

CHEMOKINE (C-C MOTIF) LIGAND 19 AND INTERLEUKIN-23 IN PATIENTS WITH POST-LYME DISEASE SYNDROME AND NEUROLOGICAL INVOLVEMENT

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Lyme borreliosis (LB) is a naturally occurring transmissible disease caused by *Borrelia burgdorferi sensu lato*. Some patients develop LB after effective treatment of the acute stage of the disease with antibiotics, which may suggest involvement of chemokines and cytokines in its pathogenesis. This study aimed to assess serum levels of chemokine (C-C motif) ligand 19 (CCL19) and interleukin-23 (IL-23) in patients with post-Lyme syndrome (PLS) and neurological involvement, and to examine their association with clinical manifestations and laboratory parameters. We examined 70 individuals (26 [37.1%] male and 44 [62.9%] female) with confirmed LB who presented with neurological symptoms persisting or recurring within 6 months following the recommended antibiotic treatment. The serum levels of CCL19 and IL-23 were determined using a solid-phase enzyme immunoassay; CCL19 was high in 12 (17.1%) participants, and IL-23 in 10 (14.3%). Significant positive correlations were established between the concentrations of CCL19 and IL-23 ($r = 0.65$, $p < 0.0001$) and their hyperproduction ($r = 0.79$, $p < 0.0001$). The likelihood of developing Lyme disease after treatment increased significantly in association with overproduction of CCL19 and, especially, IL-23: odds ratio — 5.00; 95% CI: 1.00–24.84, $p = 0.04$, and 22.42; 95% CI: 1.25–399.93, $p = 0.03$, respectively. No correlation was found between the concentration of CCL19, IL-23, and the levels CRP, IgM and IgG antibodies to *B. burgdorferi*, as well as IgG antibodies to SARS-CoV-2. A subject matter being discussed in the paper is how CCL19, IL-23 and other mechanisms participate in post-treatment pathogenesis of Lyme disease with neurological damage.

Keywords: post-Lyme syndrome, nervous system, cytokines, CCL19, interleukin 23

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ЛИГАНД 19 ХЕМОКИНА (МОТИВ С–С) И ИНТЕРЛЕЙКИН 23 У ПАЦИЕНТОВ С ПОСТЛАЙМСКИМ СИНДРОМОМ С ПОРАЖЕНИЕМ НЕРВНОЙ СИСТЕМЫ

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Лайм-боррелиоз (ЛБ) природно-очаговое, трансмиссивное заболевание, которое вызывает *Borrelia burgdorferi sensu lato*. У части пациентов после эффективного лечения острой стадии болезни антибиотиками развивается синдром болезни Лайма, в его патогенезе обсуждается участие хемокинов и цитокинов. Цель исследования — оценить концентрацию лиганда 19 хемокина (мотив С–С) (CCL19) и интерлейкина (ИЛ) ИЛ-23 в сыворотке крови у пациентов с постлаймским синдромом (ПС) с поражением нервной системы, определить связь с клиническими проявлениями болезни и лабораторными показателями. Обследовано 70 человек (26 (37,1%) мужчин и 44 (62,9%) женщины) с достоверным диагнозом ЛБ и наличием неврологической симптоматики, сохранявшейся или возникшей вновь в течение 6 месяцев после проведенного рекомендованного курса антибактериальной терапии. Концентрацию CCL19 и ИЛ-23 в сыворотке крови определяли с помощью твердофазного иммуноферментного метода. Высокие значения CCL19 выявлены у 12 (17,1%), а ИЛ-23 — у 10 (14,3%) человек. Установлены значимые положительные корреляции между концентрацией CCL19 и ИЛ-23 ($r = 0,65$, $p < 0,0001$), а также их гиперпродукцией ($r = 0,79$, $p < 0,0001$). При гиперпродукции CCL19 и, особенно, ИЛ-23 достоверно увеличивалась вероятность развития синдрома болезни Лайма после лечения (отношение шансов — 5,00; 95% ДИ: 1,00–24,84, $p = 0,04$ и 22,42; 95% ДИ: 1,25–399,93, $p = 0,03$ соответственно). Не обнаружено корреляции между концентрацией CCL19, ИЛ-23 и значениями СРБ, уровнем IgM и IgG антител к *B. burgdorferi*, IgG антител к SARS-CoV-2. Обсуждается участие CCL19, ИЛ-23 и других механизмов в патогенезе синдрома болезни Лайма после лечения у пациентов с поражением нервной системы.

Ключевые слова: постлаймский синдром, нервная система, цитокины, CCL19, интерлейкин 23

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Lyme borreliosis (LB) is a naturally occurring, transmissible disease caused by *Borrelia burgdorferi sensu lato* and transmitted by ixodid (hard) ticks; it affects multiple organs and systems and typically progresses through distinct clinical stages [1]. LB is the most common vector-borne infection both in Russia [2] and worldwide [3–6].

The term "post-treatment Lyme disease syndrome" (post-Lyme syndrome) is used to refer to patients who have recovered LB following antibiotic therapy [7]. Its clinical presentations include fatigue, pain in muscles, joints, spine, or cognitive impairment; these symptoms occur within six months after a confirmed *Borrelia burgdorferi* (*B. burgdorferi*) infection or persist for at least six months after an effective antibiotics course that arrested or eliminated the objective acute stage manifestations of the disease [8–10].

One of the common pathologies associated with PLS is neurological. Several mechanisms are involved in the pathogenesis of thereof, including persisting of infection, autonomic dysfunction, and activation of the innate and acquired immune response [10, 11]. LB patients present with high serum levels of chemokines and cytokines, in particular chemokine (C-C motif) ligand 19 (CCL19) [12, 13], interleukin-23 (IL) [14], and interferon- α (INF- α) [15]. It is believed that the identification of biomarkers of various stages and variants of LB, including PLS with neurological involvement, is important for the accuracy of the diagnosis, prediction of the development of the syndrome, and evaluation of the effectiveness of the therapy [16]. The tests for serum levels of CCL19, OspA, and INF- α in LB cases are classified as the 2nd category biological tests; they have not yet been introduced into routine laboratory practice and require further clinical evaluation [17]. Thus, establishing the concentration of CCL19, and possibly IL-23, in LB patients is potentially beneficial in the context of determining the risk of subsequent PLS, and requires further study. The papers on this topic are foreign [13–15]; no relevant studies have been conducted in the Russian Federation. This work is a continuation of our previous research effort [18].

This study aimed to evaluate serum levels of CCL-19 and IL-23 in patients with PLS with neurological involvement seeking to determine the relationship between the said levels, the specifics of clinical manifestations of the disease, and laboratory indicators.

METHODS

From September 2023 to May 2025, the study included 70 people (26 (37.1%) men and 44 (62.9%) women) with confirmed LB who presented with neurological symptoms persisting or recurring within 6 months following the recommended antibiotic treatment. The median age of the patients was 55.50 (46.00; 69.00) years, and the duration of the disease was 2.00 (1.00; 4.00) years.

Inclusion criteria: a confirmed LB diagnosis; a completed course of antibiotics for LB; disease persistence for at least 6 months after the antibiotic therapy; the patient's willingness to cooperate and the ability to comply with the requirements of this study (signed voluntary informed consent form).

Exclusion criteria: exacerbation or decompensation of chronic non-communicable diseases at the time of the patient's inclusion in the study (chronic cerebral ischemia, diabetes mellitus, acute coronary syndrome, chronic heart failure, lung pathology, chronic kidney disease, etc.); systemic rheumatic diseases (rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, systemic scleroderma, dermatitis/polymyositis, polymyalgia rheumatica, giant cell arteritis, etc.); cancer at the

time of inclusion in the study or in the medical history; SARS-COV-2 infection in the acute stage; the patient's unwillingness to continue monitoring and/or participate in certain research procedures set out in informed consent, or lack of a signed voluntary informed consent form.

At the time of the examination, five (7.1%) patients had a periodic subfebrile fever, which was interpreted as a general infection syndrome. Musculoskeletal involvement was mainly manifested as arthralgias (18 patients, 25.7%) and myalgias (8 patients, 11.4%); arthritis and myositis were less common, affecting 4 (5.7%) and 1 (1.4%) patients, respectively.

After the course of antibiotics, all patients retained or developed various pathologies of the nervous system. Thirty (42.9%) of them had radiculopathy (RP), and 22 (31.4%) — polyneuropathy (PNP), both conditions affecting the peripheral nervous system (PNS). There were three (4.3%) cases of facial nerve neuropathy (FNN). As for the central nervous system (CNS), the pathologies were encephalopathy (EP) — 54 (77.1%) cases — and encephalomyelitis (2 (2.9%) cases). Depression was diagnosed in 42 (60.0%) participants, anxiety in 10 (14.3%), and asthenia in 50 (72.5%) patients. Twenty-nine (41.4%) participants presented with a combined pathology of CNS and PNS, and isolated involvement PNS and CNS was established in 14 (20.0%) and 27 (38.6%) patients, respectively.

Based on the results of the examination, we divided the participants into four groups. The key criteria for the division were signs of continued damage to the nervous system (with partial or complete regression) or new neurological symptoms (mostly subjective or clinically pronounced) manifesting within 6 months after antibiotic treatment.

The 1st group of 39 people (55.7%) included patients with predominantly subjective, non-progressive symptoms (post-Lyme syndrome, PLS), 13 men and 26 women. Their median age of 57 (47.00; 70.00) years, and disease duration 24 (12.00; 48.00) months.

The 2nd group included 22 (31.4%) people with residual effects of neurological involvement (PLS with residual effects), 9 men and 13 women. Their median age was 55 (46.00; 64.00) years, and the duration of the disease 42 (12.00; 96.00) months.

