Clinical manifestations and issues of diagnosis of chronic cerebrovascular disease (chronic cerebral ischemia) at an early (pre-dementia) stage

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The paper presents experts' opinion on the clinical manifestations and diagnosis of chronic cerebrovascular disease (CVD) (chronic cerebral ischemia (CCI) and dyscirculatory encephalopathy (DEP)) at the pre-dementia stage. It is noted that DEP/CCI is a common diagnosis in Russian neurological practice, the criteria for which have not been updated for a long time. DEP/CCI most often develops in the presence of cerebral small artery (CSA) disease (cerebral microangiopathy (CMA)), the severity of which can be quantified by magnetic resonance imaging. The main clinical manifestation of DEP/CCI is cognitive impairment that may be subjective or moderate at the pre-dementia stage. Emotional disorders (apathy, depression, anxiety) and instability are considered as possible manifestations of CSA disease. It is noted that headache and vestibular vertigo are not caused by chronic CVD; while in patients with CMA, they are usually associated with other diseases (primary headache, peripheral vestibular vertigo, and vestibular migraine). The diagnosis of DEP/CCI should be based on the presence of cognitive impairment, reliable neuroimaging signs of CVD, and the exclusion of another cause of cognitive impairment.

Keywords: *cerebral small artery disease; chronic cerebral ischemia; dyscirculatory encephalopathy; Alzheimer's disease; headache; vestibular vertigo; non-systemic dizziness; apathy; depression.*
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For reference: *Kulesh AA, Emelin AYu, Bogolepova AN, et al. Clinical manifestations and issues of diagnosis of chronic cerebrovascular disease (chronic cerebral ischemia) at an early (pre-dementia) stage. Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics. 2021;13(1):4–12.* ***DOI:*** *10.14412/2074-2711-2021-1-4-12*

Chronic cerebral ischemia and vascular cognitive impairment. Chronic cerebral ischemia (CCI) / discirculatory encephalopathy (DEP) is one of the most common diagnoses in the Russian neurological practice. However, in most countries, these diagnoses are not used, and vascular cognitive impairment (VCI) is established. VCI are most often associated with pathology (disease) of small cerebral arteries (cerebral microangiopathy – CMA) and are regarded as the main clinical manifestation of chronic cerebrovascular disease (CVD) [1–3].

In the latest classification of mental syndromes and diseases (DSM-5), VCI is defined as mild vascular neurocognitive disorder (moderate VCI) and major vascular neurocognitive disorder (severe VCI, vascular dementia) [4]. Currently, about 50 million people suffer from dementia, its most common cause is Alzheimer's disease (AD), the second most common is vascular dementia [5]. Mild CI (MCI) are much more common (6% of the population [6]), they increase with age and are determined in one out of five people over the age of 65 [7].

Based on the data of neuroimaging and pathological studies, several possible mechanisms for the development of VCI are identified: multiple cerebral infarctions, infarction in a strategic for cognitive functions area of the brain, intracranial hemorrhage, cerebral hypoperfusion and CMA, which is recognized as the most common cause of VCI [8].

Currently, almost 100 risk factors for the development and progression of CI are known, among which the leading role is played by age and hereditary predisposition. At least ten factors are potentially reversible: arterial hypertension (AH), atrial fibrillation, diabetes mellitus (DM), hypercholesterolemia, chronic kidney disease, smoking, low education, low physical activity, obesity and depression. There is a mutual influence between many risk factors, so their combination increases the likelihood of developing CI [9].

The etiology of VCI includes atherosclerosis, cardiac, atherosclerotic and systemic embolisms, arteriolosclerosis, lipohyalinosis, amyloid angiopathy, infectious and non-infectious vasculitis, venous collagenoses, dural or parenchymal arteriovenous fistula, hereditary angiopathies (CADASIL and CARASIL), giant cell arteritis, saccular aneurysms, fibromascular dysplasia, moya-moya disease, systemic microangiopathies without inflammatory cell infiltration, cerebral venous thrombosis, etc. The main pathogenetic mechanisms of VCI include damage of large vessels or atherothrombotic disease (multiple infarctions, infarction in a strategic area), CMA (multiple lacunar infarctions in the white matter and/or subcortical nuclei, ischemic changes in the white matter of the brain, expansion of perivascular spaces, cortical microinfarctions, cortical and subcortical microbleeds), hemorrhages (intracerebral hemorrhage, cortical and subcortical microbleeds, subarachnoid hemorrhage), hypoperfusion (hippocampal sclerosis, laminar cortical sclerosis).

