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Heterogeneity of VEGF Dynamics in the Acute Period of Ischemic Stroke: Association with Disease Severity and Short-term Outcomes

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ABSTRACT

Aim. To evaluate serum vascular endothelial growth factor (VEGF) levels in the dynamics of the acute period of ischemic stroke in patients during clinical and functional recovery.

Material and methods. The study included 114 patients with ischemic stroke. Patient groups were the following: Group 1 – mild stroke (n = 57 patients), Group 2 – moderate stroke (n = 25 patients), Group 3 – severe stroke (n = 32 patients). Observation period was 14 days. Observation points included: I – the first 48–72 hours from the onset of the disease; II – the 14th day. We used the following assessment scales: National Institute of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS). VEGF was determined in blood serum on a multiplex analyzer. Statistical processing of the results was carried out using the Statistica 13.0 software package.

Results. Patients of groups 1 and 2 showed a statistically significant decrease in points on the NIHSS and mRs scales ($p < 0.001$) in the dynamics of observation, in patients of group 3, no significant changes were found ($p = 0.157$ and $p = 0.315$, respectively). VEGF in the comparison group did not show reliable differences relative to patients at points I ($p_{z-1} = 0.73$, $p_{z-2} = 0.738$, $p_{z-3} = 0.129$) and II of observation ($p_{z-1} = 0.66$, $p_{z-2} = 0.817$, $p_{z-3} = 0.276$). Analysis of the dynamics of the marker revealed an increase in VEGF between points I and II of observation in group 3 ($p = 0.021$), ΔVEGF positively correlated with a higher score on the NIHSS scale at point I ($r = 0.691$; $p = 0.027$). No relationships were found in group 1 ($p_{I–II} = 0.078$, $r_{\Delta VEGF-NIHSS\_I} = –0.294$; $p_{\Delta VEGF-NIHSS\_I} = 0.237$) and group 2 patients ($p_{I–II} = 0.285$, $r_{\Delta VEGF-NIHSS\_I} = –0.305$; $p_{\Delta VEGF-NIHSS\_I} = 0.392$).

Conclusion. Heterogeneity of ischemic stroke pathogenesis reduces the prognostic value of VEGF as an isolated biomarker. A comprehensive analysis of the temporal patterns of VEGF regulation and other angiogenic factors is needed to understand the dynamics of vascular remodeling and predict the outcomes of ischemic stroke.

Keywords: vascular endothelial growth factor, angiogenesis, biomarker, prognosis, clinical recovery

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Гетерогенность динамики VEGF в остром периоде ишемического инсульта: взаимосвязь с тяжестью заболевания и краткосрочными исходами

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РЕЗЮМЕ

Цель: оценка динамики сывороточного уровня фактора роста эндотелия сосудов (VEGF) у пациентов в остром периоде ишемического инсульта в контексте клинического и функционального восстановления, с акцентом на различия между патогенетическими подтипами и тяжестью заболевания.

Материалы и методы. Исследуемая выборка составила 114 пациентов с ишемическим инсультом головного мозга. Группы пациентов: 1-я группа – легкий инсульт (n = 57 пациентов), 2-я группа – средней степени тяжести (n = 25 пациентов), 3-я группа – тяжелый инсульт (n = 32 пациента). Период наблюдения: 14 сут. Точки наблюдения: I – первые 48–72 ч от начала заболевания; II – 14-е сут. Оценочные шкалы: шкала инсульта Национального института здоровья (NIHSS), модифицированная шкала Рэнкина (mRS). Уровень VEGF определяли в сыворотке крови на мультиплексном анализаторе. Статистическая обработка результатов проводилась с использованием пакета прикладных программ Statistica 13.0.

