UDC 617.731-002-07:57.083
DOI https://doi.org/10.32782/2226-2008-2024-4-7

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THE LEVEL OF MOLECULAR MARKERS ACTIVITY ON PERIPHERAL BLOOD LYMPHOCYTES IN PATIENTS WITH OPTIC NEURITIS

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The level of molecular markers activity on peripheral blood lymphocytes in patients with optic neuritis

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Optic neuritis (ON) is one of the frequent causes of acute damage to the optic nerve.

The research aims to determine the activation of molecular markers ICAM-1 (CD54), CD5, CD25, CD95 levels on the peripheral blood lymphocytes in patients with ON and its complications.

Materials and methods. Examinations were carried out: 1 group – 16 patients (22 eyes) with idiopathic ON (papillitis). The duration of the disease from the first symptoms to diagnosis with this examination was no more than 30 days. Group 2 – 8 patients (14 eyes) with partial atrophy of the optic nerve (PAON) as a result of ON. The duration of the disease from the first symptoms to the diagnosis ranged from 180 to 1825 days. Indicators of the molecular activation markers on CD3+ lymphocytes were determined using monoclonal antibodies by immunofluorescence method.

Results: In ON and PAON groups, the number of $CD3^+$ lymphocytes with the expression of the pro-inflammatory marker ICAM-1 (CD54) 3.4–6.3 times exceeds the norm; the expression of the marker CD25 early activation 1.9–4.6 times exceeds the norm; with the expression of the autoimmune action marker CD5 2.2–4.9 times exceeds the norm; the expression of the apoptosis marker CD95 2.4–5.1 times exceeds the norm. The expression of ICAM-1 (CD54), CD5, CD25 and CD95 markers correlates directly with the cell immunity indicators CD4+, CD8+, CD16+ and also with the level of B-lymphocytes ($CD19^+$) as an indicator of humoral immunity.

Conclusions: the level of expression of activation markers on peripheral blood lymphocytes in patients with ON and PAON was determined: the level of molecular markers of lymphocyte activation CD54, CD5, CD25, CD95 significantly exceeds the norm – 1.9–6.3 times. The expression of these markers correlates directly with the cell and humoral immunity. This determines the active participation of the markers in the immune response in ON and in its pathogenesis.

Key words: optic neuritis, partial atrophy of the optic nerve, cellular and humoral immunity, markers of lymphocyte activation.

УДК 617.731-002-07:57.083

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РІВЕНЬ МОЛЕКУЛЯРНИХ МАРКЕРІВ АКТИВАЦІЇ ЛІМФОЦИТІВ ПЕРИФЕРИЧНОЇ КРОВИ У ХВОРИХ НА НЕВРИТ ЗОРОВОГО НЕРВА

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Метою роботи було визначити рівень молекулярних маркерів активації лімфоцитів CD54, CD5, CD25, CD95 на лімфоцитах $CD3^+$ периферичної крові за допомогою моноклональних антитіл гістоімуноцитохімічним методом у двух груп хворих: з невритом зорового нерва (НЗН) та з частковою атрофією зорового нерва (ЧАЗН). Визначено, що у хворих на НЗН та ЧАЗН кількість $CD3^+$лімфоцитів з експресією прозапального маркера ICAM-1 (CD54) перевищує норму в 3,4-6,3 рази; з експресією маркера ранньої активації CD25 перевищує норму в 1,9-4,6 рази; з експресією маркера аутоімунної дії CD5 перевищує норму в 2,2-4,9 рази; з експресією маркера апоптозу CD95 перевищує норму в 2,4-5,1 рази. У хворих на НЗН та при виході в ЧАЗН експресія маркерів CD54, CD5, CD25 та CD95 на лимфоцітах периферичної крови корелює з показниками Т-клітинного імунітету ($CD4^+$, $CD8^+$, $CD16^+$), а також з рівнем В-лимфоцітів ($CD19^+$). Це показує активну участь досліджених маркерів в імунній відповіді при НЗН та в його патогенезі.

