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THE CONDITION OF THE CARDIOVASCULAR SYSTEM IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS

Abstract

The **objective** of the study was to evaluate the state of the cardiovascular system, systemic inflammation markers and oxidant/|antioxidant balance in patients with relapsing-remitting multiple sclerosis. **Material and methods.** The study included 45 patients with relapsing-remitting multiple sclerosis (17 men and 28 women), aged 28 [24; 32] years, disease duration of 5.5 [2; 7] years. The control group included practically healthy patients, aged 30 [25; 33] years. Patients with multiple sclerosis were examined neurologically using the Expanded Disability Status Scale. Instrumental methods included a comprehensive assessment of the cardiovascular system (24-hour ECG monitoring and 24-hour blood pressure monitoring with determination of the daily vascular wall stiffness, and echocardiography). Laboratory methods included complete blood count and biochemical analysis, including lipid profile, glycemia, and C-reactive protein determination. The parameters of oxidative stress (acyl hydroperoxide) and antioxidant protection (glutathione peroxidase, superoxide dismutase) were studied; a marker of endothelial dysfunction (vascular cellular adhesion molecule-1) was analyzed. **Results.** In the group of patients with multiple sclerosis, there was an increase in C-reactive protein and vascular cellular adhesion molecule-1 in comparison with the control group ($p < 0.001$). The parameters of oxidative stress and antioxidant protection were significantly increased ($p < 0.001$). According to the results of 24-hour blood pressure monitoring the variability of systolic blood pressure and diastolic blood pressure during daytime hours was reduced in comparison with the control group, ($p < 0,026$) and ($p < 0.002$), respectively. The parameters of daily vascular wall stiffness in the group of patients with multiple sclerosis were significantly increased ($p < 0.001$). According to the results of 24-hour ECG monitoring, no heart rhythm disorder was detected in both groups. In the group of patients with relapsing-remitting course of multiple sclerosis, an increase in the number of supraventricular extrasystoles was detected in comparison with the control group ($p < 0.005$). The main parameters of echocardiography were within normal values, no significant differences between the groups were found. **Conclusion.** The study showed that multiple sclerosis patients are at risk of developing cardiovascular diseases and require increased attention to prevent their development.

Key words: *multiple sclerosis, cardiovascular diseases, oxidative stress, antioxidant protection, endothelial dysfunction, vascular wall stiffness.*

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BP — blood pressure, AHP — acyl hydroperoxides, GPO — glutathione peroxidase, DBP — diastolic blood pressure, MS — multiple sclerosis, SBP — systolic blood pressure, 24-hour BPM — 24-hour blood pressure monitoring, SOD — superoxide dismutase, CRP — C-reactive protein, CVD — cardiovascular diseases, ECG HM — Holter ECG monitoring, HR — heart rate, ECG — electrocardiogram, Echo-CG — echocardiography, EDSS — Expanded Disability Status Score, VCAM-1 — vascular cell adhesion molecule-1.

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Multiple sclerosis (MS) is one of the biggest challenges facing modern neurology, and it occupies a special place among demyelinating diseases as the most prevalent one [1]. This disease mostly affects young people who lead an active working and social life [2, 3]. MS is a multifactorial disease where viral infection, genetic predisposition, as well as extrinsic factors, including environmental factors play a key role in its initiation and development [3]. Worldwide prevalence of MS is about 2.3 million people, although this figure continues to rise [4]. Prevalence of MS in Russia varies from 30 to 100 cases per 100,000 people [5].

The course of MS and its clinical symptoms are extremely diverse and labile. At the present time, MS is classified according to the activity of pathologic process reflected by the type of disease [3, 5]. Relapsing-remitting clinical course is reported in 85–90 % of patients at the onset of MS. It is characterized by distinct exacerbations alternating with remission. The primary pathogenetic mechanism of relapsing-remitting MS is immunopathological reactions [3, 6].

With an increase in overall life expectancy of patients with MS, it is necessary to consider risk data on potentially preventable diseases [7, 8]. Identification of a risk of cardiovascular diseases (CVD) in patients with MS is essential in optimizing patient management and assessment of the course of the disease. Comorbidity in MS can affect life quality, the course and approaches to treatment of the disease. There is contradictory data on the risk of cardiovascular morbidity in MS. On the one hand, a number of studies have shown that MS is a risk factor for cardiovascular pathology [8–12]. Other researchers have not found any statistically significant relationship among different types of MS and the risk of CVD [6, 13–16]. Several literary sources describe MS treatment methods with cardiotoxic effect [8, 11].

