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PLASMA LEVEL OF VON WILLEBRAND FACTOR IN PATIENTS IN THE EARLY STAGES OF RECOVERY AFTER ATHEROTHROMBOTIC STROKE

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Atherothrombotic ischemic stroke remains a leading cause of disability and mortality. The search for biomarkers of its recurrence is a key task of modern vascular neurology. Von Willebrand factor (vWF), a multimeric glycoprotein that binds platelets to damaged vessel, is considered a marker of endothelial dysfunction and platelet activity. The aim of the study was to assess the level of von Willebrand factor in the blood plasma of patients in the early stages of recovery after atherothrombotic stroke. 200 patients aged 60.42 ± 7.40 with atherothrombotic ischemic stroke and 50 people from the control group were examined. The prospective observation was conducted for 12 months to record recurrent strokes. Neurological deficit was assessed using the National Institutes of Health Stroke Scale and results were interpreted according to the generally accepted stroke grading. The level of vWF was determined by the light-transmission analysis on a laser aggregometer. The data obtained showed that the level of vWF in the early recovery period increased in parallel with the increase in disorder severity to 137.7, 155.7 and 169.7% in the groups with easy, average, and severe stroke, respectively, compared with the control indicator of 95.3%. In patients with the highest vWF level (>170%), the recurrent ischemic strokes were recorded in half of the cases. These results indicate the clinical significance and prognostic value of von Willebrand factor, in particular, for identifying the patients at high risk of recurrent vascular accidents requiring enhanced secondary prevention measures.

K e y w o r d s: von Willebrand factor, ischemic stroke, neurological deficit, early recovery period, recurrent stroke.

Atherosclerotic disease is a long-term multifactorial process that develops over decades and involves diverse cell populations at all stages – from the initial formation of an atherosclerotic plaque to the development of its complications, in particular atherothrombotic events, such as ischemic stroke. The role of platelet adhesion, activation and aggregation in these processes has been studied quite deeply, but more and more data indicate that the interaction of platelets with the endothelium plays a key role not only in thrombus formation, but also in the early stages of atherogenesis.

Among the endothelial mediators of hemostasis, a special role is played by von Willebrand factor (vWF), a high-molecular glycoprotein that ensures adhesion and aggregation of platelets in areas of endothelial damage, in particular in areas of turbulent blood flow in stenoses [1-4]. In areas of atherosclerotic vascular damage, vWF contributes to platelet fixation to the subendothelium and the formation of thrombotic masses [5-8]. Given its key role in hemostasis, changes in the level or functional activity of vWF may have a significant impact on the development and course of cardiovascular diseases, in particular ischemic stroke, making it a promising marker and potential therapeutic target [9-15].

Alice Taylor found that in patients with acute stroke and transient ischemic attack, vWF levels increased during the first four weeks after the onset of the acute event and remained stably elevated for approximately three months [7].

According to Noriyuki Okubo et al., vWF levels in patients hospitalized within 72 hours of myocardial infarction were (2151±97 IU/dL), which was 33% higher than in patients with stable ischemic heart disease (IHD) – (1445±93 IU/dL), and 34% higher than in patients with thoracalgia – (1425±76 IU/dL) [8].

In a study by Yan B. et al., which was based on a comparison of vWF levels in patients with myocardial infarction (MI) and healthy volunteers, it was found that the level of vWF in patients with MI was almost three times higher and amounted to (219.87±1.32%) compared to the indicator in healthy individuals – (78.9±0.38%) [9].

In a prospective study by Whincup P.H. et al., 1411 men without detected IHD were examined, who were distributed into tertiles depending on the level of vWF. After a maximum observation period of 16 years, it was found that the risk of developing IHD in men with the highest level of vWF (upper tertile) was 1.53 times higher compared to those with the lowest level, even after correction for traditional risk factors [10].

