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COMPARATIVE SIGNIFICANCE OF SPONTANEOUS IMMUNOGLOBULIN-SYNTHESIZING ACTIVITY OF B-LYMPHOCYTES IN VARIOUS CLINICAL VARIANTS OF REACTIVE ARTHRITIS

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СРАВНИТЕЛЬНОЕ ЗНАЧЕНИЕ СПОНТАННОЙ ИММУНОГЛОБУЛИНСИНТЕЗИРУЮЩЕЙ АКТИВНОСТИ В-ЛИМФОЦИТОВ ПРИ РАЗЛИЧНЫХ КЛИНИЧЕСКИХ ВАРИАНТАХ РЕАКТИВНОГО АРТРИТА

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Abstract. This work considers the significance of spontaneous immunoglobulin-synthesizing activity of B-lymphocytes (SIAL) in various clinical variants of reactive arthritis (ReA). It was

found that an increased level of SIAL was found in patients with autoimmune diseases (AS, RA, and SLE) from 72.2% to 88.8%, in 57.9% of patients with RHEA, only 10% of healthy individuals, and only 27.3% of patients with osteoarthritis. It was shown that Rea with a high degree of activity and a chronic course of the disease, the values of SIAL were higher than with minimal and moderate degrees of activity and acute and prolonged courses of the disease.

Аннотация. Рассматривается значение спонтанной иммуноглобулинсинтезирующей активности В-лимфоцитов (СИАЛ) при различных клинических вариантах реактивного артрита (РеА). Установлено, что повышенный уровень СИАЛ обнаружено у больных с аутоиммунными заболеваниями (АС, РА и СКВ) от 72,2 % до 88,8%, у 57,9% больных РеА, всего лишь у 10% здоровых лиц, и лишь у 27,3% больных остеоартритом. Показано, что при РеА с высокой степенью активности и хроническим течением болезни значения СИАЛ были выше, чем при минимальной и умеренной степенях активности и острой и затяжной течениях болезни.

Ключевые слова: реактивный артрит, спонтанная иммуноглобулинсинтезирующая активность, В- лимфоциты.

Keywords: reactive arthritis, spontaneous immunoglobulin-synthesizing activity, B-lymphocytes.

In the pathogenesis of reactive arthritis (ReA), one of the links is the activation of B-lymphocytes, manifested by the accumulation of circulating immune complexes and antibodies to connective tissue structures [1, p.270; 2, p.77-79; 3, p.101-103; 4, p. 528-529; 9, p. 559-562].

At the same time, a special place in the assessment of B-lymphocytic immunity is occupied by the method of studying the immunoglobulin-synthesizing (Ig) function of lymphocytes, which made it possible to establish a high spontaneous Ig-synthesizing activity of B-lymphocytes in rheumatic diseases [5, p. 66; 6, p. 557-558; 10, p. 1088-1093].

The aim of the study was to study the pathogenetic and clinical significance of spontaneous Ig-synthesizing activity of B lymphocytes (SIAL) in various clinical variants of reactive arthritis.

Materials and methods

53 RheA patients aged from 17 to 45 years (17 women and 36 men) were examined. I degree of disease activity was noted in 18 (33.9%) patients, II degree in 22 (41.5%), and III degree in 13 (24.5%) patients. An acute course of the disease was observed in 28 (52.8%) patients, a prolonged course in 15 (28.3%), and a chronic course in 10 (18.8%) patients. The urogenital form of the disease was detected in 36 (67.9%) and postenterocolitic in 17 (32.0%) patients.

As a comparison group, 18 patients with systemic lupus erythematosus (SLE), 22 patients with ankylosing spondylitis (AS), and 22 patients with osteoarthritis (OA) were examined. The control group consisted of 30 healthy individuals.

The spontaneous Ig-synthesizing activity of B lymphocytes (SIAL) was determined by quantitative cytofluorometry. Lymphocytes were isolated from peripheral heparin-stabilized blood at a density gradient of 1.007 g/cm³ verografin-ficoll. The gradient was prepared as follows: 1 part of 76% verografin solution was mixed with 4 parts of ficolla solution. After mixing, the mixture was ready for use. 2.5 ml of verografin-ficoll mixture was poured into a test tube. The test tube was left until the mixture reached room temperature. 5 ml of blood was taken from the vein. To prevent clotting, 20 units of heparin per 1.0 ml of blood were added to the blood when taken. Using a