Ключові слова: неврит зорового нерва, часткова атрофія зорового нерва, клітинний та гуморальний імунітет, маркери активації лімфоцитів.

Optic neuritis (ON), or inflammation of the optic nerve, is one of the common causes of acute optic nerve damage in both children and adults. Epidemiological data on ON vary, with incidence rates differing by more than five times, associated with the geographic distribution of immune-mediated diseases [1].

The causes of ON are diverse: autoimmune processes, infections, granulomatous disease, paraneoplastic syndromes, and demyelination. ON may also occur independently of these causes. Isolated ON, which is not associated with any specific neurological or systemic disease, is referred to as idiopathic ON. According to recent literature, most cases of ON are idiopathic [2, 3]. In recent decades [4], data have been provided on ON of unknown etiology in various countries, with incidence rates ranging from 0.7 to 33 cases per 100,000 population annually. ON can manifest clinically as papillitis, neuroretinitis, or retrobulbar neuritis. Over the last 15 years, two new biomarkers have been identified that help to further characterize atypical ON. In 2004, antibodies against aquaporin-4 (AQP-4), which are pathogenic and highly specific for neuromyelitis optica spectrum disorder, were discovered. In 2007, antibodies targeting myelin oligodendrocyte glycoprotein (MOG) epitopes were reported. These are now recognized as biomarkers for MOG-IgG-associated disease (MOGAD). According to population studies, these two forms of neuritis account for about 9% of all ON cases [5, 6]. The nomenclature defining the various subtypes of ON continues to be refined, and a consensus on expert assessment is still lacking. Advances in immunology, such as serological diagnostics with the identification of antibody biomarkers for demyelinating diseases, have expanded our understanding of some ON subtypes. However, specific serological and radiological biomarkers have not yet been established for all ON subtypes [7]. Autoimmune serology and cerebrospinal fluid analysis can provide valuable information that can either focus the differential diagnosis or clarify the primary etiology. For diagnostic purposes, antinuclear autoantibodies (ANA) are used, though they are nonspecific and do not establish the cause of optic neuritis. Testing for cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) should be included in ON cases considered for granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) [8].

More than two decades ago, studies were conducted on the characteristics of T-lymphocyte subpopulations in ON. The role of CD4+ and CD8+ T-cells and the expression of amyloid precursor protein in damaged axons during demyelination, which had a direct mutual correlation, were determined [9]. Normalization of CD4+and CD8+ T-cell levels is an important indicator of the success of many diseases [10,11].

It was shown that CD19+ B-cells play a significant role in the pathogenesis of the onset of acute demyelinating ON [12]. In our previous studies, we demonstrated the level of molecular markers of CD54, CD5, CD25, and CD95 lymphocyte activation on CD3+ lymphocytes in peripheral blood of patients with recurrent uveitis, detailing their expression patterns in relapse and remission phases of uveitis, and in cases complicated by macular edema [13]. According to the current literature, such studies have not been conducted in idiopathic ON. According to the literature, CD54, or intercellular adhesion molecule-1 (ICAM-1), is expressed on the surface of many cell populations and is activated by inflammatory stimuli, playing a crucial role in the immune system, including leukocyte adhesion to endothelium and transendothelial migration. It is an inflammation marker, with increased expression and release observed in a wide range of diseases [14]. CD5 is a signaling co-receptor expressed on the surface of all T-cells and on a significant portion of B-cells; it promotes the differentiation of T-cells into T-helper cells, enhances the activity of natural killer cells, cytotoxic T-cells, B-lymphocytes, and immunoglobulin secretion. It is recommended as a target for immune intervention in various pathologies, such as cancer, autoimmune diseases, or infections [15]. CD25 is a subunit of the interleukin-2 receptor (IL-2Rα); it is expressed on mature and activated T-lymphocytes, activated B-lymphocytes, natural killer cells, monocytes, and macrophages. It is an "early" marker of lymphocyte activation, reflecting their ability to proliferate and differentiate. Its levels change during inflammatory processes of various etiologies. CD25 competes for IL-2 binding, thereby reducing immune responses mediated by free IL-2 [16]. CD95, also known as the Fas/APO-1 antigen, belongs to the tumor necrosis factor (TNF) receptor superfamily and is involved in inducing apoptosis. CD95 is an important marker of peripheral nervous system pathology [17]. At present, researchers [18] believe that the pathophysiology and natural course of idiopathic ON remain insufficiently studied. Analyzing the expression patterns of immune cell subpopulations and their genes is essential for understanding their role and impact in the early stages of the pathological process in ON [13, 18].