There were 5 (7.1%) people in the 3rd group; they presented with progressing signs of nervous system damage — relapsing PLS, or chronic LB. This group consisted of 2 men and 3 women, their median age was 45.5 (42.00; 52.00) years, the duration of the disease 36 (30.00; 60.00) months.

The 4th group (4 patients, 5.7%; 2 men and 2 women) comprised patients with complete regression of clinical symptoms (PLS with fully resolved neurological signs). The median age of the patients was 51.5 (49.50; 57.50) years, and the duration of the disease was 24 (15.00; 30.00) months. The groups were similar in gender, age, and duration of the disease ($p > 0.05$).

The control group included 15 practically healthy donors (6 men and 9 women, median age of 50.5 (48.50; 55.50)); they met the non-inclusion criteria. Seeking to detect diseases that could affect results of the study, we examined everyone (standard neurological examination) and collected medical histories thoroughly.

Serum levels of CCL19 and IL-23 were measured by ELISA using RayBiotech reagents (Cat. No. ELH-MIP3b and ELH-IL23-1, USA), and serum C-reactive protein (CRP) was measured by a standard immunoturbidimetric method (Vector-Best, Russia; Novo C-reactive protein (latex), Cat. No. B-9501). The level of IgM antibodies to *B. burgdorferi* (anti-*B. burgdorferi*) was measured using the Anti-Borrelia ELISA (IgM) test kit (Cat. No. EI 2132-9601 M), and that of IgG antibodies to

Table 1. Clinical and laboratory characteristics by CCL19 and IL-23 concentration

Characteristic	CCL19 ≤ 293.72 pg/ml (<i>n</i> = 58)	CCL19 > 293.72 pg/ml (<i>n</i> = 12)	IL-23 ≤ 1297.41 pg/ml (<i>n</i> = 60)	IL-23 > 1297.41 pg/ml (<i>n</i> = 10)	<i>p</i>
	1	2	3	4	
Common syndromes					
General infectious syndrome, <i>n</i> (%)	4 (6.9)	1 (8.3)	5 (8.3)	0 (0.0)	n/s
Arthralgia, <i>n</i> (%)	14 (24.1)	4 (33.3)	16 (26.7)	2 (20.0)	n/s
Arthritis, <i>n</i> (%)	3 (5.2)	1 (8.3)	4 (6.7)	0 (0.0)	n/s
Myalgia, <i>n</i> (%)	5 (8.6)	3 (25.0)	6 (10.0)	2 (20.0)	n/s
Arthralgia/myalgia, <i>n</i> (%)	2 (3.5)	2 (16.7)	3 (5.0)	1 (10.0)	n/s
Myositis, <i>n</i> (%)	1 (1.7)	0 (0.0)	1 (1.7)	0 (0.0)	n/s
Nervous system damage syndromes					
RP, <i>n</i> (%)	27 (46.6)	3 (25.0)	28 (46.7)	2 (20.0)	n/s
PNP, <i>n</i> (%)	19 (32.8)	3 (25.0)	19 (31.7)	3 (30.0)	n/s
FNN, <i>n</i> (%)	3 (5.7)	0 (0.0)	3 (5.0)	0 (0.0)	n/s
EP, <i>n</i> (%)	45 (77.6)	9 (75.0)	46 (76.7)	8 (80.0)	n/s
EM, <i>n</i> (%)	1 (1.7)	1 (8.3)	2 (3.3)	0 (0.0)	n/s
Depression, <i>n</i> (%)	36 (62.1)	6 (50.0)	37 (61.7)	5 (50.0)	n/s
Anxiety, <i>n</i> (%)	8 (13.8)	2 (16.7)	7 (11.7)	3 (30.0)	n/s
Asthenia, <i>n</i> (%)	43 (75.4)	7 (58.3)	43 (72.9)	7 (70.0)	n/s
Isolated PNS involvement, <i>n</i> (%)	12 (20.7)	2 (16.7)	12 (20.0)	2 (20.0)	n/s
Isolated CNS involvement, <i>n</i> (%)	20 (34.5)	7 (58.3)	21 (35.0)	6 (60.0)	n/s
Combines involvement of PNS and CNS, <i>n</i> (%)	26 (44.8)	3 (25.0)	27 (45.0)	2 (20.0)	n/s
Laboratory indicators					
CRP, median (25 th ; 75 th percentile), (mg/l)	2.30 (0.80; 3.70)	3.00 (1.25; 3.85)	2.30 (0.80; 3.90)	2.55 (1.80; 3.60)	n/s
CRP > 5.0 mg/l, <i>n</i> (%)	11 (18.9)	1 (8.3)	11 (18.3)	1 (10.0)	n/s
IgM anti- <i>B. burgdorferi</i> , median (25 th ; 75 th percentile), RU/ml	13.90 (7.53; 105.81)	11.12 (7.17; 46.36)	13.90 (7.43; 112.49)	11.12 (7.03; 45.08)	n/s
IgM anti- <i>B. burgdorferi</i> > 22 RU/ml, <i>n</i> (%)	24 (41.4)	4 (33.3)	25 (41.7)	3 (30.0)	n/s
IgG anti- <i>B. burgdorferi</i> , median (25 th ; 75 th percentile), (RU/ml)	9.05 (4.29; 44.81)	8.17 (4.13; 12.05)	9.05 (4.32; 39.16)	8.17 (3.77; 13.39)	n/s
IgG anti- <i>B. burgdorferi</i> > 22 RU/ml, <i>n</i> (%)	18 (31.0)	0 (0.0)	18 (30.0)	0 (0.0)	p1-2* p3-4*
IgG anti-SARS-CoV-2, median (25 th ; 75 th percentile), (BAU/ml)	360.54 (209.30; 466.04)	398.66 (276.96; 614.10)	360.54 (209.50; 442.35)	468.05 (207.56; 653.33)	n/s
IgG anti-SARS-CoV-2 > 10 BAU/ml, <i>n</i> (%)	53 (91.4)	12 (100.0)	55 (91.7)	10 (100.0)	n/s

Note: * — the differences between the groups are significant, $p < 0.05$; n/s — the differences between the groups are not significant.

B. burgdorferi using the Anti-Borrelia PLUS VIsE ELISA (IgG) kit (Cat. No. EI 2132-9601 2G). According to the manufacturer's instructions, the results were considered positive if the concentration of IgM and IgG antibodies to *B. burgdorferi* was more than 22 relative units per 1 ml (OE/ml). Quantities of IgG antibodies to SARS-CoV-2 were established by evaluated by SARS-CoV-2-IgG Quantitative IFA-Best kit (Cat. No. D-5505).

Statistical processing of the results was done in Statistica 10.0 (StatSoft, USA) and MedCalc 14.8.1 (MedCalc Software, USA) using common methods of parametric and nonparametric statistical analysis. The results are presented as median (Me) with an interquartile range [25th and 75th percentiles], average value (M), and standard deviation (σ). To compare samples by qualitative attribute and to assess the proportion of occurrence of a characteristic/sign, we used the Fisher's exact test. Spearman's rank correlation coefficient was used for the correlation analysis. A ROC analysis was performed to estimate the area under the ROC curve (AUC) with a 95% confidence interval (95% CI) and to calculate the indicator's sensitivity (Hr) and specificity (C). The odds ratio (OR) was estimated with a

95% confidence interval (OR [95% CI]). The level of significance was set at $p < 0.05$.

RESULTS

Serum levels of CCL19 and IL-23 in PLS patients with neurological involvement versus donors

CCL19 concentrations in donors' serum ranged from 28.21 to 258.73 pg/ml, with a median of 112.27 (55.61; 130.64) pg/ml. The concentration of IL-23 ranged from 16.89 pg/ml to 1074.20 pg/ml, with a median of 178.34 (126.13; 594.35) pg/ml. The upper limit of the normal range ($M + 3\sigma$) in healthy donor sera was 293.72 pg/ml for CCL19 and 178.34 pg/ml for IL-23.

In LB patients with neurological involvement, the concentration of CCL19 ranged from 23.96 pg/ml to 902.50 pg/ml, with a median of 83.09 (54.71; 198.01) pg/ml. The level of IL-23 was from 15.51 pg/ml to 9759.44 pg/ml, with a median of 45.48 (22.38; 352.98) pg/ml. These values were lower than in the control group, but the differences did not reach significance ($p > 0.05$). High values (greater than $M + 3\sigma$ measured in the

Table 2. Serum concentration of CCL19, IL-23, and other immunological markers, median (25th; 75th percentile), in PLS patients with neurological involvement, all groups

