Translated by A.P. Strelkova

Research Article

https://doi.org/10.23934/2223-9022-2024-13-4-562-569

Dynamics of Oxidative Stress Indices and Endogenous Factors of Vascular Regulation in Patients with Non-Traumatic Subarachnoid Hemorrhage Due to Rupture of Cerebral Aneurysms

E.V. Klychnikova[1, 2] ✉, S.S. Petrikov[1], A.V. Prirodov[1, 2], E.Yu. Bakharev[1], S.V. Silkin[3], E.V. Tazina[1], A.A. Temnov[3], A.S. Bogdanova[1]

Scientific clinical and biochemical laboratory of emergency research methods
[1] N.V. Sklifosovsky Research Institute for Emergency Medicine
Bolshaya Sukharevskaya Sq. 3, Moscow, Russian Federation 129090
[2] N.I. Pirogov Russian National Research Medical University
Ostrovityanova Str. 1, Moscow, Russian Federation 117513
[3] Moscow Institute of Physics and Technology (National Research University)
Institutskiy per. 9, Dolgoprudny, Moscow Region, Russian Federation 141701

✉ **Contacts:** Elena V. Klychnikova, Candidate of Medical Sciences, Head of the Scientific Clinical and Biochemical Laboratory of Emergency Research Methods, N.V. Sklifosovsky Research Institute for Emergency Medicine. Email: klychnikovaev@mail.ru

INTRODUCTION The main reasons for the unsatisfactory outcome of surgical treatment of patients with non-traumatic subarachnoid hemorrhage (SAH) due to ruptured cerebral aneurysms are vascular spasm (VS) and delayed cerebral ischemia. Lysis of blood clots in the subarachnoid space leads to the release of a large number of various vasoactive factors that stimulate cytotoxic, inflammatory reactions and oxidative stress, which may be one of the reasons for the development of VS and secondary ischemic brain damage.

THE AIM OF THE STUDY Study of the dynamics of oxidative stress indicators and factors of endogenous vascular regulation in patients with non-traumatic SAH due to ruptured cerebral aneurysms.

MATERIAL AND METHODS A total of 80 patients in the acute period of SAH due to ruptured cerebral aneurysms were treated and examined. The average age of the patients was 51.7 years. The control group (norm) included 25 practically healthy people, whose average age was 32.7±8.6 years. The study used the blood serum and cerebrospinal fluid of the patients. The study points were 0, 1, 3, and 7 days after the patient's admission to the hospital. The severity of oxidative stress was assessed by the level of malonic dialdehyde (MDA) and total antioxidant activity of blood serum (TAA); vasotonic function of vascular endothelium by the content of stable metabolites of nitric oxide (NOx) and the concentration of angiotensin-converting enzyme (ACE). Biochemical studies were carried out on the biochemical analyzer "Olympus AU 2700" (Beckman Coulter, USA).

RESULTS It was revealed that patients with SAH already had pronounced oxidative stress upon admission to the hospital (increased MDA level, decreased TAA level), which led to an imbalance in the endogenous regulation of vascular tone (decreased NOx level, increased ACE concentration) and increased by the 7th day after admission to the hospital. High lactate dehydrogenase (LDH) activity was observed, the peak of which was on the 7th day of observation. Determination of LDH activity may be promising as a biomarker of ischemic brain injury and a prognostic indicator of the development of an unfavorable outcome.

CONCLUSIONS The obtained data indicate the need for a comprehensive approach to the treatment of patients with subarachnoid hemorrhage. The most relevant therapeutic goal is the removal of blood from the subarachnoid space of the brain to prevent increased oxidative stress and angiospasm.

