CONTEMPORARY APPROACH TO DIAGNOSIS OF ISCHEMIC STROKE PATHOGENETIC VARIANTS IN PATIENTS WITH ATHEROSCLEROSIS AND ARTERIAL HYPERTENSION

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The angio- and neurovisualization methods vigorously developing in recent decades determine the relevance of improvement of etiopathogenetic ischemic stroke classification used for the treatment tactics selection and for secondary prevention of the disorder. The study was aimed to clarify the capabilities of clinical diagnosis for pathogenetic variants of ischemic stroke. For that, in 125 postmortem cases, the macro and microscopic examination of brain and cardiovascular system was carried out in order to verify the stroke pathogenesis established as a result of the previous patients' examination. The study demonstrates the great potential of the major pathogenetic stroke subtypes (large-artery atherosclerosis, cardioembolism, small-artery occlusion) diagnosis using the complex of contemporary clinical and instrumental methods and the main morphological criteria of these subtypes in accordance with the TOAST classification. Moreover, the clinical and pathomorphological assessment allowed us to differentiate stroke resulting from various alterations of single cerebral artery, the atherothrombotic occlusion (44% of cases for the subtype), arterio-arterial embolism (13%) and critical stenosis (10%), as well as stroke resulting from cerebrovascular insufficiency (33%), within the "large-artery atherosclerosis" subtype. Thus, the high informativity of the existing examination methods allows for a more differentiated understanding of the cause of ischemic stroke, which is fully in line with modern personalized medicine.

Keywords: ischemic stroke, cerebral infarction, pathogenesis, atherosclerosis, arterial hypertension

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СОВРЕМЕННЫЙ ПОДХОД К ДИАГНОСТИКЕ ПАТОГЕНЕТИЧЕСКИХ ВАРИАНТОВ ИШЕМИЧЕСКОГО ИНСУЛЬТА ПРИ АТЕРОСКЛЕРОЗЕ И АРТЕРИАЛЬНОЙ ГИПЕРТОНИИ

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Активное развитие в последние десятилетия методов ангио- и нейровизуализации определяет актуальность совершенствования этиопатогенетической классификации ишемического инсульта, используемой для выбора целенаправленной тактики лечения и вторичной профилактики этого заболевания. С целью уточнить возможности клинической диагностики патогенетических вариантов ишемического инсульта в 125 случаях выполнено посмертное макро- и микроскопическое исследование мозга и сердечно-сосудистой системы для верификации патогенеза инсульта, установленного в результате предшествующего обследования пациентов. Показаны широкие возможности диагностики ведущих патогенетических подтипов инсульта (атеросклероз крупной артерии, кардиоаортальная эмболия, окклюзия мелкой артерии) при использовании комплекса современных клинико-инструментальных методов и основных морфологических критериев этих подтипов, отмеченных в общепризнанной классификации TOAST. Вместе с тем, клиническое и патоморфологическое исследование позволило выделить в подтипе «атеросклероз крупной артерии» инсульты, обусловленные различными изменениями одной церебральной артерии — атеротромботической окклюзией (44% инсультов этого подтипа), артерио-артериальной эмболией (13%) и критическим атеростенозом (10%), а также инсульты, возникающие по механизму сосудистой мозговой недостаточности (33%). Таким образом, высокая информативность существующих методов исследования позволяет более дифференцированно подходить к установлению причины ишемического инсульта, что в полной мере отвечает персонализированной направленности современной медицины.

Ключевые слова: ишемический инсульт, инфаркт головного мозга, патогенез, атеросклероз, артериальная гипертония

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Over the past decades ischemic stroke remains one of the most significant medical and social problems due to high morbidity and mortality [1, 2]. The solution to the problem is somewhat limited by the complexity of pathogenesis studies resulting from the polymorphism of the changes in cardiovascular system and brain associated with atherosclerosis and arterial hypertension (AH), which contribute to the vast majority of ischemic stroke cases. During the second half of the last century the new

classification systems based on the concept of cerebrovascular pathology heterogeneity have been developed. These were adopted for treatment tactics selection and secondary prevention of the disorder, as well as for clinical trials and epidemiological studies' standardization. The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system has been internationally recognized, inter alia in Russian Federation. [3–5]. However, the significant rate of stroke of undetermined etiology (up to 30–40%) indicates the lack of certainty in the diagnostic criteria for ischemic stroke variants defined by this classification [6, 7].