It should be noted that almost 2/3 of patients with VCI have morphological manifestations of AD, and among patients with AD, about 1/3 of cases have significant vascular lesions of the brain [10].

Neuroimaging signs of DEP/CCI in CMA

The leading method of neuroimaging in DEP/CCI is magnetic resonance imaging (MRI) of the brain, due to which a qualitative and quantitative assessment of the main manifestations of CMA is possible: white matter hyperintensity of vascular origin, lacunae, cerebral microbleeds, cortical superficial siderosis, dilated perivascular spaces and cerebral microinfarctions [11–16]. In 2013, J. Wardlaw and the STRIVE (the STandards for ReportIng Vascular changes on nEuroimaging) research group first proposed clear criteria for MRI assessment and interpretation of the manifestations (markers) of CMA, the use of which is advisable for establishing the vascular genesis of CI and, accordingly, for the diagnosis of DEP/CCI.

The clinical significance of individual markers of CMA has not been conclusively established. However, an increase in the severity of each of the MRI signs of CMA, as well as a combination of various signs (total burden), are associated with an increase in the severity of CI, other manifestations of DEP/CCI, as well as conversion to dementia and loss of independence [12–15, 17–22].

The question of the minimum sufficient severity of MRI manifestations of CMA, which is necessary to confirm the vascular genesis of CI and the presence of DEP/CCI, remains unresolved. Nevertheless, the data available in the literature suggest that the presence of at least one of the following MRI signs may serve as a basis for the diagnosis of DEP/CCI:

a) white matter hyperintensity of the 2nd and 3rd degrees according to the Fazekas scale;
b) pronounced expansion of the perivascular spaces;
c) multiple (two or more) lacunas and/or incomplete lacunar infarctions;
d) multiple (two or more) cerebral microbleeds.

In case of atrophic changes in the brain, indicating a previous ischemic stroke or intracerebral hemorrhage, it should be borne in mind that CI can be completely or partially caused by a stroke, and in the presence of positive biological markers of AD – by neurodegenerative disease.

Cognitive impairments

For CI caused by CMA, impairments of executive functions, slowness of mental activity, decreased attention with relatively preserved memory are characteristic. In cases when CVD is combined with AD, memory disorders typical of AD often prevail in the structure of CI. MCI in CMA usually has a multidomain pattern, but one in five patients is diagnosed with a monodomain (monofunctional) non-amnestic deficit [23].

Subjective CI are characterized by patient complaints of decreased memory and other cognitive functions without objective confirmation (normal results of neuropsychological testing); they are observed in 25–50% of elderly people [2]. With neuropsychological examination, even highly sensitive techniques do not reveal deviations from the average statistical standards. However, the patient feels a decrease in his intellectual abilities in comparison with the initial level. It is possible that with subjective CI, neuropsychological tests do not allow detecting disorders due to the patient's initially high cognitive potential. Subjective CI do not affect the patient's everyday, professional and social activities, even the most complex types. It should be noted that the subjective complaints of the patient and/or his relatives about poor memory and other CI often have no less prognostic value than the results of neuropsychological tests [24].

In case of subjective CI, it is advisable to assess the emotional status, to exclude the presence of depression and/or increased anxiety, which are often manifested by complaints of poor memory [25]. In the presence of depression and/or anxiety disorders, it should be borne in mind that emotional disorders can cause impairment of cognitive functions.

MCI is characterized by impaired cognitive functions, which, according to neuropsychological examination, significantly go beyond the average age norm, but do not cause adaptation disorders in everyday life, although they can lead to difficulties in complex and unusual situations [2]. The patient has to make more efforts to solve those tasks with which he previously easily coped, which causes discomfort.

VCI is characterized by a «non-amnestic» type, which is characterized by the relative preservation of memory and the predominance of executive dysfunction in the clinical picture [26]. There are problems with the organization, planning and control of voluntary activity, difficulties with the simultaneous performance of several actions, etc. Executive dysfunction includes a disorder of attention switching, goal-directed behavior, the ability to initiate, inhibit and control actions, and the formation of concepts. VCI is characterized by: 1) bradyphrenia (slowdown of the of cognitive processes), attention impairment, distraction, increased fatigue during mental work; 2) difficulties in switching

attention and changing a behavioral stereotype, inertia, perseveration; 3) lack of cognitive control, impulsivity when making a decision, reduced criticism, tactlessness, asocial behavior; 4) memory impairment with reproduction failure, while the patient experiences difficulties when it is necessary to extract the necessary information from memory, despite its safety, prompts or multiple choice can facilitate the playback process; 5) visual-spatial disorders (usually with significant severity of CI): constructive dyspraxia, spatial dysgnosia.

