ORIGINAL ARTICLE

ANEMIA IN PATIENTS WITH ANKYLOSING SPONDYLITIS, ASSOCIATION WITH THE ACTIVITY OF THE INFLAMMATORY PROCESS AND THE SEVERITY OF THE DISEASE

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ABSTRACT

The aim: To estimate the prevalence of anemia in patients with ankylosing spondylitis, major pathogenetic variants and their relationship with the activity of the inflammatory process and the severity of the disease.

Materials and methods: 118 patients with ankylosing spondylitis participated in the study, which performed hematologic, biochemical, immunological studies with general haemopoiesis and ferrokinetics parameters, plasma levels of CRP and IL-6.

Results: It was found that in Ukrainian population of patients with ankylosing spondylitis, 28.8% of patients has anemic syndrome. The anemia spectrum is represented by ACD (44.1%), ACD with iron deficiency (29.4%) and IDA (23.5%). It is shown that the severity of anemic syndrome increases with the increase of the stage of activity of the inflammatory process. The presence and severity of anemia are closely related to the severe course of the disease, evaluated by the BASDAI and ASDAS index, and laboratory markers of inflammation CRP and IL-6 of serum.

Conclusions: The obtained data is promising for the search of effective means of correction of anemic syndrome in patients with ankylosing spondylitis.

KEY WORDS: ankylosing spondylitis, anemic syndrome, iron deficiency anemia, anemia of chronic diseases, IL-6, CRP, ASDAS, BASDAI

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INTRODUCTION

Anemia of varying degrees of severity often occurs in patients with ankylosing spondylitis. According to epidemiological studies, anemic syndrome with AS occurs in 18,5-45,8% of cases [1, 2, 3, 4, 5, 6]. The main types of anemia in patients with AS are anemia of chronic disease (ACD) (33,3% – 78,7%) and iron deficiency anemia (IDA) (21,28% – 66,7%) cases [1, 3].

The pathogenesis of ACD is multifactorial, and is closely linked to the activity of the inflammatory process, which affects several key components of erythropoiesis [7, 8]. Firstly, as a result, the iron pool, circulating and available for hematopoiesis, decreases, with the development of relative iron deficiency. Secondly, under conditions of inflammation the absorption of iron in the duodenum decreases as a result of increased synthesis of the osteoplastic protein hepcidin in the liver, which creates the prerequisites for the development of absolute iron deficiency. Thirdly, due to the direct effect of the TNF-α, IL-1, IL-6 and INF-γ, the sensitivity of the erythropoiesis to erythropoietin (EPO) decreases as a result of decreasing of the expression of corresponding membrane receptors of the precursor cells and direct suppression of the differentiation and proliferation of the erythroid germ cells. Thus, the regulation of the EPO decreases and "resistance to EPO" is induced in the erythroid precursor cells.

The main causes of IDA are bleeding due to ulceration of the intestinal mucosa (especially in patients taking large doses of nonsteroidal anti-inflammatory drugs (NSAIDs)) [6], restriction of iron-containing products in food and reduced intestinal absorption of iron [4]. Inflammatory cytokines (IL-1, IL-6) may also aggravate the absorption of iron in the intestine due to hepcidin induced disintegration of ferroportin. In addition, the duodenal absorption of iron is suppressed by TNF-α through a hepcidin-independent mechanism based on the induction of TNF-α, accumulation of iron inside ferritin in enterocytes both in vitro and in vivo [9].

Thus, it is obvious that inflammation plays an important role both in the formation of ACD and IDA, which requires a profound and comprehensive study of the spectrum of anemia in patients with AS and the main mechanisms for their correction.

THE AIM

Therefore the aim of the work was to evaluate the prevalence of anemia in patients with AS, the characteristics of

the main pathogenetic variants and to study their relationship with the activity of the inflammatory process and the severity of the course of the underlying disease.