The strong growth of clinical and diagnosis capabilities in recent decades, particularly introducing the advanced modifications of magnetic resonance imaging of the brain, was followed by the TOAST classification system refining. This made it possible to reduce the rate of stroke of undetermined etiology by several times [8, 9]. The refined version of the discussed classification system, the Stop Stroke Study (SSS), defines the criteria of obvious, probable and possible variants of the following major pathogenetic subtypes of ischemic stroke: large-artery atherosclerosis, cardioembolism, and small-artery occlusion.

Introduction of a number of other classification systems is due to urgent need for improvement of etiopathogenetic stroke classification in accordance with contemporary diagnosis and treatment options [10–15]. The most significant criteria of major stroke subtypes defined by the TOAST classification continue to be the focus of discussion, however, the new classification systems propose the additional features of these subtypes. The most disputed issues are as follows: minimum severity of monofocal and multifocal intracranial atherosclerotic stenosis (atherostenosis), resulting in cerebrovascular disease; size, localization and other morphological features of infarctions in different stroke subtypes; significance of various diffuse and focal brain lesions in diagnosis of lacunar stroke resulting from hypertension, which is classified as small-artery occlusion subtype. Some classification systems propose classification of stroke with different mechanisms both as existing pathogenetic subtypes and distinct subtype based on the certain clinical and morphological features.

Pathomorphological studies make it possible to obtain extensive and most reliable data on the ischemic cerebral circulatory disorders, provided the detailed assessment of brain and cardiovascular system changes. These studies assume particular importance while being compared with the data of previous patients' examinations allowing one to clarify the criteria of clinical and instrumental diagnosis of pathogenetic stroke subtypes. The importance of pathomorphological studies, as well as the clinical and pathomorphological comparisons involving the diversity of brain ischemia pathogenesis in patients with atherosclerosis, AH and the frequent combinations of those, is emphasized by scarcity of such studies and the controversial nature of the data obtained.

The study was aimed to clarify the capabilities of clinical diagnosis for pathogenetic variants of ischemic stroke associated with atherosclerosis and AH.

METHODS

The clinical and pathomorphological comparison of 125 postmortem ischemic stroke cases observed at the Research Center of Neurology from 1990 to 2015 was carried out. Inclusion criteria: deceased men and women aged 45–74 with cerebral infarction. Exclusion criteria: no vascular disease in the form of aortic and cerebral arterial atherosclerosis, AH, coronary heart disease (CHD). Male patients predominated (78%), and the average patients' age was 62 years. Aortic and cerebral arterial atherosclerosis of various degrees together with AH was identified in all patients, and different CHD types were revealed in 64% of patients. In most cases death was caused by cerebral edema in the presence of infarctions or hemorrhages, and in the absence of such the death was due to pulmonary embolism, heart failure associated with CHD, as well as renal or multiple organ dysfunction upon severe infectious disease.

Pathogenetic stroke subtype was defined in accordance with the SSS-TOAST classification based on the appropriate subtype criteria [8]. For this purpose we assessed data obtained by computed tomography (56% of cases) or 0.5T and 1.5T magnetic resonance imaging (44%), as well as the changes in aorta and cerebral arteries revealed by color duplex sonography of the major arteries of the head, inter alia combined with transcranial Doppler embolodetection (16% of cases), computed tomography angiography (28%) or magnetic resonance angiography (34%). The history of pre-stroke episodes of cardiovascular and blood pressure (BP) instability was taken into account, as well as data of ophthalmological and endocrinological examination, electrocardiography, including Holter monitoring (24 hours and longer), and transesophageal echocardiography (22%).