Результаты. У пациентов 1-й и 2-й групп обнаружено статистически значимое снижение количества баллов по шкалам NIHSS и mRs (p < 0,001) в динамике наблюдения, у пациентов 3-й группы значимых изменений не выявлено (p = 0,157 и p = 0,315 соответственно). Уровень VEGF в группе сравнения не показал достоверных различий относительно пациентов в I (p_{z-1} = 0,73; p_{z-2} = 0,738; p_{z-3} = 0,129) и во II точке наблюдения (p_{z-1} = 0,66; p_{z-2} = 0,817; p_{z-3} = 0,276). Анализ динамики маркера выявил увеличение уровня VEGF между I и II точками наблюдения у пациентов 3-й группы (p = 0,021), ΔVEGF положительно коррелировала с более высоким баллом по шкале NIHSS в I точке (r = 0,691; p = 0,027). Корреляционных взаимосвязей в 1-й группе (p_{I-II} = 0,078, $r_{\Delta VEGF\text{-}NIHSS\_I}$ = –0,294; $p_{\Delta VEGF\text{-}NIHSS\_I}$ = 0,237) и 2-й группе пациентов (p_{I-II} = 0,285; $r_{\Delta VEGF\text{-}NIHSS\_I}$ = –0,305; $p_{\Delta VEGF\text{-}NIHSS\_I}$ = 0,392) не выявлено.

Заключение. Гетерогенность патогенеза ишемического инсульта снижает прогностическую ценность VEGF как изолированного биомаркера. Необходим комплексный анализ временных закономерностей регуляции VEGF и других ангиогенных факторов для понимания динамики сосудистого ремоделирования и прогнозирования исходов ишемического инсульта головного мозга.

Ключевые слова: фактор роста эндотелия сосудов, ангиогенез, биомаркер, прогноз, клиническое восстановление

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Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. До включения в исследование все субъекты или их ближайшие родственники были осведомлены о характере, целях, возможных рисках исследования и дали добровольное информированное письменное согласие на участие. Протокол клинического исследования разработан в соответствии с требованиями Национального стандарта РФ ГОСТ Р52379-2005 «Надлежащая клиническая практика» GCP (2005 г.) Good Clinical Practice и одобрен этическим комитетом СибГМУ (заключение № 8565/1 от 21.01.2021).

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INTRODUCTION

Strokes consistently represent a key medical and social problem worldwide, accounting for their high morbidity and mortality rates, leading to temporary disability and eventual permanent disability [1]. Scientific communities are continually developing and improving diagnostic algorithms and management strategies for patients with cerebral ischemia. However, issues of predicting the clinical and functional outcomes of the disease remain unsolved to this day. A comprehensive understanding of the neurobiological processes underlying ischemic stroke is crucial to develop early diagnostic, prognostic, and therapeutic approaches. Recently, particular attention has been paid to growth factors, which play a key role in neovascularization mechanisms and brain tissue recovery after acute ischemia [2, 3].

Vascular endothelial growth factor (VEGF) is one of the main growth factors, which is regulated by hypoxia-inducible factor (HIF) in response to acute cerebral ischemia. In cerebral stroke, VEGF is expressed on the surface of astrocytes, neurons, and endothelial cells in the infarct core and in the ischemic penumbra. Outside the central nervous system, VEGF is derived from a variety of cells, including macrophages and platelets [4]. Experimental studies on models of acute cerebral ischemia in rodents have shown that VEGF has a pleiotropic effect. On the one hand, its activation triggers angiogenesis and has a neuroprotective effect [5, 6]. On the other hand, VEGF promotes the disruption of the blood – brain barrier (BBB) and increased vascular permeability, leading to the progression of cerebral edema [7].

Despite the fact that VEGF has been studied as a prognostic marker for ischemic stroke since the 1970s, and a significant body of scientific data has been accumulated, a consensus on the role of this vascular factor in clinical and functional recovery has still not been reached. A 2013 study by R. Matsuo et al. demonstrated a sustained increase in plasma VEGF levels over a 90-day period following ischemic stroke in 171 patients, regardless of the stroke pathogenetic subtype, compared to a control group [8]. In contrast, a 2021 meta-analysis by A. Seidkhani-Nahal et al. showed that serum VEGF levels on day 1 and day 7 of acute cerebral ischemia were not statistically different between 769 patients and 621 controls [9].

The research team of A. Bhasin et al. in 2019 conducted a clinical and laboratory examination of 250 patients with cerebral ischemic stroke using the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS). In their work, the authors identified an association between VEGF levels and disease outcomes on day 7 and day 90 of cerebral ischemia [10].

