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Investigation of brain-derived neurotrophic factor and adhesion molecules in multiple sclerosis

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ABSTRACT

BACKGROUND: In recent decades, numerous papers have been published exploring various biomarkers of multiple sclerosis in body fluids. Among these, particular attention should be given to brain-derived neurotrophic factor (BDNF), intercellular adhesion molecule 1 (ICAM1), neural cell adhesion molecule (NCAM), and the ratio of their concentrations in different types of multiple sclerosis progression.

AIM: The study aimed to analyze the diagnostic significance of BDNF, ICAM1, and NCAM in patients with different courses of multiple sclerosis.

METHODS: Blood sampling and assessment of clinical pattern of the disease course were performed in the study group ($n = 66$) and the control group consisting of healthy volunteers ($n = 15$). The study group patients were divided into three subgroups according to the type of the disease course: relapsing-remitting multiple sclerosis, both treated and non-treated with disease-modifying therapies (interferons β-1b), and secondary progressive multiple sclerosis. The severity of the patient disability was determined using the Expanded Disability Status Scale. The average annual frequency of exacerbations and the rate of the disease progression were calculated. Signs of progression were assessed based on the results of magnetic resonance imaging of the brain, spinal cord, and optic nerves. BDNF, ICAM1, and NCAM levels were measured using an enzyme-linked immunosorbent assay kit (Cloud-Clone, China) on a Multiskan GO analyzer (Thermo Fisher Scientific, Finland) with a Wellwash microplate washer (Thermo Fisher Scientific, Finland) and a PST-60HL-4 plate shaker/thermostat (Biosan, Latvia).

RESULTS: BDNF was increased in the blood serum in the study group patients (all subgroups) compared with the control group. Statistically significant differences were observed in patients receiving disease-modifying therapy. In the relapsing-remitting multiple sclerosis group, there was an inverse correlation between BDNF concentration and disability severity, as measured by the Expanded Disability Status Scale. Serum levels of NCAM were significantly increased in the relapsing-remitting multiple sclerosis subgroups treated and non-treated with disease-modifying therapies, as compared with the control group. In contrast, no statistically significant differences were found in serum levels of ICAM1 among patients in the study groups.

CONCLUSION: Increased levels of BDNF and NCAM in patients with relapsing-remitting multiple sclerosis with short disease duration may indicate the neuroprotective effect of these biomarkers, but may also serve as a predictor of disease exacerbation. High levels of BDNF during interferon β-1b therapy may indicate inadequate effectiveness of this drug, necessitating a decision to escalate therapy. In patients with secondary progressive multiple sclerosis, high levels of NCAM may be associated with increasing disability.

Keywords: brain-derived neurotrophic factor; adhesion molecules; multiple sclerosis.

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Исследование мозгового нейротрофического фактора и молекул адгезии при рассеянном склерозе

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АННОТАЦИЯ

Обоснование. В последние десятилетия опубликовано большое количество работ, исследующих различные биомаркеры при рассеянном склерозе (РС) в жидкостях организма. Среди этих биомаркеров особый интерес представляют мозговой нейротрофический фактор (brain-derived neurotrophic factor, BDNF), молекулы межклеточной адгезии 1 (inter-cellular adhesion molecule 1, ICAM1), нейрональные молекулы клеточной адгезии (neural cell adhesion molecule, NCAM) и соотношение их концентрации при различных типах течения и активности РС.

Цель. Проанализировать диагностическую значимость BDNF, ICAM1 и NCAM у пациентов с различными типами течения РС.

Методы. Забор крови и оценку клинических характеристик течения заболевания проводили в основной группе (n=66) и контрольной группе, состоящей из условно здоровых добровольцев (n=15). Пациенты основной группы были разделены на три подгруппы в соответствии с типом течения заболевания: ремиттирующий РС (РРС) на фоне и без терапии препаратами, изменяющими течение заболевания (ПИТРС), — интерфероны β-1b; вторично-прогрессирующий РС. Выраженность инвалидизации пациентов определяли по расширенной шкале статуса инвалидизации. Произведён расчёт среднегодовой частоты обострений и скорости прогрессирования заболевания. Оценивались признаки активности по результатам магнитно-резонансной томографии головного, спинного мозга, зрительных нервов. Исследование концентрации BDNF, ICAM1, NCAM осуществляли с помощью набора для иммуноферментного анализа ELISA (человек; Cloud-Clone, Китай) на анализаторе Multiskan GO (Thermo Fisher Scientific, Финляндия) с использованием планшета-отмывателя для иммуноферментного анализа Wellwash (Thermo Fisher Scientific, Финляндия) и термошейкера PST-60HL-4 (Biosan, Латвия).