Characteristic	Group 1 (n = 39)	Group 2 (n = 22)	Group 3 (n = 5)	Group 4 (n = 4)	p
	1	2	3	4	
CCL19 pg/ml	119.78 (60.86; 297.35)	64.13 (48.82; 107.08)	68.14 (56.22; 89.24)	67.26 (40.45; 153.33)	p1–2**
CCL19 > 293.72 pg/ml, n (%)	10 (25.6)	1 (4.5)	1 (20.0)	0 (0)	p1–2*
IL-23, pg/ml	93.35 (23.73; 1416.73)	25.76 (18.54; 118.23)	64.21 (23.40; 352.98)	19.11 (16.04; 20.40)	p1–2* p1–4** p3–4*
IL-23 > 178.34 pg/ml, n (%)	10 (25.6)	0 (0)	0 (0)	0 (0)	p1–2**
CRP, mg/l	2.20 (0.90; 3.60)	2.40 (0.70; 5.30)	1.70 (1.50; 3.40)	3.75 (1.95; 4.52)	n/s
CRP > 5.0 mg/l, n (%)	6 (15.4)	6 (27.3)	0 (0)	0 (0)	n/s
IgM anti- <i>B. burgdorferi</i> , RU/ml	13.27 (7.33; 78.94)	12.35 (6.79; 54.29)	36.17 (25.91; 162.18)	239.11 (122.64; 247.07)	n/s
IgM anti- <i>B. burgdorferi</i> > 22 RU/ml, n (%)	15 (38.5)	6 (27.3)	4 (80.0)	3 (75.0)	n/s
IgG anti- <i>B. burgdorferi</i> (EUROIMM), RU/ml	10.66 (5.09; 19.48)	4.88 (3.95; 23.72)	10.37 (4.34; 17.86)	44.66 (5.13; 121.21)	n/s
IgG anti- <i>B. burgdorferi</i> > 22 RU/ml, n (%)	12 (30.8)	6 (27.3)	1 (20.0)	2 (50.0)	n/s
IgG anti-SARS-CoV-2, BAU/ml	346.60 (192.95; 459.48)	384.60 (245.15; 914.34)	332.78 (87.29; 362.43)	424.82 (371.57; 479.06)	n/s
IgG anti-SARS-CoV-2 > 10 BAU/ml, n (%)	37 (94.9)	20 (90.9)	4 (80.0)	4 (100.0)	n/s

Note: * — the differences between the groups are significant, $p < 0.05$; ** — the differences between the groups are significant, $p < 0.01$; n/s — the differences between the groups are not significant.

control group) of CCL19 were detected in 12 of 70 patients (17.1%), and high values of IL-23 were detected in 10 of 70 patients (14.3%).

The concentration of CCL19 did not correlate with the age of the patients ($r = 0.16$, $p > 0.05$) and the duration of the disease ($r = 0.09$, $p > 0.05$). A similar situation was observed for IL-23: its values did not depend on the patients' age ($r = -0.01$, $p > 0.05$) and the disease's duration ($r = 0.03$, $p > 0.05$).

Table 1 presents a comparative analysis of clinical and laboratory manifestations between groups with normal or high levels of CCL19 and IL-23. We observed no significant differences by gender, patient age, illness duration, or presence of common syndromes. Patients with high serum CCL19 and IL-23 were more likely to have isolated CNS damage ($p > 0.05$). By other clinical signs, the groups did not differ from each other significantly.

IgG anti-*B. burgdorferi* were significantly more often detected in patients with normal CCL19 and IL-23 values than in patients with high levels ($p = 0.02$ and $p = 0.04$, respectively). Overproduction of each cytokine was significantly related to the presence of IgG anti-*B. burgdorferi* in the blood serum (CCL19 — $r = -0.27$, $p = 0.03$; IL-23 — $r = -0.24$, $p = 0.04$).

The concentration of CRP, IgM anti-*B. burgdorferi*, IgG anti-SARS-CoV-2, and the frequency of their high values did not significantly differ in the compared groups ($p > 0.05$). We have not observed a correlation between the concentration of CCL19 and the values of CRP ($r = 0.16$, $p > 0.05$), the level of IgM anti-*B. burgdorferi* ($r = -0.12$, $p > 0.05$), IgG anti-*B. burgdorferi* ($r = 0.02$, $p > 0.05$), and IgG anti-SARS-CoV-2 ($r = 0.08$, $p > 0.05$). The level of IL-23 was also not linked to the values of CRP ($r = 0.09$, $p > 0.05$), IgM anti-*B. burgdorferi*

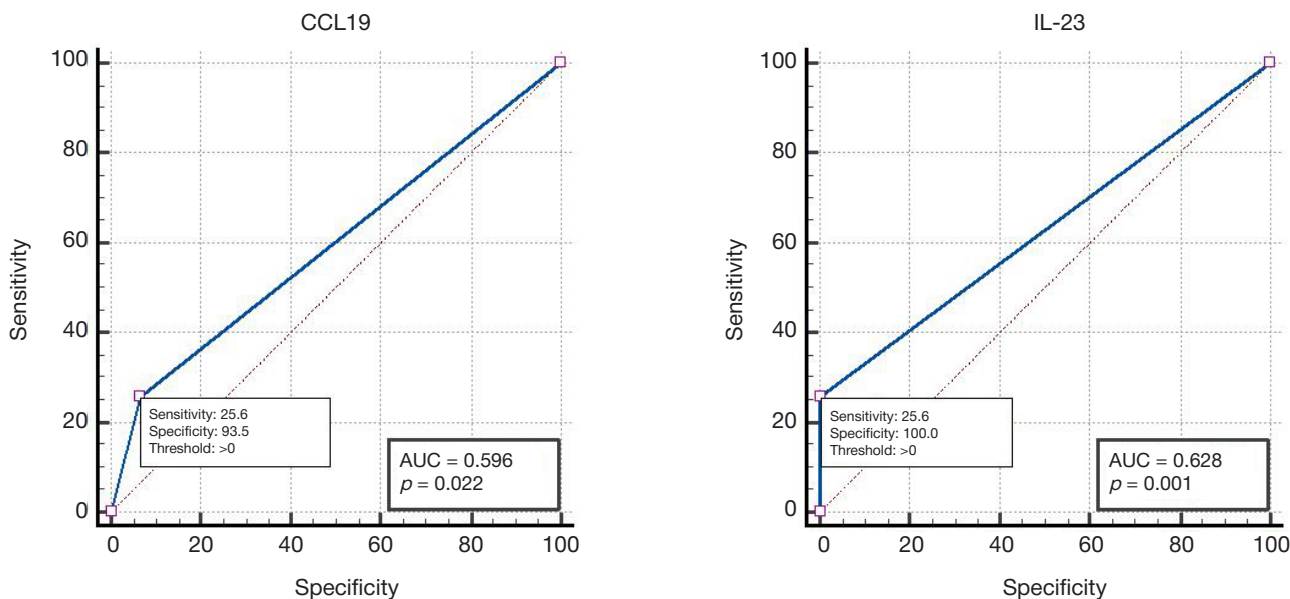
**Fig.** ROC curves showing the association between high CCL19 and IL-23 values and Group 1 patients (PLS), the cohort with PNS involvement

Table 3. Odds ratio for women and men, overproduction of CCL19, IL-23, immunological markers for groups of PLS patients with neurological involvement

Characteristic	Group 1	Group 2	Group 3	Group 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender:				
male	0,74 (0,56; 1,34), ($p = 0,50$)	1,68 (0,65; 4,33), ($p = 0,28$)	0,42 (0,08; 2,13), ($p = 0,30$)	1,54 (0,38; 6,21), ($p = 0,54$)
female	1,34 (0,56; 3,18), ($p = 0,50$)	0,59 (0,23; 1,52), ($p = 0,28$)	2,35 (0,47; 11,82), ($p = 0,30$)	0,64 (0,16; 2,60), ($p = 0,54$)
CCL19	5,00 (1,00; 24,84), ($p = 0,04$)	0,16 (0,02; 1,33), ($p = 0,09$)	1,23 (0,12; 12,06), ($p = 0,86$)	0,48 (0,02; 9,59), ($p = 0,63$)
IL-23	22,42 (1,25; 399,93), ($p = 0,03$)	0,08 (0,01; 1,46), ($p = 0,08$)	0,48 (0,02; 9,36), ($p = 0,63$)	0,59 (0,03; 11,95), ($p = 0,73$)
CRP	0,76 (0,22; 2,63), ($p = 0,66$)	2,63 (0,74; 9,34), ($p = 0,14$)	0,39 (0,02; 7,51), ($p = 0,54$)	0,48 (0,02; 9,59), ($p = 0,63$)
IgM anti- <i>B.burgdorferi</i>	0,87 (0,25; 2,15), ($p = 0,57$)	0,68 (0,24; 1,91), ($p = 0,46$)	6,83 (0,72; 64,74), ($p = 0,09$)	4,92 (0,49; 49,93), ($p = 0,18$)
IgG anti- <i>B.burgdorferi</i>	0,73 (0,33; 2,26), ($p = 0,77$)	1,13 (0,36; 3,53), ($p = 0,84$)	0,71 (0,07; 6,77), ($p = 0,76$)	3,13 (0,41; 24,02), ($p = 0,27$)
IgM anti-SARS-CoV-2	1,98 (0,31; 12,67), ($p = 0,47$)	0,67 (0,10; 4,30), ($p = 0,67$)	0,26 (0,02; 2,93), ($p = 0,28$)	0,81 (0,04; 16,98), ($p = 0,89$)

($r = -0.14$, $p > 0.05$), IgG anti-*B.burgdorferi* ($r = -0.01$, $p > 0.05$) and IgG anti-SARS-CoV-2 ($r = 0.10$, $p > 0.05$).

High values of each cytokine were not associated with elevated CRP levels (CCL19 — $r = -0.10$, $p > 0.05$ and IL-23 — $r = -0.08$, $p > 0.05$), the presence of IgM anti-*B.burgdorferi* (CCL19 — $r = -0.06$, $p > 0.05$ and IL-23 — $r = -0.08$, $p > 0.05$), and IgG anti-SARS-CoV-2 (CCL19 — $r = 0.13$, $p > 0.05$ and IL-23 — $r = 0.11$, $p > 0.05$).

We established significant positive correlations — moderately and highly strong — between concentrations of CCL19 and IL-23 ($r = 0.65$, $p < 0.0001$) and hyperproduction of these cytokines ($r = 0.79$, $p < 0.0001$).