During the pathomorphological examination, the cerebral infarction characteristics were taken into account, such as localization, size, appearance ("white" or hemorrhagic), and organization phase; arterial alterations from aortic arch to small vessels on the surface of the brain — emboli, complicated atherosclerotic lesions (intraplaque hemorrhage, plaque ulceration, thrombosis), atherosthenosis degree (in accordance with the clinical and instrumental examination method); liquor system condition; microhemorrhages and enlarged perivascular spaces (criblurs). The atherosclerosis and AH-related cardiac structure alterations, as well as cardiogenic emboli in the branch arteries of the aortic arch were detected.

During microscopic examination we clarified the complicated atherosclerotic lesions, the nature of large and small superficial arteries' occlusion, and the nature of focal brain lesion; the condition periventricular white matter was assessed. In each case, 5–10 brain tissue blocks sized 2.5 x 3 cm and 0.5 cm thick were cut out. The large arteries were examined using blocks of the same thickness, which were cut out perpendicular to the longitudinal axis of the blood vessel. Prior to microscopic examination the paraffin embedded 5–6 μm-thick brain slices were stained with Carazzi's hematoxylin and eosin using the Weigert Van Gieson method (assessment of arterial alterations) and the Kluver–Barrera method (assessment of white matter condition). Analysis of the resulting data made it possible to define the cause of each infarction.

The differences were revealed using the Mann–Whitney *U* test; the *p* values of less than 0.05 were regarded as statistically significant. The results were processed with the Statistica software (StatSoft Inc.; США), version 13.3.

RESULTS

In accordance with SSS-TOAST, 76 stroke cases (of 125) were classified as large-artery atherosclerosis based on the arterial alterations in the form of occlusion or atherostenosis, both severe (≥ 50%) and moderate (30–49%), ipsilateral to the infarction in the absence of cardiac pathology and aorta with high risk of embolism. Clinical and instrumental examination followed by pathomorphological assessment revealed

four reasons of stroke of the discussed subtype: critical atherostenosis (70–90%) of single artery — 10%; multifocal atherostenosis — 33%; atherosclerotic lesion disruption with superimposed thrombosis (atherothrombosis) — 44%; arterio-arterial embolism (13%) when the atherosclerotic plaque with parietal thrombus was found in the vessels located proximal to the occlusion area (Fig. 1).

In cases with stenosis of single artery, stroke resulted from rapid and significant increase in the volume of atherosclerotic plaque due to extensive hemorrhage or parietal thrombosis. Occlusive thrombosis resulted from atherosclerotic plaque rupture due to thinned and disrupted cap in the foci of atheromatosis and calcification. In cases of multifocal stenosis the degree of the vessel lumen narrowing ranged from 30 to 70%, moreover, in 10 observations (of 25) the maximum vessel lumen narrowing degree did not exceed 50%. We determined the diversity of the infarction size and localization with a slight predominance (by 1.5 times, $p < 0.05$) of large infarctions (Fig. 2).

It has been noted that occlusion or stenosis of single artery determine the infarctions occurring strictly in the altered blood vessel system, whereas the multifocal stenosis results in focal lesions in the areas of adjacent cerebral blood supply and lacunar infarctions. According to microscopy data, there are arteries with "recalibrated" (narrowed) lumen due to tunica intima sclerosis or tunica intima components' proliferation with formation of extra elastic membrane in the areas of infarctions occurring in the areas of adjacent blood supply and lacunar infarctions. Such patients had no diabetes mellitus, occlusions, severe atherostenoses and severe hypertensive alterations in extra- and intracerebral arteries with a diameter of 200–500 μm in the examined foci area, which are considered the major causes of focal brain ischemia [3, 14, 16, 17].

The 32 stroke cases were classified as cardioembolism subtype based on the lack of cerebral artery stenosis ≥ 50% ipsilateral to the infarction and the presence of cardiac pathology and aorta with high risk of embolism. An almost twofold prevalence of atrial fibrillation ($p < 0.05$) was detected; atrial fibrillation is considered the most common cause of cardioembolic stroke [18, 19] (Fig. 3).