Результаты. При исследовании BDNF обнаружено повышение концентрации этого фактора в сыворотке крови пациентов основной группы (всех подгрупп) по сравнению с контрольной, статистически значимые различия отмечены у пациентов, получающих терапию ПИТРС. Обнаружена обратная корреляция концентрации BDNF и выраженности инвалидизации по расширенной шкале статуса инвалидизации в группе пациентов с РРС. Концентрация NCAM в сыворотке крови статистически значимо увеличивалась по сравнению с контролем в подгруппах РРС на фоне и без терапии ПИТРС. Статистически значимых отличий концентрации ICAM1 в сыворотке крови среди пациентов исследованных групп не получено.

Заключение. Повышение концентрации BDNF и NCAM при небольшой длительности заболевания у пациентов с РРС может указывать на нейропротекторный эффект данных биомаркеров, но в то же время служить предиктором обострения заболевания. Высокая концентрация BDNF на фоне терапии интерфероном β-1b, возможно, указывает на недостаточную эффективность данного препарата, что требует принятия решения об эскалации терапии. У пациентов с вторично-прогрессирующим РС высокое содержание NCAM может быть связано с нарастанием инвалидизации.

Ключевые слова: мозговой нейротрофический фактор; молекулы адгезии; рассеянный склероз.

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BACKGROUND

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) that is characterized by immune-mediated inflammation and demyelination. It affects more than 2 million people worldwide [1]. Evaluation of personalized treatment strategies efficacy for MS requires more accurate data than simply assessing relapse rates, disease progression, and measuring early-stage disease activity with magnetic resonance imaging (MRI) [2, 3]. Therefore, numerous studies have been conducted in the last decade to identify MS biomarkers in body fluids. Currently, there is no universal serological biomarker to reliably diagnose MS [4]. It is often challenging to determine whether a flare-up is a true relapse or a pseudo-relapse induced by infection or comorbidities [5]. In addition, there are virtually no accurate biomarkers of disease progression and response to treatment. Ideally, a biomarker should have both diagnostic and prognostic value, correlate with specific disease activity such as relapse or progression, respond to treatment, and contribute to the analysis of clinical trial outcomes. Moreover, an ideal biomarker should be non-invasive, safe, reproducible, and cost-effective [6].

Identifying the balance between factors of neuroplasticity and neurodegeneration in different MS courses is of interest. Brain-derived neurotrophic factor (BDNF) is a neurotrophin protein produced in the human body. Neurotrophins influence the mechanisms of neuroplasticity, synaptogenesis, stimulate neuroregeneration, axon growth, and dendrite branching to target cells [7].

Intercellular adhesion molecule 1 (ICAM1) and neural cell adhesion molecule (NCAM) refer to the immunoglobulin superfamily. ICAM1, through its binding to αLβ2 and α4β1 integrins, plays a pivotal role in the interaction of T cells with the vascular wall endothelium. This interaction contributes to the increased permeability of the blood–brain barrier and the development of autoimmune inflammation in the CNS [8]. NCAMs (also known as CD56) are involved in cell migration, axon growth, and synapse organization and modulation. Most studies have examined the concentration of NCAMs in the cerebrospinal fluid, with their levels decreasing in patients as MS progresses [9].

AIM

The study aimed to analyze the diagnostic significance of BDNF, ICAM1, and NCAM in patients with different types of MS.

METHODS

Study Design

An interventional, single-center, cross-sectional, sampling, controlled, non-blinded, and non-randomized study was conducted.

Eligibility Criteria

The study included patients diagnosed with confirmed MS according to McDonald (2017) criteria who were hospitalized for a flare-up.

Study Setting

The study was conducted at the Research Institute of Experimental Biology and Medicine at Voronezh State Medical University, by a group of scientists, including members of the Department of Neurology. Blood samples were taken from patients undergoing inpatient treatment at the Neurology Department of Voronezh Regional Clinical Hospital No. 1 before the start of pulse glucocorticoid therapy.

Study Duration

Blood sampling and assessment of clinical characteristics of the patient groups were performed between September and December 2023.

