ATJ, 2023, №2, 110-116

AZƏRBAYCAN TİBB JURNALI
AZERBAIJAN MEDICAL JOURNAL

DOI: 10.34921/amj.2023.2.017

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ONURĞA ƏSASININ ARTERİAL HÖVZƏSİNDƏ TÖRƏNƏN İŞEMİK İNSULT ZAMANI APOPTOZUN MİTOXONDRİAL MEXANİZMLƏRİ

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Məqalədə onurğa əsasının arterial hövzəsində törənən işemik insult zamanı oksigenin aktiv formalarının, transmembran potensialının, hüceyrə ölümünün göstəricilərinin və onların insultun mərhələləri ilə qarşılıqlı əlaqəsinin öyrənilməsinə həsr edilmiş tədqiqatın nəticələri haqqında məlumat verilmişdir.

Tədqiqata onurğa əsasının arterial hövzəsinin işemik insultuna məruz qalmış 105 nəfər xəstə cəlb edilmişdir. Onlardan 49 nəfərdə xəstəliyin yarımkəskin dövrü (xəstəliyin başlanmasından sonrakı 3-6 aylar), 32 nəfərdə xronik mərhələ (6-12 ay), 14 nəfərdə xəstələnmədən 1-3 il sonrakı mərhələ olmuş, 10 nəfər isə xəstəliyin başlanmasından 3 ildən artıq sonra müşahidə edilmişdir.

Müəyyən edilmişdir ki, işemik insultun yarımkəskin və xronik dövrlərində qanda hidrogen peroksidin miqdarı kontrol qrupdakına nisbətən yüksək olmuşdur. Eyni zamanda gecikmiş yarımkəskin mərhələdə leykositlərin hüceyrə ölümü göstəricisi ən yüksək səviyyədə olmuş və həm xronik mərhələdə, həm xəstələnmə müddəti 1-3 il arası olan pasiyentlərin, həm də 3 ildən artıq xəstələnmə müddəti olan pasiyentlərin göstəricilərindən əhəmiyyətli dərəcədə fərqlənmişdir. Onurğa əsası arterial hövzəsi nahiyəsinin işemik insultunun yarımkəskin və xronik mərhələlərində (xəstəliyin başlanmasından 1-3 il və 3 ildən artıq müddət sonra) toxumalarda hidrogen peroksidin miqdarı ilə leykositlərin hüceyrə ölümünün səviyyəsi arasında birbaşa əlaqə olduğu aşkar edilmişdir.

Açar sözlər: *işemik insult, apoptoz, oksidativ stress, transmembran potensialları*

Ключевые слова: *ишемический инсульт, апоптоз, окислительный стресс, трансмембранный потенциал*

Key words: *ischemic stroke, apoptosis, oxidative stress, transmembrane potential, periods*

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MITOCHONDRIAL MECHANISMS OF APOPTOSIS DURING ISCHEMIC VERTEBROBASILAR STROKE

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Summary. *The article deals with the role of the mitochondria-mediated apoptosis pathway in the course of ischemic stroke in the vertebral-basilar basin by determining the levels of reactive oxygen species, transmembrane potential, indicators of cell death and their relationship in different periods of stroke. The study included 105 people with a diagnosis of ischemic stroke in the vertebral-basilar basin, 49 patients were in the subacute period (3-6 months), 32 patients were in the chronic period (6-12 months), 14 patients were 1-3 years after the stroke, and 10 patients were over 3 years after the stroke. It was found that in patients with ischemic stroke in the late subacute and chronic periods, the levels of* H_2O_2 *and* $\Delta\mu$ *were significantly higher, according to the control values. At the same time, the indicators of leukocyte cell death are the highest in the late subacute period. They probably differ from both control values and data in the chronic period, as well as after 1-3 years and more than 3 years of observation. A direct average relationship was established between the level of hydrogen peroxide and indicators of cell death of leukocytes in the late subacute and chronic periods of ischemic stroke in the vertebral-basilar basin, which is lost after 1-3 years and more than 3 years of observation.*