The postmortem study confirmed the presence of embologenic plaque in the aortic arch, as well as the listed forms of CHD. Focal atrial fibrosis was the morphological marker of atrial fibrillation. In the arteries located proximal to the occlusion area there were plaques, which narrowed the lumen not by more than 30%, with no alterations determining the risk of embolism.

In cases of this stroke subtype the infarctions could involve most of the internal carotid or middle cerebral artery system, but more often the infarctions occurred in the system of branches 1–2 of the middle or anterior cerebral artery (62% of cases). Systemic embolic events and infarctions with a hemorrhagic component were detected in 40% and 47% of cases respectively, and the cardiogenic emboli in the branches of the abdominal aorta with infarctions in kidney and spleen identified during the pathomorphological examination were asymptomatic due to small size of foci (1–2 cm).

SSS-TOAST classification system admits the possibility of the cardioembolism subtype establishment in case of signs of embolism from the heart or aorta, however, this can also raise some difficulties. Thus, echocardiography and postmortem examination revealed intracardiac thrombi only in 12 cases (of 31), and the cerebral artery occlusion was detected in only half of the cases, mostly during localization of emboli in the internal carotid or middle cerebral artery. It was impossible to detect the occlusion in patients admitted to hospital 4 or more days after the stroke onset due to the well known vanishing occlusion phenomenon resulting from the spontaneous emboli fragmentation and distal migration of fragments. This phenomenon was observed in a number of postmortem cases, in which the embolism of the middle or anterior cerebral artery branches was verified only by microscopy with the detection of emboli in the small arteries of pia mater near the infarction.

A small number (17) of stroke cases were classified as the small-artery occlusion subtype based in the detection of infarction with a diameter of ≤ 20 mm in the artery systems penetrating hemispheres and brainstem in the absence of the extra- and intracranial arteries alterations in the form of occlusion or stenosis (including the moderate stenosis) ipsilateral to the focal lesion. In 11 stroke cases the detected foci sized 1–2 cm were located in the knee and posterior hip area of the internal capsule, and in six cases the foci were located in thalamus and deep inside the basilar part of the pons. The foci were considered hypertensive lacunar infarctions, which was confirmed by episodes of high BP (180/110 mmHg and higher) in the medical history or upon admission to hospital, as well as by the presence of hypertensive retinopathy and left ventricular hypertrophy. According to the pathomorphological examination, the size of hypertensive lacunar infarctions along with the infarctions resulting from atherosclerosis was smaller compared to the size measured during neurovisualization (0.5–1.5 cm), which was due to their organization. Pathogenetic relationship between such infarctions and AH was confirmed,