Intervention

The clinical and anamnestic data of the patients, as well as and the MRI findings, were analyzed. The data were documented in patient case report forms.

Blood was collected in Vacuette tubes with red caps (Greiner Bio-One, Austria) before the start of pulse glucocorticoid therapy. The samples were frozen at –40 °C and stored for under 4 months.

Main Study Outcome

Serum concentrations of BDNF, ICAM1, and NCAM in the study patients were determined.

Additional Study Outcomes

Clinical and anamnestic characteristics and MRI findings of the study patients were documented.

Subgroup Analysis

Blood sampling and assessment of clinical characteristics of the disease course were performed in the study group (n = 66) and the control group consisting of apparently healthy volunteers (n = 15). The participants of the study group were divided into three subgroups by disease course: patients with relapsing-remitting MS (RRMS) without disease-modifying therapy (DMT); patients with RRMS receiving DMT (beta-1b interferons [INF]); and patients with secondary progressive MS (SPMS) with flare-ups and without DMT. The RRMS subgroup was heterogeneous, with/without MRI disease activity signs.

Outcomes Registration

The severity of patient disability was assessed using the Expanded Disability Status Scale (EDSS). The annualized relapse rate (ARR) and the progression rate

(PR) were calculated. The ARR was estimated as the ratio of the number of flare-ups to the duration of the MS course. The PR was estimated as the ratio of the EDSS annual score to the duration of the MS course. Patients with scores ⩽0.25 were designated as slow progressors, 0.25–0.75 as moderate progressors, and ⩾0.75 as high progressors [10]. Additionally, signs of the disease activity were assessed by MRI of the brain, spinal cord, and optic nerves (contrast-enhancing demyelination lesions).

The concentrations of BDNF, ICAM1, and NCAM were analyzed by enzyme-linked immunosorbent assay kit (for humans; Cloud-Clone, China) on a Multiskan GO analyzer (Thermo Fisher Scientific, Finland) using a Wellwash microplate washer (Thermo Fisher Scientific, Finland) and a PST-60HL-4 plate shaker/thermostat (Biosan, Latvia). Blood serum was obtained by standard centrifugation at 3000 rpm for 10 min using an LMC-3000 centrifuge (Biosan, Latvia).

Statistical Analysis

The sample size was not pre-calculated. Statistical analysis was performed using StatTech v. 4.1.2 (StatTech LLC, Russia). The Shapiro–Wilk test was used to evaluate the normality of distribution of the quantitative parameters. The statistical significance of observed differences in values was then determined by means of either the parametric Student's t-test ($p < 0.05$) or the non-parametric Mann–Whitney U test ($p < 0.05$). In case of normal distribution of the compared values, the direction and strength of the correlation (r) between two quantitative parameters were evaluated using the Pearson correlation coefficient. Conversely, in case of non-normal distribution of the parameters, the Spearman's rank correlation coefficient was used. The strength of the relationship was determined using the Chaddock scale, where a score of 0.1 to 0.3 indicates a weak relationship, 0.3 to 0.5 indicates a moderate relationship, 0.5 to 0.7 indicates a marked relationship, 0.7 to 0.9 indicates a high relationship, and 0.90 to 0.99 indicates a very high relationship. A predictive model characterizing the dependence of a quantitative variable on factors was developed using the linear regression method. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Participants

Women predominated in all studied groups. The mean age of patients was the lowest in the RRMS group and the highest in the SPMS group. The age of the disease onset was not significantly different between the groups but was lower in patients with RRMS. The longest disease duration was observed in the SPMS group (Table 1).

Primary Results

The BDNF levels were elevated in the blood serum of the study group patients (across all subgroups) in comparison with the control group. However, statistically significant differences were only observed in patients with RRMS who were receiving INF-beta-1b. The BDNF levels in the RRMS+DMT subgroup were higher than in patients with the natural disease course; nevertheless, the differences were not found to be statistically significant (Table 2). The same subgroup exhibited a lack of correlations between BDNF and ARR, PR, and EDSS. However, a statistically significant direct correlation between ICAM1 and BDNF concentrations was identified. In the subgroup of RRMS without DMT, a statistically significant moderate inverse correlation between EDSS scores and BDNF concentration was observed (Table 3).