The research **aims** to determine the level of molecular activation markers CD54, CD5, CD25, and CD95 on CD3+ peripheral blood lymphocytes in patients with ON and its complications.

Materials and methods. The study was conducted in the immunology laboratory, the functional ophthalmology research center, and the ocular inflammatory pathology department of the Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine. Patients were divided into two groups:

Group 1: 16 patients (22 eyes) with idiopathic ON, clinically presenting as papillitis, with disease duration from initial symptoms to diagnosis at a median (Q25-Q75) of 12 (7–30) days.

Group 2: 8 patients (14 eyes) with partial optic nerve atrophy (PAON) as a result of ON, with disease duration from initial symptoms to diagnosis at a median (Q25-Q75) of 1080 (180–1825) days.

The characteristic features of optic nerve papillitis included hyperemia, prominence of the optic nerve head, poorly defined disc margins, swelling around the disc extending into the surrounding retina, narrowed, tortuous arteries, tense, engorged veins that "sink" into the surrounding retina. As inflammation decreased, swelling gradually subsided, although moderate swelling could persist for up to three months, often on the nasal side. The optic disc gradually changed color, becoming pale, with arteries remaining tortuous and narrowed and veins tense. The mean age of patients in these groups was 37.8 ± 11.3 years. The control group consisted of 27 healthy volunteers of

similar age. The study implemented measures to ensure patient safety and rights, human dignity, and ethical standards according to the principles of the Declaration of Helsinki, the European Convention on Human Rights, and relevant Ukrainian laws. A written informed consent was obtained from each patient after thoroughly explaining the study's nature. All necessary steps were taken to maintain data anonymity following patient consent for using data from medical records. The laboratory research protocol was approved by the Ethics Committee of the Filatov Institute of Eye Diseases and Tissue Therapy (protocol No. 2, 2020). This work is a part of the research topic No. 0122U001492 (2022-2023) **"**Study of the efficacy of immunocorrection in the treatment of ischemic optic neuropathy".

All patients underwent visual acuity testing, refractometry, intraocular pressure measurement, ophthalmoscopy with pupil dilation, axial length measurement, biomicroscopy, perimetry, and assessment of optic nerve electrical sensitivity and lability using phosphene tests. Humphrey perimetry (standard 30-2SITA; Carl Zeiss Meditec) was also conducted. Macular and peripapillary retina areas were evaluated using OCT (Spectralis HRA+OCT, Heidelberg Engineering). In cases where diagnosis clarification was needed, fluorescein angiography (FA)was performed. Patients also received neurologist consultations, and MRI or CT brain imaging was conducted.

Laboratory studies were conducted before treatment. The study measured indicators of T-cell immunity (CD3+, CD4+, CD8+, CD16+ subpopulations) and humoral immunity (CD19+ B-cells).

Markers of lymphocyte activation on CD3+lymphocytes were identified using monoclonal antibodies (produced by the Kavetsky Institute of Experimental Pathology, Oncology, and Radiobiology) through indirect immunofluorescence with fluorescein isothiocyanate (FITC) according to the established method [19].

The main stages of this method are as follows: preparation of a lymphocyte suspension by centrifugation (ELMI CM-6MT centrifuge, Latvia) on a Ficoll gradient (density 1.076 g/cm³, produced by Simesta, Ukraine); double cell purification by centrifugation; preparation of smears and fixation in paraformaldehyde vapor; sequential application of specific monoclonal antibodies (MCA), rabbit serum, and FITC to the smear. Microscopy was performed at an objective magnification of x80 and an eyepiece magnification of x15 (EuromexiScope microscope, Holland). Fluorescent lymphocytes were counted on the smear per 100 free cells. The molecular markers used in the study were CD54, CD5, CD25, and CD95.

