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Peripheral Blood System Status of Rheumatoid Arthritis Patients Depending on Haptoglobin Polymorphism

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Abstract The aim of the study is to study the peripheral state of blood (PBS) in RA patients with different haptoglobin phenotypes. The study showed a connection between the course of the disease, the severity of anemia and the type of haptoglobin, which was revealed mainly in patients with the phenotype Hp 2-2. It is one of the factors of formation, development and chronization of the inflammatory process, where immunogenetic predisposition plays an important role. Clarification of these predisposing factors allows to reveal heavy forms of the flow of RA and to carry out timely preventive measures.

Keywords Rheumatoid arthritis, Haptoglobin phenotypes, Peripheral blood state, Anemia

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory rheumatic disease of unknown etiology, characterized by chronic erosive arthritis and systemic damage to internal organs [1,6]. RA is one of the most common joint diseases, occupying about 10% in the structure of rheumatological pathology, it is not only a medical, but also an economic problem, since the debut of the disease in most cases is observed in people of working age [2,5,7]. One of the extra-articular manifestations of the disease is anemia, the prevalence of which ranges from 30 to 70% of cases. Anemia in RA is based on a deficiency of hematopoiesis factors (iron, vitamin B_{12}, folic acid), a chronic inflammatory process (the so-called anemia of a chronic disease - ACH), autoimmune reactions (autoimmune hemolytic anemia) or the toxic effect of drugs (aplastic anemia) [3,4]. Anemia is accompanied by tissue hypoxia and can, on the one hand, lead to damage to various organs and systems, and on the other hand, to a deterioration in the course of the underlying disease and patient prognosis.

In recent years, the role of the genetic predisposition of RA development has been widely discussed. Most likely, the disease develops as a result of a complex and largely probable interaction of genetic factors and environmental factors [3]. Of great interest in studying the hereditary predisposition to the disease is also the determination of the HP glycoprotein α_2 -globulin fraction of whey proteins with genetic polymorphism [4,7]. The literature cites evidence that the exchange of NR is closely related to the processes occurring in the connective tissue.

The aim of our study was to study the state of UCS in patients with RA with various haptoglobin phenotypes.

2. Methods and Materials

185 patients with a diagnosis of rheumatoid arthritis (RA) for the period 2016–2019 were examined. The diagnosis of the disease was established on the basis of diagnostic criteria proposed by the American College of Rheumatologists. The average age of patients with RA was 54.8 ± 1.4 years, the duration of the disease was 8.6 ± 0.7 years (the correlation index of these indicators was r = 0.48). The determination of the haptoglobin (Hp) phenotype in the blood serum was carried out by Davis electrophoresis in the modification of N.A. Aspen. The blood serum levels of patients were also determined: iron, hepcidin, ferritin, and ADC. The data obtained were subjected to statistical processing using a software package of statistical analysis on a Pentium -4 computer. For statistically significant changes, a confidence level of $P < 0.05$ was taken.

3. Results and Discussion

As you know, in recent years, the degree of anemia is considered a prognostic indicator of RA and is included in the criteria that determine the activity of the disease. According to the literature, the greater the degree of anemia, the worse the prognosis of the disease. In our studies, anemia was observed in 102 patients (55.1%) with rheumatoid

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arthritis: in 57.3% of cases, chronic disease anemia, in 42.7% of patients, iron deficiency anemia. Hemoglobin in the peripheral blood of RA patients appeared on average 79.1 ± 1.7 g / l, the content of erythrocytes - 2,8 ±0,06h10 ^{12} / l, iron - 7,1 ± 1,41mkmol / l, ferritin - 74.5 ± 4.11 μg / L, which reflects the average degree of anemia. Change in hemoglobin content, the number of red blood cells, iron and ferritin with various phenotypes of haptoglobin are shown in table 1.

Table 1. Changes in blood picture parameters in patients with RA depending on haptoglobin carriage