Keywords: subarachnoid hemorrhage, cerebral vasospasm, oxidative stress, endogenous vascular regulation, cerebral ischemia

For citation Klychnikova EV, Petrikov SS, Prirodov AV, Bakharev EYu, Silkin SV, Tazina EV, et al. Dynamics of Oxidative Stress Indices and Endogenous Factors of Vascular Regulation in Patients with Non-Traumatic Subarachnoid Hemorrhage Due to Rupture of Cerebral Aneurysms. *Russian Sklifosovsky Journal of Emergency Medical Care.* 2024;13(4):562–569. https://doi.org/10.23934/2223-9022-2024-13-4-562-569 (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The work was carried out within the framework of the state assignment of the Ministry of Science and Higher Education (agreement No. 075-03-2022-107, project No. 0714-2020-0006)

Affiliations

Elena V. Klychnikova	Candidate of Medical Sciences, Head of the Scientific Clinical and Biochemical Laboratory of Emergency Research Methods, N.V. Sklifosovsky Research Institute for Emergency Medicine; Associate Professor, Department of General Pathology of the Medical and Biological Faculty, Pirogov Russian National Research Medical University; https://orcid.org/0000-0002-3349-0451, klychnikovaev@mail.ru; 20%, development of research design, analysis of obtained data, writing of manuscript text

Sergey S. Petrikov	Corresponding Member of the Russian Academy of Sciences, Doctor of Medical Sciences, Director of N.V. Sklifosovsky Research Institute for Emergency Medicine, Anesthesiologist and Resuscitator; https://orcid.org/0000-0003-3292-8789, petrikovss@sklif.mos.ru 20%, development of study design, editing of manuscript text
Alexandr V. Prirodov	Doctor of Medical Sciences, Head of the Neurosurgical Department, Leading Researcher, Emergency Neurosurgery Department, N.V. Sklifosovsky Research Institute for Emergency Medicine; Professor, Department of Fundamental Neurosurgery, N.I. Pirogov Russian National Research Medical University; https://orcid.org/0000-0003-2444-8136, aprirodov@yandex.ru; 15%, development of research design, analysis of obtained data, editing of manuscript text
Evgeny Yu. Bakharev	Candidate of Medical Sciences, Neurosurgeon, Senior Researcher, Emergency Neurosurgery Department, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-1525-1585, ads_nvkz@mail.ru; 10%, collection and analysis of obtained data, editing of the manuscript text
Sergey V. Silkin	Candidate of Chemical Sciences, Associate Professor, Department of Molecular and Biological Physics, Moscow Institute of Physics and Technology; https://orcid.org/0000-0002-7368-7355, silkin.sv@mipt.ru; 10%, editing the manuscript text, analysis of the obtained data
Elizaveta V. Tazina	Candidate of Pharmaceutical Sciences, Senior Researcher, Clinical and Biochemical Laboratory of Emergency Research Methods, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0001-6079-1228, ltazina@yandex.ru; 10%, editing the manuscript text, statistical processing of the material
Andrey A. Temnov	Doctor of Medical Sciences, Head of the Laboratory of Chemical and Biotechnological Synthesis, Moscow Institute of Physics and Technology; https://orcid.org/0000-0002-2141-1613, aa-temnov@yandex.ru; 10%, editing the manuscript text, analysis of the obtained data
Alina S. Bogdanova	Junior Researcher, Clinical and Biochemical Laboratory of Emergency Research Methods, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-6608-8493, bogdanovalina@mail.ru; 5%, collection of material in accordance with the study design, conducting laboratory studies

AA – arterial aneurysm
ACE – angiotensin-converting enzyme
BBB – blood-brain barrier
CA – cerebral angiospasm
CT – computed tomography
LDH – lactate dehydrogenase
MDA – malondialdehyde
NOx – stable metabolites of nitric oxide
SAH – subarachnoid hemorrhage
TAA – total antioxidant activity
TG – triglycerides
VS – vascular spasm