pipette, whole heparin-stabilized blood was carefully layered in a volume of 4 ml, avoiding mixing of the gradient and blood. Then they were centrifuged at a speed of 1500 rpm. within 30 minutes. At the same time, erythrocytes and granulocytes settled to the bottom of the test tube, and mononuclear cells were located at the interface of the gradient and blood. A layer of mononuclears was pipetted across the entire cross-sectional area of the test tube at the phase interface. Lymphocytes were transferred to a clean test tube. The isolated cells were washed twice from plasma by centrifugation in medium 199 at a speed of 1000 rpm. within 5 minutes. The appendages were removed, and the lymphocytes were resuspended with a solution of nutrient medium. Lymphocytes collected from the interphase were washed once with medium 199 by centrifugation at a speed of 1000 rpm. within 5 minutes. The appendages were removed, and the mononuclears were resuspended with 1.0 ml of medium 199. Then 0.5 ml of lymphocyte suspension was introduced into two test tubes (control and experiment) with the PPP, the composition of which is described above. The control was immediately placed in the refrigerator at t 4°C, and the experiment was placed in the thermostat at t 37°C. The samples were incubated for 18 hours. After incubation, the samples were centrifuged at a speed of 1000 rpm. Within 5 minutes, the appendages were removed, and the lymphocytes were resuspended with 2 drops of medium 199. After that, a monolayer of lymphocytes was obtained, for which a drop of lymphocytes was applied to two slides (control and experiment), incubated in a moist chamber at room temperature for 3-5 minutes. After that, the non-adhering cells were washed off with medium 199.

As a result, a clearly formed spot of viable cells remained on the glass. Immediately after receiving the monolayer, it was fixed with a 4% formaldehyde solution for 10 minutes. After fixation, the drug was washed with medium 199, dried, and stained with luminescent serum against human globulins conjugated with fluorescein isothiocyanate (FITZ serum).

After staining and thorough washing of unbound proteins and FITZ, the glasses were dried, and quantitative cytofluorometry was performed on a microscope using a photometric prefix. Measurement of the Ig-synthesizing function of lymphocytes was carried out in the region of 530 nm from the area of the preparation site. In addition to total fluorescence, total light scattering was measured at the same site of the preparation using a combination of MS-1 and NS-10 light filters that do not excite fluorescence. Light scattering under the selected measurement conditions linearly reflects the cell density of the monolayer, so the ratio of total fluorescence to light scattering is the average fluorescence on the plane of the monolayer, or the value reflecting the level of Ig per cell in the studied lymphoid population.

Taking into account that the discharge strength of the source lamp is not strictly constant and, consequently, the fluorescence intensity can vary from series of experiments to series, an amendment was introduced to the total fluorescence value by measuring the fluorescence of a reference uranium glass 2.3 mm thick—Fe—in each series of determinations. Hence, the average fluorescence (F) of the monolayer density was calculated by the ratio: $F = F_{\text{Fe}} / x_{\text{Fe}}$. This ratio reflects the average number of intracellular Ig associated with a lymphoid cell. Then, comparing the levels of Ig in the experiment and control, the SIAL indicator was derived according to the formula: $\text{SIAL} = (F_{\text{expt}} / F_{\text{control}}) \times 100$ conl. units.

Statistical processing of the obtained results was carried out according to special programs with the calculation of the arithmetic mean (M), the standard deviation (σ), the average error of the arithmetic mean (m), the confidence coefficient (t), and the probability index (P). the quadratic deviation (σ), the average error of the arithmetic mean (m), the confidence coefficient (t), the probability index (P).

Results

The levels of SIAL in the examined groups are presented in Table 1.

Table 1

The LEVEL OF SIAL IN THE EXAMINED GROUPS

Contingent	n	M±m	Number of positive results	
			Abs.	%
Control	30	115,6±1,73 (106,3-124,9)	3	10,0
OA patients	22	118,4±2,40	6	27,3
AS patients	22	129,7±3,02***	26	72,2
SLE patients	18	162,3±2,70***	16	88,8
RheA patients	53	123,8±2,71**	31	58,5

Note: 1. in parentheses, the confidence interval in healthy individuals according to the formula $M \pm \sigma$. 2*- significantly, compared with healthy individuals (*- $p < 0.05$; **- $p < 0.01$; ***- $p < 0.001$)

As can be seen from Table 1, the CIAL index in patients with RheA is significantly higher than in representatives of the control group and patients with OA, but less than in patients with AS and SLE. At the same time, the minimum value of this indicator was found in individuals of the control group, the average value of SIAL was found in patients with RheA and AS, and the maximum value of the above indicator is observed in patients with SLE. The level of SIAL in ReA patients was significantly higher than in healthy individuals ($t=2.5$; $p < 0.01$) and OA patients ($t=1.49$; $p > 0.05$). This indicator in RHEA was less than in patients with AS (in the form of a trend) and SLE ($t=3.56$; $p < 0.001$). There is the following difference in the frequency of the above indicator, which goes beyond the limits of the confidence interval of the norm. The level was found to be higher than normal in only 6.7% of individuals from the control group, whereas in RheA it was 58.5%, which is higher than in patients with OA (27.3%).