In the world, stroke ranks second among all causes of death and disability, while Ukraine occupies one of the first places in Europe regarding cerebrovascular morbidity and mortality. Cerebral stroke is diagnosed yearly in 16.8 million people, and according to reports of the World Health Organization, this figure will increase to 23 million people by 2030 [1-3]. At the same time, approximately 6.5 million deaths because of the stroke are diagnosed annually worldwide, which is second only to coronary heart disease [4]. Although stroke mortality and prevalence have decreased over the past thirty years from 40% to 33% in 2013, the results vary among populations stratified by race, geography, and comorbidities [5]. According to a report by the European Stroke Alliance (SAFE), together with the European Stroke Organization (ESO), the number of stroke cases is expected to increase by 34% by 2035 due to the ageing population [6]. Although the diagnosis and treatment of ischemic stroke have improved significantly [7, 8], the prognosis of patients with ischemic stroke is still unfavorable [9], so it is necessary to continue to study the pathophysiological mechanisms of stroke in order to choose optimal therapeutic strategies for the treatment of ischemic stroke in its different periods.

Oxidative stress plays a crucial role in the development and progression of many diseases, especially acute ischemic stroke [10-12]. Increased production of oxygen radicals can change cell structure and enzyme activity [13, 14], which leads to extravasation of blood components, increased inflammatory response, and even irreversible brain tissue damage [15].

This study aims to clarify the role of the mitochondria-mediated apoptosis pathway in the course of ischemic stroke in the vertebral-basilar basin by determining the levels of reactive oxygen species, transmembrane potential, indicators of cell death and their relationship in different periods of stroke.

Materials and methods. The study included 105 patients with a diagnosis of ischemic stroke in the vertebral-basilar basin, 49 patients were in the subacute period (3-6 months), 32 patients were in the chronic period (6-12 months), 14 patients were 1-3 years after the stroke, and 10 patients were over 3 years after the stroke. All patients were examined and treated in the neurological departments of Ternopil Regional Communal Clinical Psychoneurological Hospital. The diagnosis of cerebral infarction was verified using spiral computed tomography (CT) (Atelon 4, Toshiba) or magnetic resonance imaging (MRI) (Simens, Magnetom Avanto, 1.5 Tl). The examination was carried out according to a single scheme using formalized maps.

The research included patients with the presence of an ischemic focus according to neuro visual examination methods in the subacute and chronic periods and patients 1 year and over after a stroke. The exclusion criteria were as follows: patients in the first 3 months of ischemic stroke, having the signs of clinically significant neurological, mental, renal, hepatic, immunological, gastrointestinal, urogenital disorders, lesions of the musculoskeletal system, skin, sense organs, endocrine system or hematological diseases including uncontrolled, acute pancreatitis, unstable or life-threatening heart disease, patients with malignant neoplasms who have not been in complete remission for at least 5 years, patients having medication (drug) dependence, and alcohol addiction.

The ethical principles included in the Declaration of Human Rights, adopted in Helsinki in 1975, and revised in 2008, were fully respected in our study. The enrolled subjects participated in this study voluntarily and completed and signed written informed consent. Ethics Committee of I. Horbachevsky Ternopil National Medical University approved the study protocol.

Determination of leukocytes' number in the stage of apoptosis, and necrosis, with increased intracellular content of reactive oxygen species (ROS) and reduced membrane potential of mitochondria, was carried out with the flow cytometry method in peripheral blood. Under the microscope, the cells were counted with Goryaev's camera and adjusted to $1x10^6$ cells/ml. The apoptosis determination was executed using a software system on flow cytometer Epics XL (Beckman Coulter, USA). Results are expressed as a percentage of cells which have attached FITC Annexin V or PI. The cells are alive when they are FITC Annexin V and PI negative. The cells are apoptotic when FITC Annexin V is positive, and PI is negative. The cells are in the stage of irreversible apoptosis (necrosis) when they are FITC Annexin V and PI positive.

Analysis of cell samples to determine ROS of neutrophils was evaluated with the flow cytometry method by Epics XL (Beckman Coulter, USA), using 2.7-dichlorodihydrofluorescein diacetate (hydrogen peroxide) and Dichlorethidium (superoxide anion-radical). The value of the studied parameter was expressed as a percentage (ratio of cells with ROS overproduction to general cell count×100%).

The number of neutrophils with low transmembrane mitochondrial potential ($\Delta\psi$) was evaluated by the flow cytometry method, using a kit of reagents "MitoScreen" ("BD Pharmigen", USA) on flow cytometer Epics XL (Beckman Coulter, USA). The value of the studied parameter was expressed as a

percentage (ratio of cells with low Δψ to general cell count×100%).