Cytokines in PLS patients with neurological involvement (various groups)

As noted above, we divided the sample of LB patients into four groups based on the results of clinical examination. High levels of CCL19 and IL-23 (compared to normal range values) were common among group 1 patients (CCL19 — 83.3 and 50.0%, $p = 0.03$; IL-23 — 100 and 48.3%, $p = 0.001$). Overproduction of CCL19 was detected in only one (8.3%) group 2 patient and one (8.3%) participant from group 3. High levels of IL-23 were recorded only in the patients from the 1st group.

Table 2 presents the results of intergroup comparison. The highest concentrations of CCL19 and IL-23 were observed in group 1 (PLS); Overproduction of each of these cytokines was significantly associated with this group (CCL19 — $r = 0.25$, $p = 0.03$; IL-23 — $r = 0.36$, $p = 0.001$), and there was no such association detected for other groups.

Compared to other groups, group 4 exhibited a clear pattern of increased concentration of CRP, IgM and IgG antibodies to *B. burgdorferi*, and IgG anti-SARS-CoV-2 ($p > 0.05$). By these indicators, groups 1, 2, and 3, did not differ significantly ($p > 0.05$ for all parameters).

The diagnostic significance of overproduction of these immunological markers was established only for clinical manifestations seen in group 1 patients (Fig.). For CCL19, the area under the ROC curve was 0.596 (sensitivity 25.64%, specificity 93.55%, $p = 0.022$), and for IL-23, it was 0.628 (sensitivity 25.64%, specificity 100.00%, $p = 0.0003$).

Odds ratio for gender, overproduction of CCL19, IL-23, and immunological markers in PLS groups

We determined the OR for men and women, high concentrations of CCL19, IL-23, CRP, presence of IgM and IgG antibodies to *B. burgdorferi*, IgG anti-SARS-CoV-2, and various groups of PLS patients neurological involvement (Table 3).

The OR did not depend on gender in all 4 groups. Significant associations were found only between CCL19, IL-23, and group 1. With high values of CCL19, the risk of PLS significantly increased (OR 5.00; 95% CI — from 1.00 to 24.84; $p = 0.04$) especially with overproduction of IL-23 in the background (OR 22.42; 95% CI — from 1.25 to 399.93; $p = 0.03$).

DISCUSSION

Dysregulation of the innate and acquired immune responses, accompanied by increased production of chemokines and cytokines, is a widely discussed possible cause of PLS [10, 11]. Several authors reported detecting high spinal fluid concentration of CCL19 and IL-23 in the acute stage of neuroborreliosis [15, 19]. Thus, one team of researchers observed significant (compared to the control) increase of CCL19 levels before and after antibiotic therapy [12]. Subsequently, this team confirmed its discovery in a larger cohort of patients [13]. However, these findings were not revalidated by other scholars investigating CCL19 concentration in LB patients [20].

European researchers, almost simultaneously with scientists from the USA, also reported an increase in serum IL-23 in neuroborreliosis cases [14], which was later confirmed by other authors [15]. However, similar to another research group [21], we did not detect serum IL-23 in patients with acute-stage neuroborreliosis [22].

We found high levels of CCL19 levels 17.1% of patients, and high IL-23 in 14.3% of cases; the concentrations of these cytokines were not related to the patients' age and duration of the disease. Previously, other researchers also have not identified an association of CCL19 with the gender, age of patients, and disease's duration [13]. The absence of a link between IL-23 concentration and gender has been noted in other studies [14, 20].

We did not find associations between overproduction of CCL19/IL-23 and common LB syndromes with the majority of clinical manifestations of neurological involvement. However, their high values suggested more frequent occurrence of isolated CNS damage, mainly in the form of EP. Other authors also point to the lack of connection between the production of CCL19/IL-23 and the clinical signs of PLS [13–15, 20]. Similar to several researchers [13, 15], we did not register an increase in the concentration of CRP 6 months after the start of antibiotic therapy in all groups of PLS patients with neurological involvement. There is, however, one study that reported a significant growth of the level of CRP in PLS patients compared with the values established in convalescents [23].

There are three generally recognized outcomes of LB following a course of antibiotics: recovery, development of resistance to antibiotics (including progressing forms of the

disease), and PLS [10, 11]. A number of papers describe an established connection between the development of PLS and high values of either CCL19 [13] or IL-23 [14]; other studies, on the contrary, report no such links [15, 20]. We found that high levels of CCL19 and IL-23 (compared with normal range values) indicate a significantly more frequent occurrence of PLS. There is evidence that high serum CCL19 6 months after the start of the antibiotic therapy translates into PLS development OR of 1.84 (95% CI: from 1.12 to 3.02, $p < 0.05$) [13]. In this study, we demonstrated that elevated CCL19 and IL-23 levels were of prognostic and diagnostic significance in group 1 participants (PLS patients).

The assumed reason for the differing results between the US and European PLS studies — a confirmed link to CCL19 in the former and to IL-23 in the latter — is differences in the genospecies of *B. burgdorferi*: the predominant strain in the USA is *B. burgdorferi sensu stricto*, while in Europe it is *B. afzelii* and *B. garinii* [13]. However, in our opinion, this is not the only valid explanation. In the Russian Federation, the predominant strains are *B. afzelii* and *B. garinii*, same as in Europe [24], and in this work, we observed increase of both CCL19 and IL-23 in the PLS group. The differences may also stem from the peculiarities of the formation of clinical groups in each study.

CCL19 and IL-23 are also known to spike during the acute stage of Covid-19 and suggest adverse outcomes [25]. Our sample did not include acute-stage Covid-19 patients. Since there were no intergroup differences in the frequency of occurrence and the levels of IgG anti-SARS-CoV-2, we believe that this infection did not affect the LB-related patterns we have identified. Moreover, high values of CCL19 and IL-23 were not associated with detection or increased serum counts of IgG anti-SARS-CoV-2.

An important component of LB diagnosis is the determination of specific IgM and IgG antibodies to *B. burgdorferi*. With this in mind, we analyzed the connections between them and the studied biomarkers. IgG anti-*B. burgdorferi* was significantly more often detected in patients with normal CCL19 and IL-23 values than in those with high levels thereof. No correlation was found between the concentration of CCL19/IL-23 and levels of IgM and IgG antibodies to *B. burgdorferi*. Other authors also did not identify a relationship between the serum level of IL-23 and the amount of antibodies to *B. burgdorferi* [14].

IgM or IgG anti-*B. burgdorferi* were found in all groups of patients with neurological involvement. We believe that the frequent detection of specific IgM and IgG antibodies to *B. burgdorferi* in group 1 was not associated with an active *B. burgdorferi* infection. According to the literature, in LB cases, specific IgM and IgG anti-*B. burgdorferi* detectable with a two tests (ELISA and Western blotting) can persist for a long time — from 10 to 20 years after treatment [26]. However, their presence is not associated with a persisting infection. It was found that high concentrations of these IgM and IgG is associated with rapid resolution of LB symptoms (compared with low levels thereof) [27]. These data partially explain the high incidence and level of specific anti-*B. burgdorferi* immunoglobulins as well as IgG anti-SARS-CoV-2 in group 4 patients (full recovery).

Considering the possible mechanisms of PLS development, it should be noted that in case of *B. burgdorferi*, a complex of interrelated reactions develops in response to infection, including activation of the effector components of innate and acquired immune defenses aimed at limiting the pathogenic load, minimizing tissue damage, and preventing subsequent reinfection [28]. The production of pro-inflammatory chemokines and cytokines by dendritic cells (DC) and macrophages is an integral part of this process aimed at enhancing the innate

immune system response and initiating the acquired immunity [28]. CCL19 and IL-23 are instrumental to these processes. CCL19 is involved in T cell activation, initiation of acquired immunity, and maintenance of immune tolerance. It is produced by DC, macrophages, neutrophils, etc. [29]. This antibody, which targets CCR7 (C-C chemokine receptor type 7), plays an important role in recruitment of CCR7⁺ naive and memory T cells, dendritic cells, and B lymphocytes to lymphoid organs and the central nervous system [30, 31]. CCL19 is continuously expressed in the CNS for rapid immune surveillance [32]. After infection with *B. burgdorferi*, animal models exhibit increased CCL19 mRNA expression in the lymph nodes [33] accompanied by intensive CCL19 production by activated DC.

The main sources of IL-23, as with CCL19, are activated dendritic cells and macrophages [29, 34]. IL-23 is also produced by B cells and type 3 innate lymphoid cells. It is obvious that CCL19 and IL-23, playing an important role in inflammatory processes, act synergistically in some cases, enhancing each other's production and effects. In experimental studies, CCL19 binding to CCR7 on cells in the spleen and bone marrow of mice activated the PI3K and NF- κ B signaling pathways, induced transcription of IL-23p19, and increased production of IL-23 [35]. This may explain the combined increase in serum CCL19 and IL-23 in group 1 patients (PLS) we observed.

The activation of DC in LB has a number of significant features. The examination of the bacterial immunopeptidome during culture of live *B. burgdorferi* with dendritic cells derived from monocytes of healthy donors revealed a unique gene-expression signature distinct from that induced by the TLR agonist 2-lipoteichoic acid [36]. There was registered an increased expression of negative checkpoint inhibitors PD-L1, TIM3, LAG3 and indolamine-2,3-dioxygenase by monocytic DC. It is believed that pathogens use the PD-L1 pathway to evade the host's response [37]. An experimental LB model showed that the PD-1/PD-L1 pathway is induced during *B. burgdorferi* infection [38]. Induction of LAG-3 expression, which is mainly restricted to regulatory T cells (Tregs), was detected in monocytic DCs [39]. The latter affect the balance of pro- and anti-inflammatory processes caused by infection, including LB [40].

