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## CEREBRAL PERIVASCULAR SPACES AS AN IMPORTANT DIAGNOSTIC MARKER OF CEREBRAL SMALL VESSEL DISEASE AND BRAIN PATHOLOGY

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### Abstract

**Objective.** To assess the association of enlarged perivascular spaces (EPVS) with cerebral small vessel disease (CSVD), some basic metabolic tests, brain atrophy and clinical outcome after territorial stroke.

**Methods.** 90 patients with acute stroke (<24 hours of onset) were recruited. Modified Rankin scale and Bartel index were used to assess stroke outcome. Cerebral MRI was performed to assess white matter lesions (WML), lacunes, cerebral atrophy and EPVS in basal ganglia and cortical-subcortical area with a validated four-point visual rating scale. Total CSVD burden was calculated with summation of lacunes, WML and EPVS with a validated scale. Spearman correlation and logistic regression were used to identify association between EPVS, total CSVD burden, CSVD features and some basic metabolic tests (creatinine, urea, cholesterol, bilirubin, fibrinogen, erythrocyte sedimentation rate).

**Results.** There was a very strong correlation between EPVS and total CSVD burden ( $r = 0.9$ ,  $p < 0.000$ ) and with Fazekas score scale ( $r = 0.9$ ,  $p < 0.000$ ). A strong correlation was

found between EPVS and global cortical atrophy ( $r = 0.7$ ,  $p < 0.000$ ), and a moderate correlation with presence of lacunes ( $r = 0.4$ ,  $p < 0.05$ ). EPVS in basal ganglia had a significant correlation with the degree of extracranial carotid stenosis ( $r = 0.4$ ,  $p < 0.05$ ). The severity of EPVS was associated with a more severe neurological deficit on the NIHSS scale ( $r = 0.5$ ,  $p < 0.05$ ) and an increased degree of disability by Bartel's index ( $r = 0.5$ ,  $p < 0.05$ ) in patients on discharge. Creatinine was associated with CSVD features.

**Conclusions.** EPVS is highly associated with total CSVD burden and others its features as well as with stroke outcome. EPVS in different brain regions may lead to the distinguish of two main type of CSVD – hypertensive arteriolosclerosis and beta-amyloid angiopathy.

**Key words: perivascular spaces; cerebral small vessel disease; stroke; MRI**

### **Introduction**

With the development of neuroimaging techniques for the diagnosis of brain pathology, practitioners and researchers are increasingly able to early diagnose cerebrovascular changes, predict, prevent and monitor the effectiveness of the treatment. Enlarged perivascular spaces of the brain is an important neuroimaging indicator of vascular changes, in particular the pathology of cerebral small vessel disease and the risk of lacunar strokes [1, 2]. In addition, EPVS may reflect changes in large vessels - there is a relationship between arterial pulsatility and EPVS that allows identification of individuals at increased risk of territorial stroke [3, 4]. The study of EPVS «in space and time» is a promising predictor of clinical and biological changes.

Perivascular spaces (Virchow-Robin spaces) surround small perforating arteries, arterioles, capillaries, venules of the brain and are a drainage system that helps to eliminate products of neurons metabolism, in particular - beta-amyloid, subtypes of which are a pathological substrate for the development of amyloid angiopathy or Alzheimer's disease. This system is known as Glyphatic (Glia and Lymph), which is analogous to the body's lymphatic system. It is most active at night during sleep [5, 6, 7, 8].

Present-day scientific data show that EPVS of different brain areas, namely, cortical-subcortical and deep, in the area of basal ganglia, have anatomical and physiological differences, and their enlargement may have different ethio-pathogenesis and different prognostic value [9]. The arteries of the basal ganglia are surrounded by two layers of leptomeninx, separated by perivascular spaces, which are a direct extension of the Virchow-Robin spaces in the subarachnoid space. The inner layer closely contacts the adventitia of the

vascular wall and the outer layer with the border glial membrane of the astrocytic processes and is a continuation of the pia mater. The cortical and subcortical arteries have only one periarterial layer, and surrounded by which arteries penetrate the cortex and white matter. Drainage of the interstitial fluid from the brain to the lymph nodes of the neck can mainly pass through the cortical-subcortical PVS, but not through the PVS of basal ganglia [10]. This, in turn, gives rise to the idea of certain differential-diagnostic disparities of EPVS of different brain areas.