INTRODUCTION

The incidence of non-traumatic subarachnoid hemorrhage (SAH) due to ruptured cerebral - aneurysms ranges from 2 to 20 cases per 100,000 people per year [1]. The need for surgeries for cerebral aneurysms in the Russian Federation is 5 per 100,000 population per year, i.e. approximately 7,325 surgeries per year [2]. The main cause of unsatisfactory surgical outcomes in this category of patients is cerebral vascular spasm (CVS) and delayed cerebral ischemia [3]. Cerebral CVS is a specific complication of SAH that occurs in response to blood entering the cisterns of the base of the brain [1]. Subsequent lysis of blood clots in the subarachnoid space leads to the release of a large number of various vasoactive factors (erythrocytes, hemoglobin, blood coagulation factors), which stimulate cytotoxic, inflammatory reactions and oxidative stress, which leads to the development of SAH and secondary ischemic brain injury [3–7]. One

of the mechanisms of SAH development is the disruption of the nitric oxide/nitric oxide synthase (NO/NOS) metabolic pathways [8–10]. Thus, understanding the role of oxidative stress, in particular, lipid peroxidation, the antioxidant system, endothelial dysfunction (factors of endogenous vascular regulation of nitric oxide and angiotensin-converting enzyme) in the pathology of SAH may become a new target for therapeutic intervention.

The aim of the study was to investigate the dynamics of oxidative stress indicators and factors of endogenous vascular regulation in patients with non-traumatic SAH due to rupture of cerebral aneurysms.

MATERIAL AND METHODS

The study included 80 patients in the acute period of SAH due to rupture of an aneurysm of the cerebral arteries, who were treated at the N.V. Sklifosovsky Research Institute for Emergency Medicine.

The study included patients who underwent microsurgical surgery at the Department of Emergency Neurosurgery of the N.V. Sklifosovsky Research Institute for Emergency Medicine due to ruptured arterial aneurysms (AA) within the first 72 hours from the onset of the disease. This study was conducted with the approval of the Ethics Committee of the N.V. Sklifosovsky Research Institute for Emergency Medicine. The inclusion criteria for the study were:

— the presence of AA, confirmed by angiography;

— the period of surgical intervention is no later than 72 hours from the moment of hemorrhage;

— severity of the condition upon admission according to the *Hunt–Hess classification* I–IV st.;

— massive basal SAH according to the *Fisher classification* type III–IV, higher than score 15 according to the *A. Hijdra classification*;

— absence of signs of vascular spasm according to preoperative examination methods (CT angiography, digital subtraction cerebral angiography, transcranial Doppler ultrasound).

Before surgical treatment, a physical examination (with assessment of the respiratory, cardiovascular, digestive and genitourinary systems) was mandatory, neurological status was assessed, transcranial Doppler sonography, CT of the brain (with assessment of the severity of hemorrhage according to the *Fisher* and *A. Hijdra classifications*), CT angiography or digital subtraction cerebral angiography, and laboratory examination were performed.

Among the patients, there were 42 men (52.5%) and 38 women (47.5%). The average age was 51.7 years (from 30 to 75). Distribution of patients by severity of the condition according to the *Hunt–Hess scale* was as follows: severity stage II — 21 patients (26.25%), severity stage III — 47 patients (58.75%), severity stage IV — 12 patients (15%). There were no patients with severity stage I among these patients. The severity of hemorrhage according to the *Hijdra classification* averaged score 22.7 (minimum score 15, maximum score 30).

The control group (norm) included 25 healthy people, whose average age was 32.7±8.6 years, the male/female ratio was 17/8.

Blood serum and cerebrospinal fluid of patients were used for the study. The study points were: 0 — admission (before surgery), 1 — day 1, 3 — day 3, 7 — day 7 after the patient's admission to the hospital.

The severity of oxidative stress was assessed by the level of malondialdehyde (MDA) using a fluorimetric method [11], and the total antioxidant activity (TAA) of blood serum and cerebrospinal fluid using a photometric method with a biochemical analyzer ˝*Olympus AU* 2700˝ (*Beckman Coulter,* USA) using reagents of Randox *(*UK), and the oxidative stress coefficient MDA/OAA, calculated using the formula:

$$(MDA_p : MDA_c) : (OAA_p : OAA_c),$$

where MDA_p, OAA_p are the values of MDA and OAA in the examined patients; MDA_c, OAA_c are the average values of MDA and OAA in the control group (normal).