In a prospective study of approximately 10,000 healthy men, 296 developed coronary heart disease (CHD) during a 5-year follow-up period, including 158 myocardial infarction (MI) and 142 stable or unstable angina. It was found that baseline vWF levels were statistically higher in patients who subsequently developed MI (129.2 ± 53.1 IU/dL) compared with healthy participants (115.9 ± 41.8 IU/dL). The risk of developing MI in men with vWF levels in the fourth quartile was 3.34 times higher than in men with vWF levels in the first quartile [6].

In the prospective ECAT study of 3043 patients with angina, baseline vWF levels were found to be higher in patients who subsequently developed MI or sudden cardiac death over a 2-year follow-up period. Participants were stratified by quartiles of vWF levels, and the risk of adverse cardiovascular events was found to be 1.85-fold higher in patients with the highest vWF levels (upper quartile) compared with those in the lower quartile [11].

In another study of 123 patients aged <70 years who had had an MI, vWF levels were measured 3 months after the acute event. A follow-up period of 4.9 years showed that elevated vWF levels were an independent predictor of recurrent MI and cardiovascular death [13]. T. Nowakowski, et al. published the results of studies describing increased vWF levels in patients with peripheral atherosclerosis, especially in patients in the restenosis group [14].

However, not all studies confirm the prognostic clinical value of vWF. For example, in the SMILE study, which included 560 men aged 18–70 years with stable coronary artery disease (after an MI at least 6 months before inclusion) and 646 healthy individuals, no significant differences in vWF levels were found between the groups (138% vs. 135%, respectively), which does not confirm the presence of an association between vWF levels and coronary artery disease in this cohort [15].

In the large-scale ARIC study, which included 14,477 participants aged 45–64 years, it was found that elevated vWF levels are associated with an increased risk of coronary artery disease. However, as the results of the analysis showed, the inclusion of vWF indicators in models that take into account traditional risk factors only slightly improves the predictive accuracy in predicting the development of the disease.

Given the conflicting results of previous studies, we set the goal of determining the prognostic value and clinical significance of vWF in patients in the early recovery period of atherothrombotic stroke by observing these patients for a year with recording cases of repeated ischemic stroke against the background of a full range of secondary prevention measures.

Based on the above, the issue of studying circulating blood predictors of the occurrence of atherothrombotic complications in patients with ischemic stroke in the early recovery period is relevant and of significant scientific interest.

The aim of the study is to assess the clinical significance and prognostic value of von Willebrand factor in the blood of patients in the early recovery period of atherothrombotic stroke.

Material and Methods

A clinical and laboratory analysis of 200 patients in the early recovery period of atherothrombotic stroke was conducted. Among the examined there were 116 men and 84 women aged (60.42±7.4) years. The control group consisted of 50 practically healthy people (26 men and 24 women) without severe somatic pathology and history of cerebral circulation disorders, aged (58.7±6.3) years.

The study was conducted on the basis of the stroke center of the Ivano-Frankivsk Regional Clinical Hospital in the period from 2021 to 2025. The inclusion criteria were a confirmed diagnosis of atherothrombotic ischemic stroke according to the TOAST classification. Exclusion criteria were: cardioembolic stroke, decompensated heart, respiratory, liver and kidney failure, oncological pathology, cognitive impairment (<20 MMSE). The study was approved by the Bioethics Commission of the IFNMU (protocol No. 149/25 of 01/23/2025) and was

performed in accordance with the provisions of the Declaration of Helsinki of 1964. Upon inclusion in the study, all patients signed a voluntary informed consent.

All participants underwent a clinical and neurological examination, instrumental methods of examination (MRI or CT of the brain, ultrasound of extracranial vessels, ECG, EchoCG) and laboratory determination of the level of von Willebrand factor in blood plasma by the method of turbidimetric aggregation (light-transmission, LTA) on the Biola Aggregation Analyser laser aggregometer. Blood sampling to determine the level of von Willebrand factor (vWF) was performed by venipuncture on an empty stomach 30-35 days after the development of ischemic stroke. The reference range of von Willebrand factor (vWF) level for the method used is 50–150%.