According to existing data, EPVS increase the risk of stroke, more lacunar than large territorial ones, correlate with vascular dementia, hypertension, and sleep disorders [11, 12, 13]. EPVS is one of the key signs of CSVD (along with white matter lesion and lacunes), observed in cerebral amyloid angiopathy, and is probably associated with brain atrophy [14, 15]. However, the pathogenesis of EPVS and its role in the development of cerebrovascular dysfunction and stroke have not been thoroughly studied.

Experimental studies have shown that systemic inflammation also plays a certain role in the progression of EPVS. Inflammatory markers accumulate around the vessels in the perivascular spaces, disrupt the integrity of the blood-brain barrier, increase extravasation of blood plasma components, provoke macrophage migration, and impede the clearance of brain wastes. These processes lead to oxidative stress, endothelial dysfunction, impaired myelin integrity and progression of WML. Inflammation can cause a decrease in blood flow, hypoperfusion, hypoxia of brain tissue and become a central mechanism of the development of CSVD [16, 17].

Movement of the cerebrospinal fluid along the perivascular drainage pathways is driven by the arterial pulse wave (pulsatility), so increasing the stiffness of the vascular wall decrease it and leads to deceleration clearance of metabolites and enlargement of perivascular spaces. Arterial hypertension contributes to the stiffness of the walls of the large arteries, which leads to increased pulse wave on small vessels, with subsequent development of arteriosclerosis, which may be another link of the pathogenesis of CSVD [18].

Thus, key factors in the progression of CSVD are vascular dysfunction (including impairment of cerebrovascular reactivity), inflammation, and dysfunction of the blood-brain barrier. Therefore, the enlargement of PVS can be a significant indicator of vascular changes with some prognostic potential.

### **Objectives**

1. Establish the association and diagnostic value of EPVS with CSVD and its individual features (WML, lacunes, atrophy).

2. To determine whether EPVS is associated with the severity of neurological deficits and with the degree of disability in patients with acute territorial stroke.

3. Investigate the relationship between EPVS and the biochemical markers of dysfunction of the other body systems.

### **Methods**

The study was conducted at the specialized stroke unit of Vinnitsia Regional Clinical Psychoneurological Hospital named after acad. O.I. Yushchenko. Patients were hospitalized within 24 hours of disease onset. All subjects were diagnosed with a stroke based on the TOAST criteria [37]. The whole cohort of participants was performed brain CT (immediately, upon admission - to determine the type of stroke), brain MRI, carotid duplex scan to determine the degree of extracranial carotid stenosis, biochemical analyses of blood (urea, creatinine, bilirubin, fibrinogen, prothrombin time, cholesterol). Clinical-neurological evaluation of patients was carried out by using the rating scales: the severity of neurological deficits on the National Institute of Health Stroke Scale (NIHSS) [38] on admission, during the intermediate treatment period and on discharge; level of consciousness on the Glasgow coma scale (GCS) on admission, intermediate treatment and on discharge; cognitive function was evaluated using the Mini-Mental State Examination (MMSE) [39]; the degree of disability with modified Rankin scale (mRS) [40] on admission, on discharge, and at 90 days after discharge (telephone interview); index of daily activity of Bartel at the time of discharge and at 90 days after the discharge (in telephone interview). Demographic indicators and risk factors were recorded: age, gender, place of residence, level of education, hypertension, atrial fibrillation, diabetes mellitus, concomitant kidney disease, lungs diseases, gastrointestinal tract diseases, varicose veins, previous stroke.

### **MRI protocol and assessment**

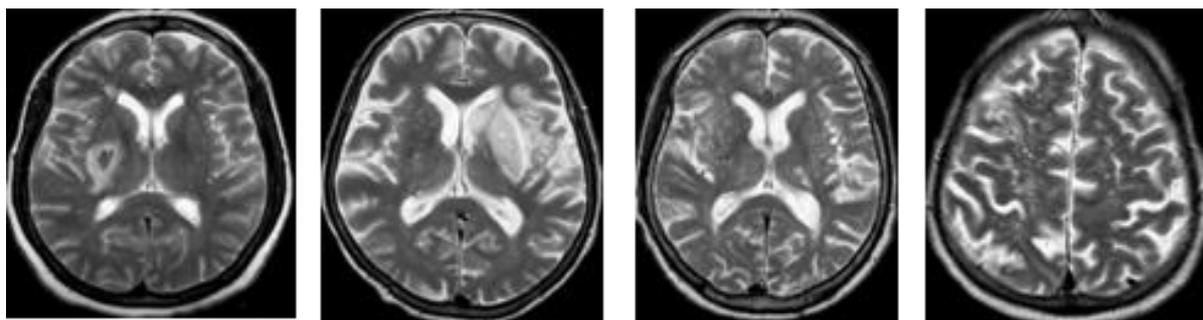
MRI was performed on a Philips Achieva 1.5T scanner of our hospital's MRI center.