Study objective: to study the condition of the cardiovascular system in patients with relapsing-remitting multiple sclerosis, with assessment of vascular injury markers and oxidant/antioxidant balance.

Materials and methods

The study included 45 patients (17 males and 28 females) aged 28 [24; 32] years who had suffered from relapsing-remitting MS diagnosed in accordance with the international McDonald criteria (2010), with the disease duration of 5.5 [2; 7] years, the annual incidence of exacerbations of 0.8 [0.38; 1] (Group 1). The control group (Group 2) included 15 individuals (10 females and 5 males) of comparable age (30 [25; 33] years) without clinical signs of nervous system diseases, i.e., apparently healthy individuals.

None of the study patients and control individuals had a history of CVD, diabetes mellitus, ischemic heart disease (IHD), or hypertension.

Patients with multiple sclerosis were examined neurologically with rating of disability according to the Expanded Disability Status Score (EDSS), a 10-point severity scale obtained by assessing separate neurological areas. This figure was 2.54 [1; 3.5] points.

Patients of both groups underwent general clinical examination: complete blood count and biochemical analysis, including lipid profile (total cholesterol, triglycerides, high- and low-density lipoproteins), glycemia, and high-sensitivity C-reactive protein (CRP). The following parameters were also identified: endothelial dysfunction marker (vascular adhesion molecule-1 (VCAM-1)), oxidative stress (acyl hydroperoxides (AHP)) and antioxidant defense (superoxide dismutase (SOD) and glutathione peroxidase (GPO)) indices.

Daily blood pressure monitoring (24-hour BPM) was performed using BpLab portable monitors capable of identifying the 24-hour vascular wall stiffness (mean PWVao).

Holter ECG monitoring (ECG HM) was performed using Microvit MT-101/200 Holter ECG monitoring system (SCHILLER, Switzerland). The analyzed parameters included basic rhythm, medium, maximum and minimum heart rate (HR) for 24 hours, presence of pauses, number of extrasystoles, and ST segment dynamics.

Central hemodynamics was studied by echocardiography (Echo-CG) using Vivid 7 Expert echocardiograph (GE Medical Systems) according to

the generally accepted method. Wall thickness, left ventricular (LV) cavity dimension, left atrial (LA) longitudinal size were assessed from the parasternal access along the LV long axis. Diastolic thickness of interventricular septum (IVST, cm) and left ventricular posterior wall (LVPW, cm), left ventricular end-diastolic (EDD, cm) and end-systolic diameters (ESD, cm), left ventricular end-diastolic (EDV) and end-systolic volumes (ESV) were measured. Also, left ventricular ejection fraction (EF, %) was assessed according to Simpson's rule. Left ventricular mass (LVM) was calculated by the formula of R.B. Devereux et al. Left ventricular mass index (LVMI) was calculated based on LVM indexed to the body surface index of the examined patient (S, m^2). LVMI was calculated to assess the left ventricular hypertrophy (LVH), with the upper limit of normal of 95 g/m^2 for females and 115 g/m^2 for males.

Statistical processing and analysis of the data obtained were performed using SPSS 22.0 software. The type of data distribution was identified by the Kolmogorov — Smirnov test. Sampling was described using the median, the first and third quartiles, as the data was not primarily normally distributed. The comparison in the groups was performed using the Mann — Whitney test. Differences were considered significant with $p < 0.05$.

Results and discussion

Patients from both groups were comparable on basic anthropometric and general clinical parameters. Clinical and laboratory characteristics of MS patients and control group patients are shown in **Table 1.**

All of the patients had normal office blood pressure (BP), with no anamnestic signs of hypertension.

According to the results of 24-hour BPM, no statistically significant difference was found in day- and night-time BP in both groups. Comparison of 24-hour BPM figures in groups 1 and 2 is provided in **Table 2.**

The BP variability assessment draws attention to the significant reduction in variability of daytime systolic blood pressure (VarSBP) in MS patients as compared to the control group ($p < 0.026$). However, these figures were within the normal range. A similar trend was found when assessing the variability of daytime diastolic blood pressure (VarDBP) in MS patients as compared to the control group ($p < 0.002$).