All of the data were processed using the software package Statistica 6.1 for Windows. The median (Me) and interquartile range (IQR [Q25-Q75]) were deduced. Quantitative indicators comparative analysis of three and more groups were conducted using the Kruskal-Wallis criterion, which is considered statistically significant at $p < 0.05$. Intergroup comparisons were performed using the Mann-Whitney-Wilcoxon U test while evaluating equal statistical significance. Correlation analysis was performed with the Spearman method. The coefficient of linear correlation (r) and its reliability (p) was calculated and demonstrated in the tables (correlation matrices). If the index r=0 the linkage was considered to be absent; in the range, 0-0.29 – the linkage was considered to have weak correlation; the interval of index 0.30-0.69 described linkage as having medium strength, and interval of 0.70-1.00 pointed to strong correlation interaction. The correlation coefficient was significant at $p<0.05$.

Results and discussion. Among the indicators of free radical oxidation, the level of hydrogen peroxide in the leukocytes of patients of all experimental groups probably differed when analyzing the rank variations of Kruskal-Wallis (p=0.003). It was found that the level of H_2O_2 was probably higher by 104.81% in the group of patients 3-6 months after the stroke, and by 23.72% in the group of patients 6-12 months after the stroke, compared to the control group. At the same time, the obtained data of the 1st group were probably higher compared to the results of the 3rd (by 85.76%) and the 4th (by 98.45%) experimental groups (table 1).

The indicator of leukocyte Δψ in patients of all experimental groups also probably differed when analyzing Kruskal-Wallis rank variations (p=0.046). At the same time, it was established that Δμ was probably higher by 137.65% in the group of patients who were 3-6 months after the stroke and by 69.95% in the group of patients after 6-12 months after the stroke compared to the control values. The obtained data of the 1st group were probably higher compared to the results of the 3rd (by 118.10%) and the 4th (by 142.11%) experimental groups (table 1).

Indicators of blood leukocyte cell death, namely live leukocytes and leukocytes with early and late signs of apoptosis in patients of all experimental groups, also probably differed when analyzing Kruskal-Wallis rank variations. The level of leukocytes with signs of necrosis in all experimental groups probably did not differ when performing the Kruskal-Wallis rank variation analysis. It was established that in the late subacute period, cell death rates of blood leukocytes were significantly different vs control values: live leukocytes were lower by 40.23%, while V^+/PI^- and V^+/PI^+ exceeded accordingly 7.15 and 3.91 times. At the same time, the obtained results of cell death indicators of blood leucocytes in the late subacute period were probably higher than the data in the chronic period, as well as after 1-3 years and more than 3 years (table 2).

Table 1. *Indicators of the intracellular level of free oxygen radicals and transmembrane potential in patients who suffered an ischemic stroke in the vertebral-basilar basin, Me (Q_{25} - Q_{75})*

Catamnesis	H_2O_2 (%)	$O_2^{\bullet-}$ (%)	Δμ
3-6 months (1)	31.95 (30.80; 32.98) ^	5.55 (5.15; 5.95)	10.12 (9.68; 11.17) ^
6-12 months (2)	19.30 (18.68; 20.25) ^	3.01 (2.88; 3.14)	7.24 (7.05; 7.36) ^
1-3 years (3)	17.20 (16.13; 17.70) #	1.87 (1.79; 1.94)	4.64 (4.35;4.72) #
more than 3 years (4)	16.10 (15.80; 16.20) #	1.80 (1.70; 1.90)	4.18 (4.02;4.31) #
control (5)	15.60 (14.23; 16.95) #	1.89 (1.59; 2.01)	4.26 (4.13; 4.31) #
Kruskal-Wallis criterion, p			
	H=15.85 P=0.003*	H=8.61 p=0.07	H=9.94 p=0.046*
Note: * – statistically significant results; ^ – the probability of differences in relation to the control values (5); # – the probability of differences in relation to (1).			