EPVS were defined as point foci of circular, ovoid shape (if perpendicular to the slice plane) or linear foci (if detected along the slice plane) having characteristics of a signal identical to the cerebrospinal fluid in all slices, from 1 to 3 mm in diameter (in some cases they may be bigger). We differentiated them from lacunes by size - lacunes larger than 3 mm in diameter and surrounded by a ring of hyperintense signal on fluid-attenuated inversion recovery. The amount of EPVS was counted separately at the level of basal ganglia and the cortex / subcortical white matter. To assess the severity, a validated four-point visual rating scale (0 = none; 1 = 1-10; 2 = 11-20; 3 = 21-40; 4 => 40) was used [19]. To calculate the EPVS of individual regions, we found a slice from the most vulnerable one hemisphere at

both levels. The total burden of EPVS was also calculated by summing the EPVS of areas of basal ganglia and subcortical white matter (0 to 8).

Lacunae were defined as round or ovoid lesions of 3 to 20 mm in diameter having characteristics of a signal identical to the cerebrospinal fluid and surrounded by a hyperintense ring on fluid-attenuated inversion recovery. They were distinguished from recent lacunar infarcts by the absence of signal on diffusion-weighted imaging [20].

White matter lesion (leucoaraiosis) was determined and evaluated on a visual scale by Fazekas et al. [21]. The severity of periventricular WML was calculated as follows: none (0, no signs), light (1, thin periventricular "caps" or pencil-thin lining), moderate (2, smooth "halo"), severe (3, large confluent areas). The scale of Klarenbeek et al. was used to determine the global CSVD burden [22], which has been validated in a number of large studies [24-27]. According to the scale, in the case of one or more lacunae, there was one score awarded, if there was no lacuna - none. If the Fazekas scale of leucoaraiosis was 3, there was one point awarded, if the level of leucoaraiosis was within the range of 0-2 - none. If the severity of the EPVS was 2 or higher, one point was scored, and if the severity of the EPVS was less than two, none points were awarded. Three data points (presence of lacunae, degree of WML, severity of EPVS) were summed to calculate the total CSVD burden, which could be from 0 to 3. The degree of cortical, external atrophy was determined by a valid visual rating scale, from 0 to 3 (absence, mild, moderate, severe) [41]. Mediotemporal hippocampal atrophy was estimated by using the Sheltens scale [23]. Internal brain atrophy was evaluated by the following ventriculometric indices: index of anterior horns of lateral ventricles (Evans index) - the ratio of the maximum diameter between the outer walls of the anterior horns of lateral ventricles and the maximum bitemporal diameter of the skull; the index of the third ventricle was estimated by the ratio of its maximum width in the posterior third at the level of the pineal body to the largest transverse diameter of the skull, multiplied by 100; Schlattenbrandt-Nurenberger index (index of third ventricle) is the ratio of the maximum transverse diameter of the skull to the width of the III ventricle; the index of the fourth ventricle was calculated by the ratio of its largest width to the maximum internal diameter of the posterior cranial fossa on the same section; bicaudal index - the ratio of the width of the frontal horns at the level of the caudate nucleus to the diameter of the brain at the same level [28, 29].



**Fig. 1** view of EPVS in basal ganglia (a-c) and cortex (d) (a, grade 1, 1–10 EPVS; b, grade 2, 11-20 EPVS; c, grade 3, 21–40 EPVS; d, grade 4, >40 EPVS).

### Statistical analysis

Statistical data processing was performed in IBM SPSS 25.0 (IBM Corp., Armonk, NY, USA). Student's T-test or Mann-Whitney U-test was used to analyze differences between two groups, ANOVA or Kruskal-Wallis test (in case of normal distribution or non-normal, respectively). Spearman or Pearson correlation analysis and logistic regression were used to establish the relationship between EPVS and other clinical-instrumental data.