The assessment of neurological deficit was carried out using the standardized NIHSS scale (National Institutes of Health Stroke Scale). The results were interpreted according to the generally accepted grading: mild stroke: 1–4 points; moderate: 5–15 points; severe stroke: 16–20 points; very severe stroke: > 21-42 points.

For secondary prevention, all patients received antiplatelet agents, statins, antihypertensive and hypoglycemic drugs if indicated. If hemodynamically significant stenoses of cerebral vessels were detected, patients were consulted by a vascular surgeon with further recommendations for carotid endarterectomy and continuation of standard therapy for secondary stroke prevention. Further prospective observation lasted 12 months with recording of cases of recurrent ischemic stroke and analysis of baseline vWF levels in these patients.

For statistical data processing, STATISTICA 8 software was used. The frequency of qualitative indicators was presented in absolute (*n*) and relative (%) values. During the analysis of quantitative data, the nature of the distribution of indicators was determined using the Shapiro-Wilk test. For quantitative data with a normal distribution, the results were presented in the form of M (σ), where M is the mean value and σ is the standard deviation; for data with a non-normal distribution, in the form of Me (Q1; Q3), where Me is the median and Q1 and Q3 are quartiles. Quantitative indicators with a normal distribution in two independent groups were compared using the Student test.

Results and Discussion

The level of vWF in patients in the early recovery period of atherothrombotic stroke was 147.3 (135.6; 178.8)%, which was significantly higher compared to the control group – 95.3 (87.6; 105.8)% ($P < 0.05$). The obtained data indicate significant activation of the endothelium and increased prothrombotic activity in the early stages of recovery after stroke. The detected trend towards a significant increase in vWF levels is consistent with the results of a study by Yan B. et al., who demonstrated an almost threefold increase in its concentration in acute vascular accidents compared to healthy individuals [9].

The analysis of vWF levels was performed depending on age, gender and leading etiological factors of stroke. A significant increase in vWF levels was found depending on age compared to the control group ($P < 0.05$), so in middle-aged patients (45-59 years, $n = 24$) it was (141.7 (135.5; 160.8)%), elderly (60-74 years, $n = 153$), - (163.7 (152.5; 174.7)%) and senile (75-90 years, $n = 23$), - (180.3 (176.5; 190.1)%). These results indicate that age is a significant physiological factor affecting the level of vWF. According to the literature, even in healthy people, the level of vWF increases by approximately 10% for each decade of life, which is associated with the gradual aging of the vascular endothelium. The researcher D. Larkin [16] found that with age the activity of the enzyme ADAMTS13, which cleaves large vWF multimers, decreases, as a result of which more active forms of FV circulate in the blood, which contribute to platelet aggregation.

We did not find statistically significant gender differences between vWF levels. However, T. N. Bongers [17] indicate that sex differences exist, although they are leveled with age.

When analyzing the influence of stroke risk factors on the level of vWF, it was found that patients with comorbidity of cerebral atherosclerosis and arterial hypertension had moderate vWF expression (155.7 (135.4; 164.7)%), while patients with cerebral atherosclerosis, arterial hypertension, and diabetes mellitus had significantly higher vWF levels (170.3 (165.5; 185.1)%).

Analysis of the dependence of vWF concentration on the severity of neurological deficit according to the NIHSS scale demonstrated its clear tendency to increase in parallel with the increase in the severity of disorders (Table 1). This pattern indicates a relationship between the deepening of ischemic

damage to brain tissue, caused by atherosclerotic occlusion or critical stenosis of the cerebral artery, and the development of endothelial dysfunction, which is manifested by increased release of vWF from endothelial cells, which, in turn, can be considered as a marker of the severity of ischemic-reperfusion injury and the progression of the pathological process.