Table 2. *Indicators of blood leukocytes cell death in patients who suffered an ischemic stroke in the vertebral-basilar basin, Me (Q_{25} - Q_{75})*

Catamnesis	Live leukocytes, %	Leukocytes with early signs of apoptosis (V^+/PI^-), %	Leukocytes with late signs of apoptosis (V^+/PI^+), %	Leukocytes with signs of necrosis (V^-/PI^+), %
3-6 months (1)	68.01 (67.00; 68.81) ^	30.40 (29.30; 31.25) ^	0.86 (0.80; 0.92) ^	0.96 (0.90; 1.10)
6-12 months (2)	79.59 (78.46; 80.65)	19.60 (18.68; 20.80) # ^ &	0.53 (0.49; 0.58) ^	0.18 (0.15; 0.20)
1-3 years (3)	88.01 (87.77; 88.46) #	11.70 (11.20; 11.88) # ^	0.21 (0.18; 0.23) #	0.11 (0.09; 0.14)
more than 3 years (4)	92.29 (92.27; 92.50) #	7.32 (7.18; 7.34) # ^ &	0.20 (0.18; 0.22) #	0.16 (0.15; 0.17)
control (5)	95.37 (94.99; 95.97) #	4.25 (3.70; 4.60) #	0.22 (0.16; 0.25) #	0.14 (0.11; 0.16)
Kruskal-Wallis criterion, p				
	H=29.33 p<0.001*	H=25.30 p=0.0004*	H=10.49 p=0.03*	H=4.69 p=0.32
Note: * – statistically significant results; ^ – the probability of differences concerning the control values (5); # – the probability of differences concerning (1), & – the probability of differences concerning (3).				

In order to clarify the metabolic relationships between the investigated indicators, a correlation analysis was conducted. There was established a positive average relationship between hydrogen peroxide and indicators of programmed leukocytes cell death, as well as a direct average relationship between Δμ, apoptotic and necrotic peripheral blood leukocytes in patients who suffered an ischemic stroke in the vertebral-basilar basin in the late sub-acute period. After 6-12 months, there is a medium-strength positive relationship between the percentage of leukocytes with early and late signs of apoptosis, on the one hand, and the level of H_2O_2 and Δμ, on the other. Established correlations are being lost in experimental groups after 1-3 years and more than 3 years (table 3). The obtained data indicate the implementation of the mitochondria-mediated pathway of leukocyte cell death in patients with ischemic stroke in the vertebral-basilar basin in the late subacute and chronic periods.

Table 3. *Correlations between selected indicators of oxidative stress, transmembrane potential, and programmed leukocytes cell death in patients with ischemic stroke in the vertebral-basilar basin*

	Indicators of programmed cell death of leukocytes			
Indicators of oxidative stress and transmembrane potential	Live leukocytes, %	V^+/PI^-, %	V^+/PI^+, %	V^-/PI^+, %
	3-6 months			
H_2O_2	0.58*	0.61*	0.54*	0.49*
$O_2^{\bullet-}$	0.32	0.28	0.41	0.35
Δμ	0.42	0.59*	0.54*	0.51*
	6-12 months			
H_2O_2	0.38	0.47*	0.51*	0.32
$O_2^{\bullet-}$	0.21	0.19	0.33	0.17
Δμ	0.29	0.55*	0.54*	0.36
	1-3 years			
H_2O_2	0.26	0.21	0.25	0.17
$O_2^{\bullet-}$	0.19	0.12	0.09	0.16
Δμ	0.22	0.26	0.16	0.24
	more than 3 years			
H_2O_2	0.28	0.12	0.08	0.11
$O_2^{\bullet-}$	0.14	0.23	0.12	0.18
Δμ	0.26	0.28	0.16	0.05

It has been established that almost a fourth of all transient ischemic attacks and strokes occur in the vertebral-basilar basin [16]. Although stroke in the vertebral-basilar basin has traditionally been considered to have a more favorable prognosis compared to stroke in the intracranial internal carotid artery, the data are still controversial; some studies show significantly more severe impairment in patients having a stroke in the vertebral-basilar basin, and also 21% of patients with mortality or disability [17].

From the pathogenetic point of view, atherosclerosis is the main pathological process in stroke [18]. Previous studies have shown that vertebral-basilar occlusion is associated with intracranial atherosclerosis [19, 20]. Atherosclerosis, hyperlipidemia, or rupture of the plaque leads to focal ischemia [21, 22]. Low oxygen saturation leads to excessive production of ROS; as a result, neuronal cells initiate inflammatory answer, and in the end, they undergo apoptosis [23].