### Results

All clinical and demographic characteristics of patients are shown in table 1. MRI characteristics of patients are shown in table 2. A peculiar, different from the population distribution of types of ischemic stroke was due to the specific practice of the unit stroke, which is intended for urgent thrombolysis and the selection of patients is performed in favor of moderate and severe territorial stroke. 28 (31%) patients had increased fibrinogen, 13 (14.6%) – increased urea, 8 (9%) - increased creatinine, 9 (10%) - increased bilirubin, 53 (59%) - increased cholesterol, 34 (38 %) - increased erythrocyte sedimentation rate.

**Table 1** Clinical-demographical characteristics

Total number of patients, n	90
Age	60,57±11,029
Sex, male	48 (53,3 %)
Related diseases::	
- Hypertension	88 (97,8 %)
- Diabetes	20 (22 %)
- Varicose	21 (23,3 %)
- Chronic kidney disease	7 (7,8 %)

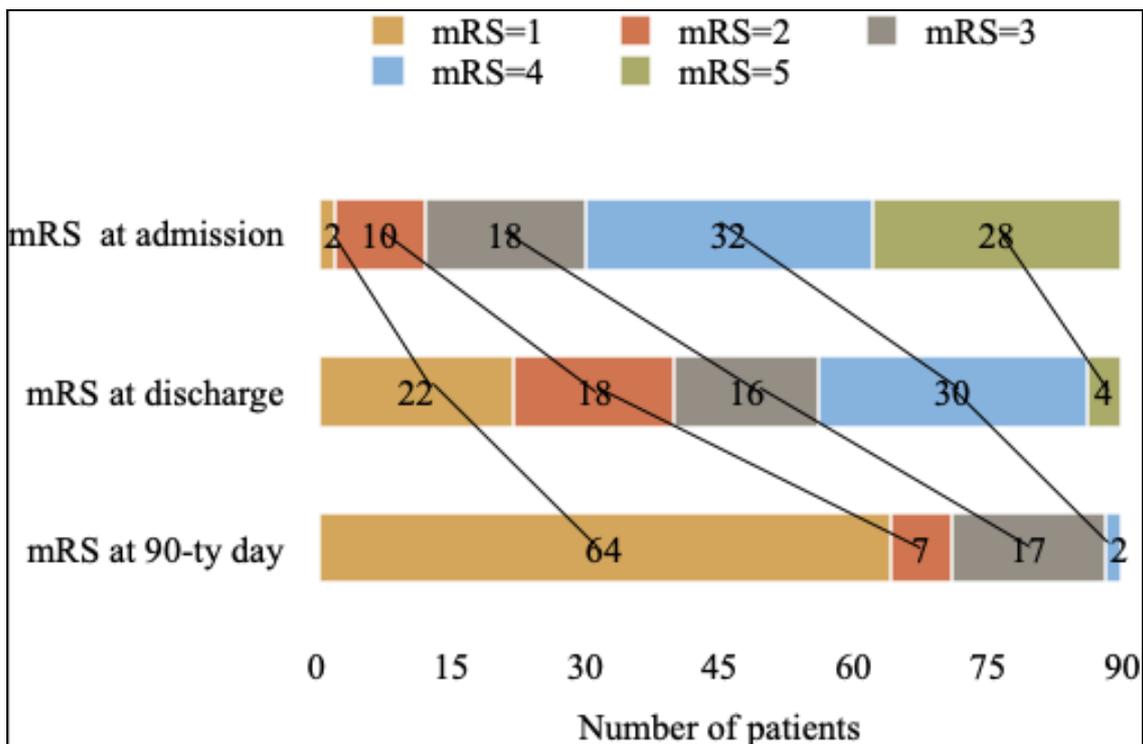
- Chronic gastrointestinal diseases	10 (11,1 %)
- Chronic lungs disease	16 (17,8 %)
Smoking	19 (21,1 %)
Previous stroke	33 (36,8 %)
Hypertension: - stage 1	14 (15,4 %)
- stage 2	58 (64,8 %)
- stage 3	15 (16,5 %)
Weight for BMI: - overweight	29 (32,2 %)
- obese class I	26 (28,9 %)
- obese class II	9 (10 %)
- obese class III	5 (5,6 %)
Extracranial carotid artery stenosis:	
- < 50%	67 (75 %)
- 50-75%	19 (21 %)
- > 75%	4 (4 %)
Ischemic stroke	81 (90 %)
Hemorrhagic stroke	9 (10 %)
TOAST-classification of ischemic stroke:	
- large-artery atherosclerosis	58 (64 %)
- cardioembolism	20 (22 %)
- small-vessel occlusion	5 (5,4 %)
- stroke of undetermined etiology	7 (7,5 %)
- stroke of other determined etiology	1 (1,1 %)
NIHSS at admission:	
minor-moderate (1 – 8)	33 (36,7 %)
moderate (9 – 12)	24 (26,7 %)
moderate-severe (13 – 15)	10 (11,1 %)
severe (> 15)	23 (25,3 %)
NIHSS at discharge:	
minor-moderate (1 – 8)	52 (57,8 %)
moderate (9 – 12)	25 (27,8 %)
moderate-severe (13 – 15)	3 (3,3 %)
severe (> 15)	10 (11,1 %)
GCS at admission:	
coma (3 – 8)	1 (1,1%)
sopor (9 – 12)	22 (24,4%)
confusion (13 – 14)	31 (34,4%)
fully alert (15)	36 (40%)
GCS at admission:	
coma (3 – 8)	2 (2,2%)
sopor (9 – 12)	6 (6,7%)
confusion (13 – 14)	21 (23,3%)
fully alert (15)	61 (67,8%)