A number of studies show data on the relationship between blood pressure variability and cardiovascular complications. On the one hand, it was noted that the increase in BP variability contributes to the development of endothelial dysfunction due

Table 1. *Clinical and laboratory characteristics of patients with relapsing-remitting MS (group 1) and patients of the control group (group 2)*

Parameter	Group 1, n = 45	Group 2, n = 15	P
Age, years	28 [24; 32]	30 [25; 33]	0.282
BMI	22.75 [20.5; 23.7]	24.66 [20.76; 26.32]	0.021
Total cholesterol, mmol/l	4.1 [3.8; 4.33]	4.33 [3.87; 4.68]	0.2
Triglyceride, mmol/l	1.3 [0.89; 1.63]	0.88 [0.67; 1.3]	0.03
HDL, mmol/l	1.4 [1.088; 1.6]	1.48 [1.17; 1.67]	0.497
LDL, mmol/l	2.31 [1.73; 2.69]	2.39 [2.2; 2.79]	0.272
Total protein, g/l	72 [68; 74.25]	74 [70; 78]	0.185
Creatinine, μmol/l	72.5 [60.75; 83]	72 [64; 78]	0.821
Urea, mmol/l	4.35 [3.725; 4.925]	4.1 [3.7; 4.7]	0.712
Total bilirubin, μmol/l	17 [14; 19]	12 [8.7; 15.2]	0.012
ALT, U/l	24 [21; 28.25]	11 [9; 17]	0.001
AST, U/l	22 [19; 26.25]	15 [11; 17]	0.001
Glucose, mmol/l	4.55 [4.2; 5.1]	4.7 [4.5; 4.9]	0.382

Note: ALT — alanine aminotransferase, AST — aspartate aminotransferase, BMI — body mass index, HDL — high-density lipoprotein, LDL — low-density lipoprotein, p — significance of differences (Mann — Whitney test).

Table 2. *Parameters of 24-hour blood pressure monitoring in patients with relapsing-remitting MS (group 1) and patients of the control group (group 2)*

Parameter	Group 1, n = 45	Group 2, n = 15	P
Mean daytime SBP, mm Hg	117 [110; 127.25]	115 [106; 123]	0.96
Variability of daytime SBP, mm Hg	10 [8; 13]	13 [10; 17]	0.026
Mean daytime DBP, mm Hg	73 [67; 78]	75 [70; 82]	0.314
Variability of daytime DBP, mm Hg	9 [7; 10]	10 [9; 16]	0.002
Mean nighttime SBP, mm Hg	107 [97.5; 117]	101 [92; 118]	0.519
Variability of nighttime SBP, mm Hg	10 [8; 12]	9 [7; 12]	0.19
Mean nighttime DBP, mm Hg	66 [58.25; 71]	64 [56; 71]	0.933
Variability of nighttime DBP, mm Hg	8 [7; 9]	8 [7; 12]	0.665
Degree of nighttime decrease in SBP, %	7.75 [4.2; 11.11]	13 [6; 14]	0.15
Degree of nighttime decrease in DBP, %	9.655 [4.79; 16.42]	18 [11; 22]	0.017
Mean 24-hour SBP, mm Hg	115 [107; 124.25]	111 [102; 121]	0.718
Mean 24-hour DBP, mm Hg	71.5 [64.9; 76]	73 [65; 78]	0.788

Note: DBP — diastolic blood pressure, SBP — systolic blood pressure, ρ — significance of differences (the Mann — Whitney test).

to suppressed production of nitric oxide and effect on vascular intima, which, in turn, can result in atherogenesis [17]. On the other hand, patients with high variability show increased activity of the sympathetic nervous system, as a result of which vascular tone increases, especially during morning hours, which leads to a higher risk of cardiovascular complications [10, 18–19].

Considering the study data (reduced blood pressure variability in MS patients as compared to the control group), it can be assumed that the decrease of BP variability in MS shows the lack of effect of the above-mentioned mechanisms on the risk of development of cardiovascular complications.

According to the night-time reduction in diastolic blood pressure (DBP night), most MS patients showed insufficient reduction in diastolic blood pressure (DBP) (non-dippers), and normal nighttime DBP (dippers) prevailed in the control group ($\rho < 0.017$).