Oxidative stress is one of the causes of the pathogenesis of ischemic damage to nerve cells, mediated by a violation of calcium homeostasis [24, 25]. An uncontrolled calcium increase in nerve cells makes ROS active. Damaged mitochondria can also produce ROS constitutively. ROS are formed during ischemia and reperfusion phases, leading to brain damage in patients with acute ischemic stroke. ROS can also lead to other intracellular damage, i.e., inactivate enzymes, cause structural changes in carbohydrate molecules, and, as a result, apoptosis appears [26-28].

Neuronal loss occurs during stroke due to cerebral ischemia or hemorrhage, triggering a complex series of biochemical events that lead to complete disruption of cell integrity and cell death. A post-stroke lesion is characterized by a focus of necrotic cell death that is formed rapidly after injury presenting the tissue that is irreversibly lost, as well as a penumbra that surrounds the focus and is defined as a moderately hypoperfused metastable area that maintains structural integrity but has lost or impaired function. This penumbra is the leading risk zone and can be saved with appropriate treatment [29]. The changes we obtained in the late subacute and chronic periods may be associated with residual phenomena after an acute ischemic stroke and gradual recovery of tissues. In our study signs of necrosis were recorded 3-6 months after the stroke.

Our results showed a relationship between oxidative stress and indicators of leukocyte cell death in the late subacute and chronic periods of ischemic stroke in the vertebral-basilar basin, which is lost after 1-3 years and over 3 years after the stroke. Scientists have shown that a change in the activity of phagocytes is also observed in the chronic phase after a stroke, that is, in this case, phagocytes demonstrate increased adhesive properties. At the same time, the presence of vascular damage after a stroke leads to the generation of radicals by endothelial cells, which initiate the lipid peroxidation of cell membrane components and cause the release of pro-inflammatory mediators, including phagocytes [30]. Adhering to the vascular endothelium, phagocytes release various toxic products that exacerbate vascular damage and increase the likelihood of a subsequent stroke within one year. The obtained data give reason to conclude that the absence of a relationship between oxidative stress and indicators of leukocyte cell death after 1 year and later indicates the effectiveness of the therapy in the early stages of ischemic stroke.

Conclusions

1. In patients with ischemic stroke in the late subacute and chronic periods, the levels of H_2O_2 and $\Delta\mu$ were significantly higher, according to the control values. At the same time, the indicators of leukocyte cell death are the highest in the late subacute period. They probably differ from both control values and data in the chronic period, as well as after 1-3 years and more than 3 years of observation.

2. A direct average relationship was established between the level of hydrogen peroxide and indicators of cell death of leukocytes in the late subacute and chronic periods of ischemic stroke in the vertebral-basilar basin, which is lost after 1-3 years and more than 3 years of observation.

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МИТОХОНДРИАЛЬНЫЕ МЕХАНИЗМЫ АПОПТОЗА В ТЕЧЕНИИ ИШЕМИЧЕСКОГО ИНСУЛЬТА В ВЕРТЕБРО-БАЗИЛЯРНОМ БАССЕЙНЕ

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В статье рассмотрена роль митохондрий-опосредованного пути апоптоза в течении ишемического инсульта в вертебро-базилярном бассейне путем определения уровней активных форм кислорода, трансмембранного потенциала, показателей клеточной гибели и их взаимосвязи в разные периоды инсульта.

В исследование было включено 105 человек с диагнозом ишемического инсульта в вертебро-базилярном бассейне, из них в подостром периоде (3-6 месяцев) – 49 больных, хроническом периоде (6-12 месяцев) – 32 больных, через 1-3 года – 14 больных и более 3 лет – 10 больных.

Установлено, что у больных ишемическим инсультом в позднем подостром и хроническом периодах уровень H_2O_2 и $\Delta\mu$ были вероятно выше, относительно контроля. В то же время, в позднем подостром периоде показатели клеточной гибели лейкоцитов самые высокие и вероятно отличаются как от контрольных значений, так и данных в хроническом периоде, а также через 1-3 года и более 3 лет наблюдения. Установлена прямая средняя связь между уровнем гидрогена пероксида и показателями клеточной гибели лейкоцитов в позднем подостром и хроническом периодах ишемического инсульта в вертебро-базилярном бассейне, который теряется через 1-3 года и более 3 лет наблюдения.

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