Serum NCAM levels showed an increase in the RRMS subgroups with and without DMT in comparison with the control group. Statistically significant differences were identified in the RRMS subgroup without DMT (See Table 2). Within the RRMS group, a statistically significant increase in NCAM levels was observed in patients with active MRI lesions in contrast to patients without evidence of the disease activity as determined by neuroimaging data ($p = 0.02$, Mann–Whitney U test). A markedly close inverse correlation between disease duration and NCAM levels was observed in SPMS patients, although the absolute values of this parameter did not differ from those of the control group. In the same group, a statistically significant direct correlation was found between NCAM levels and PR, as well as between NCAM levels and EDSS score (See Table 3).

No statistically significant differences in serum ICAM1 levels among study group patients were observed (See Table 2). A positive correlation between ICAM1 levels and ARR was found in the RRMS subgroup without DMT, and a statistically

Table 1. Clinical characteristics of patients (M±*m*)

Clinical characteristics	Control (*n*=15)	RRMS (*n*=24)	RRMS+DMT (*n*=33)	SPMS (*n*=9)
Age, years	33.4±1.8	37.2±2.1	38.1±1.8	49.8±2.6*†
Number of women, %	66.67	67	57	55
Age at first attack, years	—	29.8±2.3	33.3±1.9	32.5±2.8
Disease duration, years	—	6.7±1.0	5.3±0.8	17.3±3.0†

Note: RRMS, relapsing-remitting multiple sclerosis; RRMS+DMT, RRMS treated with disease-modifying therapy; SPMS, secondary progressive multiple sclerosis; * differences are statistically significant compared with the control group, $p < 0.05$; † differences are statistically significant compared with the RRMS group, $p < 0.05$.

Table 2. Concentration of brain-derived neurotrophic factor and adhesion molecules (M±*m*)

Parameters	Control	RRMS	RRMS+DMT	SPMS
BDNF, pg/mL	464.4±55.6	643.7±96.4	817.0±79.0*	666.9±100.9
ICAM1, pg/mL	287.0±27.1	266.7±20.3	283.0±26.1	253.6±31.4
NCAM, ng/mL	1407.7±269.4	2048.6±401.7*	1803.6±326.1	1456.5±318.8

Note: RRMS, relapsing-remitting multiple sclerosis; RRMS+DMT, RRMS treated with disease-modifying therapy; SPMS, secondary progressive multiple sclerosis; BDNF, brain-derived neurotrophic factor; ICAM1, intercellular adhesion molecules 1; NCAM, neural cell adhesion molecules; * differences are statistically significant compared with the control group, $p < 0.05$.

Table 3. Correlations of serum BDNF, ICAM1, and NCAM levels in patients with different types of MS course and clinical characteristics

Parameters	RRMS		RRMS+DMT		SPMS	
	r	*p*	*r*	*p*	*r*	*p*
BDNF and ICAM1	0.148	0.491	0.546	0.002*	–0.103	0.791
BDNF and NCAM	0.262	0.217	0.136	0.474	0.233	0.546
BDNF and ARR	0.173	0.418	0.279	0.135	0.192	0.62
BDNF and PR	–0.196	0.358	–0.148	0.435	0	1
BDNF and EDSS score	–0.41	0.046*	–0.03	0.876	–0.261	0.498
ICAM1 and NCAM	0.236	0.268	0.384	0.036*	–0.45	0.224
ICAM1 and ARR	0.349	0.095	0.38	0.039*	0.176	0.651
ICAM1 and PR	0.296	0.16	0.025	0.897	–0.333	0.381
ICAM1 and EDSS score	0.062	0.772	–0.244	0.194	–0.41	0.273
NCAM and ARR	–0.023	0.916	0.196	0.3	0.243	0.529
NCAM and PR	–0.146	0.497	–0.097	0.608	0.7	0.036*
NCAM and EDSS score	0.293	0.165	–0.135	0.475	0.671	0.048*
NCAM and disease duration	–0.042	0.844	–0.073	0.701	–0.7	0.036*

Note: RRMS, relapsing-remitting multiple sclerosis; RRMS+DMT, RRMS treated with disease-modifying therapy; SPMS, secondary progressive multiple sclerosis; BDNF, brain-derived neurotrophic factor; ICAM1, intercellular adhesion molecules 1; NCAM, neural cell adhesion molecules; ARR, annualized relapse rate; PR, progression rate; EDSS, Expanded Disability Status Scale; * differences are statistically significant, $p < 0.05$.

significant relationship was observed in the RRMS subgroup receiving INF-beta-1b. In the RRMS subgroup without DMT, a statistically significant moderate direct correlation between ICAM1 and NCAM levels was observed. Conversely, in the SPMS subgroup, a negative correlation between these parameters was found. Furthermore, a moderate inverse correlation between ICAM1 and disease duration in patients with RRMS was revealed (See Table 3).