MATERIALS AND METHODS

118 patients (102 (86.4%) males and 16 (13.6%) females) aged 19 to 75 years who suffered from AS within 1-25 years were selected for the study. The average age of the surveyed was 43.67 ± 0.97 years. The installation and verification of the previously established clinical diagnosis of AS was conducted in accordance with the modified New York criteria. All patients were divided into three groups: patients with AS without anemic syndrome, patients with AS with anemic syndrome and a control group that included practically healthy people without autoimmune systemic diseases. The control group comprised 26 practically healthy persons, representative by age and gender to the main group. In 84 (71.2%) the central form of AS was registered, in 34 (28.8%) the peripheral one.

In 27 (79,4%) anemia of mild severity, in 7 (20,6%) – average degree. Anemia was diagnosed in patients with a decrease in hemoglobin concentration of less than 120 g / L and was established based on the diagnostic criteria [9]. To determine the activity of the disease, the Ankylosing Spondylitis Disease Activity Score (ASDAS) [10] and BASDAI (Bath ankylosing spondylitis disease activity index) [11] were used.

To evaluate the degree of joint syndrome, the number of edematous joints and the number of joints with existing pain were counted. Investigation of joints included physical examination, palpation and an objective assessment of the pain with VAS. The severity of joint pain and the assessment of the general condition of patients were determined based on a 10-point visual analog scale (VAS), where 0 is the best possible health condition, 10 is the worst condition.

All laboratory tests were determined by commonly accepted methods. Hematologic parameters were determined on the ERMA PCE-210 device (Japan), biochemical parameters were determined on the hardware (Humalyzer 2000 biochemical analyzer) and the enzyme immunoassay using Stat Fax 303 / Plus using standard reagents. Determination of the content of soluble transferrin receptors (sTfR) in serum was determined by the method of immunoassay analysis in the Soluble transferrin receptors (sTfR) test system "Monobind Inc.", (USA), the ferritin content was determined using an enzyme-linked ELISA method "ORGENTEC Diagnostika", (Germany). According to manufacturer's instructions, to assess the activity of the inflammatory process in serum, the content of C-reactive protein (CRP) should be quantitatively determined by immuno-enzymatic method using the standard set of the company "Diagnostic Automation Inc." (USA) and determination of erythrocyte sedimentation rate (ESR). The content of proinflammatory cytokine – IL-6 in blood plasma was determined by the immune enzyme method using the standard set of firm "Calbiotech", (Germany). X-ray diagnostics was carried out in accordance with the existing criteria for determination of the AS. Detection of reliable sarcoilliitis (on the second and further stages) is one of the alternative visualization criteria for diagnostics of the AS.

The statistical analysis was carried out using generally accepted methods of statistics using the package of statistical programs "Microsoft Office Excel 2007". The significance of the results was estimated using Student's criterion (the differences were considered with $p < 0.05$) and with Fischer's criterion. In accordance with the requirements of the Ukrainian legislation, patients who participated in the study received full information about the study and signed informed consent to participate in the clinical trial. During the research, the rules were followed in accordance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine and the relevant laws of Ukraine.

RESULTS

Among the 118 patients with AS, anemia was detected in 34 (28.8%) patients. In 27 (79.4%), it was mild severity, in 7 (20.6%) – moderate. Latent iron deficiency was registered in 10 (11.9%) people with a hemoglobin level of not less than 120 g / l. Among all anemic patients, 15 patients (44.1%) had signs of ACD, 10 (29.4%) – ACD with functional deficiency of iron and 8 (23.5%) – IDA (Table I). One more patient had signs of B12 / folio deficiency anemia. The hemoglobin level and the number of erythrocytes in all groups of patients were significantly lower than in the control group. When comparing the pathogenetic groups of patients with these indicators, it should be noted that the level of hemoglobin was lowest in patients with IDA, but probably did not differ from patients with ACD and ACD with iron deficiency. However, these groups of patients significantly differed in MCV magnitude. The smallest (73,49 ± 3,14) average red blood cell size was in patients with IDA, which was significantly higher (87,30 ± 3,06) in patients with a combination of ACD and iron deficiency, and the highest (95,17 ± 1, 92) in patients with ACD. In the latter group, it was significantly higher than in patients with iron deficiency anemia. According to cytometric characteristics of IDA in 75% of patients, it was microcytic in 25% normocytic, ACD with iron deficiency in 60% normocytic in 20% micro / and macrocytic, and ACD in 73% normocytic, in 20% macrocytic. Similar differences between groups were found for ferrokinetics.