Thus, the current clinical data on the role of VEGF as a potential marker for outcomes of ischemic stroke do not allow for definitive conclusions. The study of VEGF – a key factor in angiogenesis and vascular remodeling in the recovery processes of patients with ischemic stroke – is of significant scientific and practical interest. Such research is important both to understand the pathogenetic mechanisms of cerebral ischemia and to find new effective tools for forecasting rehabilitation potential, aiming for a future personalized treatment approach.

The aim of the study was to assess the changes in serum VEGF levels in patients during the acute phase of ischemic stroke in the context of clinical and functional recovery, with a focus on differences between pathogenetic subtypes of stroke and disease severity.

MATERIALS AND METHODS

This study was conducted at the Neurology and Neurosurgery Division of the Siberian State Medical University (SibSMU) in collaboration with the Laboratory of Molecular Genetics and Biochemistry at the Mental Health Research Institute, Tomsk National Research Medical Center. The study included 114 patients (51 women, 63 men) with ischemic stroke, hospitalized at the Regional Vascular Center of Tomsk Regional Hospital within 48–72 hours after the onset of focal neurological symptoms.

The median patient age was 65 (59; 70) years. The diagnosis of stroke was verified according to the WHO clinical criteria and confirmed by neuroimaging data. The nosological form of the disease was established in accordance with the International Classification of Diseases, 10th Revision (ICD-10). An informed consent was obtained from the patients or their immediate family members prior to inclusion in the study. Exclusion criteria were as follows: transient ischemic attack, hemorrhagic stroke, history of stroke, nervous system damage of other etiology (traumatic, autoimmune, neurodegenerative, neoplastic, or epilepsy), and extracranial pathology (connective tissue diseases, musculoskeletal system diseases, hereditary disorders, or neoplasms).The patient population was divided into three groups based on the severity of neurological deficit assessed using the NIHSS scale (Goldstein et al., 2011): group 1 – mild stroke (NIHSS score 1–6, $n = 57$); group 2 – moderate stroke (NIHSS score 7–13, $n = 25$); group 3 – severe stroke (NIHSS score 14–42, $n = 32$) [11]. The clinical and demographic characteristics of the patient cohort are presented in Table 1. The comparison group consisted of 13 volunteers with a median age of 64 (58; 71) years, with no history of cerebrovascular or other organic lesions of the central nervous system, comparable to the study population in terms of sex, age, and cardiovascular risk factors.

Table 1

Clinical and Demographic Characteristics of the Study Population

Characteristic	Group 1, *n* = 57	Group 2, *n* = 25	Group 3, *n* = 32
Gender, *n* (%) – men – women	 34 (59.6%) 23 (40.4%)	 12 (48%) 13 (52%)	 17 (53.1%) 15 (46.9%)
Age, years Me [Q_1;Q_3]	65 [59; 69]	66 [59; 68]	69 [62; 74]
Body mass index, kg/m^2, Me [Q_1;Q_3]	28.26 [25.95; 30.85]	28.13 [25,25; 35.14]	27.99 [23.15; 31.22]
Arterial hypertension, *n* (%)	57 (100%)	25 (100%)	32 (100%)
Atherosclerosis of the aorta and heart valves, *n* (%)	45 (78.9%)	15 (60%)	20 (62.5%)
Diabetes mellitus, *n* (%)	12 (21.1 %)	6 (24%)	8 (25%)
Coronary heart disease, *n* (%)	15 (26.3%)	7 (28%)	14 (43.8%)
Myocardial infarction, *n* (%)	6 (10.5%)	3 (12%)	5 (15.6%)
Stenting and artificial heart valves, *n* (%)	2 (3.5%)	1 (4%)	2 (6.3%)
Atrial fibrillation, *n* (%)	13 (22.8%)	3 (12%)	13 (40.6%)
Dyslipidemia, *n* (%)	48 (84.2%)	19 (76%)	18 (56.25%)
Smoking, *n* (%)	15 (26.3%)	5 (20%)	2 (6.3%)
Affected cerebral hemisphere – right, *n* (%) – left, i (%)	 29 (50.9%) 28 (49.1%)	 15 (60%) 9 (40%)	 16 (50%) 16 (50%)
Stroke subtype according to TOAST criteria: – atherothrombotic, *n* (%) – cardioembolic, *n* (%) – lacunar, *n* (%) – other established etiology, *n* (%) – unknown etiology, *n* (%)	 8 (14%) 13 (22.8%) 3 (5.3%) 0 33 (57.9%)	 8 (32%) 3 (12%) 1 (4%) 0 13 (52%)	 10 (31.3%) 13 (40.6%) 0 0 9 (28.1%)