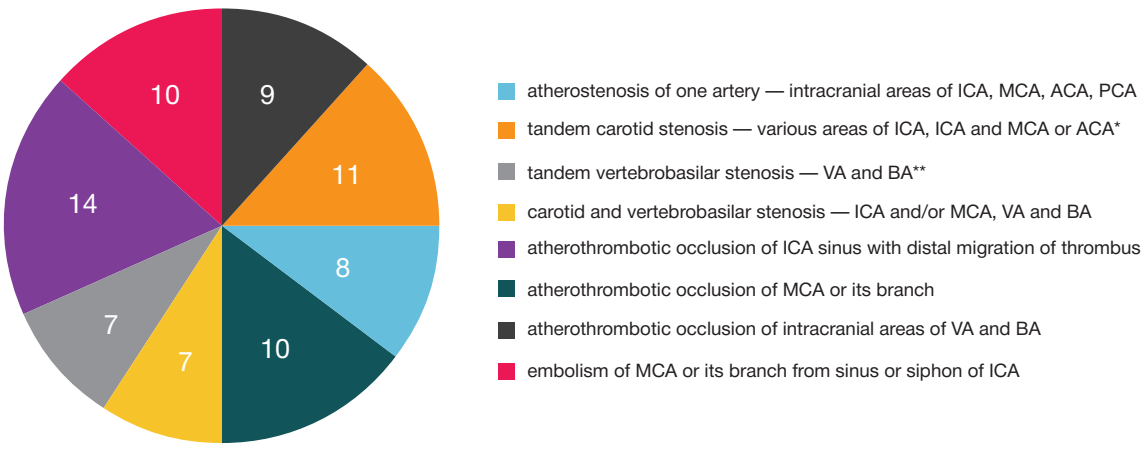

Fig. 1. Causes of stroke of the large-artery atherosclerosis subtype. ICA — internal carotid artery, MCA — middle cerebral artery, ACA — anterior cerebral artery, PCA — posterior cerebral artery, VA — vertebral arteries, BA — basilar artery; * — in combination with contralateral stenosis of ICA or MCA, ** — in combination with contralateral stenosis of VA

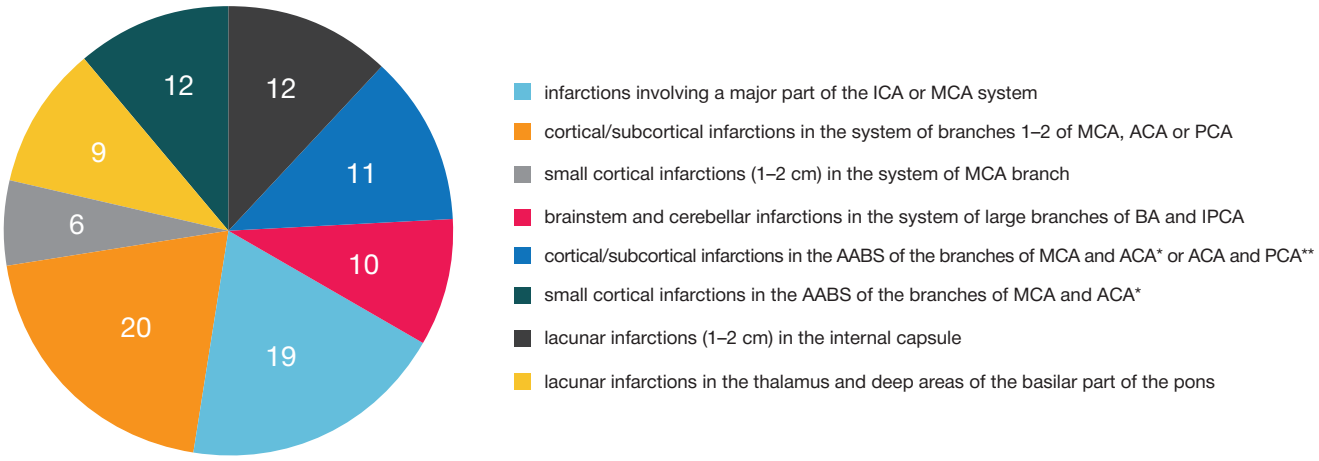

Fig. 2. Infarctions in patients with stroke of the large-artery atherosclerosis subtype. ICA — internal carotid artery, MCA — middle cerebral artery, ACA — anterior cerebral artery, PCA — posterior cerebral artery, BA — basilar artery, IPCA — inferior posterior cerebellar artery, AABS — area of adjacent blood supply; * — in the area of superior frontal sulcus and on the border between the superior and middle thirds of the central gyri, ** — in the area of intraparietal sulcus and in the inferior temporal gyrus

since the arteries with specific alterations (hyalinosis or plasmorrhagia with foci of fibrinoid necrosis associated with sharp narrowing of the lumen until the closure is complete) were detected in the close proximity to the foci.

Mention should be made of multiple infarctions, including the silent ones, within the same arterial system, detected in 49% stroke cases or the large-artery atherosclerosis subtype. The majority of silent ischemic foci were represented by single and multiple lacunar infarctions (54 of 78), the relationship of which with AH was excluded by microscopy. The other asymptomatic infarctions were small cortical infarctions, which resulted from critical atherostenoses and occlusions in the small arteries of the brain surface, and, much like lacunar infarctions, most often resulted from severe stenoses of larger arteries.