In a simplified form, the criteria for non-demented VCI can be presented as follows (Table 1).

Variability of the severity of CI with a similar volume of cerebral damage may be associated with the presence of a combined neurodegenerative disease, metabolic disorders (diabetes mellitus, renal and hepatic dysfunction) and individual factors (education, gender, environmental factors and genetic predisposition) [27].

Medical history data, CT and MRI may not be characteristic of VCI, which suggests the presence of another disease (Table 2).

VCI can be classified into probable in presence of clinical, anamnestic, CT or MRI signs of chronic CVD and possible, when there are clinical and anamnestic signs of VCI and CVD, but CT or MRI was not performed, or no signs of significant CVD were detected.

Emotional Disorders

Anxiety and depressive disorders can be a manifestation of both chronic CVD and primary emotional disorders. Unfortunately, in our country, a significant part of patients suffering from primary anxiety and depressive disorders are mistakenly diagnosed with DEP or CCI, without receiving adequate treatment.

In patients with mild VCI, sleep disturbances (27%), depression (23%), changes in appetite (15%), anxiety (11%), irritability (9%) and apathy (9%) are found [28]. Apathy and depression are common in patients with CMA (73%) but combined in only 34% of patients; 18% of patients has apathy in the absence of depression [29]. Apathy, but not depression regarded as a prodromal symptom of dementia in CMA [30] and associated with disruption of cortico-subcortical neuronal networks involved in emotional regulation, positive reinforcement and goal-directed behavior [29].

The problem of emotional disorders in DEP/CCI can be considered in the context of the hypothesis of vascular depression – a disease characterized by onset after 65 years of age, no family history of depression, a clinical picture in the form of loss of energy, subjective feelings of sadness, anhedonia, motivational problems and progressive VCI, the presence of cardiovascular risk factors and diseases, as well as resistance to therapy [31, 32].

A recent meta-analysis of 68 studies confirmed the association between white matter hyperintensity and the development of depression in later life [33]. In patients with MCI over 50 years of age, depressive symptoms are observed in 51.4% of cases, and the appearance of new episodes of depression is associated with a pronounced hyperintensity of the subcortical white matter [34]. In a large population study, it was shown that in elderly people with CMA without dementia, an increase in the severity of vascular MRI changes increases the risk of developing depression [35].

Balance disorders and vestibular (systemic) dizziness

Balance disorders are not typical for pre-dementia VCI. It should be borne in mind that instability, imbalance in patients with chronic CVD may be the result of concomitant diseases. Many patients with chronic CVD complain of non-systemic dizziness, which can be caused by the presence of neurological disorders in the patient, such as paresis, impaired sensitivity or coordination. For the advanced stage of the disease (CCI or DEP stage III), frontal dysbasia is characteristic («walking apraxia», frontal ataxia, etc.), but it is not observed in its earlier stages.

CMA is associated with imbalance and gait disturbances, especially in elderly patients [36]. Walking speed in healthy elderly individuals is associated with gender, age, AH, white matter hyperintensity, and total CMA burden [37]. In elderly population white matter hyperintensity is negatively associated with the motor function of the upper (pronation-supination time) and lower (walking speed and time to get up from the chair)

Table 1. *Non-dementia vascular cognitive impairment (VCI) (Stages I–II CCI or DEP)*

Parameter	Vascular cognitive impairment	
	subjective	mild
Complaints of the patient and/or people close to him/her	On memory and other cognitive functions impairment	
Neuropsychological methods	Absence of significant changes	Presence of mild CI
History, clinical examination, CT or MRI of the brain	Presence of risk factors, signs and manifestations of CVD; lack of data indicating the presence of other diseases that can cause CI	
Assessment of daily activity	Absence o f any disorders	Problems in performing complex mental activities, absence of dementia

Table 2. *The signs uncharacteristic of VCI*

Category	Signs
Natural history	Early appearance of memory disorders or a progressive deterioration of memory and other cognitive functions, as well as speech disorder, motor functions (praxis), perception (gnosis) in the absence of corresponding signs of a stroke as per CT, MRI
Anamnesis	Presence of other diseases that can cause CI, (e.g., AD, neurodegenerative disease, multiple sclerosis, encephalitis, toxic or metabolic disease)
CT or MRI	Absence of lesion or minimal vascular brain injury

limbs [38]. CMA may underlie non-systemic vertigo (unsteadiness) in elderly patients; it can be associated with instability due to dissociation of the cortical vestibular centers, thalamo-cortical connections, frontal gait centers and basal ganglia, and a discrepancy between the planned motor act and sensory feedback [39].