Thus, in the group of patients with IDA, the level of serum iron was significantly lower (not only from ACD, but also ACD with iron deficiency). In the same group, the highest (by 29% and 37%, respectively) was the TIBC. Patients with IDA were also characterized by the lowest transferrin saturation and hematocrit. The TS in the latter group was 46% lower than in the iron deficiency group and 88% in the ACD group than in the patients with ACD. The analysis of levels of ferritin in blood serum, depending on the type of anemia, showed that in patients with IDA in comparison with ACD, the level of ferritin was the

Table I. Comparison of indicators of hemopoiesis and ferrokinetics in patients with AS with different pathogenetic variants of anemia (M ± m)

Indexes	Control, n=26	IDA, n=8	ACD with iron deficiency, n=10	ACD, n=15
Hemoglobin, g / l	134,85±1,86	92,88±5,78*	103,20±2,71*	102,53±2,20*
Erythrocytes, 1012/ l	4,29±0,08	3,69±0,25*	3,70±0,10*	3,61±0,08*
MCV, fl	92,17±1,26	73,49±3,14*	87,30±3,06#	95,17±1,92#&
Iron, μmol / l	15,67±0,86	8,30±0,21*	9,52±0,12*#	11,51±0,21*#&
TIBC, μmol / l	54,60±1,92	74,81±3,18*	58,09±1,16#	54,54±0,64#&
TS,%	27,48±1,60	11,22±0,49*	16,43±0,30*#	21,10±0,24*#&
Ferritin, μg / l	29,77±2,33	21,98±1,53*	28,03±5,02	34,37±3,03#
sTfR, мг/л	3,29±0,14	8,35±0,81*	4,72±0,43*#	3,77±0,25#
Hematocrit	0,37±0,00	0,27±0,02*	0,32±0,00*#	0,34±0,00*#&

Notes: * - significance of differences with the group of healthy individuals; # - significance of differences with the group of patients with IDA; & - significance of differences with the group of patients with ACD with iron deficiency (P <0.05).

Table II. Communication of the form of the AS with the form, degree of anemia and its cytometric characteristic (M ± m)

Groups	Groups Duration of AS, years	Forms	
		central	peripheral
		n (%)	n (%)
Patients without anemia, n = 84	8,50±0,57	66 (78,6%)	18 (21,4%)
Patients with anemia, n = 34	7,87±1,08	18 (53,0%)&	16 (47,0%)&
Including:			
ACD, n = 15	7,00±0,92	7 (46,7%)	8 (53,3%)
ACD with iron deficiency, n=10	10,30±2,81	5 (50,0%)	5(50,0%)
IDA, n = 8	5,81±2,25	6 (75%)	2 (25%)
Including:			
Anemia 1st degree, n = 27	8,80±1,28	15 (55,6%)	12 (44,4%)
Anemia 2nd degree, n = 7	4,29±1,02*	3 (42,9%)	4 (57,1%)
Including anemia:			
Normocytic, n = 19	9,63±1,64	9 (47,4%)	10(52,6%)
Microcytic, n = 9	4,50±1,38#	5 (55,6%)	4 (44,4%)
Macrocytic, n = 6	7,33±1,67	4 (66,7%)	2(33,3%)

Notes: & - significance of differences with the group of patients with in patients without anemia; * - significance of differences with the group of patients with anemia of the first degree of gravity; # - significance of differences with the group of patients with normocytic anemia (P <0.05).

lowest, and the soluble receptors to the transferrin were the highest. Patients with ACD with iron deficiency with these indicators occupied an intermediate position between patients with IDA and ACD.

The development of anemia in patients with AS significantly depended on the severity of the course of the disease (Table II). So, almost every second patient with anemia had a peripheral form of AS. Among patients with a peripheral form, the proportion of people with more severe (anemia of the 2nd degree) anemia was also higher than among those with central form. There was a tendency to increase in the group of patients with peripheral form of the proportion of people with ACD and the combination of ACD with iron deficiency, while in the central form predominant patients with IDA.

