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New features of the pathogenesis of a disease of cerebral small vessels

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Abstract

The etiopathogenesis of Binswanger's disease (cerebral vascular disease) is still the least studied cause of the disease. It is believed that endothelial, capillary and venular dysfunction, pathology of pericyte function, and increased BBB permeability lead to this condition. Moreover, essential arterial hypertension is not a cause, but a secondary compensatory-adaptive process in relation to cerebral microcirculatory disorders. As a result, lacunar infarction, microbleeding, leukoaraiosis and cerebral atrophy occur in the brain. Due to the lack of in-depth studies of etiopathogenesis - the Binswanger disease clinic, there are currently no means and solutions for effective treatment. Thus, an acute shortage of research and the need to continue scientific work in this direction are revealed.

Keywords: Binswanger disease, small vessel disease, systemic inflammation, endothelial dysfunction, pericytes, capillary dysfunction, clinic, treatment.

INTRODUCTION

Approximately 45% of cases of dementia are caused by cerebral vascular disease or Binswanger disease. According to WHO, in 2017 there were more than 47 million patients with dementia worldwide, according to forecasts, by 2030 this number will reach 75.6 million, and by 2050 it will almost triple and reach 135.5 million. Such growth will occur largely due to the increase in the number of people with dementia in low- and middle-income countries [12]. The disease was first described by Swiss doctor Otto Binswanger in 1894. The name of the disease in 1902 was given by his student A. Alzheimer, who studied pathology more deeply. At the time the disease was discovered, the diagnosis was made posthumously after an autopsy, but the question of timely diagnosis and targeted treatment is still open.

Cerebral small blood vessel disease (BCMS) is a group of diseases with certain neuroimaging changes on MRI tomograms of the brain [1], caused, as a rule, by a systemic lesion of small vessels from 5 microns to 2 mm in size. Small cerebral vessels mean small perforating arteries, arterioles, capillaries, venules, and small veins [9] located in the substance of the brain (parenchymal) and subarachnoid space (leptomeningeal).

Etiology and pathogenesis. **Endothelial dysfunction.** Local damage to the body leads to local activation of the endothelium, which is manifested by the production of vasoconstrictor and blood coagulating substances by these cells to stop bleeding, as well as inflammatory mediators and growth factors to eliminate the pathogenic agent and ensure the repair process. But with a modern human lifestyle, many factors lead not to local, but to systemic and chronic irritation of the endothelium, to which he responds with systemic vasoconstriction, increased thrombogenicity and systemic production of adhesion molecules and cytokines, that is, a systemic sluggish inflammatory process is triggered. As a result, arterial hypertension develops.

Capillary dysfunction is “oxygen starvation of the brain against the background of normal and hyperperfusion.” The heterogeneity of the flow rates through the capillary bed limits the pure extraction of oxygen - a biophysical property called functional shunting. In a normal brain, capillary blood flow patterns are homogenized when local cerebral blood flow increases due to activation of the cortex and thereby contributes to more efficient oxygen extraction [8]. And paradoxically, drugs that enhance cerebral blood flow during discirculatory encephalopathy (in the

English literature “small vessels disease”) can contribute to increased brain hypoxia, and in extreme cases, can lead to “malignant vasodilation” and provoke acute cerebrovascular accident.

Pericytes – analogues of MMC in capillaries and postcapillary venules, regulate their tone. Pericitis is an important component of the BBB, a 50% reduction in the number of pericytes increases three times the amount of extravascular fibrinogen, which has a toxic effect on neurons, which leads to point necrosis of the white matter and disruption of myelin production by oligodendrocytes [8].

Venular dysfunction. Normally, cerebral venules provide both a sufficient outflow and prevent its excessiveness. In cerebral disease of small vessels, cerebral venous dysfunction is preceded by capillary dysfunction and the earliest preclinical changes in cerebral blood flow autoregulation, such as resting hyperemia and maintaining capillary blood flow heterogeneity during functional loading, are caused by the primary cerebral venous vasomotion disorder. If we consider that the endothelium of venules has the highest adhesive ability, then it is possible that with endothelial dysfunction, it is the endothelium of the venules that is the first to be affected when exposed to reactive oxygen species and proteolytic enzymes produced by adhered leukocytes. In patients who do not have hemodynamically significant stenosis of the carotid arteries, it is probably not a compensatory process for limiting functional bypass surgery, but is a manifestation of a severe degree of violation of the venous outflow of blood. recent studies have shown that venotonicdiosmin accelerates the clearance of amyloid beta through the glyphatic system and improves cognitive abilities [10].

BBB permeability increase. Violation of the BBB with the migration of plasma proteins through the damaged vascular wall, contributes to disruption of the circulation of intercellular fluid in perivascular spaces [5] and impaired clearance of amyloid beta through the glyphatic system.

Clinical signs. The most common clinical manifestation of endothelial dysfunction is arterial hypertension, therefore it is not surprising that arterial hypertension is considered the main cause of BCMS, although the established cause-effect relationships are not convincing and need to be reviewed. We believe that essential hypertension is not the cause, but a secondary compensatory-adaptive process in relation to cerebral microcirculatory disorders in Binswanger disease.