Dizziness in the domestic literature is regarded as a possible manifestation of DEP/CCI and is usually defined as vestibulo-atactic syndrome or vertebrobasilar insufficiency. For a long time, hemodynamic causes were assumed as the cause of circulatory disorders in the vertebrobasilar system, however, studies of the last 25 years, which used modern diagnostic methods (MRI, MR-angiography, CT, digital subtraction angiography), showed that in the pathogenesis of circulatory disorders in the vertebrobasilar system the role of hemodynamic disorders (vertebrobasilar insufficiency) is extremely small. If vestibular dizziness (vertigo) is repeated for 3 weeks or more, without being accompanied by other neurological disorders, then it is almost never caused by ischemic damage in the vertebrobasilar system [40]. Therefore, the term «vertebrobasilar insufficiency» available in the 10th revision of the International Classification of Diseases is currently not regarded as common variant of vascular brain pathology.

The presence of vestibular dizziness is not typical for chronic CVD [41]. In cases where a patient with a diagnosis of DEP/CCI has vertigo, two options are possible. In the first, there is a combination of CVD and vestibular disease (benign paroxysmal positional vertigo, vestibular migraine, Meniere's disease, or other peripheral vestibulopathy). In such cases, most often vestibular diseases are the reason for contacting a neurologist, and the examination reveals CI and signs of vascular pathology of the brain according to CT or MRI. In the second variant, the patient has only vestibular disease, and the diagnosis of CVD was made incorrectly. Unfortunately, at present, a large number of middle-aged or elderly patients suffering from vestibular dizziness are mistakenly diagnosed with chronic CVD and do not receive effective treatment [42, 43]. The identification of diseases that cause dizziness and their treatment can help many patients who are undergoing long-term and unsuccessful treatment for DEP or CCI.

Headache

Headache in the domestic literature is regarded as a possible manifestation of CCI/DEP already in the early stages of the disease. This assumption arose long ago and remains unchanged in many Russian books and articles. However, at present, no convincing data has been received to support it.

In the latest International Classification of Headaches (2013), in the «Secondary headaches» section, a special subsection is dedicated to the possible causes of headaches in CVD.

Headache attributed to cranial or cervical vascular disorder [44]

6.1 Headache attributed to cerebral ischaemic event
- 6.1.1 Headache attributed to ischaemic stroke (cerebral infarction)
- 6.1.2 Headache attributed to transient ischaemic attack (TIA)

6.2 Headache attributed to non-traumatic intracranial haemorrhage
- 6.2.1 Headache attributed to non-traumatic intracerebral haemorrhage
- 6.2.2 Acute headache attributed to non-traumatic subarachnoid haemorrhage (SAH)
- 6.2.3 Acute headache attributed to non-traumatic acute subdural haemorrhage (ASDH)
- 6.2.4 Persistent headache attributed to past non-traumatic intracranial haemorrhage

6.3 Headache attributed to unruptured vascular malformation
- 6.3.1 Headache attributed to unruptured saccular aneurysm
- 6.3.2 Headache attributed to arteriovenous malformation (AVM)
- 6.3.3 Headache attributed to dural arteriovenous fistula (DAVF)
- 6.3.4 Headache attributed to cavernous angioma
- 6.3.5 Headache attributed to encephalotrigeminal or leptomeningeal angiomatosis (Sturge Weber syndrome)

6.4 Headache attributed to arteritis
- 6.4.1 Headache attributed to giant cell arteritis (GCA)
- 6.4.2 Headache attributed to primary angiitis of the central nervous system (PACNS)
- 6.4.3 Headache attributed to secondary angiitis of the central nervous system (SACNS)

6.5 Headache attributed to cervical carotid or vertebral artery disorder
- 6.5.1 Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection
- 6.5.2 Post-endarterectomy headache
- 6.5.3 Headache attributed to carotid or vertebral angioplasty or stenting

6.6 Headache attributed to cranial venous disorder
- 6.6.1 Headache attributed to cerebral venous thrombosis (CVT)
- 6.6.2 Headache attributed to cranial venous sinus stenting

6.7 Headache attributed to other acute intracranial arterial disorder
- 6.7.1 Headache attributed to an intracranial endarterial procedure
- 6.7.2 Angiography headache
- 6.7.3 Headache attributed to reversible cerebral vasoconstriction syndrome (RCVS)
- 6.7.4 Headache attributed to intracranial artery dissection

6.8 Headache attributed to genetic vasculopathy
- 6.8.1 Headache attributed to Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
- 6.8.2 Headache attributed to Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes (MELAS)
- 6.8.3 Headache attributed to Moyamoya angiopathy (MMA)
- 6.8.4 Migraine-like aura attributed to cerebral amyloid angiopathy (CAA)
- 6.8.5. Headache attributed to syndrome of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCLSM)
- 6.8.6 Headache attributed to other chronic intracranial vasculopathy

6.9 Headache attributed to pituitary apoplexy

As can be seen from the presented data, chronic CVD are not considered as a possible cause of headache. Headache is uncommon in the vast majority of cases of VCI, with the exception of rare cases of hereditary vasculopathy and other diseases.