The observation period was 14 days. Assessment time points were as follows: I – the acute stroke period (first 48–72 hours), II – the subacute period (day 14 of the disease). Neurological deficit was assessed using the NIHSS, and functional disability was evaluated with the mRS scale. Patient serum was used as the biological material for analysis. VEGF concentration was measured using the MAGPIX multiplex analyzer (Luminex, USA) and the HNDG3MAG-36K panel from MILLIPLEX MAP (Merck, Darmstadt, Germany). The results were expressed in pg/mL. Statistical analysis was performed using the Statistica 13.0 software package. The critical significance level for testing statistical hypotheses was set at 0.05 (p is the obtained significance level). Categorical variables were presented as absolute numbers and relative frequencies *n* (%). Quantitative and ordinal variables were presented as median and interquartile range, Me [Q_1; Q_3].

The Kruskal–Wallis test was used to compare multiple independent groups, with the Mann–Whitney *U* test and Bonferroni correction used for pairwise comparisons. Changes between the two time points were assessed using the Wilcoxon signed-rank test. Correlation analysis between variables was performed using non-parametric methods.

Table 2

Dynamics of Clinical and Laboratory Parameters in Acute Ischemic Stroke across Observation Groups

Criteria	Patient Groups			Comparison			
				Evaluation of dynamics, $p_{I\text{-}II}$			Intergroup comparison, $p_{1,2,3}$
	1 (*n*=57)	2 (*n*=25)	3 (*n*=32)	Groups			
				1	2	3	
mRs_I	3 [2; 3]	4 [4; 5]	5 [5; 5]	<0.001*	<0.001*	0.157	<0.001*
mRs_II	2 [1; 2]	4 [3; 4]	5 [5; 5]				<0.001*
NIHSS_I	4 [3; 5]	10 [2; 3]	18 [16; 21]	<0.001*	<0.001*	0.315	<0.001*
NIHSS_II	3 [2; 3]	7 [5; 8]	20 [12; 23]				<0.001*
VEGF_I pg/mL	83.0 [35.3; 113.6]	70.2 [47.6; 88.1]	53.5 [25.4; 90.6]	0.078	0.285	0.021*	0.377
VEGF_II pg/mL	90.3 [47.6; 150.2]	100.1 [64.8; 113.6]	110.9 [61.8; 228.2]				0.724
Δ VEGF pg/mL	18 [–5; 53]	13 [5; 17]	68 [38; 105]				0.065

* $p < 0.05$.

RESULTS

During the study, patients at point I demonstrated significant differences in the severity of neurological deficit according to the NIHSS and functional impairment according to the mRS across all groups.

In patients of groups 1 (mild stroke) and 2 (moderate stroke), a statistically significant decrease in NIHSS and mRS scores was found ($p_{I\text{-}II} < 0.001$), indicating a regression of neurological deficit and functional recovery by day 14 of the disease (Table 2). Moderate positive correlations between ΔNIHSS and ΔmRS further confirmed the clinical improvement and functional independence of patients in groups 1 and 2 at the second observation point ($r_1 = 0.645$, $p_1 < 0,001$ and $r_2=0.507$, $p_2=0.001$, respectively).

In group 3 patients with severe stroke, no significant quantitative changes in the studied scores were found at the observation points (Table 2). At the same time, ΔNIHSS significantly correlated with mRs_II, reflecting the degree of disability in patients with severe stroke in the absence of recorded clinical improvement on day 14 of the disease ($r_3 = 0.418$, $p_3 = 0.019$).