Bartel index at admission:	
Severe disability (0 – 45)	28 (21%)
Moderate disability (46 – 75)	17 (19%)
Minimal disability (76 – 100)	45 (50%)
Bartel index at discharge:	
Severe disability (0 – 45)	18 (20%)
Moderate disability (46 – 75)	8 (9%)
Minimal disability (76 – 100)	64 (71%)
(MMSE < 26) (at discharge)	70 (77,8%)

**Table 2** MRI characteristics

Total EPVS burden:	
1	0 (0%)
2	5 (5,6%)
3	15 (16,9%)
4	22 (24,7%)
5	34 (38,2%)
6	10 (11,2%)
7	3 (3,4%)
8	0 (0%)
Severity of EPVS at basal ganglia:	
1	27 (30,3%)
2	49 (55,1%)
3	13 (14,6%)
4	0 (0%)
Severity of EPVS at subcortical regions:	
1	7 (7,9%)
2	29 (32,6%)
3	37 (52,8%)
4	6 (6,7%)
Severity of WML (Fazekas scores):	
1	18 (20%)
2	32 (35,6%)
3	39 (43,3%)
Total CSVD burden:	
0	22 (24,7%)
1	32 (36%)
2	26 (29,2%)
3	9 (10,1%)
Presence of lacunes:	
yes	24 (27%)
no	66 (73%)
Global cortical atrophy (0-3):	
0	5 (5,6%)
1	43 (47,8%)
2	27 (30%)
3	15 (16,7%)

Mediotemporal hippocampal atrophy (0-4):	
0	27 (30%)
1	42 (46,7)
2	12 (13,3%)
3	8 (8,9%)
4	1 (1,1%)
Increased Evans index	41 (45,6%)
Enlarged of third ventricle	58 (64%)



**Fig. 2** dynamics of mRS changes

Total EPVS burden had a very strong correlation with total CSVD burden ( $r = 0.9$ ,  $p < 0.000$ ) and with Fazekas score scale ( $r = 0.9$ ,  $p < 0.000$ ). A strong correlation was found between EPVS and global cortical atrophy ( $r = 0.7$ ,  $p < 0.000$ ), and a moderate correlation with presence of lacunes ( $r = 0.4$ ,  $p < 0.05$ ), but with mediotemporal hippocampal atrophy the association wasn't found ( $r = 0.4$ ,  $p > 0.05$ ), as with the internal cerebrospinal spaces (by the index of the anterior horns of the lateral ventricles ( $r = 0.3$ ,  $p = 0.9$ ) and the index of the third ventricle ( $r = 0,3$ ,  $p = 0.6$ )). There was a tendency of association between total EPVS burden and the degree of hypertension ( $r = 0.5$ ), but it didn't have sufficient significance ( $p = 0.09$ ).