DISCUSSION

The study had shown the diversity of ischemic brain lesions and cardiovascular system alterations in cases of cerebral artery atherosclerosis combinations with CHD and AH. Clinical diagnosis or these alterations requires the use of a set of methods, which, according to our study, should be applied during the first 1–3 days after the stroke onset. Contemporary research methods make it possible to obtain considerable information on the ischemic stroke morphology. Thus, color duplex sonography of the major arteries of the head allows not only to define the degree of stenosis with accuracy of 95%, but also to reveal ulceration, hemorrhages and other structural features of atherosclerotic plaques associated with high risk of stroke [20]. Active use of echocardiography and Holter monitoring, as well as implementation of prolonged ambulatory ECG monitoring (during 30 days and more) and cardiac magnetic resonance imaging possesses great potential for verification of cardioembolism [21–23]. Neurovisualization methods provide a comprehensive source of information on acute focal brain lesions, diffuse white matter changes and cerebral perfusion, and also allow one to visualize the complicated atherosclerotic lesions [24–26]. Magnetic resonance angiography has become the method of choice for the diagnosis of intracranial artery alterations, including the occlusions and stenoses of perforating arteries in the areas of their origin, which are considered one of the main causes of focal brain lesion [27].

This study is one of the few Russian studies showing the great potential of the use of contemporary clinical and instrumental methods, as well as the stroke subtypes defined by the SSS-TOAST classification system, for diagnosis of major stroke pathogenetic subtypes (large-artery atherosclerosis, cardioembolism, small-artery occlusion) based on the pathomorphological verification. Furthermore, the study highlights inconsistency of the discussed in the literature additional features of cardioembolism (systemic embolic events and infarctions with a hemorrhagic component) and large-artery atherosclerosis (multiple infarctions, including the silent ones, occurring within the same arterial system) subtypes [8, 28]. Small number of lacunar stroke cases resulting from hypertension made it impossible to evaluate the significance of other features reported as additional markers of this type of stroke (diffuse loss of white matter and criblures caused by persistent edema, dilated ventricular system and subarachnoid space in the region of hemisphere sulci, microhemorrhages, combination of clinically significant lacunar infarctions with similar silent infarctions located in the other arterial system) [13]. All features were detected in no more than two cases both by neurovisualization and pathomorphological examination.

In our opinion, high informativity of currently available clinical and instrumental methods allows for a more in-depth diagnosis of pathogenetic stroke variants. The in-depth differential diagnosis is particularly important for the large-artery atherosclerosis subtype, which, according to the clinical, instrumental and pathomorphological data, includes stroke types of different etiology, i.e. resulting from critical atherostenosis or arterio-arterial embolism of intracranial artery, atherothrombotic occlusion of an extra- or intracranial artery, as well as from maximum degree (≥ 50%) of multifocal atherostenosis. Lower degree of maximum stenosis in patients with multiple atherosclerotic lesions compared to monofocal stenosis may be associated with local obstacles to collateral circulation through the circle of Willis anastomotic system and the arterial network of the brain surface. It seems that we should accept the opinion that in case of stroke resulting from multifocal stenosis the total cerebral arteries plaque burden should be assessed rather than maximum stenosis degree [15].

In cases of multifocal atherostenoses infarctions evolved in accordance with the cerebrovascular insufficiency mechanism, the doctrine of which was developed in the 50s by D. Denny-Brown and E. Corday. According to the doctrine, the development of infarctions depends not only on local obstacles to blood supply, but also on hemodynamics. According to the well known Schneider–Zulch's "last meadow" concept, in cases of general hemodynamic disorders ischemic lesions occur in the periphery of vascular territory, i.e. in the areas of adjacent blood supply to the branches of the internal carotid and/or