Statistical Analysis: Data accumulation, correction, visualization, and systematization of the obtained results, along with statistical analysis, were conducted using STATISTICA 8.0 software (StatSoft.Inc). Nominal data were described with absolute values and percentages. Quantitative indicators were assessed according to normal distribution with the Shapiro–Wilk test. Normally distributed data were grouped into variation series, and mean (M) and standard deviation (SD) were calculated. Comparisons of mean values of normally distributed data used the Student's t-test, while non-normally distributed quantitative indicators were described with the median and interquartile ranges(Q25-Q75) and compared using the Mann-Whitney U-test. Spearman's coefficient was used to examine the strength of correlations. Statistical significance was considered when $p \leq 0.05$.

Results. The average leukocyte count in peripheral blood in Group 1 with acute ON was 8.5 x 10^6/L, with a 95% confidence interval (CI) of (7.3–9.7) x10^6/L, which was 41.6% higher than in Group 2, where the count was 6.12 x 10^6/L with a 95% CI of (3.4–8.8) x 10^6/L (p=0.039). It was also 57% higher than in the control group, which had an average of 5.4 x 10^6/L with a 95% CI of (5.1–5.7) x 10^6/L (p = 0.000).

The absolute lymphocyte count in peripheral blood, presented as median (Q25-Q75), was as follows: in Group 1 – 2.43 (1.98–2.82) cells/μL; in Group 2 – 1.8 (1.59–2.91) cells/μL; and in the control group – 1.59 (1.25–1.89) cells/μL. Comparisons showed that the absolute lymphocyte count in Group 1 was higher than in the control group (p = 0.0003), while there were no significant differences between Groups 1 and 2.

The absolute number of CD3+ cells (cells/μL) in peripheral blood, presented as median (Q25-Q75), was: Group 1 – 1462 (1230-2154) cells/μL; Group 2 – 1098 (954–1517) cells/μL; and the control – 1020 (851-1124) cells/μL. Comparison indicated that the absolute count of CD3+ cells was higher in Group 1 than in the control (p = 0.00014), with no significant difference between Groups 1 and 2. Notably, the CD3+ count in Group 2 did not differ significantly from that in the control.

The relative CD3+ cell count (%) in peripheral blood was: Group 1 – (59.5 ±7.0)%; Group 2 – (60 ± 1.7)%; control – (62.7 ± 5.8)%. No significant differences were found between the groups.

The absolute count of ICAM-1 (CD54) marker-positive lymphocytes (cells/μL) in peripheral blood was significantly higher in patients with ON and PAON than in the control group – 6.7 times (p = 0.00002) and 5.9 times (p =0.0004), respectively. The relative count of ICAM-1 (CD54) positive lymphocytes (%) was also 3.4 times higher in these groups than in the control group (p =0.0000) (Table 1).

The absolute count of CD25 marker-positive lymphocytes (cells/μL) in peripheral blood of patients with ON and PAON was 4.0 times higher (p =0.00003) than in the control group. The relative count of lymphocytes with this marker was also 1.9 times higher in these groups than in the control group (p =0.0000) (Table 1).

The absolute count of CD5 marker-positive lymphocytes (cells/μL) in peripheral blood was significantly higher in patients with ON and PAON – 5.2 times (p = 0.00003) and 4.6 times (p = 0.002), respectively, compared to the control group (Table 2).

The relative number of CD5-positive lymphocytes (%) was 2.2 times higher in these groups than in the control group (p = 0.0000) (Table 2).

The absolute number of CD95-positive lymphocytes (cells/μL) in peripheral blood in ON and PAON patients was significantly greater – 5.3 times (p =0.00002) and 4.9 times (p = 0.0004), respectively, compared to the control group.

The relative number of CD95-positive lymphocytes (%) was 2.4 times higher in these groups compared to the control group (p = 0.0000) (Table 2).