B. burgdorferi stimulates the production of indolamine-2,3-dioxygenase by monocytic DC (an enzyme that destroys tryptophan and suppresses the formation of effector T cells) and stimulates the generation of CD4-Treg cells [41]. Thus, DC exposed to *B. burgdorferi* alter the T cell response of the human body [36]. It is believed that dysregulation and aberrant response of T cells is a feature of LB that partially conditions clinical outcomes of the disease [11]. In patients with elevated levels of IL-23, an impaired immune response associated with Th17 increases the risk of subsequent PLS [14].

In recent years, new data have emerged revealing additional mechanisms of CCL19 and IL-23 involvement in the formation of clinical manifestations of PLS. These data are potentially interesting in terms of understanding the pathogenesis of the syndrome and devising its treatment strategies. The findings include involvement of choroid plexus cells and the meningeal lymphatic system, dysregulation of immune-cell migration between the CNS and peripheral compartments, and dysfunction of the glymphatic system, impaired expression of transcription factors that maintain vascular endothelial homeostasis and T-lymphocyte function, in particular Kruppel-like factor 2 (KLF2).

B. burgdorferi can affect epithelial cells of the vascular plexus in the human CNS, inducing changes that promote chemotaxis of activated T lymphocytes into CNS parenchyma [42]. During

incubation of *B. burgdorferi* with epithelial cells of the human vascular plexus, a significant increase in the expression of immune and inflammatory chemokine genes, including CCR7 and INF types I and II, was observed. Researchers registered a decrease in the expression of key genes encoding proteins involved in tight junctions (*cln14*) and adhesion (*cdh2*), as well as the β -subunit of the sodium–potassium transporter (*atp1b1*) [43]. The meningeal lymphatic system plays an important role in local immune homeostasis of the meninges and participates in the migration of immune cells — particularly DC and T cells — from the central nervous system to meningeal borders and, subsequently, via afferent lymphatic vessels, to the cervical lymph nodes [44]. Disruption of T-cell migration from the CNS may be accompanied by pathological changes therein [44].

It is possible that the dysfunction of the glymphatic system after the acute stage of LB may be an additional factor in the pathogenesis of PLS with neurological involvement. Its key element is aquaporin-4 [45]. It is involved in brain inflammation, cerebrospinal fluid clearance, synaptic plasticity and memory formation, regulation of extracellular space volume, and potassium homeostasis [46, 47]. Aquaporin-4 participates in the migration of immune cells to the CNS, in the formation of an effective acquired T- and B-cell immune response; it is needed to complete activation of T cells [48, 49].

Mice with aquaporin-4 deficiency show cognitive impairments in object location memory test [50] and worsened spatial memory in the Morris water maze [51]; both of these disruptions are important neurological manifestations of PLS. Dysregulation of the glymphatic system is considered to be the main factor in the development of myalgic encephalomyelitis/chronic fatigue syndrome, the clinical signs of which, especially "brain fog," are characteristic of PLS with neurological involvement [52].

It is known that CCR7 expression for CCL19 is regulated by the zinc-finger transcription factor KLF2, which maintains vascular endothelial homeostasis and T-lymphocyte function [53]. Genes regulated by KLF2 are important for the survival, migration, and functioning of T cells. A drop in KLF2 levels is associated with the development of endothelial dysfunction,

a cytokine storm triggered by some infections [53]. KLF2 prevents the development of endothelial dysfunction caused by the SARS-Cov-2 virus [54]. Several drugs, in particular atorvastatin, resveratrol, metformin, liraglutide, and trichostatin D, can increase the level of KLF2 mRNA in endothelial cells and are its activator [55]. Their effects have also been associated with inhibition of the NOD-like receptor protein 3 (NLRP3) signaling pathway/caspase-1/IL-1 β involved in the pathogenesis of a number of neurological diseases.

KLF2 suppresses inflammation caused by NF- κ B [56], provides expression of the L-selectin receptor (CD62L), and determines the direction of differentiation of T lymphocytes into effector CXCR1+ or depleted CD101+T cells [57]. Previously, some authors investigated the possible role of T cell depletion and their aberrant state in the pathogenesis of PLS [11, 13, 20]. It is possible that in some LB patients, antibiotic therapy leads to impaired transmigration of T lymphocytes and DC into and out of the CNS, caused by altered aquaporin-4 polarization in astrocytes and by suppression of KLF2 expression and activity in CNS endothelial and epithelial cells; these changes may underlie PLS symptoms.

Generally, in LB it is crucial to identify biomarkers with adequate diagnostic specificity and sensitivity to predict the development of PLS [16]; tests of CCL19 may be useful for screening such patients [17]. According to our data, measuring IL-23 levels is as important diagnostically and prognostically as measuring CCL19 levels. Further research is needed to establish definitive reference intervals and optimal thresholds so these biomarkers can be introduced into clinical practice and results from different technologies compared reliably.

CONCLUSIONS

Our study confirmed the involvement of chemokine CCL19 and cytokine IL-23 in the pathogenesis of PLS with neurological involvement. The results of this work and literature data indicate that in some LB patients, the clinical signs of PLS stem from aberrant changes in the functioning of the body's innate and acquired immune response to *B. burgdorferi*.

References

1. Klinicheskie rekomendacii. Bolezn' Lajma u vzroslyh. 2025. Dostupno po ssylke: <http://medelement.com/disease/bolezni-lajma-u-vzroslyh-kr-rf-2025/19081> (data obrashcheniya: 10.03.2026). Russian.
2. Rudakova SA, Teslova OE, Mutalnova NE, Rudakov NV, Penevskaya NA, Kuzmenko YuF, et al. Epidemiologicheskaya situatsiya po iksodovym kleshchevym borreliozam v Rossijskoj Federacii v 2010–2024 gg. i prognoz na 2025 g. Problemy osobo opasnyh infekcij. 2025; 2: 39–46. DOI: 10.21055/0370-1069-2025-2-39-46. Russian.
3. Steere AC, Strle F, Wormser GP, Hu LT, Branda JA, Hovius JW, et al. Lyme borreliosis. Nat Rev Dis Primers. 2016; 2: 16090. DOI: 10.1038/nrdp.2016.90. Erratum in: Nat Rev Dis Primers. 2017; 3: 17062. DOI: 10.1038/nrdp.2017.62.
4. Radolf JD, Strle K, Lemieux JE, Strle F. Lyme Disease in Humans. Curr Issues Mol Biol. 2021; 42: 333–84. DOI: 10.21775/cimb.042.333.
5. Schwartz AM, Kugeler KJ, Nelson CA, Marx GE, Hinckley AF. Use of commercial claims data for evaluating trends in Lyme disease diagnoses, United States, 2010–2018. Emer Infect Dis. 2021; 27 (2): 499–507. DOI: 10.3201/eid2702.202728.
6. Steinbrink A, Brugger K, Margos G, Kraiczky P, Klimpel S. The evolving story of *Borrelia burgdorferi* sensu lato transmission in Europe. Parasitol. Res. 2022; 121 (3): 781–803. DOI: 10.1007/s00436-022-07445-3.
7. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006; 43: 1089–134. DOI: 10.1086/508667.
8. Weitzner E, McKenna D, Nowakowski J, Scavarda C, Dornbush R, Bittker S, et al. Long-term assessment of post-treatment symptoms in patients with culture-confirmed early Lyme disease. Clin Infect Dis. 2015; 61: 1800–6. DOI: 10.1093/cid/civ735.
9. Shor S, Green C, Szantyr B, Phillips S, Liegner K, Burrascano JJ Jr, et al. Chronic Lyme disease: an evidence-based definition by the ILADS working group. Antibiotics (Basel). 2019; 8: 269. DOI: 10.3390/antibiotics8040269.
10. Zafar K, Azuama OC, Parveen N. Current and emerging approaches for eliminating *Borrelia burgdorferi* and alleviating persistent Lyme disease symptoms. Front Microbiol. 2024; 15: 1459202. DOI: 10.3389/fmicb.2024.1459202.
11. Steere AC. Posttreatment Lyme disease syndromes: distinct pathogenesis caused by maladaptive host responses. J Clin Invest. 2020; 130 (5): 2148–51. DOI: 10.1172/JCI138062.
12. Soloski MJ, Crowder LA, Lahey LJ, Wagner CA, Robinson WH, Aucott JN. Serum inflammatory mediators as markers of human Lyme disease activity. PLoS One. 2014; 9 (4): e93243. DOI: 10.1371/journal.pone.0093243.