Other neurological disorders

Focal neurological disorders are not typical for mild VCI, but they can be caused by a previous stroke or other neurological disease.

Dysfunctions of the pelvic organs are also not typical for VCI at the pre-dementia stage; they are usually caused by combined neurological disorders. Urinary disorders are typical for patients with CMA, observed mainly at the stage of a major neurocognitive defect and include nocturia, incontinence, frequency and urgency [45]. White matter lesions in the areas of the anterior thalamic radiance and the superior longitudinal fasciculus can dissociate centers involved in urinary control (such as the anterior cingulate gyrus, right insular cortex, accessory motor cortex, inferior, medial, and dorsolateral orbitofrontal cortex) and cause urinary incontinence in the elderly women [46]. In a population study in China in elderly people (65 years and older) with white matter hyperintensity (in half – grade 1 according to Fazekas), no associations were found between white matter pathology and urinary complaints [47], which may indicate the preservation of pelvic functions for the initial stages of the CMA.

Differential diagnosis with AD

AD is the most common degenerative brain disease leading to the development of CI. In the early stages of AD, memory impairments dominate and remain the only cognitive symptom while the criticism, intelligence and other higher mental functions remain intact [48]. In more rare cases, AD debuts with a non-amnestic syndrome, which is manifested by visual-spatial impairments, impairment of executive functions, or speech impairments with difficulty in naming objects [49]. For accurate diagnosis of AD, along with clinical and neuropsychological studies, instrumental and laboratory methods are used, which make it possible to make a diagnosis even at the stage of mild CI. In the cerebrospinal fluid, the concentration of beta-amyloid decreases due to its deposition in the brain, but the level of tau protein increases, which reflects a neurodegenerative process. Positron emission tomography of the brain with the introduction of a special substance into the patient's blood, which binds to beta-amyloid and makes it visible, is informative. In many patients, CI is caused by a combination of vascular and neurodegenerative brain damage, mainly AD. AD by itself increases the risk of stroke development due to cerebral amyloid angiopathy, which is characteristic of this disease [3, 48].

Clinical manifestations of chronic CVD

Clinical manifestations of chronic CVD are summarized in Table. 3.

Conclusion

Only the presence of VCI serves as a clinical basis for the diagnosis of chronic CVD (DEP/CCI). It should be noted that in the 11th revision of the International Classification of Diseases [16], in the section «Diseases of the nervous system», «Cerebrovascular disorder with neurocognitive impairments» is highlighted, which largely corresponds to the clinical manifestations of DEP/CCI. In chronic CVD, there is often a combination of CVD and AD. In our country, AD is rarely diagnosed, the majority of AD patients are observed with a diagnosis of DEP or

Table 3. *Clinical manifestations of chronic CVD*

Clinical manifestations	DEP/CCI	
	Stage I	Stage II
Cognitive impairment	Subjective	Mild
Depression	Possible, but often is caused by a primary emotional disorder	
Apathy, fatigue	Possible, but more often caused by primary emotional disorders	
Non-systemic dizziness (unsteadiness)	Not typical, more often caused by other reasons	Possibly mild, more often caused by other causes
Headaches (cephalgic syndrome)	Not typical, except in cases of hereditary vasculopathies and other rare diseases, more often caused by primary headaches	
Vestibular dizziness	Not typical, more often caused by peripheral vestibulopathy, migraine or other diseases	
Sleep disturbance	Possible, but more often caused by another cause	
Pelvic dysfunction	Not common, caused by another cause	
Focal neurological disorders	Not common, may be caused by stroke o r other neurological disease	

CCI. Excessive diagnosis of DEP/CCI is largely due to the fact that neither neuropsychological research, which allows diagnosing CI, nor otoneurological examination (diagnosis of vestibular disorders), a special survey to identify primary headaches, diagnosis of anxiety and/or depressive disorders are carried out.

On the other hand, many cases of VCI (DEP/CCI) are not diagnosed because patients do not seek advice for impaired memory and other cognitive functions, considering them «normal age-related changes», while neuropsychological research and neuroimaging data (CT or MRI of the brain) in these patients, typical manifestations of VCI are revealed.