The severity of neurological deficit in the examined patients was pathogenetically caused by obliteration of cerebral arteries of the corresponding caliber by atherothrombotic masses. This relationship became the basis for the analysis of the concentration of vWF in comparison with the degree of atherosclerotic lesion of extracranial vessels. We established a progressive increase in the level of vWF in accordance with the intensity of the stenosing process in the extracranial part of the cerebral arteries. In particular, with stenosis (30–50%) the concentration of vWF was – (143.7 (132.5; 155.8)%); with stenosis (50–75%) the indicator reached – (155.7 (142.5; 175.8)%), and in the group with critical stenosis (>75%), – (170.7 (165.5; 190.5)%). The obtained data demonstrate a statistically significant difference compared to the control group ($P < 0.05$), confirming the role of vWF as a marker of endothelial dysfunction in progressive atherosclerosis.

During the year of observation, recurrent ischemic stroke in the study cohort was registered in 56 patients (28%). In five of them, a change in the pathogenetic subtype of stroke to cardioembolic was recorded due to the first detection of atrial fibrillation. This indicates the need for careful dynamic cardiological monitoring of etiological factors of cerebrovascular disorders after the primary stroke. In 72% of cases, recurrent stroke occurred in the same vascular basin as the primary one, which reflects the persistence of the local atherothrombotic process.

To assess the prognostic value of vWF, all patients were divided into four quartiles depending on its level: I (≤ 120%), II (121–145%), III (146–170%), IV (>170%) (Table 2.). The frequency of recurrent strokes increased in accordance with the increase in vWF levels, so, in patients in the I quartile, recurrent stroke occurred in 6 (11,5%) patients; in the II quartile – 11 (21,5%); in the III – 18 (37,5%); and in the IV – 21 (43%).

The study found that extremely high concentrations of von Willebrand factor (vWF >170%, IV quartile) are associated with a critical increase in the risk of recurrent vascular accidents: recurrences of ischemic stroke were recorded in almost 50% of cases. This pattern allows us to consider vWF as a validated predictor of secondary cardiovascular events, which pathogenetically justifies the need to intensify secondary prevention strategies in this group of patients.

Our results correlate with the data of the multicenter ICARAS study, which demonstrated a twofold increase in the frequency of cardio- and cerebrovascular episodes in patients with vWF values corresponding to the upper quartile. Similar conclusions are given by Fuchs and Frossard, noting that with a factor concentration in the IV quartile, the frequency of recurrent infarctions and strokes increases by 6 times. It is noteworthy that fatalities (10%) were recorded exclusively among individuals belonging to the 3rd and 4th quartiles of the distribution.

Modern genetic and molecular studies [18] prove that vWF is not only a passive biomarker of endothelial dysfunction and atherosclerosis, but also a direct predictor and participant in the pathogenetic

Table 1. Concentration changes of von Willebrand factor in patients in the early recovery period of atherothrombotic stroke

Von Willebrand factor (%), Me (Q1; Q3)	Neurological deficit score (NIHSS)			Control group, $n = 50$
	easy (≤4 points), $n = 72$	average (5–15 points), $n = 78$	severe (≥16 -20 points), $n = 50$	
	137.7 (120.5; 140.8) $P < 0.05$	155.7 (142.5; 161.8) $P < 0.001$; $P_1 < 0.05$	169.7 (165.5; 187.5) $P < 0.001$; $P_1 < 0.05$; $P_2 < 0.05$	95.3 (87.6; 105.8)

Note: P – significance of differences in indicators compared to the control group; P_1 – significance of differences in indicators with moderate and severe stroke severity to mild; P_2 – significance of differences in indicators with moderate stroke severity to severe.

Table 2. Distribution of patients by quartile depending on the level of von Willebrand factor and the frequency of recurrent ischemic strokes during the year

Quartile	VWF level, %	Number of patients	Number of recurrent ischemic strokes (within 1 year)
I	≤120	52	6 (11.5%)
II	121–145	51	11 (21.5%)
III	146–170	48	18 (37.5%)
IV	>170	49	21 (43%)

cascade of ischemic stroke. Our results indicate a complex interaction between endothelial destruction and activation of the platelet link of hemostasis against the background of systemic atherosclerosis. This functional connection ensures the integration of cellular and vascular mechanisms of thrombogenesis [19, 20].