There are literary data on the increased nighttime activity of sympathoadrenal system in patients with impaired 24-hour BP profile. It has been established that non-dippers had disturbed circadian rhythm of the autonomic nervous system activity, higher nighttime activity of the sympathetic nervous system, as well as inadequate activity of the parasympathetic nervous system [20].

Changes in the circadian rhythm of BP in patients with relapsing-remitting MS, who have normal BP figures, require separate study, since, according to the Ohasama study (1997, 2002), non-dippers without essential hypertension are characterized by higher risk of cardiovascular mortality, which is comparable to the relative risk for dippers with essential hypertension and can be even greater.

The assessment of 24-hour vascular wall stiffness can be used as screening to detect preclinical atherosclerosis and identify high cardiac risk groups. A number of studies show that persistent increase in pulse velocity in hypertension and other CVD is associated with high cardiovascular risk and adverse outcome [9, 16, 17, 21].

In our study, 24-hour vascular wall stiffness figures were significantly higher in MS patients as compared to the control group: mean PWVao: 9.2 [8.5; 9.8] m/sec and 7 [6.4; 7.8] m/sec, respectively ($\rho < 0.001$). However, these figures were within the normal range.

In assessing the Holter ECG monitoring (ECG HM) data, the average daily, minimum, and maximum HR figures were within the normal range. No significant difference was found in both groups. What is noticeable is that the level of supraventricular arrhythmia is higher in MS patients as compared to the control group ($\rho < 0.005$). The number of ventricular extrasystoles (VES) did not exceed the normal limit; there were no significant differences between the

Table 3. *Parameters of systemic inflammation, endothelial dysfunction, oxidative stress and antioxidant protection in patients with relapsing-remitting MS (group 1) and patients of the control group (group 2)*

Parameter	Group 1, n = 45	Group 2, n = 15	P
CRP, mg/l	1.1 [0.49; 2.28]	0.6 [0.3; 0.8]	0.001
VCAM-1, ng/ml	590 [412.18; 894.75]	446.7 [385.3; 542.7]	0.017
AHP, nmol/mg	6.05 [4.55; 7.6]	3.45 [2.84; 4.61]	0.001
SOD, UA/g	1,633 [951.5; 1,916]	1,487.8 [1,285.3; 1,634.1]	0.001
GPO, UA/g	82.4 [74.2; 88.38]	46.3 [36.4; 62.4]	0.001

Note: AHP — acyl hydroperoxides, CRP — C-reactive protein, GPO — glutathione peroxidase, SOD — superoxide dismutase, VCAM-1 — vascular cell adhesion molecule-1, p — significance of differences (the Mann — Whitney test).

groups. No significant changes were found for ST segment in both groups. The increased level of supraventricular arrhythmia in MS patients reflects an imbalance in the sympathetic/parasympathetic regulation.

According to echocardiography, left atrial longitudinal dimension, left ventricular linear dimensions (ESD, EDD, IVS, LVPWT, EDV, ESV) and LV systolic function indices (EF) were within the normal range in both groups. LVM and LVMI also did not exceed threshold values both in MS patients and in the control group. No statistically significant differences in the above-mentioned figures were found in both groups.

The leading role in the pathogenesis of multiple sclerosis belongs to immune inflammation, activated oxidative stress and impaired antioxidant defense mechanisms. In MS, humoral immunity is activated, activity of macrophages is higher. As a result, non-specific mechanisms of phagocytosis become active and oxidative stress develops in nerve and glial cells, which leads to the destruction of myelin sheath of axons and reduction in their number [3, 22–24].

Non-clinically significant increase of CRP was found in the group of patients with relapsing-remitting MS as compared to the control group ($p < 0.001$). Comparative characteristics of the study groups according to the markers of systemic inflammation, endothelial dysfunction and oxidant/antioxidant system are presented in **Table 3.**

Comparison of the two groups showed a significant increase of endothelial dysfunction marker of VCAM-1 in MS patients ($p < 0.017$). This increase is associated with more pronounced endothelial injury processes in patients with multiple sclerosis, which developed under the effect of oxidative stress, which results in endotheliocytes being activated and adhesion molecules being expressed [25, 26].

Oxidative stress was assessed based on AHP, and was higher in MS patients as compared to the control group ($p < 0.001$). Antioxidant defense indicators were also significantly higher in MS patients as compared to the control group: GPO ($p < 0.001$), SOD ($p < 0.001$).