The vasotonic function of the vascular endothelium was assessed by the content of stable metabolites of nitric oxide (NOx) and the concentration of angiotensin-converting enzyme (ACE). NOx was determined using the Griess reaction [12], ACE — by a photometric method on a biochemical analyzer ˝*Olympus AU* 2700˝ (*Beckman Coulter*, USA). Reagents of *Audit Diagnostics*, Ireland, were used. The coupling of the interaction of NOx and ACE was assessed by the NOx/ACE coefficient, reflecting the imbalance between endothelium-dependent vasodilation and vasoconstriction, which was calculated using the formula:

$(NOx_p : NOx_c) : (ACE_p : ACE_c)$,

where NOx_p, ACE_p are the values of NOx and ACE in the examined patients; NOx_c, ACE_c are the average values of NOx and ACE in the control group (normal).

Biochemical studies were carried out with a biochemical analyzer ˝*Olympus AU* 2700˝ (*Beckman Coulter*, USA) using reagents of ˝*Beckman Coulter*˝ (USA).

Statistical processing was performed using the *Statistica* 13.3 *TIBCO Software Inc. program*. The data were presented as median (*Me*) and interquartile range (*Q*1; *Q*3). The study groups were compared with each other using the Mann–Whitney *U* test. The level of statistical significance was considered to be $p<0.05$.

RESULTS

When assessing the severity of oxidative stress in the examined patients, it was found that the initial level of MDA in the blood serum upon admission (3.507 μmol/l) was 1.5-fold ($p<0.05$) higher than the normal MDA values (2.27 μmol/l). The level of TAA in the blood serum (1.37 mmol/l) was 1.2-fold lower than the normal value (1.61 mmol/l) (Table 1). The oxidative stress coefficient MDA/TAA (0.96), reflecting the balance in the prooxidant/antioxidant system, was 3.4-fold ($p<0.05$) higher than the normal values (3.27) (Table 1). In the study of endogenous factors of vascular regulation, it was found that the concentration of NOx in the blood serum (6.4 μmol/l) of patients with non-traumatic SAH was 2.9-fold lower than the normal value (18.61 μmol/l), while the concentration of ACE (62.4 μmol/l) was 1.4-fold higher than the normal values of this indicator (45 μmol/l) ($p<0.05$). The NOx/ACE coefficient, reflecting the ratio between vasodilating and vasoconstrictor components of the blood, was reduced 4.8-fold ($p<0.05$) (Table 1).

Table 1

Dynamics of oxidative stress indices and endogenous factors of vascular regulation in blood serum of patients with non-traumatic subarachnoid hemorrhages in critical condition

Indicators	Norm, *Me* (*Q*1; *Q*3)	Day, *Me* (*Q*1; *Q*3)			
		0	1	3	7
MDA, μmol/l	2.27 (2.11; 2.47)	3.507 (3.130; 3.592)*	3.766 (3.507; 3.781)*	4.112 (3.652; 4.113)*	4.559 (4.535; 4.583)*
OAA, mmol/l	1.61 (1.56; 1.68)	1.37 (1.23; 2.74)	1.39 (1.1; 2.78)	1.42 (1.2; 2.86)	1.31 (1.1; 2.51)
MDA/OAA ratio	0.96 (0.91; 1.11)	3.27 (2.39; 4.43)*	3.74 (2.9; 4.55)*	3.22 (2.33; 5.36)*	3.02 (2.31; 5.06)*
NOx, μmol/l	18.61 (17.70; 23.62)	6.40 (3.33; 6.47)*	4.84 (3.19; 6.24)*	5.34 (4.09; 6.79)*	5.85 (4.89; 6.80)*
ACE, μmol/l	45.00 (36.45; 55.15)	62.4 (60.7; 62.7)*	40.9 (39.6; 43.6)	37.7 (36.3; 40.2)	31.1 (30.4; 31.9)
NOx/ACE ratio	1.02 (0.85; 1.25)	0.21 (0.11; 0.21)*	0.24 (0.16; 0.29)*	0.31 (0.22; 0.38)*	0.38 (0.32; 0.43)*
Albumin, g/l	43.12 (41.69; 44.53)	38.11 (37.99; 40.06)*	42.29 (37.86; 42.44)	35.53 (35.41; 35.79)*	34.38 (33.98; 34.78)*
Glucose, mmol/l	5.00 (4.55; 5.26)	4.38 (3.58; 5.15)	3.96 (3.72; 4.93)	5.38 (3.46; 6.82)	13.32 (12.65; 13.98)*
LDH, U/L	155.40 (140.19; 177.20)	243.05 (196.35; 247.85)	213.29 (191.89; 244.09)*	205.70 (181.22; 231.77)	261.50 (252.06; 270.95)*