The data shown in Table III indicates that the activity of the inflammatory process is a factor that increases the likelihood of anemia in patients with AS. In particular, patients with anemic syndrome were characterized by larger values of BASDAI, ASDAS, and VAS.

Thus, the smallest values of BASDAI and ASDAS were in the case of IDA, whereas ACD and a ACD with iron deficiency were characterized by larger (higher) changes in total disease activity rates. In particular, in comparison with IDA, individuals with ACD and ACD with iron deficiency had a total BASDAI activity of 37 and 25%, respectively.

The severity of anemia was also associated with higher disease activity. In persons with anemia of the 2nd degree, the magnitude of BASDAI, ASDAS, and pain in the VAS, prevailed in patients with 1st degree anemia by 6-11%, respectively. There was no close associative connection between the severity of the disease with the morphological variant of anemia.

Table III. The connection of the activity of the inflammatory process with the questionnaires BASDAI, ASDAS, VAS with the type, degree and cytometric variant of anemia in patients with AS (M ± m)

Groups	Activity of the inflammatory process		
	BASDAI, points	ASDAS, points	VAS, points
Patients without anemia, n = 84	5,37±0,18	3,80±0,07	7,08±0,20
Patients with anemia, n = 34	6,67±0,24*	4,16±0,10*	7,97±0,25*
Including:			
ACD, n = 15	5,40±0,46	3,95±0,29	7,75±0,56
ACD with iron deficiency, n=10	6,76±0,38$	4,04±0,15	8,60±0,43
IDA, n = 8	7,42±0,25$	4,44±0,11$	7,80±0,35
Including:			
Anemia 1st degree, n = 27	6,59±0,27	4,06±0,12	7,58±0,28
Anemia 2nd degree, n = 7	7,00±0,49	4,57±0,07#	8,43±0,57
Including anemia:			
Normocytic, n = 19	6,01±0,54	4,08±0,25	7,67±0,50
Microcytic, n = 9	6,81±0,26	4,24±0,13	7,95±0,31
Macrocytic, n = 6	7,22±0,65	4,07±0,24	8,50±0,72

Notes: * - significance of differences with the group of patients with in patients without anemia; $ - significance of differences with the group of patients with IDA; # - significance of differences with the group of patients with anemia of the first degree of gravity (P <0.05).

Table IV. The connection of the activity of the inflammatory process with the levels of CRP, ESR, IL-6 with the type, degree and cytometric variant of anemia in patients with AS (M ± m)

Groups	Activity of the inflammatory process		
	CRP, ng/ml	ESR, mm/h	IL-6, g/ml
Patients without anemia, n = 84	9,99±0,89	20,69±1,25	18,19±1,51
Patients with anemia, n = 34	15,34±0,80*	34,15±2,23*	25,44±1,44*
Including:			
ACD, n = 15	13,13±1,60	31,13±2,12	16,15±1,98
ACD with iron deficiency, n=10	12,20±0,69	33,00±4,77	24,38±2,39
IDA, n = 8	18,83±0,98#	37,13±3,75	30,85±1,43#
Including:			
Anemia 1st degree, n = 27	14,65±0,91	33,11±2,20	24,98±1,55
Anemia 2nd degree, n = 7	18,0±1,31¥	38,14±6,95	27,24±3,75
Including anemia:			
Normocytic, n = 19	13,40±1,86	30,11±2,15	18,03±2,90
Microcytic, n = 9	16,65±1,00	33,05±2,15	27,26±1,33&
Macrocytic, n = 6	14,08±1,32	43,67±9,88	30,80±3,53&

Notes: * - significance of differences with the group of patients with in patients without anemia; # - significance of differences with the group of patients with ACD and iron deficiency and IDA; ¥ - significance of differences with the group of patients with anemia of the first degree of gravity; & - significance of differences with the group of patients with microcytic anemia (P <0.05).