In general, early diagnosis and effective treatment of VCI (DEP/CCI) is becoming increasingly important, since the timely implementation of adequate therapeutic measures can slow down the progression of the disease, its individual manifestations and lead to a decrease in the incidence of stroke and dementia.

REFERENCES

1. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. *Lancet Neurol.* 2003 Feb;2(2):89-98. doi: 10.1016/s1474-4422(03)00305-3

2. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011;42:2672-713. doi: 10.1161/STR.0b013e3182299496

3. Zhou J, Yu JT, Wang HF, et al. Association between stroke and Alzheimer's disease: systematic review and meta-analysis. *J Alzheimers Dis.* 2015;43(2):479-89. doi: 10.3233/JAD-140666

4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association; 2013.

5. WHO/Dementia (2017). Available from: http://www.who.int/mediacentre/factsheets/fs362/en/ (accessed 3 Mar 2018).

6. Sachdev PS, Lipnicki DM, Kochan NA, et al. The prevalence of mild cognitive impairment in diverse geographical and ethnocultural regions: the COSMIC collaboration. *PLoS One*. 2015 Nov 5;10(11):e0142388. doi: 10.1371/journal.pone.0142388. eCollection 2015.

7. Lopez OL, Kuller LH, Becker JT, et al. Incidence of dementia in mild cognitive impairment in the cardiovascular health study cognition study. *Arch Neurol.* 2007 Mar;64(3):416-20. doi: 10.1001/archneur.64.3.416

8. Cuadrado-Godia E, Dwivedi P, Sharma S. Cerebral Small Vessel Disease: A Review Focusing on Pathophysiology, Biomarkers, and Machine Learning Strategies. *J Stroke.* 2018;20(3):302-20. doi: 10.5853/jos.2017.02922. Epub 2018 Sep 30.

9. Markus HS, Schmidt R. Genetics of Vascular Cognitive Impairment. *Stroke*. 2019;50(3):765-72. doi: 10.1161/STROKEAHA.118.020379

10. Gong L, Liu XY, Fang M. Recent progress on small vessel disease with cognitive impairment. *Int J Clin Exp Med.* 2015 May 15;8(5):7701-9.

11. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration: a united approach. *Lancet Neurol.* 2013 Aug;12(8):822-38. doi: 10.1016/S1474-4422(13)70124-8

12. Charidimou A, Linn J, Vernooij MW, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. *Brain*. 2015;138 (Pt 8):2126-39. doi: 10.1093/brain/awv162

13. Van Veluw SJ, Shih AY, Smith EE, et al. Detection, risk factors, and functional consequences of cerebral microinfarcts. *Lancet Neurol.* 2017 Sep;16(9):730-40. doi: 10.1016/S1474-4422(17)30196-5. Epub 2017 Jul 14.

14. Debette S, Schilling S, Duperron MG, et al. Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and metaanalysis. *JAMA Neurol.* 2019 Jan 1;76(1):81-94. doi: 10.1001/jamaneurol.2018.3122

15. Кулеш АА, Дробаха ВЕ, Шестаков ВВ. Церебральная болезнь мелких сосудов: классификация, клинические проявления, диагностика и особенности лечения. *Неврология, нейропсихиатрия, психосоматика.* 2019;11(Прил. 3):4-17. doi: 10.14412/2074-2711-2019-3S-4-17 [Kulesh AA, Drobakha VE, Shestakov VV. Cerebral small vessel disease: classification, clinical manifestations, diagnosis, and features of treatment. *Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics.* 2019;11(Suppl. 3):4-17. doi: 10.14412/2074-2711-2019-3S-4-17 (In Russ.)].

16. МКБ-11 (Международная классификация болезней 11-го пересмотра). Доступно по ссылке: https://icd11.ru [ICD (International Classification of Diseases 11). Available from: https://icd11.ru/ (In Russ.)].

17. Charidimou A, Shams S, Romero JR, et al. Clinical significance of cerebral microbleeds on MRI: A comprehensive meta-analysis of risk of intracerebral hemorrhage, ischemic stroke, mortality, and dementia in cohort studies (v1). *Int J Stroke.* 2018;13(5):454-68. doi: 10.1177/1747493017751931

18. Francis F, Ballerini L, Wardlaw JM. Perivascular spaces and their associations with risk factors, clinical disorders and neuroimaging features: A systematic review and meta-analysis. *Int J Stroke.* 2019 Jun;14(4):359-71. doi: 10.1177/1747493019830321. Epub 2019 Feb 14.