Notes: * — p<0.05 relative to the Control group (norm). ACE — angiotensin-converting enzyme; LDH — lactate dehydrogenase; MDA — malonic dialdehyde; TAA — total antioxidant status; NOx — nitrogen oxide

Thus, this study revealed that in patients with SAH, activation of oxidative stress and disruption of the vasotonic function of the endothelium already occurs upon admission.

By the 3rd–7th day of observation, an increase in free radical processes was noted, which was manifested by an increase in the MDA level on the 3rd and 7th days relative to the norm ($p<0.05$) (Table 1). Also during this period, a statistically significant decrease in the NOx level in the blood serum and the NOx/ACE coefficient ($p<0.05$) was recorded, which indicated the development of vascular dysfunction in patients with SAH.

In patients with SAH, a statistically significant increase in lactate dehydrogenase (LDH) levels was observed on the 1st and 7th days of observation ($p<0.05$) (Table 1).

On day 7, patients with SAH showed a statistically significant increase in serum glucose levels.

When studying the oxidative stress indices and endogenous factors of vascular regulation in the cerebrospinal fluid, an increase in the MDA level was revealed, with the maximum increase in this index recorded on the 1st and 7th days of the study ($p<0.05$) (Table 2). The NOx index statistically significantly increased by day 7 ($p<0.05$), while ACE did not statistically significantly differ from the norm (Table 2).

When studying LDH activity in the cerebrospinal fluid, a statistically significant increase was found on the 1st and 7th days of observation ($p<0.05$) (Table 2). It should also be noted that LDH activity on day 7 was 13.1-fold higher than normal ($p <0.008$).

Thus, the obtained data indicate that in patients with SAH due to rupture of cerebral aneurysm there is a marked increase in oxidative stress, which leads to an imbalance in the endogenous regulation of vascular tone. These changes can be markers of the development of cerebral angiospasm (CA) and secondary cerebral ischemia. An increase in LDH activity both in the blood serum and in the cerebrospinal fluid indicates the development of a hypoxic state in patients with SAH, which is most pronounced by the day 7 from the moment of admission to the hospital.

DISCUSSION

The presented results indicate significant metabolic disturbances occurring in patients with non-traumatic SAH due to ruptured cerebral aneurysms. A number of studies emphasize the important role of the coagulation cascade, oxidative stress, neuroinflammation and hemolysis in the pathogenesis of secondary brain injury, which affects the clinical outcome of diseases accompanied by spontaneous intracerebral hemorrhage [13, 14]. Studying the pathophysiology of secondary brain

Table 2

Dynamics of oxidative stress indices and endogenous factors of vascular regulation in cerebrospinal fluid in patients with non-traumatic subarachnoid hemorrhage in critical condition