EPVS in basal ganglia had a significant correlation with the degree of extracranial carotid stenosis ( $r = 0.4, p < 0.05$ ), while EPVS of the cortical-subcortical regions had no such correlation ( $r = 0.1, p = 0.9$ ). A moderate correlation was found between stage of hypertension and global cortical atrophy ( $r = 0.4, p < 0.05$ ), but association of stage of hypertension and mediotemporal hippocampal atrophy wasn't found. Severity of WML ( $r = 0.8, p < 0.000$ ), lacunes ( $r = 0.7, p < 0.05$ ), global cortical atrophy ( $r = 0.7, p < 0.05$ ), total CSVD burden ( $r = 0.7, p < 0.05$ ) increased with age. The history of previous strokes was associated with total CSVD burden ( $r = 0.4, p = 0.002$ ), presence of lacunae ( $r = 0.4, p < 0.05$ ), and WML ( $r = 0.4, p < 0.05$ ). Increase in creatinine level ( $r = 0.4, p < 0.01$ ) and smoking ( $r = 0.55, p = 0.002$ ) were associated with the presence of lacunes ( $r = 0.6, p = 0.002$ ). Chronic kidney disease, as well as creatinine and urea were associated with other signs of CSVD (WML, EPVS), but such relationship was not significant ( $p = 0.052-0.06$ ). Elevated cholesterol was moderately correlated only with EPVS in the subcortical white matter ( $r = 0.4, p < 0.05$ ). Widening of the anterior horns of the lateral ventricles (Evans index) was correlated with increased creatinine ( $r = 0.3, p < 0.05$ ) and body mass index ( $r = 0.5, p < 0.05$ ). Mediotemporal hippocampal atrophy was associated with a history of stroke ( $r = 0.4, p < 0.05$ ), degree of WML ( $r = 0.6, p < 0.05$ ), and total CSVD burden ( $r = 0.5, p < 0.05$ ), Evans index ( $r = 0.4, p < 0.05$ ), third ventricle index ( $r = 0.7, p < 0.000$ ), creatinine ( $r = 0.4, p < 0.05$ ). The degree of Fazekas score increased in patients with history of traumatic brain injury ( $r = 0.4, p < 0.000$ ). The presence of lacunes correlated with other signs of CSVD: ( $r = 0.7, p < 0.000$ ), WML ( $r = 0.4, p < 0.01$ ), EPVS in basal nuclei ( $r = 0.4, p = 0.003$ ) and total CSVD burden as well as decrease GCS score on admission ( $r = 0.3, p < 0.05$ ) and a higher degree of disability on a modified Rankin scale (mRS) on discharge ( $r = 0.4, p < 0.05$ ). Total CSVD burden was associated with the severity of cognitive deficits ( $r = 0.3, p < 0.05$ ). The severity of EPVS was associated with a more severe neurological deficit on the NIHSS scale ( $r = 0.5, p < 0.05$ ) and an increased degree of disability by Bartel's index ( $r = 0.5, p < 0.05$ ) in patients on discharge. No correlation was found between global cortical atrophy and mediotemporal hippocampal atrophy ( $r = 0.4, p = 0.5$ ), between extracranial carotid stenosis and mediotemporal hippocampal atrophy ( $r = 0.3, p = 0.6$ ), between EPVS in basal ganglia and mediotemporal hippocampal atrophy ( $r = 0.2, p = 0.7$ ).

## **Discussion**

Our results confirmed a very strong correlation between total EPVS burden and total CSVD burden, between total EPVS burden and separate CSVD signs - WML (very strong correlation), external cortical atrophy (strong correlation), presence of lacunes (significant

correlation). Thus, EPVS have a high diagnostic value and can be a prognostic marker and criterion for the effectiveness of therapeutic interventions. Today, it is considered that a single number of EPVS is not pathological. However, it is possible that their increase, even in small numbers, may reflect "blind", preclinical changes, preclinical stage of pathological changes, which over time may manifest of a variety of known symptoms and syndromes of CSVD. Therefore, EPVS can be assumed as a sign of CSVD debut. EPVS is also observed in other diseases (eg, multiple sclerosis) [31], so it is necessary to compare EPVS with other vascular risk factors.

The results of our study showed that EPVS of different brain areas may have a different etiopathogenesis, which coincided with a number of other studies [9, 42-44]. Cortical, convexital vessels of the brain are known to have much broader cerebral autoregulation limits and blood circulation depending on the metabolic needs of neurons, which may increase or decrease tenfold [36]. They are more resistant to blood pressure changes, while lenticular vessels in basal nucleus area are more limited. Therefore, stenosis of extracranial vessels and changes in blood pressure will progress the rigidity of the walls of large vessels, which will lead to increased pulse wave effects on arterioles and capillaries, dysfunction of the blood-brain barrier and widening of perivascular spaces. Considering the above, vessels and PVS will mostly suffer in the area of basal ganglia. Basal ganglia EPVS can be used to identify one of the major subtype of CSVD - hypertensive arteriosclerosis.