19. Jokinen H, Koikkalainen J, Laakso HM, et al. Global Burden of Small Vessel Disease-Related Brain Changes on MRI Predicts Cognitive and Functional Decline. *Stroke*. 2020 Jan;51(1):170-8. doi: 10.1161/STROKEAHA.119.026170. Epub 2019 Nov 8.

20. Jie W, Lin G, Liu Z, et al. The Relationship Between Enlarged Perivascular Spaces and Cognitive Function: A Meta-Analysis of Observational Studies. *Front Pharmacol.* 2020;11:715. doi: 10.3389/fphar.2020.00715

21. Левин ОС, Дамулин ИВ. Диффузное поражение белого вещества и проблема сосудистой деменции. В кн.: Яхно НН, редактор. Достижения нейрогериатрии. Ч. 2. Москва; 1995. С. 189-228. [Levin OS, Damulin IV. Diffuse white matter lesion and vascular dementia problem. In: Yakhno NN, editor. *Dostizheniya neyrogeriatrii* [Achievements of neurogeriatrics]. Pt 2. Moscow; 1995. P. 189-228 (In Russ.)].

22. Араблинский АВ, Макотрова ТА, Левин ОС. Церебральные микрокровоизлияния при сосудистых и дегенеративных заболеваниях головного мозга. *Журнал неврологии и психиатрии им. С.С. Корсакова.* 2013;113(7-2):45-51. [Arablinskiy AV, Makotrova TA, Levin OS. Cerebral microbleeds in vascular and degenerative diseases of the brain. *Zhurnal nevrologii i psikhiatrii im. S.S. Korsakova.* 2013;113(7-2):45-51 (In Russ.)].

23. Salvadori E, Poggesi A, Valenti R, et al. Operationalizing mild cognitive impairment criteria in small vessel disease: the VMCI-Tuscany Study. *Alzheimers Dement.* 2016 Apr;12(4):407-18. doi: 10.1016/j.jalz.2015.02.010. Epub 2015 Jun 13.

24. Rabin LA, Smart CM, Crane PK, et al. Subjective Cognitive Decline in Older Adults: An Overview of Self-Report Measures Used Across 19 International Research Studies. *J Alzheimers Dis.* 2015 Sep 24;48 Suppl 1 (0 1):S63-86. doi: 10.3233/JAD-150154

25. Rogne S, Vangberg T, Eldevik P, et al. Magnetic Resonance Volumetry: Prediction of Subjective Memory Complaints and Mild Cognitive Impairment, and Associations with Genetic and Cardiovascular Risk Factors. *Dement Geriatr Cogn Dis Extra.* 2016 Nov 25;6(3):529-40. doi: 10.1159/000450885

26. Яхно НН, Захаров ВВ, Локшина АБ и др. Деменции. Москва: Медпресс-информ; 2011. [Yakhno NN, Zakharov VV, Lokshina AB, et al. *Dementsii* [Dementia]. Moscow: Medpress-inform; 2011 (In Russ.)].

27. Gurol ME, Sacco RL, McCullough LD. Multiple Faces of Cerebral Small Vessel Diseases. *Stroke*. 2020 Jan;51(1):9-11. doi: 10.1161/STROKEAHA.119.027969. Epub 2019 Nov 22.

28. Tiel C, Sudo FK, Alves GS, et al. Neuropsychiatric symptoms in Vascular Cognitive Impairment: a systematic review. *Dement Neuropsychol*. Jul-Sep 2015;9(3):230-6. doi: 10.1590/1980-57642015DN93000004

29. Hollocks MJ, Lawrence AJ, Brookes RL, et al. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. *Brain*. 2015;138(Pt 12):3803-15. doi: 10.1093/brain/awv304

30. Tay J, Morris RG, Tuladhar AM, et al. Apathy, but not depression, predicts all-cause dementia in cerebral small vessel disease. *J Neurol Neurosurg Psychiatry*. 2020 Sep;91(9):953-9. doi: 10.1136/jnnp-2020-323092. Epub 2020 Jul 10.

31. Aizenstein HJ, Baskys A, Boldrini M, et al. Vascular depression consensus report – a critical update. *BMC Med*. 2016 Nov 3;14(1):161. doi: 10.1186/s12916-016-0720-5

32. Боголепова АН. Сосудистая депрессия и когнитивная дисфункция. *Неврология, нейропсихиатрия, психосоматика*. 2019;11(Прил. 3):26-31. doi: 10.14412/2074-2711-2019-3S-26-31
[Bogolepova AN. Vascular depression and cognitive dysfunction. *Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics*. 2019;11(Suppl. 3):26-31. doi: 10.14412/2074-2711-2019-3S-26-31 (In Russ.)].