The serum VEGF concentration in the comparison group was 70.2 [47.6; 138.6] pg/mL and did not statistically significantly differ in the patient groups, either within the first 48–72 hours of ischemic stroke ($p_{z\text{-}1} = 0.73$, $p_{z\text{-}2} = 0.738$, $p_{z\text{-}3} = 0.129$) or on day 14 of stroke ($p_{z\text{-}1} = 0.66$, $p_{z\text{-}2} = 0.817$, $p_{z\text{-}3} = 0.276$). No significant differences in the marker levels in the peripheral blood of patients with varying severity of ischemic stroke were found either (Table 2).

A comparative analysis at observation point II revealed a significant increase in serum VEGF concentrations during the dynamics of the acute period in group 3 patients with severe stroke ($p_{I\text{-}II} = 0.021$). Here, ΔVEGF was 68 [38; 105] pg/mL and positively correlated with a higher NIHSS_I score ($r = 0.691$; $p = 0.027$).

Within the study, patients were also divided into stroke subtypes according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification [12]. This resulted in the following groups: atherothrombotic stroke ($n = 26$), cardio-embolic stroke ($n = 29$), and a combined group including patients with lacunar stroke and stroke of unspecified etiology ($n = 59$), due to the insufficient number of patients in the first category. No cases of stroke of other established etiologies were registered in the cohort.

The results of the comparative analysis showed that in the group of patients with the cardioembolic subtype of stroke, VEGF levels in the first 48–72 hours of the disease were significantly lower compared to the control group ($p = 0.039$).

Correlation analysis revealed significant relationships between clinical and laboratory parameters exclusively in the group of patients with atherothrombotic stroke, where ΔVEGF was 10 [–22; 63] pg/mL and positively correlated with the NIHSS score at both observation points I ($r = 0.754$; $p = 0.012$) and II ($r = 0.695$; $p = 0.026$). A similar correlation was found between ΔVEGF and mRs_II ($r = 0.695$; $p = 0.026$). The obtained results indicate the presence of a reliable relationship between the changes in VEGF growth, the severity of neurological deficit, and the degree of functional impairment by the end of the 14-day observation period.

DISCUSSION

In acute ischemic brain injury, VEGF is one of the main regulators of angiogenesis and neuronal survival, determining the clinical outcome of stroke [13]. Immunohistochemical studies conducted on experimental models of middle cerebral artery occlusion in rats showed that VEGF expression in astrocytes in the ischemic core increased after 2 hours and then gradually decreased over 6 hours. Increased VEGF immunoreactivity in hypertrophied astrocytes and endothelial cells was also detected in the ischemic penumbra zone 24 hours after the onset of ischemia and persisted for 14 days [14].

The results of the present study showed that serum VEGF concentrations in patients during the first 48–72 hours of ischemic stroke remained at a level comparable to those in the comparison group. It is likely that the neuroprotein content in the peripheral blood does not reflect the level of expression in the ischemic focus. VEGF produced locally in brain tissue in response to ischemic injury does not reach the systemic circulation in equal concentrations during the first 48–72 hours, accumulating within the infarct zone. Furthermore, the neuroinflammatory process that develops during acute cerebral ischemia can modulate VEGF expression, counteracting its predicted increase [15]. Clinical studies presented in the international literature demonstrate a negative correlation between leukocyte levels and C-reactive protein compared to angiogenic growth factors, including VEGF, supporting the hypothesis of a negative impact of neuroinflammatory responses on angiogenesis [16].

Of particular interest are the differences in VEGF changes depending on the subtype of ischemic stroke. In cardioembolic stroke, hypoxia develops rapidly, which can lead to suppression of VEGF expression due to severe energy deficit in neurons and glial cells. In contrast to atherothrombotic stroke, in which occlusion develops gradually, the sudden cessation of blood flow in cardioembolism limits the activation time of HIF-1α, a key regulator of VEGF synthesis. As a result, in the first 48–72 hours of cardioembolic stroke, VEGF-dependent pathways likely remain functionally inactive [17]. An additional pathogenetic factor affecting VEGF expression in cardioembolic stroke is the concomitant systemic inflammatory response and hypercoagulability characteristic of atrial fibrillation and other cardiac sources of embolism. Elevated levels of proinflammatory cytokines (in particular, interleukin-6 and tumor necrosis factor-α) in combination with markers of coagulation cascade activation (such as D-dimer) create a microenvironment that suppresses angiogenic processes, which further inhibits VEGF production [18, 19]. In contrast, atherothrombotic stroke, which develops against the background of progressive stenosis of large cerebral arteries, is characterized by chronic hypoxia, which induces persistent compensatory VEGF expression. In lacunar stroke, caused by damage to small arteries, the ischemic response is minimal, which explains the absence of significant changes in VEGF levels [20, 21].

