidin result in suppression of nutritional iron absorption in the duodenum and impairment of endogenous iron recirculation due to its sequestration in cells of the macrophage – monocyte system [4, 5]. TNF-α directly inhibits intestinal iron absorption by the hepcidin-independent mechanism, reduces the erythrocyte life span, promotes erythrophagocytosis, suppresses proliferation of erythroid progenitor cells via implementation of proapoptoptic effects, and inhibits erythropoietin production [4, 5]. Following the combined effect of hepcidin and cytokines, functional iron deficiency develops, accompanied by hypoferremia with normal or elevated serum ferritin, heme synthesis is disrupted, and erythropoiesis decreases [4, 5].

Spondyloarthritis (SpA) is a chronic autoimmune disease characterized by persistent systemic inflammation, damage to the axial skeleton, entheses, and peripheral joints, and possible extra-articular manifestations, such as psoriasis, uveitis, Crohn's disease or ulcerative colitis [6]. SpA is highly prevalent in the general population, but currently there is no convincing evidence of the incidence and features of anemia in this category of patients. Proper identification of the pathogenetic type of anemia contributes to the choice of the optimal therapeutic strategy for correcting anemia in SpA. The presence of ACD is considered as a marker of the activity of systemic inflammation, its severity and pathogenetic features may influence the choice of backbone antirheumatic therapy, determining a personalized approach to SpA treatment. Therefore, it is of interest to study the relationship between anemia and inflammation in SpA.

The aim of the study was to evaluate the relationship between hemoglobin levels and markers of SpA activity, such as serum concentrations of TNF-α, IL-6, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

MATERIALS AND METHODS

The study included 92 patients with SpA (55 males and 37 females aged 42.9 ± 11.6 years, SpA duration – 14.8 ± 9.6 years), who were admitted to the Department of Rheumatology at Saratov Regional Hospital from 2017 to 2019. Inclusion criteria were the following: people aged 18 years and older, a confirmed diagnosis of SpA according to the Assessment of Spondyloarthritis International Society (ASAS) classification criteria (2009) [7], a signed informed consent to participate in the study. Exclusion criteria included therapy with biological disease-modifying antirheumatic drugs (bDMARDs); true iron deficiency, posthemorrhagic, megaloblastic or hemolytic anemia; cancers; tuberculosis, HIV, HBV and HCV infections; stage 3–5 chronic kidney disease; pregnancy and lactation.

The study was carried out according to the principles set out in the Declaration of Helsinki and approved by the local Ethics Committee at V.I.Razumovsky Saratov State Medical University (Protocol No. 3 of 07.11.2017).

The SpA activity was determined by calculating the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP). Complete blood count (CBC) and serum biochemistry parameters, including iron status and CRP, were evaluated. Serum TNF-α and IL-6 levels were measured in all patients by enzyme-linked immunosorbent assay (ELISA) using alpha-TNF-EIA-BEST and Interleukin-6-EIA-BEST reagent kits (Vector-Best, Russian Federation). According to the instructions, the reference concentrations were TNF-α < 6 pg / ml and IL-6 < 10 pg / ml.

Anemia was defined at a hemoglobin concentration of < 130 g / l for men and < 120 g / l for women. ACD was diagnosed when serum ferritin was > 100 ng / ml, transferrin saturation (TSAT) was < 20%, and CRP was > 5 mg / l. Combined ACD / IDA was diagnosed when serum ferritin was 30–100 ng / ml, TSAT was < 20%, and CRP was > 5 mg / l [8].

Statistical processing of the data was performed using SPSS version 26.0 software (IBM SPSS Statistics, USA). Normality of sample distribution was examined by the Shapiro –Wilk and Kolmogorov – Smirnov tests, the distribution was considered

normal at $p > 0.05$. Normally distributed, quantitative variables were presented as the mean and standard deviation ($M \pm SD$). Variables characterized by non-normal distribution were presented as the median and the upper and lower quartiles Me [Q_1; Q_3]. Depending on the type of data distribution, parametric and non-parametric methods were used. To compare the differences between quantitative variables in two independent groups, the Student's t-test was used for normally distributed variables, and the Mann – Whitney test was used for non-normally distributed variables. To assess the differences between the categorical variables, the Pearson's chi-square test χ^2 or Fisher's exact test was used. The odds ratio (OR) with 95% confidence interval (CI) was used for assessing the effect of cytokine overproduction on the development of anemia in patients with SpA. Relationships between variables were tested using the Spearman's rank correlation coefficient. The Chaddock scale was used to determine the strength of the relationship. The differences were considered statistically significant at $p < 0.05$; $p < 0.1$ was considered as a trend toward a difference.

RESULTS

Anemia was detected in 52 (57%) patients included in the study: ACD was found in 13 (25%) patients, combined ACD / IDA was detected in 39 (75%) patients. In 47 (90%) patients, the severity of the disease was mild, in 5 (10%) patients, the severity of anemia was moderate. SpA patients with and without anemia were comparable in gender, age, disease duration, and SpA activity, and according to the BASDAI and ASDAS-CRP scores, the majority of patients had high disease activity (Table 1). In SpA patients with anemia, a trend toward more frequent use of multiagent therapy, including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and synthetic disease-modifying antirheumatic drugs (DMARDs), was observed. Among SpA patients without anemia, in most cases (70%), NSAID therapy was prescribed without the additional use of glucocorticoids, and synthetic DMARDs were used in 40% of patients (Table 1).