Thus, in MS patients, the activation of antioxidant systems occurs in response to the increased oxidative stress, with the formation of the oxidant/antioxidant balance at a new level. These processes are typical for the early stages of various diseases, including cardiovascular pathology. It has been established that, in patients with progressive MS, oxidant/antioxidant imbalance occurs in response to the continuous production of reactive oxygen intermediates due to inhibited activity of antioxidant enzymes [27, 28].

Conclusions

Based on the examination performed when comparing patients with relapsing-remitting MS and the control group, the average daily BP figures are within the normal range, without significant differences between the groups. There are no statistically and clinically significant differences in morphofunctional characteristics of the cardiovascular system (Echo-CG and ECG HM).

Increase in oxidative stress (AHP), antioxidant defense (SOD, GPO), CRP, endothelial dysfunction marker (VCAM-1) is observed in MS patients,

which demonstrates the systemic damaging effect of reactive oxygen intermediates and activation of antioxidant defense, with the development of systemic inflammation and endothelium dysfunction.

Increased vascular wall stiffness is reported in MS patients, despite the absence of day- and nighttime SBP and DBP abnormalities, which demonstrates increased risk of cardiovascular complications in these patients.

Considering the study results, markers of a higher risk of developing cardiovascular diseases were found in patients with MS, thus indicating the need to pay special attention to this group of patients to develop strategies for prevention and early diagnosis of a cardiovascular pathology. At the same time, the systemic pathology of small vessels may be one of pathogenetic mechanisms of multiple sclerosis and may increase with the disease progression [21, 24].

Conflict of interests

The authors declare no conflict of interests.

References:

1. Thompson A.J., Baranzini S.E., Geurts J. et al. Multiple sclerosis. Lancet. 2018; 391 (10130): 1622-1636. doi: 10.1016/S0140-6736(18)30481-1.
2. Boiko A., Kesselring J., Paty D.W. et al. Multiple sclerosis and public health. Educational and management implications. World Health Organization, Department of Mental Health, Neuroscience and Neurological Disorders. 1999; 2: 1–11.
3. Gusev E.I., Boiko A.N., Zavalishin I.A. Multiple sclerosis. Clinical Guideline. M.: Real Time. 2011; 43–45, 140–141, 161–162 [in Russian].
4. Atlas of MS 2013. URL: http://www.msif.org/wpcontent/uploads/2014/09/Atlas-of-MS.pdf (date of the application: 04/02/2019).
5. Gusev E.I., Boiko A.N., Zavalishin I.A. et all. Epidemiological studies of multiple sclerosis. Methodical recommendation MZ RF № 2003/82. Moscow. 2003; 20–45 [in Russian].
6. Zavalishin I.A. et all. Multiple sclerosis: modern aspects of etiology and pathogenesis. Journal of Neurology and Psychiatry. Special Issue Multiple Sclerosis. 2003; 2: 10–17 [in Russian].
7. Stuifbergen A.K. Physical activity and perceived health status in persons with multiple sclerosis. J Neurosci Nurs. 2007; 29: 238–243. doi: 10.1097/01376517-199708000-00004.
8. Warren S.A., Turpin K.V.L., Pohar S.L. et al. Comorbidity and health-related quality of life in people with multiple sclerosis. Int J MS Care. 2009; 11: 6–16. doi: 10.7224/1537-2073-11.1.6.
9. Jadidi E., Mohammadi M., Moradi T. High risk of cardiovascular diseases after diagnosis of multiple sclerosis. Mult Scler. 2013 Sep; 19(10):1336–1340. doi: 10.1177/1352458513475833.
10. Marrie R.A., Rudick R., Horwitz R. et al. Vascular comorbidity in associated with more rapid disability progression in multiple sclerosis. Neurology 2010; 74: 1074-1047. doi: 10.1212/WNL.0b013e3181d6b125.
11. Murray T.J. The cardiac effects of mitoxantrone: Do the benefits in multiple sclerosis outweigh the risks? Expert Opin Drug Saf. 2006; 5: 265–274. doi: 10.1517/14740338.5.2.265.
12. Wei L., MacDonald TM. and Walker B.R. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med. 2004; 141: 764–770. doi: 10.7326/0003-4819-141-10-200411160-00007.
13. Kang J.H., Chen Y.H. and Lin H.C. Comorbidities amongst patients with multiple sclerosis: A population-based controlled study. Eur J Neurol. 2010; 17: 1215–1219. doi: 10.1111/j.1468-1331.2010.02971.x.
14. Sternberg Z., Leung C., Sternberg D., Li F., Karmon Y., Chadha K., Levy E. The prevalence of the classical and non-classical cardiovascular risk factors in multiple sclerosis patients. CNS Neurol Disord Drug Targets. 2013; 12: 104–111. doi: 10.2174/18715273113120100016.
15. Lutskiy M.A., Esaulenko I.E. Oxidative stress in the pathogenesis of multiple sclerosis. Multiple sclerosis. 2006; 3: 26–30 [in Russian].
16. Marrie R.A., Reider N., Cohen J., Stuve O., Trojano M., Cutter G. et al. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. Mult Scler. 2015 Mar; 21(3): 263–81. doi: 10.1177/1352458514564491.
17. Trifonova S.S., Gaysenok O.V., Sidorenko B.A. Application of methods for assessing the stiffness of the vascular wall in clinical practice: the possibility of cardiovascular index. Cardiology. 2015; (4): 55-61. doi: 10.18565/cardio.2015.4.61-66 [in Russian].