13. Aucott JN, Soloski MJ, Rebman AW, Crowder LA, Lahey LJ, Wagner CA, et al. CCL19 as a chemokine risk factor for posttreatment Lyme disease syndrome: a prospective clinical cohort study. *Clin Vaccine Immunol.* 2016; 23 (9): 757–66. DOI: 10.1128/CVI.00071-16.
14. Strle K, Stupica D, Drouin EE, Steere AC, Strle F. Elevated levels of IL-23 in a subset of patients with post-lyme disease symptoms following erythema migrans. *Clin Infect Dis.* 2014; 58 (3): 372–80. DOI: 10.1093/cid/cit735.
15. Hernández SA, Ogrinc K, Korva M, Kastrin A, Bogović P, Rojko T, et al. Associated of persistent symptoms after Lyme Neuroborreliosis and increased levels of interferon- α in blood. *Emerg Infect Dis.* 2023; 29 (6): 1091–101. DOI: 10.3201/eid2906.221685.
16. Adkison H, Embers ME. Lyme disease and the pursuit of a clinical cure. *Front Med (Lausanne).* 2023; 10: 1183344. DOI: 10.3389/fmed.2023.1183344.
17. Raffetin A, Saunier A, Bouiller K, Caraux-Paz P, Eldin C, Gallien S, et al. Unconventional diagnostic tests for Lyme borreliosis: a systematic review. *Clin Microbiol Infect.* 2020; 26 (1): 51–59. DOI: 10.1016/j.cmi.2019.06.033.
18. Baranova NS, Ostapenko YaS, Ovsyannikova LA, Spirin NN, Baranov AA, Bykanova MA. Clinical characteristics of neurological involvement in post-treatment Lyme disease syndrome: part 1. *RMJ.* 2026; 4: 7–12. DOI: 10.32364/2225-2282-2026-4-2. Russian.
19. Rupprecht TA, Plate A, Adam M, Wick M, Kastenbauer S, Schmidt C, et al. The chemokine CXCL13 is a key regulator of B cell recruitment to the cerebrospinal fluid in acute Lyme neuroborreliosis. *J Neuroinflammation.* 2009; 6: 42. DOI: 10.1186/1742-2094-6-42.
20. Girgis AA, Cimbro R, Yang T, Rebman AW, Sewell T, Villegas de Flores D, et al. Aberrant T-cell phenotypes in a cohort of patients with post-treatment Lyme disease. *Front Immunol.* 2025; 16: 1607619. DOI: 10.3389/fimmu.2025.1607619.
21. Eckman EA, Pacheco-Quinto J, Herdt AR, Halperin JJ. Neuroimmunomodulators in neuroborreliosis and Lyme encephalopathy. *Clin Infect Dis.* 2018; 67 (1): 80–88. DOI: 10.1093/cid/ciy019.
22. Baranova NS, Ovsyannikova LA, Ostapenko YaS, Spirin NN, Baranov AA, Gris MS, et al. Cytokine levels in patients with multiple sclerosis and chronic neuroborreliosis. *Neurology, Neuropsychiatry, Psychosomatics.* 2024; 16 (Suppl.2): 57–64. DOI: 10.14412/2074-2711-2024-2S-57-64. Russian.
23. Uhde M, Ajamian M, Li X, Wormser GP, Marques A, Alaadini A. Expression of C-reactive protein and serum amyloid A in early to late manifestations of Lyme disease. *Clin Infect Dis.* 2016; 63: 1399–404. DOI: 10.1093/cid/ciw599.
24. Rudakova SA, Rudakov NV, Shtrek SV, Teslova OE, Kaneshova NE. Genovidovaya harakteristika kleshchevyh borreliozov v Rossii. *Fundamental'naya i klinicheskaya medicina.* 2021; 6 (3): 94–99. DOI: 10.23946/2500-0764-2021-6-3-94-99. Russian.
25. Tveita A, Murphy SL, Holter JC, Kildal AB, Michelsen AE, Lerum TV, et al. High circulating levels of the homeostatic chemokines CCL19 and CCL21 predict mortality and disease severity in COVID-19. *J Infect Dis.* 2022; 226 (12): 2150–60. DOI: 10.1093/infdis/jiac313.
26. Kalish RA, McHugh G, Granquist J, Shea B, Ruthazer R, Steere AC. Persistence of immunoglobulin M or immunoglobulin G antibody responses to *Borrelia burgdorferi* 10–20 years after active Lyme disease. *Clin Infect Dis.* 2001; 33 (6): 780–5. DOI: 10.1086/322669.
27. Blum LK, Adamska, J Z, Martin DS, Rebman, AW, Elliott SE, Cao RRL, et al. Robust B cell responses predict rapid resolution of Lyme disease. *Front. Immunol.* 2018; 9: 1634. DOI: 10.3389/fimmu.2018.01634.
28. Bockenstedt LK, Wooten RM, Baumgarth N. Immune response to *Borrelia*: lessons from Lyme Disease spirochetes. *Curr Issues Mol Biol.* 2021; 42: 145–190. DOI: 10.21775/cimb.042.145.
29. Nakano K, Whitehead GS, Lyons-Cohen MR, Grimm SA, Wilkinson CL, Izumi G, et al. Chemokine CCL19 promotes type 2 T-cell differentiation and allergic airway inflammation. *J Allergy Clin Immunol.* 2024; 153 (2): 487–502.e9. DOI: 10.1016/j.jaci.2023.10.024.
30. Yan Y, Chen R, Wang X, Hu K, Huang L, Lu M, et al. CCL19 and CCR7 expression, signaling pathways, and adjuvant functions in viral infection and prevention. *Front Cell Dev Biol.* 2019; 7: 212. DOI: 10.3389/fcell.2019.00212.
31. Bielecki B, Jatzczak-Pawlik I, Wolinski P, Bednarek A, Glabinski A. Central nervous system and peripheral expression of CCL19, CCL21 and their receptor CCR7 in experimental model of multiple sclerosis. *Arch Immunol Ther Exp (Warsz).* 2015; 63 (5): 367–76. DOI: 10.1007/s00005-015-0339-9.
32. Krumbholz M, Theil D, Steinmeyer F, Cepok S, Hemmer B, Hofbauer M, et al. CCL19 is constitutively expressed in the CNS, up-regulated in neuroinflammation, active and also inactive multiple sclerosis lesions. *J Neuroimmunol.* 2007; 190 (1–2): 72–9. DOI: 10.1016/j.jneuroim.2007.07.024.
33. Hastey CJ, Ochoa J, Olsen KJ, Barthold SW, Baumgarth N. MyD88- and TRIF-independent induction of type I interferon drives naive B cell accumulation but not loss of lymph node architecture in Lyme disease. *Infect Immun.* 2014; 82: 1548 –8. DOI: 10.1128/IAI.00969-13.
34. Li Y, Yu X, Ma Y, Hua S. IL-23 and dendritic cells: What are the roles of their mutual attachment in immune response and immunotherapy? *Cytokine.* 2019; 120: 78–84. DOI: 10.1016/j.cyto.2019.02.018.
35. Kuwabara T, Tanaka Y, Ishikawa F, Kondo M, Sekiya H, Kakiuchi T. CCR7 ligands up-regulate IL-23 through PI3-kinase and NF- κ B pathway in dendritic cells. *J Leukoc Biol.* 2012; 92 (2): 309–18. DOI: 10.1189/jlb.0811415.
36. Gutierrez-Hoffmann M, Fan J, O'Meally RN, Cole RN, Florea L, Antonescu C, et al. The Interaction of *Borrelia burgdorferi* with Human Dendritic Cells: Functional Implications. *J Immunol.* 2023; 211 (4): 612–25. DOI: 10.4049/jimmunol.2300235.
37. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nat Immunol.* 2007; 8 (3): 239–45. DOI: 10.1038/ni1443.
38. Helble JD, McCarthy JE, Sawden M, Starnbach MN, Hu LT. The PD-1/PD-L1 pathway is induced during *Borrelia burgdorferi* infection and inhibits T cell joint infiltration without compromising bacterial clearance. *PLoS Pathog.* 2022; 18 (10): e1010903. DOI: 10.1371/journal.ppat.1010903.
39. Anderson AC, Joller N, Kuchroo VK. Lag-3, Tim-3, and TIGIT: co-inhibitory receptors with specialized functions in immune regulation. *Immunity.* 2016; 44 (5): 989–1004. DOI: 10.1016/j.immuni.2016.05.001.
40. Lochhead RB, Strle K, Arvikar SL, Weis JJ, Steere AC. Lyme arthritis: linking infection, inflammation and autoimmunity. *Nat Rev Rheumatol.* 2021; 17 (8): 449–61. DOI: 10.1038/s41584-021-00648-5.
41. Harden JL, Egilmez NK. Indoleamine 2,3-dioxygenase and dendritic cell tolerogenicity. *Immunol Invest.* 2012; 41 (6–7): 738–64. DOI: 10.3109/08820139.2012.676122.
42. Thompson D, Sorenson J, Greenmyer J, Brissette CA, Watt JA. The Lyme disease bacterium, *Borrelia burgdorferi*, stimulates an inflammatory response in human choroid plexus epithelial cells. *PLoS One.* 2020; 15 (7): e0234993. DOI: 10.1371/journal.pone.0234993.
43. Barwe SP, Skay A, McSpadden R, Huynh TP, Langhans SA, Inge LJ, et al. Na,K-ATPase β -subunit cis homo-oligomerization is necessary for epithelial lumen formation in mammalian cells. *J Cell Sci.* 2012; 125 (Pt 23): 5711–20. DOI: 10.1242/jcs.108795.
44. Laaker C, Baenen C, Kovács KG, Sandor M, Fabry Z. Immune cells as messengers from the CNS to the periphery: the role of the meningeal lymphatic system in immune cell migration from the CNS. *Front Immunol.* 2023; 14: 1233908. DOI: 10.3389/fimmu.2023.1233908.
45. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci Transl Med.* 2012; 4 (147): 147ra111. DOI: 10.1126/scitranslmed.3003748.
46. Cai Y, Zhang Y, Leng S, Ma Y, Jiang Q, Wen Q, et al. The relationship between inflammation, impaired glymphatic system, and neurodegenerative disorders: A vicious cycle. *Neurobiol Dis.* 2024; 192: 106426. DOI: 10.1016/j.nbd.2024.106426.
47. Mader S, Brimberg L. Aquaporin-4 Water Channel in the Brain and Its Implication for Health and Disease. *Cells.* 2019; 8 (2): 90. DOI: 10.3390/cells8020090.
48. Morley SC. T cells go with the flow: aquaporin 4 is required for