Table 1

Absolute (cells/μL) and relative (%) expression levels of ICAM-1 (CD54) and CD25 markers on peripheral blood lymphocytes in patients with ON

Indicator	ON	Transition of ON to PAON	Control Group
	1	2	3
	N=16	N=8	N=27
CD54, (cells/μL) Median (Q_{25}-Q_{75})	761 (494–1227)	669 (593–1432)	113 (87–168)
p*	p_{1-3} =0.00002; p_{2-3}=0.0004		
CD54(%), M±SD	29.2±1.7	28.2±3.8	8.5±2.0
p^T	p_{1-3} =0.0000; p_{2-3}=0.0000		
CD25, (cells/μL) Median(Q_{25}-Q_{75})	535 (366–990)	595 (512–1054)	136 (105–211)
p*	p_{1-3} =0.00003; p_{2-3}=0.001		
CD25 %, M±SD	19.6±5.0	21.0±1.6	10.7±2.2
p^T	p_{1-3} =0.0000; p_{2-3}=0.0000		

Note: M – arithmetic mean, SD – standard deviation; N – number of patients; Median (Q25-Q75) – median, lower and upper quartiles (25–75%);
* – Mann–Whitney U-test; T – Student's t-test, PAON – partial atrophy of optic nerve, ON – optic neuritis.

Table 2

Absolute (cells/μL) and relative (%) expression levels of CD5 and CD95 markers on peripheral blood lymphocytes in ON patients

Indicator	ON	Transition of ON to PAON	Control Group
	1	2	3
	N=16	N=8	N=27
CD5, (cells/μL) Median(Q_{25}-Q_{75})	733 (583–1069)	641 (508–1271)	140 (114–176)
p*	p_{1-3} =0.00003; p_{2-3}=0.002		
CD5 (%), M±SD	23.8±4.5	23.5±5.5	10.3±2.0
p^T	p_{1-3} =0.00003; p_{2-3}=0.0000		
CD95 (cells/μL) Median (Q_{25}-Q_{75})	633 (619–696)	582 (466–655)	120 (88–227)
p*	p_{1-3} =0.00002; p_{2-3}=0.0004		
CD95%, M±SD	22.8±4.3	22.8±2.3	9.6±2.8
p^T	p_{1-3} =0.0000; p_{2-3}=0.0000		

Note: M – arithmetic mean, SD – standard deviation; N – number of patients; Median (Q25-Q75) – median, lower and upper quartiles (25–75%);
* – Mann–Whitney U-test; T – Student's t-test, PAON – partial atrophy of optic nerve, ON – optic neuritis.

Significant differences between ON and PAON groups were not statistically observed in the analysis of expression levels of all four markers.

Analyzing the correlation using Spearman rank criterion(r), the number of CD4+ lymphocytes showed significant correlation with all lymphocyte activation markers, with the strongest correlation (r = 0.95) observed with CD54 and CD5 (Table 3).

Thus, the absolute count of CD4+ T-helper cells (cells/μL) in peripheral blood in ON patients correlates with the expression levels (cells/μL) of markers CD54, CD5, CD25, and CD95 on lymphocytes.

The CD8+ indicator (cells/μL), representing the absolute count of T-suppressor/cytotoxic cells in peripheral blood, showed correlation with the expression levels (cells/μL) of markers CD54, CD25, and CD95 on lymphocytes, though weaker ($p \leq 0.05$) than with CD4+ (r = 0.58-0.7) (Table 3).

The CD19+ (cells/μL), representing the absolute count of B-cells, correlated with the expression levels (cells/μL) of markers CD54, CD25, and CD95 on lymphocytes, with the strongest correlation observed with CD54 (r=0.84) (Table 3).

The absolute count of natural killer cells (CD16+) (cells/μL) had correlations with the expression levels (cells/μL) of markers CD54, CD5, CD25,and CD95 on lymphocytes, with the strongest correlation observed with CD54 (Table 3). The immunoregulatory index (CD4+/CD8+) correlated with the expression levels (cells/μL) of markers CD54, CD5, and CD95 on lymphocytes (Table 3).