Of particular note is the observation that patients with mild to moderate stroke demonstrated better short-term outcomes of ischemic stroke on day 14 of disease without a significant increase in VEGF over time. This finding may indicate the activation of alternative signaling pathways regulating neuronal recovery and clinical outcomes that do not require vascular remodeling and a significant increase in VEGF expression. Recent research data support the hypothesis that activation of neuronal plasticity mechanisms, and in particular brain-derived neurotrophic factor (BDNF), plays a key role in the motor recovery of patients with ischemic stroke during the first 14 days [22].

In patients with severe ischemic stroke, a significant increase in VEGF in the absence of significant clinical and functional recovery was observed on the 14^{th} day of disease. This increase is likely due to the need for continuous VEGF expression during the acute period to stimulate angiogenesis and neurogenesis [23]. However, angiogenesis may have limited efficacy in restoring lost functions in the short term. In severe stroke, accompanied by deeper damage to the conduction pathways located below the ischemic focus, the need for angiogenesis to restore impaired functions is presumably higher compared to mild or moderate strokes. Activation of angiogenic pathways in response to neuronal damage during acute brain tissue ischemia likely requires a certain amount of time, which explains the absence of a significant increase in VEGF concentration in the peripheral blood, indicating a delayed activation of vascular remodeling reactions [24, 25]. Thus, VEGF may be a potential marker of functional outcomes in more remote periods of ischemic stroke (end of acute and early recovery).

The identified relationship between increased serum VEGF levels and worsening clinical and functional outcomes in atherothrombotic stroke can be explained by a complex of pathophysiological mechanisms characteristic of this subtype of stroke. The chronic nature of atherosclerotic vascular lesions creates conditions for prolonged hypoxia, which leads to sustained activation of HIF-1α and continuous expression of VEGF. This leads to the development of vascular preconditioning manifested by increased expression of VEGF-R2 receptors and changes in their sensitivity, which, in combination with the activation of matrix metalloproteinase-9 releasing matrix-bound VEGF creates the preconditions for increased vascular permeability [26, 27].

These changes contribute to the development of vasogenic edema due to destabilization of endothelial tight junctions and lead to extravasation of proinflammatory cytokines, which increases the risk of hemorrhagic transformation. It is important to note that atherothrombotic lesions are accompanied by pathological angiogenesis, producing functionally immature vessels, which exacerbates ischemic damage. Chronic hypoxia maintains constant activation of VEGF-dependent signaling pathways, which contributes to prolonged damage to the BBB and more pronounced neurological deficits [20, 28]. Increased VEGF expression in patients with the atherothrombotic subtype of ischemic stroke may serve as a marker of persistent pathophysiological processes, including a progressive increase in the volume of the ischemic lesion [29]. This explains the association we identified between increased VEGF and worse clinical and functional outcomes in this pathogenetic subtype of stroke.

CONCLUSION

The heterogeneity of the pathogenetic mechanisms of ischemic stroke limits the prognostic value of VEGF expression levels as a standalone biomarker during the acute phase of the disease. The prognostic value of VEGF is limited by the variability of the response depending on the severity and pathogenetic subtype of stroke. This study highlights the need to investigate the temporal changes in VEGF regulation and other angiogenic factors to understand the mechanisms of vascular remodeling and functional recovery after cerebral ischemia. Comprehensive analysis of VEGF in combination with other neuron-specific proteins may facilitate a more accurate assessment of compensatory processes in ischemic stroke and will become a valuable tool for predicting disease outcomes.

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