- full T-cell activation. *J Leukoc Biol.* 2023; 113 (6): 541–3. DOI: 10.1093/jleuko/qiad041.
49. Nicosia M, Lee J, Beavers A, Kish D, Farr GW, McGuirk PR, et al. Water channel aquaporin 4 is required for T cell receptor mediated lymphocyte activation. *J Leukoc Biol.* 2023; 113 (6): 544–54. DOI: 10.1093/jleuko/qiad010.
 50. Skucas VA, Mathews IB, Yang J, Cheng Q, Treister A, Duffy AM, et al. Impairment of select forms of spatial memory and neurotrophin-dependent synaptic plasticity by deletion of glial aquaporin-4. *J Neurosci.* 2011; 31: 6392–7. DOI: 10.1523/JNEUROSCI.6249-10.2011.
 51. Zhang J, Li Y, Chen ZG, Dang H, Ding JH, Fan Y, et al. Glia protein aquaporin-4 regulates aversive motivation of spatial memory in Morris water maze. *CNS Neurosci Ther.* 2013; 19: 937–44. DOI: 10.1111/cns.12191.
 52. Nemat-Gorgani M, Jensen MA, Davis RW. Glymphatic system dysregulation as a key contributor to myalgic encephalomyelitis/chronic fatigue syndrome. *Int J Mol Sci.* 2025; 26 (23): 11524. DOI: 10.3390/ijms262311524.
 53. Turpaev KT. Transkripcionnyj faktor KLF2 i ego rol' v reguljacii vospalitel'nyh processov. *Obzor. Biohimiya,* 2020; 85 (1): 64–79 DOI: 10.31857/S0320972520010054. Russian.
 54. Xu S, Liu Y, Ding Y, Luo S, Zheng X, Wu X, et al. The zinc finger transcription factor, KLF2, protects against COVID-19 associated endothelial dysfunction. *Signal Transduct Target Ther.* 2021; 6 (1): 266. DOI: 10.1038/s41392-021-00690-5.
 55. Lei L, Chen M, Wang C, Jiang X, Li Y, Wang W, et al. Trichostatin D as a Novel KLF2 Activator Attenuates TNF α -Induced Endothelial Inflammation. *Int J Mol Sci.* 2022; 23 (21): 13477. DOI: 10.3390/ijms232113477.
 56. Jha P, Das H. KLF2 in Regulation of NF- κ B-Mediated Immune Cell Function and Inflammation. *Int J Mol Sci.* 2017; 18 (11): 2383. DOI: 10.3390/ijms18112383.
 57. Tsui C, Heyden L, Wen L, Gago da Graça C, Potemkin N, Frolov A, et al. Lymph nodes fuel KLF2-dependent effector CD8 $^{+}$ T cell differentiation during chronic infection and checkpoint blockade. *Nat Immunol.* 2025; 26 (10): 1752–65. DOI: 10.1038/s41590-025-02276-7.

Литература

1. Клинические рекомендации. Болезнь Лайма у взрослых. 2025. Доступно по ссылке: <http://medelement.com/disease/болезнь-лайма-у-взрослых-к-р-р-р-2025/19081> (дата обращения: 10.03.2026).
2. Рудакова С. А., Теслова О. Е., Муталинова Н. Е., Рудаков Н. В., Пеневская Н. А., Кузьменко Ю. Ф. и др. Эпидемиологическая ситуация по иксодовым клещевым боррелиозам в Российской Федерации в 2010–2024 гг. и прогноз на 2025 г. *Проблемы особо опасных инфекций.* 2025; 2: 39–46. DOI: 10.21055/0370-1069-2025-2-39-46.
3. Steere AC, Strle F, Wormser GP, Hu LT, Branda JA, Hovius JW, et al. Lyme borreliosis. *Nat Rev Dis Primers.* 2016; 2: 16090. DOI: 10.1038/nrdp.2016.90. Erratum in: *Nat Rev Dis Primers.* 2017; 3: 17062. DOI: 10.1038/nrdp.2017.62.
4. Radolf JD, Strle K, Lemieux JE, Strle F. Lyme Disease in Humans. *Curr Issues Mol Biol.* 2021; 42: 333–84. DOI: 10.21775/cimb.042.333.
5. Schwartz AM, Kugeler KJ, Nelson CA, Marx GE, Hinckley AF. Use of commercial claims data for evaluating trends in Lyme disease diagnoses, United States, 2010–2018. *Emerg Infect Dis.* 2021; 27 (2): 499–507. DOI: 10.3201/eid2702.202728.
6. Steinbrink A, Brugger K, Margos G, Kraicz P, Klimpel S. The evolving story of *Borrelia burgdorferi* sensu lato transmission in Europe. *Parasitol. Res.* 2022; 121 (3): 781–803. DOI: 10.1007/s00436-022-07445-3.
7. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2006; 43: 1089–134. DOI: 10.1086/508667.
8. Weitzner E, McKenna D, Nowakowski J, Scavarda C, Dornbush R, Bittker S, et al. Long-term assessment of post-treatment symptoms in patients with culture-confirmed early Lyme disease. *Clin Infect Dis.* 2015; 61: 1800–6. DOI: 10.1093/cid/civ735.
9. Shor S, Green C, Szantyr B, Phillips S, Liegner K, Burrascano JJ Jr, et al. Chronic Lyme disease: an evidence-based definition by the ILADS working group. *Antibiotics (Basel).* 2019; 8: 269. DOI: 10.3390/antibiotics8040269.
10. Zafar K, Azuama OC, Parveen N. Current and emerging approaches for eliminating *Borrelia burgdorferi* and alleviating persistent Lyme disease symptoms. *Front Microbiol.* 2024; 15: 1459202. DOI: 10.3389/fmicb.2024.1459202.
11. Steere AC. Posttreatment Lyme disease syndromes: distinct pathogenesis caused by maladaptive host responses. *J Clin Invest.* 2020; 130 (5): 2148–51. DOI: 10.1172/JCI138062.
12. Soloski MJ, Crowder LA, Lahey LJ, Wagner CA, Robinson WH, Aucott JN. Serum inflammatory mediators as markers of human Lyme disease activity. *PLoS One.* 2014; 9 (4): e93243. DOI: 10.1371/journal.pone.0093243.
13. Aucott JN, Soloski MJ, Rebman AW, Crowder LA, Lahey LJ, Wagner CA, et al. CCL19 as a chemokine risk factor for posttreatment Lyme disease syndrome: a prospective clinical cohort study. *Clin Vaccine Immunol.* 2016; 23 (9): 757–66. DOI: 10.1128/CVI.00071-16.
14. Strle K, Stupica D, Drouin EE, Steere AC, Strle F. Elevated levels of IL-23 in a subset of patients with post-lyme disease symptoms following erythema migrans. *Clin Infect Dis.* 2014; 58 (3): 372–80. DOI: 10.1093/cid/cit735.
15. Hernández SA, Ogrinc K, Korva M, Kastrin A, Bogovič P, Rojko T, et al. Associated of persistent symptoms after Lyme Neuroborreliosis and increased levels of interferon- α in blood. *Emerg Infect Dis.* 2023; 29 (6): 1091–101. DOI: 10.3201/eid2906.221685.
16. Adkison H, Embers ME. Lyme disease and the pursuit of a clinical cure. *Front Med (Lausanne).* 2023; 10: 1183344. DOI: 10.3389/fmed.2023.1183344.
17. Raffetin A, Saunier A, Bouiller K, Caraux-Paz P, Eldin C, Gallien S, et al. Unconventional diagnostic tests for Lyme borreliosis: a systematic review. *Clin Microbiol Infect.* 2020; 26 (1): 51–59. DOI: 10.1016/j.cmi.2019.06.033.
18. Баранова Н. С., Остапенко Я. С., Овсянникова Л. А., Спиринов Н. Н., Баранов А. А., Быканова М. А. Клинические особенности поражения нервной системы при постлаймском синдроме. Часть 1. *ПМЖ.* 2026; 4: 7–12. DOI: 10.32364/2225-2282-2026-4-2.
19. Rupprecht TA, Plate A, Adam M, Wick M, Kastenbauer S, Schmidt C, et al. The chemokine CXCL13 is a key regulator of B cell recruitment to the cerebrospinal fluid in acute Lyme neuroborreliosis. *J Neuroinflammation.* 2009; 6: 42. DOI: 10.1186/1742-2094-6-42.
20. Girgis AA, Cimbro R, Yang T, Rebman AW, Sewell T, Villegas de Flores D, et al. Aberrant T-cell phenotypes in a cohort of patients with post-treatment Lyme disease. *Front Immunol.* 2025; 16: 1607619. DOI: 10.3389/fimmu.2025.1607619.
21. Eckman EA, Pacheco-Quinto J, Herdt AR, Halperin JJ. Neuroimmunomodulators in neuroborreliosis and Lyme encephalopathy. *Clin Infect Dis.* 2018; 67 (1): 80–88. DOI: 10.1093/cid/ciy019.
22. Баранова Н. С., Овсянникова Л. А., Остапенко Я. С., Спиринов Н. Н., Баранов А. А., Григорьев М. С. и др. Уровень цитокинов у пациентов с рассеянным склерозом и хроническим нейроборрелиозом. *Неврология, нейропсихиатрия, психосоматика.* 2024; 16: 57–64. DOI: 10.14412/2074-2711-2024-2S-57-64.
23. Uhde M, Ajamian M, Li X, Wormser GP, Marques A, Alaedini A. Expression of C-reactive protein and serum amyloid A in early to late manifestations of Lyme disease. *Clin Infect Dis.* 2016; 63: 1399–404. DOI: 10.1093/cid/ciw599.
24. Рудакова С. А., Рудаков Н. В., Штрек С. В., Теслова О. Е., Канешова Н. Е. Генотипическая характеристика клещевых боррелиозов в России. *Фундаментальная и клиническая медицина.* 2021; 6 (3): 94–99. DOI: 10.23946/2500-0764-2021-6-3-94-99.
25. Tveita A, Murphy SL, Holter JC, Kildal AB, Michelsen AE, Lerum TV, et