33. Salo KI, Scharfen J, Wilden ID, et al. Confining the Concept of Vascular Depression to Late-Onset Depression: A Meta-Analysis of MRI-Defined Hyperintensity Burden in Major Depressive Disorder and Bipolar Disorder. *Front Psychol*. 2019;10:1241. doi: 10.3389/fpsyg.2019.01241

34. Kim S, Woo SY, Kang HS, et al. Factors related to prevalence, persistence, and incidence of depressive symptoms in mild cognitive impairment: vascular depression construct. *Int J Geriatr Psychiatry*. 2016;31(7):818-26. doi: 10.1002/gps.4400

35. Van Sloten TT, Sigurdsson S, van Buchem MA, et al. Cerebral Small Vessel Disease and Association With Higher Incidence of Depressive Symptoms in a General Elderly Population: The AGES-Reykjavik Study. *Am J Psychiatry*. 2015 Jun;172(6):570-8. doi: 10.1176/appi.ajp.2014.14050578. Epub 2015 Mar 3.

36. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010 Jul;9(7):689-701. doi: 10.1016/S1474-4422(10)70104-6

37. Pinter D, Ritchie SJ, Doubal F, et al. Impact of small vessel disease in the brain on gait and balance. *Sci Rep*. 2017 Jan 30;7:41637. doi: 10.1038/srep41637

38. Su N, Zhai FF, Zhou LX, et al. Cerebral Small Vessel Disease Burden Is Associated with Motor Performance of Lower and Upper Extremities in Community-Dwelling Populations. *Front Aging Neurosci*. 2017;9:313. doi: 10.3389/fnagi.2017.00313

39. Kaski D, Rust HM, Ibitoye R, et al. Theoretical framework for «unexplained» dizziness in the elderly: The role of small vessel disease. *Prog Brain Res*. 2019;248:225-40. doi: 10.1016/bs.pbr.2019.04.009. Epub 2019 May 20.

40. Caplan L. Posterior circulation ischemia: then, now, and tomorrow. The Thomas Willis Lecture-2000. *Stroke*. 2000 Aug;31(8):2011-23. doi: 10.1161/01.str.31.8.2011

41. Brandt T, Dieterich M. Vertigo and dizziness: common complains. London: Springer; 2004. 208 p.

42. Парфенов ВА, Захаров ВВ, Преображенская ИС. Когнитивные расстройства. Москва: Ремедиум; 2014.
[Parfenov VA, Zakharov VV, Preobrazhenskaya IS. *Kognitivnyye rasstroystva* [Cognitive Disorders]. Moscow: Remedium; 2014 (In Russ.)].

43. Парфенов ВА. Дисциркуляторная энцефалопатия и сосудистые когнитивные расстройства. Москва: ИМА-ПРЕСС; 2017.
[Parfenov VA. *Distsirkulyatornaya entsefalopatiya i sosudistyye kognitivnyye rasstroystva* [Dyscirculatory encephalopathy and vascular cognitive disorders]. Moscow: IMA-PRESS; 2017 (In Russ.)].

44. Olesen J, Bes A, Kunkel R, et al. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013 Jul;33(9):629-808. doi: 10.1177/0333102413485658

45. Li Q, Yang Y, Reis C, et al. Cerebral Small Vessel Disease. *Cell Transplant*. 2018 Dec; 27(12): 1711-22. doi: 10.1177/0963689718795148. Epub 2018 Sep 25.

46. Tadic SD, Griffiths D, Murrin A, et al. Brain activity during bladder filling is related to white matter structural changes in older women with urinary incontinence. *Neuroimage*. 2010;51(4):1294-302. doi: 10.1016/j.neuroimage.2010.03.016

47. Yee CH, Leung C, Wong YY, et al. Lower Urinary Tract Symptoms in Subjects with Subclinical Cerebral White Matter Lesions. *J Aging Res*. 2018 Jul 30;2018:1582092. doi: 10.1155/2018/1582092. eCollection 2018.

48. Chertkow H, Feldman HH, Jacova C, Massoud F. Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: consensus from the Canadian conference on diagnosis of dementia. *Alzheimers Res Ther*. 2013 Jul 8;5(Suppl 1):S2. doi: 10.1186/alzrt198. Epub 2013 Jul 8.

49. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011 May;7(3):263-9. doi: 10.1016/j.jalz.2011.03.004

Received/Reviewed/Accepted
1.11.2020/10.12.2020/15.12.2020

Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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