Secondary Results

Statistically significant differences in EDSS scores were observed between the groups. Patients with SPMS demonstrated the highest scores (Fig. 1). In the RRMS and RRMS+DMT subgroups, a statistically significant inverse correlation between disease duration and ARR scores was revealed ($r = –0.717$; $p < 0.001$, and $r = –0.625$; $p < 0.001$, respectively). In addition, an increase in EDSS score was expected with increasing PR and disease duration in all groups, with statistically significant values in the SPMS subgroup ($r = –1.000$; $p < 0.005$). Furthermore, male sex was associated with higher PR in the RRMS natural course group ($p = 0.043$, Mann–Whitney U test) and with higher ARR in the RRMS+DMT group ($p = 0.010$, Mann–Whitney U test).

Adverse Events

No adverse events were registered.

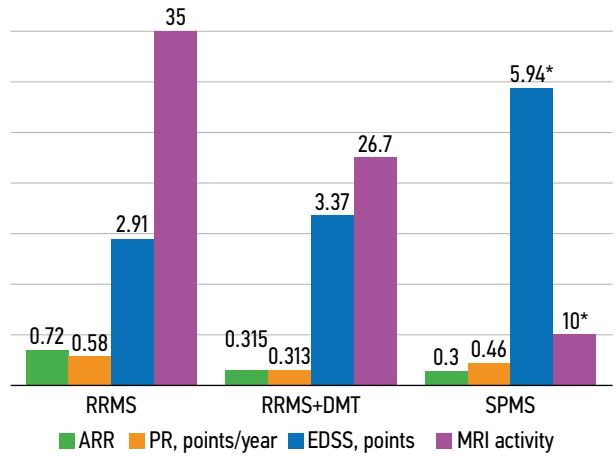

Fig. 1. Clinical characteristics of patients. RRMS, relapsing-remitting multiple sclerosis; RRMS+DMT, RRMS treated with disease-modifying therapy; SPMS, secondary progressive multiple sclerosis; ARR, annualized relapse rate; PR, progression rate; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; * differences are statistically significant compared with the RRMS group, $p < 0.05$.

DISCUSSION

Summary of Primary Results

An increase in BDNF levels was found in the study group (all subgroups) compared with the control group. NCAM serum levels were increased in patients with RRMS. ICAM1 serum levels did not show statistically significant differences between subgroups or compared with controls.

Interpretation

An increase in BDNF levels was observed in the subgroups of patients compared with the control group. The results suggest that elevated BDNF levels are associated with reduced disability severity in patients with RRMS as measured by EDSS. This may indicate the neuroprotective and neurotrophic role of this biomarker in disease exacerbation. Notably, the main sources of BDNF during flare-ups are CNS neurons and activated T cells and B cells [11]. Conversely, high BDNF levels in RRMS patients may serve as a flare-up marker. A statistically significant increase in BDNF levels was observed in the RRMS subgroup while on INF-beta-1b therapy. The data on the effect of INF drugs on the production of this biomarker are ambiguous. However, several studies have shown a significant increase in BDNF levels in the blood of patients receiving INF-beta, which has been attributed to the activation of T cells and the production of this factor [12–14]. However, the absence of correlations with the primary clinical characteristics of the disease course (PR, ARR, and EDSS score) in the present study may indicate a lack of efficacy of this therapy.

The findings of this study are consistent with those of previous investigations, thus establishing a correlation between the inflammatory activity of MS and BDNF production. During periods of exacerbation, immune cells secrete neurotrophic factors and engage in interactions with neurons and glial cells, protecting them from damage and promoting growth and repair. This phenomenon has been designated as protective autoimmunity. BDNF, a pivotal neurotrophin in this context, has been shown to modulate neuroinflammation and provide neuroprotection in MS [15]. The available data show that, when BDNF production by unstimulated peripheral blood mononuclear cells was determined in patients with RRMS in different disease phases, it was significantly higher during flare-ups, which correlated with better reversibility of clinical manifestations [16]. A study of BDNF levels in the blood of patients with RRMS found a significant overexpression in this parameter during relapse compared with remission [17].