- al. High circulating levels of the homeostatic chemokines CCL19 and CCL21 predict mortality and disease severity in COVID-19. *J Infect Dis.* 2022; 226 (12): 2150–60. DOI: 10.1093/infdis/jiac313.
26. Kalish RA, McHugh G, Granquist J, Shea B, Ruthazer R, Steere AC. Persistence of immunoglobulin M or immunoglobulin G antibody responses to *Borrelia burgdorferi* 10–20 years after active Lyme disease. *Clin Infect Dis.* 2001; 33 (6): 780–5. DOI: 10.1086/322669.
27. Blum LK, Adamska J Z, Martin DS, Rebman AW, Elliott SE, Cao RRL, et al. Robust B cell responses predict rapid resolution of Lyme disease. *Front. Immunol.* 2018; 9: 1634. DOI: 10.3389/fimmu.2018.01634.
28. Bockenstedt LK, Wooten RM, Baumgarth N. Immune response to *Borrelia*: lessons from Lyme Disease spirochetes. *Curr Issues Mol Biol.* 2021; 42: 145–190. DOI: 10.21775/cimb.042.145.
29. Nakano K, Whitehead GS, Lyons-Cohen MR, Grimm SA, Wilkinson CL, Izumi G, et al. Chemokine CCL19 promotes type 2 T-cell differentiation and allergic airway inflammation. *J Allergy Clin Immunol.* 2024; 153 (2): 487–502.e9. DOI: 10.1016/j.jaci.2023.10.024.
30. Yan Y, Chen R, Wang X, Hu K, Huang L, Lu M, et al. CCL19 and CCR7 expression, signaling pathways, and adjuvant functions in viral infection and prevention. *Front Cell Dev Biol.* 2019; 7: 212. DOI: 10.3389/fcell.2019.00212.
31. Bielecki B, Jatzak-Pawlik I, Wolinski P, Bednarek A, Glabinski A. Central nervous system and peripheral expression of CCL19, CCL21 and their receptor CCR7 in experimental model of multiple sclerosis. *Arch Immunol Ther Exp (Warsz).* 2015; 63 (5): 367–76. DOI: 10.1007/s00005-015-0339-9.
32. Krumbholz M, Theil D, Steinmeyer F, Cepok S, Hemmer B, Hofbauer M, et al. CCL19 is constitutively expressed in the CNS, up-regulated in neuroinflammation, active and also inactive multiple sclerosis lesions. *J Neuroimmunol.* 2007; 190 (1–2): 72–9. DOI: 10.1016/j.jneuroim.2007.07.024.
33. Hastey CJ, Ochoa J, Olsen KJ, Barthold SW, Baumgarth N. MyD88- and TRIF-independent induction of type I interferon drives naive B cell accumulation but not loss of lymph node architecture in Lyme disease. *Infect Immun.* 2014; 82: 1548–8. DOI: 10.1128/IAI.00969-13.
34. Li Y, Yu X, Ma Y, Hua S. IL-23 and dendritic cells: What are the roles of their mutual attachment in immune response and immunotherapy? *Cytokine.* 2019; 120: 78–84. DOI: 10.1016/j.cyto.2019.02.018.
35. Kuwabara T, Tanaka Y, Ishikawa F, Kondo M, Sekiya H, Kakiuchi T. CCR7 ligands up-regulate IL-23 through PI3-kinase and NF- κ B pathway in dendritic cells. *J Leukoc Biol.* 2012; 92 (2): 309–18. DOI: 10.1189/jlb.0811415.
36. Gutierrez-Hoffmann M, Fan J, O'Meally RN, Cole RN, Florea L, Antonescu C, et al. The Interaction of *Borrelia burgdorferi* with Human Dendritic Cells: Functional Implications. *J Immunol.* 2023; 211 (4): 612–25. DOI: 10.4049/jimmunol.2300235.
37. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nat Immunol.* 2007; 8 (3): 239–45. DOI: 10.1038/ni1443.
38. Helble JD, McCarthy JE, Sawden M, Starnbach MN, Hu LT. The PD-1/PD-L1 pathway is induced during *Borrelia burgdorferi* infection and inhibits T cell joint infiltration without compromising bacterial clearance. *PLoS Pathog.* 2022; 18 (10): e1010903. DOI: 10.1371/journal.ppat.1010903.
39. Anderson AC, Joller N, Kuchroo VK. Lag-3, Tim-3, and TIGIT: co-inhibitory receptors with specialized functions in immune regulation. *Immunity.* 2016; 44 (5): 989–1004. DOI: 10.1016/j.immuni.2016.05.001.
40. Lochhead RB, Strle K, Arvikar SL, Weis JJ, Steere AC. Lyme arthritis: linking infection, inflammation and autoimmunity. *Nat Rev Rheumatol.* 2021; 17 (8): 449–61. DOI: 10.1038/s41584-021-00648-5.
41. Harden JL, Egilmez NK. Indoleamine 2,3-dioxygenase and dendritic cell tolerogenicity. *Immunol Invest.* 2012; 41 (6–7): 738–64. DOI: 10.3109/08820139.2012.676122.
42. Thompson D, Sorenson J, Greenmyer J, Brissette CA, Watt JA. The Lyme disease bacterium, *Borrelia burgdorferi*, stimulates an inflammatory response in human choroid plexus epithelial cells. *PLoS One.* 2020; 15 (7): e0234993. DOI: 10.1371/journal.pone.0234993.
43. Barwe SP, Skay A, McSpadden R, Huynh TP, Langhans SA, Inge LJ, et al. Na,K-ATPase β -subunit cis homo-oligomerization is necessary for epithelial lumen formation in mammalian cells. *J Cell Sci.* 2012; 125 (Pt 23): 5711–20. DOI: 10.1242/jcs.108795.
44. Laaker C, Baenen C, Kovács KG, Sandor M, Fabry Z. Immune cells as messengers from the CNS to the periphery: the role of the meningeal lymphatic system in immune cell migration from the CNS. *Front Immunol.* 2023; 14: 1233908. DOI: 10.3389/fimmu.2023.1233908.
45. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci Transl Med.* 2012; 4 (147): 147ra111. DOI: 10.1126/scitranslmed.3003748.
46. Cai Y, Zhang Y, Leng S, Ma Y, Jiang Q, Wen Q, et al. The relationship between inflammation, impaired glymphatic system, and neurodegenerative disorders: A vicious cycle. *Neurobiol Dis.* 2024; 192: 106426. DOI: 10.1016/j.nbd.2024.106426.
47. Mader S, Brimberg L. Aquaporin-4 Water Channel in the Brain and Its Implication for Health and Disease. *Cells.* 2019; 8 (2): 90. DOI: 10.3390/cells8020090.
48. Morley SC. T cells go with the flow: aquaporin 4 is required for full T-cell activation. *J Leukoc Biol.* 2023; 113 (6): 541–3. DOI: 10.1093/jleuko/qiad041.
49. Nicosia M, Lee J, Beavers A, Kish D, Farr GW, McGuirk PR, et al. Water channel aquaporin 4 is required for T cell receptor mediated lymphocyte activation. *J Leukoc Biol.* 2023; 113 (6): 544–54. DOI: 10.1093/jleuko/qiad010.
50. Skucas VA, Mathews IB, Yang J, Cheng Q, Treister A, Duffy AM, et al. Impairment of select forms of spatial memory and neurotrophin-dependent synaptic plasticity by deletion of glial aquaporin-4. *J Neurosci.* 2011; 31: 6392–7. DOI: 10.1523/JNEUROSCI.6249-10.2011.
51. Zhang J, Li Y, Chen ZG, Dang H, Ding JH, Fan Y, et al. Glia protein aquaporin-4 regulates aversive motivation of spatial memory in Morris water maze. *CNS Neurosci Ther.* 2013; 19: 937–44. DOI: 10.1111/cns.12191.
52. Nemat-Gorgani M, Jensen MA, Davis RW. Glymphatic system dysregulation as a key contributor to myalgic encephalomyelitis/chronic fatigue syndrome. *Int J Mol Sci.* 2025; 26 (23): 11524. DOI: 10.3390/ijms262311524.
53. Турпаев К. Т. Транскрипционный фактор KLF2 и его роль в регуляции воспалительных процессов. Обзор. *Биохимия.* 2020; 85 (1): 64–79 DOI: 10.31857/S0320972520010054.
54. Xu S, Liu Y, Ding Y, Luo S, Zheng X, Wu X, et al. The zinc finger transcription factor, KLF2, protects against COVID-19 associated endothelial dysfunction. *Signal Transduct Target Ther.* 2021; 6 (1): 266. DOI: 10.1038/s41392-021-00690-5.
55. Lei L, Chen M, Wang C, Jiang X, Li Y, Wang W, et al. Trichostatin D as a Novel KLF2 Activator Attenuates TNF α -Induced Endothelial Inflammation. *Int J Mol Sci.* 2022; 23 (21): 13477. DOI: 10.3390/ijms232113477.
56. Jha P, Das H. KLF2 in Regulation of NF- κ B-Mediated Immune Cell Function and Inflammation. *Int J Mol Sci.* 2017; 18 (11): 2383. DOI: 10.3390/ijms18112383.
57. Tsui C, Heyden L, Wen L, Gago da Graça C, Potemkin N, Frolov A, et al. Lymph nodes fuel KLF2-dependent effector CD8+ T cell differentiation during chronic infection and checkpoint blockade. *Nat Immunol.* 2025; 26 (10): 1752–65. DOI: 10.1038/s41590-025-02276-7.