Lacunar infarction is a small cerebral infarction of 3-20 mm in diameter, located in the deep parts of the hemispheres or in the subcortical white matter (in the pool of one perforating artery), detected by neuroimaging, which often does not manifest an acute acute neurological deficit and subsequently transforms into a small cavity - the lacuna [11].

Hyperintensity of white matter (leukoaraiosis) of vascular etiology is diagnosed on the basis of abnormal signals of various sizes in the white matter of the hyperintense brain in a T2-weighted image, without cavity formation [11], detected in ≈ 15% of adults without neurological symptoms older than 70 years and in ≈ 2 / 3 patients with dementia.

The expansion of perivascular spaces (Virchow – Robin) is a space filled with CSF located along vessels in gray and white matter and having a signal similar to CSF in all MRI sequences. Since they follow along the vessels, they can appear linearly, rounded or oval in the images with a diameter of usually not more than 3 mm, when the section is perpendicular to the vessel [11], they are often found in elderly people and are often mistaken for lacunar infarctions, they can occur as a result inflammation of the vascular wall, impaired integrity of the blood-brain barrier, amyloid accumulation along the vessel wall, brain atrophy and other causes.

Cerebral microbleeds are small, hypo-intense lesions with a diameter of 2-5 mm, which are visible on T2-weighted gradient echo (GRE) or sensitive-weighted sequences (SWI). Most often, CMCs are localized in the cortico-subcortical junction, the deep sections of the gray or white matter of the hemispheres, the brain stem and cerebellum. It is believed that the MRI signal is due to macrophages loaded with hemosiderin in the perivascular tissue due to diapedesis [6]; lacunae may be the outcome of these microbleeds.

Cerebral atrophy (in the context of BCMS) is a decrease in the volume of brain matter that is not associated with macroscopic focal injuries, such as trauma or heart attacks [11], tissue loss is replaced by an increase in ventricles and subarachnoid spaces (replacement external and internal hydrocephalus).

Treatment and prevention. The appropriateness of isolating BMS in a separate group is due to the fact that the prevention of cardiovascular diseases, approved for diseases of large arteries and cardioembolism, including antiplatelet, antihypertensive drugs and statins, may be ineffective for BCMS, and intensive antiplatelet therapy can be dangerous for BMS increased risk of hemorrhage [2]. Potential prevention methods for BMS may include exposure of the small vessels to the endothelium, the blood-brain barrier (BBB), microcirculation, and neuroinflammation [1].

There is no convincing data on the effectiveness of acetylcholinesterase and memantine inhibitors in BCMS patients [2]. Anticoagulants increase the risk of intracerebral hemorrhage in patients with BCMS [2].

Anticoagulants (warfarin, dabigatran, apixaban and rivaroxaban) reduce the risk of stroke in patients with atrial fibrillation. In the SPIRIT study, high doses of warfarin (INR 3.0–4.5) were associated with a high risk

of intracranial hemorrhage, especially in patients with extensive HIHB [2].

A study of steroidal and non-steroidal anti-inflammatory drugs (NSAIDs) has shown a protective effect against cerebral functions. Non-selective NSAIDs (aspirin, ibuprofen, naproxen) reduce the synthesis of pro-inflammatory prostaglandins, but their complications are gastrointestinal bleeding. Selective COX-2 inhibitors (coxibs) increase the risk of vascular events [2].

Antiplatelet agents - extra-platelet effects, in particular, the effect on endothelial dysfunction and activity of leukocytes and smooth muscle cells of arteries. Data from randomized trials confirm the effectiveness of antiplatelet agents in the prevention of re-stroke and transient ischemic attacks. [3].

Experimental studies have shown that dipyridamole, cilostazole and pentoxifylline can modulate BBB permeability, but there is no clinical evidence for this. Statins reduce the risk of primary and secondary stroke. Although there have not been large-scale studies of their use in LI, atorvastatin reduces the risk of re-stroke in both BMS and large arterial diseases (SPARCL study). [2].

Antihypertensive drugs of different classes are likely to have different effects on the prevention of stroke and cardiovascular events, but this information is not yet available [4].

One of the promising strategies is the use of flavonoid glycosides, which have a cytoprotective effect on many tissues. The leading drug containing these substances is the standardized extract of the ginkgo biloba plant Egb761 that has been used for over 50 years. One of the latest reviews on the effectiveness of EGb761, published by pharmacologists at the University of Toledo, USA, where the drug is known as tanakan or tebonin, has shown high efficiency (for cognitive impairment, cardiovascular and cerebrovascular diseases) and safety due to the absence of ginkgolic acids [7]. The ability of EGb761 in cerebral ischemia to activate cerebral stem cells and their migration to the lesion, including due to activation of cerebral neurotrophic and vascular endothelial growth factors, is noted.

CONCLUSION

Thus, it can be justifiably said that the continuation of the study of the etiopathogenesis of Binswinger's disease will lead to finding the most effective means of treatment.

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