No.	Indicators	Nr 1-1	Nr 2-1	Nr 2-2
1.	Hemoglobin, g / l	81.5 ±2.6	81.9 ±2.2	76.7 ±2.8 *
2.	Red blood cells, ×10 ^{12} / l	2.98 ±0.11	2.97 ±0.09	2.73 ±0.08
3.	White blood cells ×10 ^{9} / L	4.97 ±0.48	5.14 ±0.29	4.95 ±0.22
4.	Lymphocytes,%	24.85 ±2.51	27.36 ±1.28	23.51 ±1.15
5.	Ferritin	90 ±1.87	74 ±1.86	59 ±2.08
6.	Iron	10.9 ±1.1	7.82 ±1.615	6.1 ±1.23
9.	ESR, mm / hour	29.54 ±3.24	26.51 ±1.59	41.81 ±2.21 *
10.	CRP, mg / l	39.19 ±4.22	44.18 ±1.59	80.13 ±6.76 *
11.	Haptoglobin, g / l	2.98 ±0.38	2.80 ±0.19	3.36 ±0.22 *
12.	Fibrinogen, g / l	4.37 ±0.20	4.75 ±0.24	5.24 ±0.8 *
13.	ADC	48.4 ±3.2	96, 9 ±4.3	185.1 ±4.8
14.	Hepsidin	2.88 ±0.2	4.28 ±1.2	7.12 ±1.72

Note: the differences between the indicators of the group of patients with Hp1-1 and the rest are significant, P <0.05.

The results showed that the content of hemoglobin, erythrocytes, iron and ferritin is most pronounced reduced in patients with the phenotype Hp 2-2 (up to 76.7 ± 2.8 g / l, 2.73 ±0.08 ×10 ^{12} / l, 59 ± 2.08 μmol / L and 6.1 ± 1.23 μg / L), respectively, which confirms the idea of a severe course of RA in patients with this form of HP. Among 102 patients with anemia, a severe form was not detected with Hp 1-1 carriage, with the Hp 2-1 phenotype in 7% of patients, while in patients with the Hp 2-2 phenotype, 24.1%. As can be seen from the above data, the severity of anemia depended on the type of haptoglobin and was detected mainly in patients with the phenotype Hp 2-2. In the group of patients with anemia, the serum hepcidin content was significantly higher than in patients with normal hemoglobin in the blood.

We have established a relationship between the activity of the inflammatory process and the carriage of Nr. Indeed, this is confirmed by the highest rates of ESR, fibrinogen, CRP and ADCP.

So, if with Hp 1-1 the ESR indicator increased significantly 3.02 times, with Hp 2-1 - 2.7 times and the highest values (an increase of 4.2 times) - in patients with Nr 2-2. Confirmation of this is an increase in the proteins of the acute phase.

The level of fibrinogen also increased significantly, and its severity depended on the haptoglobin phenotype. The greatest increase in fibrinogen level was characteristic of patients with Nr 2-2 carriage. So, its level increased statistically significantly at 1.97; 2.14 and 2.36 times, respectively, to the phenotypes Hp1-1, Hp 2-1 and Hp 2-2.

As you know, ESR are used to determine the concentration of the components of the "acute phase" and allow you to quantify the inflammatory process. The value of ESR depends on many factors and, therefore, its specificity is low. However, the concentration of CRP reflects the content of a particular protein of the "acute phase", which is more specific. Its concentration increases and decreases faster (decreases by 50% in 24 hours) than ESR, which is characterized by long-lasting high rates (decreases by 50% in 1 week) after the attenuation of inflammation.

Indeed, in patients with the type of haptoglobin Nr 1-1, the average CRP content (increased in 84.6% of patients) was 39.19 + 4.22 mg / L, in patients with the type of haptoglobin Nr 2-1 (was high in 89, 5% of patients) - 44.18 + 1.59 mg / l, in patients with the type of haptoglobin Hp 2-2 (was increased in 96.3% of patients) - 80.15 ±6.76 mg / l (P <0, 02 and P <0.01).

The level of ACCP in the blood of patients with RA increased significantly, and its values literally depended on the haptoglobin phenotype. The greatest increase in the level of ADC was characteristic of patients with carriage Nr 2-2. So, its level increased statistically significantly at 4.8; 9.6 and 18.5 times, respectively, the phenotypes Hp1-1, Hp 2-1 and Hp 2-2. At the same time, we found a correspondence between the activity of the pathological process, high values of CRP, ESR, ADCP and carriage of haptoglobin.

Thus, a study of the state of UCS in patients with RA with various haptoglobin phenotypes. indicates the presence of a relationship between the course of the disease, the severity of anemia, such as haptoglobin and a genetic predisposition to the development of RA, which was detected mainly in patients with the Np 2-2 phenotype. This confirms the available literature data considering the immunological concept of RA as one of the factors in the formation, development, and chronicity of the inflammatory process, where the immunogenetic predisposition plays an important role. This is confirmed by the presence of severe RA in patients with HP. 2-2. These factors determine the severity of the pathology, significant changes in the homeostasis of the

body. Elucidation of these predisposing factors makes it possible to identify severe forms of the course of RA and conduct timely preventive measures.

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