Indicators	Norm, *Me* (*Q*1; *Q*3)	Day, *Me* (*Q*1; *Q*3)			
		0	1	3	7
MDA, μmol/l	0.248 (0.184; 0.257)	0.317 (0.291; 0.371)*	0.538 (0.371; 0.644)*	0.317 (0.283; 0.348)*	0.471 (0.429; 0.512)*
NOx, μmol/l	5.16 (2.66; 8.97)	18.61 (11.37; 18.95)*	14.55 (8.56; 17.92)	19.42 (11.39; 20.91)*	20.04 (19.55; 20.53)*
ACE, μmol/l	4.3 (4.2; 4.5)	6.8 (5.2; 7.7)*	4.4 (3.9; 4.6)	2.7 (2.6; 3.4)	4.8 (4.5; 5.0)
Albumin, g/l	0.08 (0.07; 0.11)	0.43 (0.40; 1.10)*	0.18 (0.17; 0.28)*	0.10 (0.08; 0.11)	0.25 (0.13; 0.36)*
Glucose, mmol/l	4.17 (3.89; 4.28)	3.46 (3.43; 3.84)	4.20 (4.18; 4.45)	3.53 (3.27; 3.64)	3.65 (3.15; 4.16)
LDH, U/L	5.48 (4.75; 7.46)	12.69 (11.29; 14.10)*	12.25 (7.71; 12.82)	10.92 (7.65; 16.33)*	72.01 (53.80; 90.21)*

Notes: * — $p<0.05$ relative to the Control group (norm). ACE – angiotensin-converting enzyme; LDH – lactate dehydrogenase; MDA – malonic dialdehyde; NOx – nitrogen oxide

injury after SAH will help identify promising cellular and molecular targets for treatment, identify the most sensitive biomarkers of blood serum and cerebrospinal fluid to predict the development and assess the effect of various types of therapy (surgical or pharmacological) on the development of secondary brain injury after SAH. Our study found that patients with SAH had a statistically significant increase in the MDA level and the MDA/OAA ratio, recorded immediately upon admission and persisting up to 7 days of observation. Increased lipid peroxidation contributes to the destabilization and damage of cell membranes and may be one of the causes of the development of vasogenic, cytotoxic or mixed cerebral edema. One of the main mechanisms of activation of free radical processes and the development of CA is an increase in the concentration of metals of variable valence, in particular, trivalent iron is formed during the breakdown of hemoglobin, which is a powerful activator of free radical processes. Both divalent (Fe^{2+}) and trivalent (Fe^{3+}) iron can generate a very destructive hydroxyl radical (OH^{-}*) through the Fenton reaction and the Haber-Weiss cycle, respectively. The production of oxygen radicals catalyzed by free iron can also disrupt the blood-brain barrier (BBB), leading to increased vasogenic edema and increased intracranial pressure [15]. This fact proves the increase of albumin level in cerebrospinal fluid immediately upon admission and its decrease in blood serum of patients with SAH already upon admission, which may indicate the violation of BBB. On the first day of the study, the decrease of NOx level and the increase of ACE were also observed, which indicated the violation of vasotonic function of the endothelium already upon admission. The prevalence of vasoconstriction processes over vasodilation was also indicated by the statistically significant decrease of NOx/ACE coefficient. The development of delayed cerebral ischemia is a multifactorial process that develops over time. This hypothesis is confirmed by the dynamics of LDH activity, which statistically significantly increases on the 1st and 7th days of observation (p<0.05). LDH is a cytoplasmic enzyme involved in the anaerobic metabolic pathway and is present in almost all tissues of the body in the form of various isomers. High serum LDH levels may be observed in the presence of organ injury, hypoxic conditions, and some well-defined diseases. High serum LDH values have been associated with the area of brain injury in patients [16]. In a population of patients with SAH, high serum LDH values before microsurgical clipping were found to be associated with poor neurological outcome at 3 months [17], and in another cohort of patients with SAH, high serum LDH values were associated with early mortality [18]. Thus, determination of LDH activity in serum and cerebrospinal fluid may be promising as a biomarker of ischemic brain injury and a prognostic indicator for the development of poor outcome, which requires further study.