Patients with anemia were characterized by higher values of CRB, ESR and IL-6 than patients without anemia (Table IV).In particular, in the last group the level of CRP was lower by 34.9%, ESR – by 39.4% and IL-6 – by 28.5% compared with patients with such presence. At the same time, the smallest value of CRP, ESR and IL-6 was again inherent in IDA, whereas ACD and ACD with iron deficiency were characterized by higher activity in these indicators. Compared to IDA in patients with ACD, CRP levels were higher by 43%, respectively, ESR by 19%, and IL-6 by 91%, respectively. Patients with ACD with iron deficiency occupy an intermediate position between patients with IDA and ACD.

The severity of anemia was also associated with a more severe course of AS, assessed by laboratory markers of disease activity. In patients with anemia of the 2nd degree, CRP levels were significantly higher than in patients with anemia of the 1st degree of 22.8%, respectively, with other

activity indicators only a tendency to increase them with an increase in the degree of anemia was noted.

According to cytometric characteristics, the most severe indicators of CRP, ESR and IL-6 were recorded in macrocytic anemia, the easiest – in microcytic, and patients with normocytosis had intermediate indices.

DISCUSSION

Thus, the results of our studies clearly indicate that among the 118 patients with an AS, anemia was diagnosed in 34 (28,8%) cases, other 84 (71,2%) patients had no signs of anemia. Among persons with anemic syndrome, only 44,1% of patients had ACD, and 23,5% of patients had IDA. According to Russian researchers [1], among patients with AS 78,72% had ACD, and 21,28% of patients had IDA. According to the Korean population of patients with AS, first place (66,7% of patients) in frequency was taken by IDA, the second by ACD (33,3% of patients) [3]. Twice lower (15%) frequency of ACD was found in the Italian population of patients with AS [5]. In our opinion, this difference in frequency of anemia can exist due to different socio-economic status of the population, the features of treatment, the severity of the inflammatory process, etc. Another feature of the part of patients with acute respiratory system is the presence of a distinct functional deficiency of iron, which leads to the development of microcytosis (MCV < 80 ft) and hypochromia in peripheral blood of some patients, which requires the determination of iron metabolism parameters for differential diagnosis of functional deficiency of iron with its absolute deficit and therefore the objection (IDA). Therefore, according to our data, ACD with iron deficiency was detected in 29,4% of cases.

The study did not reveal any significant differences, connected with hemoglobin content and the number of red blood cells, in different groups of patients . However, the patients probably differed in MCV magnitude. The highest average size of erythrocytes was found in patients with ACD, probably the patients with combination of ACD with iron deficiency had it lower, and the lowest values of MCV were found in patients with IDA. According to cytometric characteristics of IDA, in 75% of cases patients had microcytic, patients with ACD with iron deficiency had in 60% normocytic, and ACD – in 73% of normocytic. The similarity of the cytometric picture was described in the study [1].

It was discovered that in 62,5% of cases patients with IDA had anemia of moderate severity, whereas in the groups with ACD and ACD with iron deficiency there were only 10% of them. According to [3] among AS patients, patients with ACD in the overwhelming majority have a slight degree of anemia, whereas an IDA is more often of an average or severe degree.

Our studies have shown that the main indicators of ferrokinetics were significantly dependent on the pathogenetic variant of anemia. In particular, the level of serum iron in patients with IDA was significantly lower than in patients with ACD. It was during iron deficiency that the TIBC was highest, the transferrin saturation, and the level of ferritin were the lowest, compared with patients with ACD. However, the highest level of soluble transferrin receptors was detected in patients with IDA, and in individuals with ACD, respectively, the lowest. At the same time, patients with ACD with iron deficiency with these indicators occupied an intermediate position between patients with IDA and ACD. Literature data clearly indicates that soluble transferrin receptors are an important indicator of iron deficiency [12, 13]. In cases of its lack, bone marrow enhances the production of receptors for transferrin, and thus sends iron with transferrin to bone marrow cells for normal erythropoiesis [13]. According to [4], levels of soluble transferrin receptors are highest in people with IDA, and they are among the most sensitive differential diagnostic criteria for iron deficiency in conditions of high activity of the inflammatory process in patients with AS.

We found that the severity of the course of the AS influenced the development of anemia. Thus, among patients with peripheral form, there were more people with more severe (anemia II degree) anemia, as well as a greater proportion of people with ACD and ACD with iron deficiency than among patients with central form.