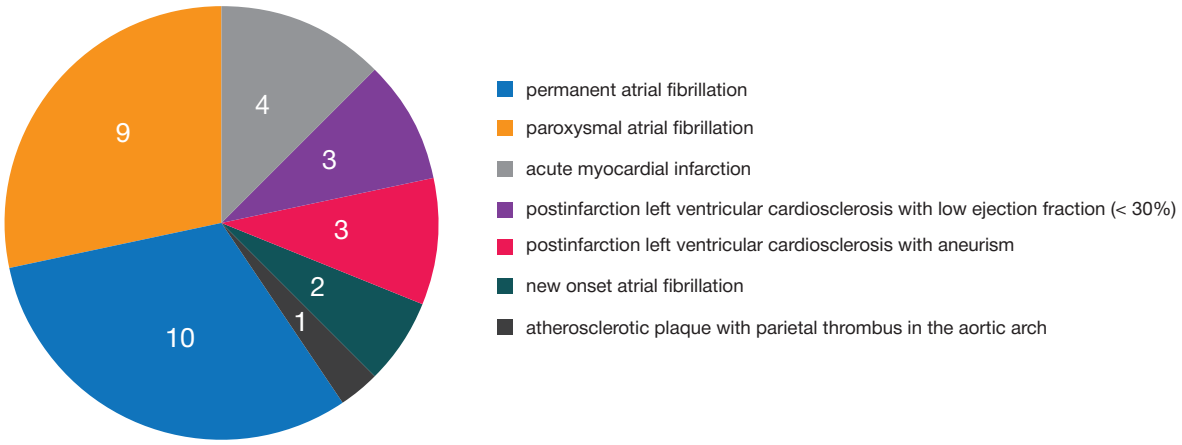

Fig. 3. Pathology with high risk of cerebral artery embolism

vertebral arteries, which remain intact with a sufficient level of systemic BP and total blood flow. The areas furthest away from arteries of the brain surface are the regions located deep in the cerebral hemispheres and pons, which determines the possibility of lacunar infarctions in the listed regions. In cases with multifocal stenoses the following signs of infarctions in the areas of adjacent blood supply or lacunar infarctions resulting from cerebrovascular insufficiency were observed: pre-stroke episodes of fluctuations in BP with a tendency to hypotension resulting from angina attack, decompensated heart failure in patients with postinfarction cardiosclerosis, and the taking the excessive dose of antihypertensive drug. Stenotic arteries with sclerotic wall changes were the pathomorphological feature of the detected infarctions, which may be considered the adaptive response to reduced blood flow resulting from atherostenosis of proximal large arteries. Pathogenesis features and clear signs of stroke resulting from cerebrovascular insufficiency made it possible to classify these infarctions as the distinct hemodynamic subtype in accordance with classification system developed in the Research Center of Neurology [11, 28].

The importance of in-depth differential diagnosis of pathogenetic stroke variants is reflected in other classifications of stroke. In one of those there is a distinct group within the large-artery atherosclerosis subtype which includes stroke resulting not only from cerebrovascular insufficiency, but also from atherostenosis or atherothrombosis of the brain surface artery with occlusion of penetrating artery in the area of its origin, and the aorto- and arterio-arterial embolism [14]. Such distinct pathogenetic variants of stroke have been assessed in some recent clinical trials aimed at further development of targeted treatment methods and prevention of brain ischemia, which is quite reasonable in terms of modern personalized medicine [29, 30].

CONCLUSION

The study has shown the diversity of ischemic brain lesion pathogenesis in cases of cerebral artery atherosclerosis combined with coronary heart disease and arterial hypertension. It has also shown the possibility of effective clinical diagnosis of the major ischemic stroke pathogenetic subtypes based on the criteria defined in the latest version of the TOAST classification. In our opinion, high informativity of the existing examination methods allows for a more differentiated understanding of the cause of ischemic stroke, which is fully in line with modern personalized medicine. Such approach should be used for the large-artery atherosclerosis subtype, which includes stroke resulting from various alterations of single cerebral artery (critical atherostenosis, atherothrombotic occlusion and arterio-arterial embolism) and stroke resulting from cerebrovascular insufficiency. The latter deserve special attention, since their pathogenetic features are defined by the following triad: cortical and cortical/subcortical infarctions in the areas of adjacent blood supply or lacunar infarctions in the regions located deep in the cerebral hemispheres and pons; multifocal atherostenoses (incuding the contralateral ones) the maximum degree of which may not exceed 50%; pre-stroke extracerebral factors of cerebral blood flow reduction.

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