CONCLUSION

The results obtained in this work are of a general pathophysiological nature and can be extrapolated to other pathologies. Understanding the role of oxidative stress, in particular, lipid peroxidation, the antioxidant system and endothelial dysfunction (factors of endogenous vascular regulation of nitric oxide and angiotensin-converting enzyme) in the pathology of SAH may become a new target for therapeutic intervention. In addition, recently there has been an active search for new diagnostic systems and therapeutic drugs for the diagnosis and treatment of tumors with high vascularization, such as glioblastoma. In particular, vascular endothelial growth factor (*VEGF*) has been identified as a critical regulator of angiogenesis. The researchers' data convincingly indicate that vascular remodeling induced by anti-*VEGF treatment* leads to a more hypoxic tumor microenvironment. This contributes to a metabolic change in tumor cells towards glycolysis, which leads to a decrease in their invasion into the brain.

The data obtained in our study indicate the need for a comprehensive approach to the treatment of patients with subarachnoid hemorrhages. The most relevant therapeutic goals are the removal of blood from the subarachnoid space of the brain to prevent increased oxidative stress and angiospasm (surgically and with pharmaceuticals).

FINDING

1. In patients with subarachnoid hemorrhages, a statistically significant increase in the level of malondialdehyde in the blood serum and cerebrospinal fluid 1.5- and 1.3-fold, respectively (p<0.05), and the oxidative stress coefficient 3.4-fold (p<0.05) was revealed, which indicates the activation of free radical processes in this category of patients already upon admission to the hospital.

2. The maximum increase in the level of malondialdehyde in the blood serum and cerebrospinal fluid in patients with subarachnoid hemorrhages is noted on the 3rd and 7th days of observation (p<0.05 relative to the norm), which may indicate the important role of oxidative stress in the development of cerebral angiospasm.

3. The concentration of stable nitric oxide metabolites in the blood serum of patients with subarachnoid hemorrhage was initially 2.9 times lower than normal, the concentration of angiotensin-converting enzyme was 1.4-fold higher than normal values upon admission to hospital (p<0.05), and the stable nitric oxide metabolites/angiotensin-converting enzyme ratio, reflecting the ratio between vasodilating and vasoconstrictor blood components, was reduced 4.8-fold (p<0.05). By the 7th day of observation, a statistically significant 3.9-fold increase in the level of stable nitric oxide metabolites (p<0.05) in the cerebrospinal fluid was noted. The obtained data indicate a violation of the vasotonic function of the cerebral vascular endothelium, which may also have a significant impact on the development of cerebral angiospasm.

4. In patients with subarachnoid hemorrhages, a statistically significant increase in the level of lactate dehydrogenase was observed on the 1st and 7th days of observation (p <0.05), both in the blood serum and in the cerebrospinal fluid; this indicator may be a marker of ischemic brain damage.