The main CBC and iron status parameters and markers of systemic inflammation in SpA patients included in the study are shown in Table 2. Anisocytosis and a trend toward microcytosis and hypochromia of red blood cells were detected according to the obtained values in the patients with anemia. These patients were characterized by a higher platelet count, reduced TSAT, and a trend toward a decrease in serum iron, which is typical of ACD. A trend toward an increase in serum IL-6 concentrations and a significant increase in CRP and ESR values were identified in anemic patients compared with patients without anemia ($p = 0.051$, $p = 0.001$, and $p < 0.001$, respectively). Nevertheless, no significant differences in the TNF-α concentrations in patients with and without anemia were revealed ($p = 0.245$).

Table 1

Main demographic and clinical characteristics of SpA patients

Parameter	All patients with SpA ($n = 92$)		p
	Without anemia ($n = 40$)	With anemia ($n = 52$)	
Age, years, M SD	45.113.0	41.310.3	0.139
Males, n (%)	25 (63)	30 (58)	0.641
Disease duration, years, Me [Q_1–Q_3]	12.3 [7.4–20.3]	15.8 [8.7–21.6]	0.521
BASDAI, M SD	4.82.2	5.62.1	0.117
BASDAI > 4, n (%)	22 (55)	33 (64)	0.799
ASDAS-CRP, M SD	3.31.0	3.81.2	0.062
ASDAS-CRP 2.1, n (%)	27 (68)	42 (81)	0.434
SpA treatment, n (%):	–	–	–
NSAIDs	28 (70)	26 (50)	0.053
NSAIDs + glucocorticoids	11 (28)	24 (46)	0.068
Synthetic DMARDs, including:	16 (40)	31 (60)	0.103
Methotrexate	8 (50)	14 (45)	0.472
Sulfasalazine	7 (44)	12 (39)	0.608
Methotrexate + sulfasalazine	1 (6)	4 (13)	0.383
Hydroxychloroquine	–	1 (3)	–

A correlation analysis was performed to determine the relationship between markers of systemic inflammation, disease activity scores, and hemoglobin levels (Table 3). The hemoglobin was inversely correlated with CRP and ESR ($p = 0.001$ and $p < 0.001$, respectively). A positive correlation between serum IL-6 concentration and other markers of systemic inflammation, such as TNF-α, CRP, and ESR, was observed ($p < 0.001$ for all).

The analysis of the frequency of anemia depending on excess serum levels of TNF-α and IL-6 is presented in Table 4. The odds for anemia were 5.3 times higher with elevated IL-6 concentration > 10 pg / ml (95% CI: 1.4–19.9). Moderate strength of the relationship between the compared features was noted (Cramer's V = 0.281).

Table 2

Hematological and ferrokinetic parameters and systemic inflammatory markers in patients with SpA

Parameter	All patients with SpA (n = 92)				p
	without anemia (n = 40)		with anemia (n = 52)		
	n	Me [Q_1–Q_3]	n	Me [Q_1–Q_3]	
Hemoglobin, g / l	40	139 [134–149]	52	116 [107–120]	<0.001*
Mean corpuscular volume (MCV), fl	40	90.4 [88.9–92.9]	52	85.3 [79.3–91.0]	0.002*
Mean corpuscular hemoglobin (MCH), pg	40	30.3 [29.5–30.9]	52	27.3 [24.6–29.7]	<0.001*
Red cell distribution width (RDW), %	40	13.5 [12.9–14.3]	52	15.1 [13.6–16.8]	<0.001*
Platelets, 10^9 / l	40	278 [236–319]	52	297 [265–362]	0.028*
ESR, mm / h	40	10 [6–15]	52	23 [12–32]	<0.001*
Serum iron, μmol / l	16	13.8 [10.5–14.0]	52	8.7 [6.3–13.7]	0.071
Ferritin, ng / ml	16	69 [49–162]	52	70 [46–98]	0.640
Transferrin, g / l	16	2.2 [2.0–2.3]	52	2.2 [2.1–2.3]	0.688
TSAT, %	16	24.9 [18.0–27.5]	52	15.7 [11.2–23.0]	0.038*
CRP, mg / l	40	9.0 [3.9–16.6]	52	17.8 [9.5–30.5]	0.001*
TNF-α, pg / ml	40	3.0 [2.4–4.0]	52	3.4 [2.7–4.1]	0.245
IL-6, pg / ml	40	4.1 [2.0–6.7]	52	5.4 [2.4–11.7]	0.051

* $p < 0.05$

Table 3

Correlation analysis of systemic inflammatory markers and clinical and laboratory parameters in patients with SpA