Table 2

SIAL IN VARIOUS CLINICAL VARIANTS OF REA

Examined subgroups of RheA patients	n	M±m	Frequency of positive results		
			Abs.	%	
I deg.	18	120,2±3,41	7	38,9	$t_1=1,27$; $p_1 < 0,05$
II deg.	22	126,1±3,15	13	59,1	$t_2=0,47$; $p_2 > 0,05$
III deg.	13	138,3±2,09	11	84,6	$t_3=3,23$; $p_3 < 0,001$
Acute current	28	118,9±2,38	13	46,4	$t_4=1,60$; $p_4 > 0,05$
Prolonged course	15	125,8±3,58	9	60,0	$t_5=2,24$; $p_5 < 0,05$
Chronic course	10	135,2±2,19	9	90,0	$t_6=5,04$; $p_6 < 0,001$
Urogenital form	36	125,1±3,08	22	61,1	$t_7=0,67$; $p_7 > 0,05$
Postenterocolitic form	17	122,3±2,81	9	52,9	

Notes: 1. t_1 and p_1 – the difference between the indicators at RheA I and II degrees of activity; 2. t_2 and p_2 - the difference between the indicators at RheA II and III degrees of activity; 3. t_3 and p_3 - the difference between the indicators at RheA I and III degrees of activity; 4. t_4 and p_4 – the difference between the indicators of acute and prolonged RheA; 5. t_5 and p_5 - the difference between the indicators of prolonged and chronic RheA; 6. t_6 and p_6 – the difference between the indicators of acute and chronic RheA; 7. t_7 and p_7 - the difference between the indicators of urogenital and postenterocolitic RheA

From the data presented in Table 2, it can be seen that the level of SIAL in ReA patients with grade III activity was higher than in I ($t_3=3.23$; $p_3 < 0.001$) and II degree of activity ($t_2=0.47$; $p_2 > 0.05$). The same pattern has been established for the frequency of positive SIAL results, so the SIAL index above the norm was found in 84.6% of patients with III degree of activity, which is

much higher than in patients with II (59.1%) and I (38.9%) degrees of disease activity. When comparing SIAL levels depending on the course of the disease (acute, prolonged, chronic), the highest level of SIAL was found in patients with a chronic course of the disease, significantly exceeding the same indicator in patients with acute and prolonged currents ($t_6=5.04$; $p_6<0.001$ and $t_5=2.24$; $p_5<0.05$, respectively). Analysis of the level of SIAL in RHEA patients with urogenital and postenterocolitic pathology revealed almost the same value of this phenomenon in both forms of the disease ($t_7=0.67$; $p_7>0.05$).

Discussion

The above data indicate that the level of SIAL in RheA patients is higher than in healthy individuals and OA patients and lower than in SLE and AS patients. It is also noted that the quantitative values of immune disorders correspond to the severity of the inflammatory process in rheumatic diseases, which is consistent with the works of other authors [7, pp. 23-24; 8, pp. 632-634] and our previous works [4, pp. 528-529; 5, pp. 66; 6, pp. 557-559].

As follows from the literature data, the Ig-synthesizing activity of lymphocytes correlates with the presence and degree of inflammatory changes, and the high Ig-synthesizing activity of B-lymphocytes against the background of a deficiency in the suppressor function of T-lymphocytes is characteristic of inflammatory rheumatic diseases. The presence of B-lymphocytes with high immunoglobulin-synthesizing activity, which we found in RheA, obviously underlies the production of antichlamydia, antiyersiniosis, and other antibodies by the latter with the formation of immune complexes that cause immune inflammation. The revealed high level of SIAL in RheA patients, in comparison with healthy individuals and RheA patients, proves a higher activity of B-lymphocytes and other immune disorders in RheA [4, pp. 528-529; 5, pp. 66; 6, pp. 557-559]. On the other hand, a significantly high level of SIAL in the chronic course of RheA, compared with acute ($t=5.04$; $p<0.001$) and prolonged ($t=2.24$; $p<0.05$) courses of the disease, indicates that autoimmune disorders, namely activation of B-lymphocytes, are mainly characteristic of the chronic variant of the disease.

At the same time, lower SIAL parameters in RHEA compared with SLE and AS once again confirm the lower severity of autoimmune shifts in this disease, which subsequently determine less vivid clinical and laboratory manifestations in RHEA patients than in patients with SLE and AS. [4, pp. 528-529; 5, pp. 66; 6, pp. 557-559].

The important clinical significance of SIAL in RHEA is that this indicator, increasing from a minimum degree of activity to a high one, allows us to determine not only the presence of an exacerbation of the pathological process in RHEA but also to clarify the degree of activity of the disease. Another important clinical significance of the STRENGTH indicator is that this phenomenon in RHEA patients with a chronic course of the disease was much higher compared to the acute and prolonged course of the disease.

Conclusions:

The level of SIAL in patients with RheA was significantly higher than in healthy individuals but less than in patients with AS and SLE.

The value of the SIAL indicator in RheA depends on the activity and course of the disease: the higher the activity and duration of the disease, the greater the value of SIAL.

Assessment of SIAL can be used to determine the activity of the pathological process in RheA.

Patients with chronic RheA may benefit from immunosuppressive therapy if their SIAL level is high.

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