REFERENCES

1. *Hemorrhagic insul't. Clinical recommendations.* Ministry of Health of the Russian Federation, 2022. Available at: https://cr.minzdrav.gov.ru/schema/523_2 [Accessed Dec 20, 2023]
2. Krylov VV, Dash`yan VG, Shetova IM, Kordonskii AYu, Grin' AA, Parfenov VE, et al. Neurosurgical Care for Patients with Cerebrovascular Pathology in Russian Federation. *Russian Journal of Neurosurgery* . 2017;(4):11–20. (In Russ.)
3. Krylov VV, Dash'yan VG (eds.) *Surgery for head brain aneurysm in massive subarakhnoid blood leakage.* Moscow: ABV-Press Publ.; 2021. (In Russ.)
4. Campbell BCV, Khatri P. Stroke. *The Lancet.* 2020;396(10244):129–142. PMID: 32653056 https://doi.org/10.1016/S0140-6736(20)31179-X
5. Hua W, Chen X, Wang J, Zang W, Jiang C, Ren H, et al. Mechanisms and potential therapeutic targets for spontaneous intracerebral hemorrhage. *Brain Hemorrhages.* 2020;1(2):99–104. https://doi.org/10.1016/j.hest.2020.02.002
6. Chen Y, Chen S, Chang J, Wei J, Feng M, Wang R. Perihematomal edema after intracerebral hemorrhage: an update on pathogenesis, risk factors, and therapeutic advances. *Frontiers Immunol* . 2021;12:740632. https://doi.org/10.3389/fimmu.2021.740632
7. Jiang C, Guo H, Zhang Z, Wang Y, Liu S, Lai J, et al. Molecular, pathological, clinical, and therapeutic aspects of perihematomal edema in different stages of intracerebral hemorrhage. *Oxid Med Cell Longev* . 2022:3948921. PMID: 36164392 https://doi.org/10.1155/2022/3948921
8. Dodd WS, Laurent D, Dumont AS, Hasan DM, Jabbour PM, Starke RM, et al. Pathophysiology of delayed cerebral ischemia after subarachnoid hemorrhage: a review. *J Am Heart Assoc* . 2021;10(15):e021845. PMID: 34325514 https://doi.org/10.1161/JAHA.121.021845
9. Pluta RM. Delayed cerebral vasospasm and nitric oxide: review, new hypothesis, and proposed treatment. *Pharmacol Ther* . 2005;105(1):23–56. PMID: 15626454 https://doi.org/10.1016/j.pharmthera.2004.10.002
10. Sehba FA, Bederson JB. Nitric oxide in early brain injury after subarachnoid hemorrhage. *Acta Neurochir Suppl*. 2011;110(Pt 1):99–103. PMID: 21116923 https://doi.org/10.1007/978-3-7091-0353-1_18
11. Gavrilov VB, Gavrilova AR, Mazhul' LM. Methods of determining lipid peroxidation products in the serum using a thiobarbituric acid test. *Vopr Med Khim.* 1987;33(1):118–122. PMID: 2437702. (In Russ.).
12. Golikov PP, Nikolaeva NIu. Analysis of nitrites/nitrates (NOx) in serum. *Biomed Khim* . 2004;50(1):79–85. PMID: 15108630. (In Russ.)
13. Leclerc JL, Garcia JM, Diller MA, Carpenter AM, Kamat PK, Hoh BL, et al. A comparison of pathophysiology in humans and rodent models of subarachnoid hemorrhage. *Front Mol Neurosci* . 2018:11:71. PMID: 29623028 https://doi.org/10.3389/fnmol.2018.00071
14. Hayman EG, Patel AP, James RF, Simard JM. Heparin and heparin-derivatives in post-subarachnoid hemorrhage brain injury: a multimodal therapy for a multimodal disease. *Molecules* . 2017;22(5):724. PMID: 28468328 https://doi.org/10.3390/molecules22050724

15. Loftspring MC. Iron and early brain injury after subarachnoid hemorrhage. *J Cereb Blood Flow Metab* . 2010;30(11):1791–1792. PMID: 20736954 https://doi.org/10.1038/jcbfm.2010.139
16. Cavalli I, Stella C, Stoll T, Mascia L, Salvagno M, Coppalini G, et al. Serum LDH levels may predict poor neurological outcome after aneurysmal subarachnoid hemorrhage. *BMC Neurol* . 2023;23(1):228. PMID: 37312033 https://doi.org/10.1186/s12883-023-03282-8
17. Zheng S, Wang H, Chen G, Shangguan H, Yu L, Lin Z, et al. Higher serum levels of lactate dehydrogenase before microsurgery predict poor outcome of aneurysmal subarachnoid hemorrhage. *Front Neurol* . 2021:12:720574. PMID: 34456854 https://doi.org/10.3389/fneur.2021.720574
18. Zan X, Deng H, Zhang Y, Wang P, Chong W, Hai Y, et al. Lactate dehydrogenase predicting mortality in patients with aneurysmal subarachnoid hemorrhage. *Ann Clin Transl Neurol* . 2022;9(10):1565–1573. PMID: 35984334 https://doi.org/10.1002/acn3.51650

Received on 19/01/2024
Review completed on 02/27/2024
Accepted on 17/09/2024