Discussion. In our study, the number of lymphocytes expressing the pro-inflammatory marker ICAM-1 (CD54) in patients with ON and PAON exceeded the control group level by 3.4–6.3 times. It is known that the concentration of soluble ICAM-1 in cerebrospinal fluid (CSF) is elevated in patients with demyelinating diseases and meningoencephalitis [20]. Furthermore, a significant increase in ICAM-1 in serum, compared to normal levels, is observed in patients with optic neuromyelitis [21]. Therefore, the observed increase in the

Table 3

Significant Correlation Coefficients (r) for Expression Levels of Lymphocyte Activation Markers and Immunity Indicators (absolute lymphocyte count cells/μL)

Indicator	CD54 (cells/μL)	CD5 (cells/μL)	CD25 (cells/μL)	CD95 (cells/μL)
CD4+(cells/μL)	0.95	0.95	0.7	0.87
CD8+(cells/μL)	0.7	–	0.58	0.58
CD4+/ CD8+	0.7	0.8	–	0.73
CD16+(cells/μL)	0.88	0.87	0.66	0.77
CD19+(cells/μL)	0.84	–	0.68	0.68

number of lymphocytes expressing the pro-inflammatory marker ICAM-1 in this study is a specific marker for ON and PAON.

According to our data, the number of lymphocytes expressing the autoimmune marker CD5 in ON and PAON patients 2.2–4.9 times exceeded the control group. However, the literature indicates that CD5 expression in patients with optic neuritis lacks diagnostic significance [22].

We found that the number of lymphocytes expressing the early activation marker CD25 on CD3+ lymphocytes in patients with ON and its transition to PAON exceeded the normal level by 1.9–4.6 times, with no significant differences between ON groups. According to the literature, induction of CD25 expression on CD4+ lymphocytes prevents autoimmune-mediated demyelination in experimental autoimmune neuritis [23]. Therefore, the increase in CD25-expressing lymphocytes in ON and PAON patients may indicate activation of immune response-suppressing mechanisms.

In idiopathic ON patients and in cases progressing to PAON, the number of CD95-expressing CD3+ lymphocytes exceeded the normal level by 2.4–5.1 times, possibly reflecting enhanced processes of nervous system damage, including optic nerve damage. Although no significant differences were observed between ON and PAON patient groups, there was a tendency towards a slight decrease in CD54, CD5, and CD95 expression when comparing ON and PAON patients, which could indicate a reduction in inflammation intensity as ON transforms in to PAON; this is further suggested by an increase in CD25 expression. The expression levels (cells/μL) of CD54 and CD95 markers on peripheral blood lymphocytes correlated strongly with cellular immunity indicators (particularly CD4+), as well as with B-lymphocyte levels, a measure of humoral immunity. This demonstrates the active involvement of these markers in immune response and ON pathogenesis. The weakest correlation with cellular and humoral immunity indicators was observed for CD25 expression, a marker for immune response suppression mechanisms.

Conclusions

1. In ON patients and those with its sequelae (progressing to PAON), the number of CD3+ lymphocytes expressing the pro-inflammatory marker ICAM-1 (CD54) exceeds the normal level 3.4–6.3 times; the early activation marker CD25 exceeds the normal level 1.9–4.6 times; the autoimmune marker CD5 exceeds the normal level 2.2–4.9 times; and the apoptosis marker CD95 exceeds the normal level 2.4–5.1 times. No statistically significant differences were found between ON and PAON groups, suggesting the persistence of a low-grade inflammatory process in the clinical picture of optic nerve dystrophic changes.

2. In ON patients, CD54 and CD5 expression on peripheral blood lymphocytes strongly correlates with T-cell immunity indicators (CD4+, CD8+, CD16+) as well as with B-lymphocyte levels (CD19+), a measure of humoral immunity. This indicates active involvement of these markers in the immune response and ON pathogenesis.

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Надійшла до редакції 29.05.2024 р.
Прийнята до друку 28.11.2024 р.
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