18. Motl R.W., Arnett P.A., Smith M.M. et al. Worsening of symptoms is associated with lower physical activity levels in individuals with multiple sclerosis. Mult Scler. 2008; 14: 140–142. doi: 10.1177/1352458507079126.
19. Ohkubo T., Imai Y., Tsuji I. et al. Relation between nocturnal decline in blood pressure and mortality. The Ohasama study. Am. J. Hypertens. 2007; (2): 1201–1207. doi: 10.1016/S0895-7061(97)00274-4.
20. Witte K., Engelhard S., Janssen B.J. et al. Circadian and short-term regulation of blood pressure and heart rate in transgenic mice with cardiac over expression of the beta1-adrenoreceptor. Chronobiol. Int. 2004; 21(2): 205–216. doi: 10.1081/CBI-120037801.
21. Wens I., Dalgas U., Stenager E., Eijnde B.O. Risk factors related to cardiovascular diseases and the metabolic syndrome in multiple sclerosis — a systematic review. Mult Scler. 2013 Oct; 19(12):1556–64. doi: 10.1177/1352458513504252.
22. Geraldes R., Esiri M.M., DeLuca G.C., Palace J. Age-related small vessel disease: a potential contributor to neurodegeneration in multiple sclerosis. Brain Pathol. 2017; 27(6): 707-722. doi: 10.1111/bpa.12460.
23. Jakimovski D., Gandhi S., Paunkoski I., Bergsland N., Hagemeier J., Ramasamy D.P., Hojnacki D., Kolb C., Benedict R.H.B., Weinstock-Guttman B., Zivadinov R. Hypertension and heart disease are associated with development of brain atrophy in multiple sclerosis: a 5-year longitudinal study. Eur J Neurol. 2019; 26(1): 87-e8. doi: 10.1111/ene.13769.
24. Zavalishin I.A., Piradov M.A., Boyko A.N. et al. Autoimmune diseases in neurology. Clinical guideline. M: ROOI «Human Health». 2014; 592 p.
25. Lutskiy M.A. et all. Oxidant stress in the pathogenesis of multiple sclerosis. Journal of neurology and psychiatry named after S. S. Korsakov (Application «Stroke»). 2009: 109:5. 73-80. doi: 10.1007/s11055-007-0003-x [in Russian].
26. Spirina N.N., Spirin N.N., Boiko A.N. Effect of alpha-lipoic acid on the severity of endothelial dysfunction in multiple sclerosis. Journal of Neurology and Psychiatry named after S.S. Korsakov. 2018; 8(2): 162 [in Russian].
27. Krotenko N.V., Aliferova V.M., Ivanova S.A. Oxidative stress — a characteristic feature of the pathogenesis of multiple sclerosis. Bulletin of Siberian medicine. 2008; 7(5): 208–214 [in Russian].
28. Spirina N.N., Spirin N.N., Fadeeva O.A. et al. Multiple sclerosis and endothelial dysfunction. 2013; 10 (2): 32–42 [in Russian].

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