Parameter	CRP	ESR	IL-6	TNF-α
BASDAI	r = 0.147 p = 0.202	r = 0.105 p = 0.362	r = –0.094 p = 0.417	r = 0.102 p = 0.378
ASDAS-CRP	r = 0.489 p < 0.001*	r = 0.358 p = 0.001*	r = 0.160 p = 0.167	r = 0.208 p = 0.071
Hemoglobin	r = –0.327 p = 0.001*	r = –0.527 p < 0.001*	r = –0.155 p = 0.142	r = –0.104 p = 0.323
TNF-α	r = 0.153 p = 0.146	r = 0.233 p = 0.025*	r = 0.431 p < 0.001*	1
IL-6	r = 0.361 p < 0.001*	r = 0.369 p < 0.001*	1	r = 0.431 p < 0.001*

* $p < 0.05$

Table 4

Comparison of the frequency of anemia depending on increased serum concentrations of TNFα and IL6

Risk factor	Frequency of anemia		p	OR (95% CI)
	The presence of the factor, n (%)	The absence of the factor, n (%)		
TNF-α > 6 pg / ml	4 (80.0)	48 (55.2)	0.383	3.3 (0.3–30.3)
IL-6 > 10 pg / ml	16 (84.2)	36 (50.0)	0.009*	5.3 (1.4–19.9)

* $p < 0.05$

DISCUSSION

In this study, we attempted to assess the contribution of systemic inflammation to the development of anemia in patients with SpA. No significant differences in the TNF-α levels in patients with and without anemia were revealed. At the same time, a trend toward an increase in the serum IL-6 concentrations in patients with reduced hemoglobin levels was observed, and overproduction of this cytokine caused a more than five-fold increase in the odds for developing anemia. The traditional inflammatory markers, CRP and ESR, were significantly higher in SpA patients with anemia, and these parameters were correlated with ASDAS-CRP score, hemoglobin level, and serum IL-6 concentration.

It was found that serum IL-6 concentration in patients with SpA was significantly higher than in healthy individuals [9, 10]. However, according to the results of clinical trials reported by J. Sieper et al. [11, 12], the efficacy of IL-6 inhibitors (tocilizumab, sarilumab) in the treatment of ankylosing spondylitis (AS) has not been confirmed. Despite a significant decrease in the laboratory markers of disease activity, no improvement in symptoms related to the axial skeleton and peripheral joints in patients and no significant differences in the ASAS20 and ASAS40 response rate compared with the control group were identified. It is worth noting that these studies did not analyze the relationships between hemoglobin and IL-6 concentrations and did not evaluate the hematological response to treatment with IL-6 inhibitors. At the same time, IL-6 inhibitors are preferred in patients with rheumatoid arthritis who have anemia and other signs of IL-6-dependent inflammation due to their proven high clinical efficacy [13]. It should be assumed that the use of IL-6 inhibitors in SpA patients with severe ACD may be justified.

Anti-TNF-α therapy in patients with psoriatic arthritis [14] and AS [15] with isolated ACD without signs of true iron deficiency led to a significant increase in hemoglobin levels and a decrease in serum CRP and ferritin concentrations. It is known that cytokines are able to potentiate the effects of each other, especially this is typical of the triad of inflammatory mediators – TNF-α, IL-1β, and IL-6. The opposite effect is also realized – TNF-α blockade in the cytokine ensemble can reduce IL-6 expression playing a key role in the development of ACD.

Long-term use of NSAIDs as first-line drug treatment is recommended in patients with axial SpA. Y. Yan et al. in their study [16] demonstrated a significant decrease in laboratory inflammatory markers in AS patients treated with NSAIDs: statistically significant reduction in the levels of ESR, CRP, IL-6, and TNF-α was shown. Taking into account the pathogenesis of anemia, it is obvious that appropriate anti-inflammatory therapy with NSAIDs can prevent the development of anemia in patients with SpA. On the other hand, continuous NSAID requires monitoring of potential side effects, especially developing drug-induced gastrointestinal bleeding and IDA. In this study, 75% of patients were diagnosed with combined ACD / IDA, but had no signs of NSAID-induced enteropathy. Previously, there were no data confirming the association between IDA and the use of NSAIDs in patients with SpA [17]. The presence of iron deficiency in anemia should be considered as a consequence of hepcidin-induced alteration of iron homeostasis under the conditions of chronic systemic inflammation.

The results of this study confirm the existence of a relationship between the activity of systemic inflammation and hemoglobin levels in patients with SpA. Taking into account the above, correction of anemia in patients with SpA should be based on suppression and, if impossible, minimization of disease activity, which is the immediate therapeutic goal, provided appropriate basic antirheumatic therapy is chosen.

CONCLUSION

The study confirmed the relationship between the activity of systemic inflammation and anemia in patients with SpA. The majority of patients had mixed anemia (ACD / IDA) with a slight or moderate decrease in hemoglobin levels. Inflammation should be considered as the main component in the development of anemia. Taking into account the pathogenesis of ACD, the basis of antianemic therapy is to achieve remission, and if impossible, minimal SpA activity. Additional studies are required to determine the effect of NSAIDs and synthetic and biological DMARDs on the development and course of anemia in patients with SpA.

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