Conversely, other studies have found decreased levels of BDNF in the body fluids of MS patients. According to the findings by Russian research, low plasma BDNF levels (pg/mL) were found more often in RRMS patients than in age-matched healthy individuals. However, a statistically significant positive correlation between BDNF levels and the induced anti-inflammatory cytokine IL-10 suggested its possible immune-modulating properties [18]. Another study found a decrease in serum BDNF levels (indicating brain levels of this neurotrophic factor) in MS patients, regardless of age, sex, and disease duration [19]. A further study demonstrated an 8% decrease in mean BDNF levels ($p < 0.001$) in MS patients compared with controls, with lower BDNF levels observed in patients with SPMS than in patients with RRMS ($p = 0.004$) [20]. Preliminary results of a meta-analysis of 13 studies demonstrated that MS patients exhibited statistically significantly lower BDNF levels compared with control subjects. In addition, a univariate meta-regression analysis revealed that disease duration and the proportion of males had a significant negative and positive correlation with BDNF levels, respectively [21].

The correlation of ICAM1 levels with increased ARR observed in this study is probably explained by the pathogenesis of blood–brain barrier damage and is supported by the published data. With greater disease duration, a decrease in serum ICAM1 levels would be expected, probably due to neurodegeneration and a decrease in the severity of inflammatory changes in the CNS. Previous studies have found significant differences in ICAM1 levels in patients from different groups depending on the type of the disease course and its activity [22]. A study comparing ICAM1 levels in cerebrospinal fluid and blood plasma of MS patients and controls showed a statistically significant increase in the concentration of this marker in MS patients ($p = 0.001$). In addition, this marker levels were significantly increased in patients with an exacerbation of the disease compared to the non-exacerbation group [23].

The findings indicate a statistically significant direct correlation between MRI disease activity and NCAM levels in patients with RRMS, suggesting an elevated NCAM content during MS flare-up. Furthermore, a study documented an increase in NCAM plasma levels in patients during exacerbation, followed by its substantial decrease 2–3 weeks after remission onset [24]. In SPMS, the concentration of this biomarker decreases over time, and there is a statistically significant correlation of NCAM levels with increasing PR and a degree of disability shown by EDSS scores, which may be regarded as a lower potential of neuroprotection in these patients [25].

Study Limitations

The study was limited by the lack of standardized assessment of interlaboratory comparisons of test results and reference levels of the studied biomarkers.

CONCLUSION

Elevated levels of BDNF and NCAM, together with a short disease duration and active autoimmune inflammation in RRMS, may indicate the readiness of the CNS defense mechanisms to activate in response to myelin destruction. This may be regarded as a neuroprotective effect of these

biomarkers, but also as a predictor of disease exacerbation. High levels of BDNF during INF-beta-1b therapy may indicate inadequate efficacy of these drugs, necessitating a decision to escalate therapy. As the duration of MS increases and patients progress to the SPMS stage, high NCAM levels may be associated with increasing disability.

ADDITIONAL INFORMATION

Author contributions. N.A. Ermolenko, A.V. Budnevsky — conceptualization, methodology, review, editing; V.V. Shishkina, L.N. Antakova — resources, investigation, review, editing; V.A. Bykova, A.O. Khoroshikh, M.V. Popova — investigation, formal analysis, visualization, writing — review, editing; N.V. Tkachenko, O.V. Bragina — resources, investigation, review, editing. All authors have approved the manuscript (version for publication) and have also agreed to be responsible for all aspects of the work, ensuring that issues related to the accuracy and integrity of any part of it are properly addressed and resolved.

Ethics approval. The study was approved by the Local Ethical Committee of the N.N. Burdenko Voronezh State Medical University (protocol No. 3 of 12.10.2016). All study participants signed a voluntary informed consent form prior to enrollment.

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Statement of originality. The authors did not use previously published information (text, figures, and data) in this study.

Data availability statement. All data obtained in this study are available in the article.

Generative AI. Generative AI technologies were not used for this article creation.

Provenance and peer-review. This paper was submitted to the journal on an initiative basis and reviewed according to the usual procedure. Two members of the editorial board, a member of the editorial board and the scientific editor of the publication participated in the review.

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