From a pathophysiological perspective, endothelial damage under ischemic conditions stimulates massive release of vWF, which initiates platelet adhesion and aggregation [21, 22]. In response, activated platelets secrete a spectrum of vasoactive and proinflammatory mediators (including thromboxane A_2 and serotonin), which potentiates endothelial destruction and closes the pathogenetic "vicious circle" of atherothrombosis [23].

Conclusions. In patients in the early recovery period of atherothrombotic stroke, the level of von Willebrand factor significantly exceeds the indicators of the control group. His significantly increases with age ($P < 0.05$), reaching a peak in old age (180.3% (176.5; 190.1)%), which is due to age-related involution of the endothelium. No statistically significant differences in the concentration of vWF depending on gender were found, which indicates the leveling of the gender effect against the background of pronounced vascular pathology. The concentration of vWF showed a progressive increase in accordance with the severity of the condition according to the NIHSS scale. The highest values were recorded in severe deficiency, which has a statistically significant difference compared to both the control group ($P < 0.001$).

High values of vWF (III–IV quartiles) are associated with an increased risk of recurrent ischemic stroke within a year, which indicates its prognostic value as a biomarker of vascular complications.

The use of vWF in clinical practice allows identifying a group at high risk of recurrent vascular catastrophes and intensifying secondary prevention measures.

Prospects for further research. In our opinion, it would be interesting to investigate the dependence of the level of von Willebrand factor on the subtype of ischemic stroke.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http:// ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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РІВЕНЬ ФАКТОРА ФОН ВІЛЛЕБРАНДА У ПЛАЗМІ КРОВІ ПАЦІЄНТІВ НА РАННІХ СТАДІЯХ ВІДНОВЛЕННЯ ПІСЛЯ АТЕРОТРОМБОТИЧНОГО ІНСУЛЬТУ

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Атеротромботичний ішемічний інсульт залишається провідною причиною інвалідності та смертності. Пошук біомаркерів його рецидиву є ключовим завданням сучасної судинної неврології. Фактор фон Віллебранда (vWF), мультимерний глікопротеїн, що зв'язує тромбоцити з пошкодженою судиною, вважається маркером ендотеліальної дисфункції та активності тромбоцитів. Метою дослідження була оцінка рівня фактора фон Віллебранда в плазмі крові пацієнтів на ранніх стадіях відновлення після атеротромботичного інсульту. Було обстежено 200 пацієнтів віком 60,42 ± 7,40 років із атеротромботичним ішемічним інсультом та 50 осіб із контрольної групи. Проспективне спостереження проводилося протягом 12 місяців для

реєстрації рецидивів інсультів. Неврологічний дефіцит оцінювали за допомогою шкали інсульту Національного інституту здоров'я, а результати інтерпретували відповідно до загальноприйнятої градації важкості інсульту. Рівень vWF визначали за допомогою світлопропускаючого аналізу на лазерному агрегометрі. Отримані дані показали, що рівень фактора фон Віллебранда (ФВ) у ранньому періоді одуження зростав паралельно зі збільшенням тяжкості захворювання до 137,7, 155,7 та 169,7% у групах із легким, середнім та тяжким інсультом відповідно, порівняно з контрольним показником 95,3%. У пацієнтів із найвищим рівнем ФВ (>170%) рецидивні ішемічні інсульти реєструвалися у половині випадків. Ці результати свідчать про клінічну значущість та прогностичну цінність фактора фон Віллебранда, зокрема, для виявлення пацієнтів із високим ризиком рецидивних судинних катастроф, що потребують посилених заходів вторинної профілактики.

Ключові слова: фактор фон Віллебранда, ішемічний інсульт, неврологічний дефіцит, ранній відновний період інсульту, рецидивуючий інсульт.

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