Individuals with anemia have a greater activity in the inflammatory process by the BASDAI, ASDAS, VAS questionnaires than patients without anemic syndrome. In particular, the index of BASDAI and ASDAS activity in anemic patients was significantly higher than in patients without anemia. The study also found that the presence of IDA in patients with AS was clearly associated with minimal activity in the BASDAI and ASDAS indices, while the presence of ACD clearly depended on the higher activity of these questionnaires. In particular, the BASDAI index in patients with hypertension was significantly (37%) higher than in patients with IDA.

Patients with anemia were characterized by significantly higher values and laboratory (CRP, ESR and IL-6) indicators of disease activity than patients without anemia. At the same time, the smallest value of these markers of inflammation was determined in patients with IDA, whereas patients with ACD and ACD with iron deficiency were characterized by higher levels of indicators.

The degree of severity of anemia was also associate.d with greater activity, both in terms of aggregate BASDAI and ASDAS and laboratory markers of inflammation. In particular, in patients with anemia of the 2nd degree of severity, the levels of CRP, ESR and IL-6 were predominant in patients with anemia of the 1st degree of severity of 22,8%, 15% and 8%, respectively. There was no close correlation between the activity of the disease and morphological variants of anemia. Summing up the results obtained, it should be noted that anemia in patients with AS is partly due to high activity of the inflammatory process, and on the other hand, it is a marker of the severity of the disease.

The personal data is similar to the results of other researchers. Thus, it has been shown that individuals with a

peripheral form are more likely to have registered anemic syndrome, with BASDAI and CRP, more often arthritis, entezite and / or dactylitis [14].

According to [3], with the use of immunobiotic (anti-TNF-α) therapy, the levels of ESR, CRP, and BASDAI decrease with the simultaneous growth of the average hemoglobin level. Anemia has been cured in all patients with ACD, except for one, whereas in patients with IDA only three levels of anemia were leveled, while the rest were iron supplements to restore hemoglobin levels. Even non-anemic patients experienced an increase in hemoglobin levels (from 14,7 ± 1,0 g / dl to 15,0 ± 1,2 g / dl). Improvement of the hemoglobin level correlated positively with changes in ESR and CRP($r=0,608$, $p<0,001$ i $r=0,588$, $p<0,001$, respectively).

Similar results were obtained in other studies [2, 15]. In particular, according to [2], normalization of hemoglobin levels occurred in 70,3% of patients receiving infliximab and only 27,3% of the patients that received traditional treatment. It should be noted that in subjects with very high levels of CRP and / or IL-6, at baseline, there was a marked improvement in hemoglobin levels than in patients with a relatively normal level of these parameters.

Thus, the high frequency and complexity of the formation of anemia in patients with AS, its close relationship with the activity of the disease requires personified ways of correction.

CONCLUSIONS

1. Anemia in patients with AS is found in 28,8% of cases, and in another 10 (11,9% of cases) was registered latent deficiency of iron. The anemia spectrum is represented by ACD (44,1%), ACD with iron deficiency (29,4%), and IDA (23,5%).
2. According to cytometric characteristics of IDA, in 75% of cases patients had microcytic, patients with ACD with iron deficiency had in 60% of cases normocytic, and ACD – in 73% of cases normocytic.
3. The direction of changes in haemopoiesis and ferrokinetics in patients with AS is due to the type of anemia. Patients with IDA have the highest levels of erythrocytes, TIBC and sTfR, microcytosis and the lowest levels of serum iron, TS and ferritin. In patients with ACD only moderate changes in iron metabolism were registered, patients with ACD with iron deficiency with these indicators occupy intermediate positions.
4. The presence and severity of anemia is closely associated with the severe course of the disease assessed by the BASDAI and ASDAS index, laboratory markers of inflammation – ESR, CRP, and IL-6 in serum. Characteristic for ACD are the highest levels of activity of the disease, the lowest for IDA, the patients with ACD with iron deficiency in the indicators of inflammatory process occupy an intermediate position.

Directions of further researches provide the search for effective means of correction of anemia in patients with ankylosing spondylitis.

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