Our results showed that global cortical atrophy and mediotemporal hippocampal atrophy are not related. This is consistent with the fact that mediotemporal hippocampal atrophy reflect neurodegenerative processes (for example, Alzheimer's disease) [34], but cortical atrophy may have a vascular origin. This is also evidenced by our reliable correlation between extracranial vessels stenosis and cortical atrophy. In contrast to hippocampal atrophy, cortical was associated with both total EPVS burden and EPVS of subcortical regions and basal ganglia. According to the results of our study, WML was correlated with mediotemporal hippocampal atrophy. According to existing scientific data, WML is associated with the preclinical and clinical stage of Alzheimer's disease and neurodegeneration even more than other biomarkers of neurodegeneration [35]. Therefore, we can assume that revealed association reflects not only vascular changes, but also neurodegenerative processes. Therefore, EPVS, along with the presence or absence of the additional features mentioned above, may be important diagnostic features for determining vascular or Alzheimer's type of dementia.

Interestingly, such a simple and routine biochemical indicator, such as cholesterol, was significantly correlated with the EPVS of the cortical and subcortical areas, but there was no such association with the EPVS of basal ganglia. Cortical neurons have a high level of metabolism and, as a consequence, metabolic wastes, one of which is beta amyloid. In the central nervous system (CNS), cholesterol is known to be a major component of the myelin sheath, but in non-myelinated neurons (for example, the hippocampus) it is located in the plasma membrane in the form of specific membrane domains and takes part in various cellular processes, sorting proteins, forming different signaling pathways. Since the level of cholesterol in the brain is five to ten times higher than in other organs, and its exchange in the brain is 6 times slower than in other tissues, it is not surprising that the homeostasis of cholesterol in neurons is different from other cell types. To date, there is strong evidence that most of CNS cholesterol is synthesized locally, rather than imported from blood lipoproteins. In addition, CNS cholesterol homeostasis is regulated by genes encoding ApoE proteins. However, several studies have shown that elevated plasma cholesterol has been associated with an increase in beta-amyloid accumulation in the brain in Alzheimer's disease [30]. It can be assumed that with beta-amyloid angiopathy, elevated blood plasma cholesterol promotes the accumulation of beta-amyloid in the walls of microvessels and plays a certain pathogenetic role. Therefore, EPVS of the cortical-subcortical regions, along with increase in blood cholesterol level, may suggest beta-amyloid clearance impairment through the glymphatic system and may be a cause of development of beta-amyloid angiopathy, which is the second most common type of CSVD.

Our research demonstrates the relationship between chronic kidney disease, indicators of renal dysfunction (creatinine, urea) and signs of CSVD, including EPVS. Therefore, they may be additional diagnostic satellites for cerebrovascular pathology. It is known that the structure of brain microvasculature is most similar to the structure of the renal microvasculature [32]. Therefore, cerebrovascular and renal pathologies (according to some reports, along with changes in the retinal vessels [45-47]) share a common pathophysiological background. At the same time, renal dysfunction, which leads to the accumulation of toxic metabolites, can independently lead to cerebrovascular disorders. A number of studies have shown that creatinine can get into and accumulate in the CNS due to dysfunction of blood-brain barrier [33]. Therefore, pathological changes in the cerebral small vessels, as well as the renal vessels are reflection of a number of systemic disorders of the body, but isn't isolated pathology.

## **Conclusions**

1. EPVS is a valuable diagnostic marker of cerebral vascular changes and may be a neuroimaging criterion of debut and progression of CSVD. And play a role in differentiation of vascular and neurodegenerative brain changes.
2. EPVS in different brain regions is a sign of distinction between the two major subtypes of CSVD - hypertensive arteriolosclerosis and beta-amyloid angiopathy.
3. EPVS is associated with more severe neurological deficits and degree of disability in patients with acute territorial stroke.
4. EPVS and CSVD are a reflection of systemic changes in the body, but is not isolated pathologies.

## **Further perspectives**

The combination of various vascular, metabolic, genetic, and other factors in progression of EPVS and CSVD should be investigated in much more detail and in large population groups. Further studies are needed to identify and differentiate EPVS in various brain diseases. Currently, there is no effective specific treatment for EPVS and CSVD and further development of therapeutic approaches to cure these pathologies is needed.

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