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Modern Approaches to Studying the Mechanisms of Cognitive Impairment in Patients With Cardiovascular Diseases and the Possibility of their Correction

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Summary: With increasing life expectancy in modern society, the problem of age-related diseases is becoming urgent, among which cardiovascular diseases (CVD) and cognitive disorders occupy an important place. The article discusses the key pathogenetic mechanisms of cognitive impairment in elderly people with various cardiovascular diseases, such as hypertension, coronary heart disease, atrial fibrillation, chronic heart failure, and type 2 diabetes mellitus (DM2). The concept of diagnosis of chronic cerebral ischemia is highlighted and the prospects of the main therapeutic approaches aimed at improving cognitive functions in patients with CVD and type 2 diabetes are discussed. The spectrum of action and clinical effects of the drug Cereton (choline alfoscerate) are also analyzed in detail in this category of patients.

Keywords: cognitive impairment, cardiovascular diseases, Cereton

According to the World Health Organization, in most countries of the world there is a clear trend towards a change in the demographic situation, manifested in an increase in the proportion of elderly and senile people. Currently, about 20% of the population in Russia is elderly. Given these data, we can expect a further increase in the prevalence of age-related diseases. Old age is an important unmodifiable risk factor for many chronic and acute diseases, which in turn contributes to the development of comorbidity. The number of chronic diseases in the elderly varies from 2 to 10, depending on lifestyle and the level of preventive measures carried out over the previous years.

The most common diseases among the elderly are cardiovascular diseases (CVD), cerebrovascular diseases (CVD), type 2 diabetes mellitus (DM2), osteoarthritis, osteoporosis and oncological diseases. Since these diseases significantly increase the risk of disability and negatively affect the quality of life, their timely detection and prevention of complications become extremely important.

Cardiovascular diseases can lead to cognitive decline, up to dementia. Blood pressure (BP) is particularly closely associated with the development of cognitive impairment, especially in hypertension (AH).

Both elevated and excessively low blood pressure levels caused by excessive antihypertensive therapy can contribute to the development of hypertension. It is important to note that arterial hypertension in middle age plays a significant role in the subsequent development of dementia. According to the Scientific Center of Neurology in Moscow, 74% of middle-aged patients with recently uncomplicated hypertension of the 1-2 degree had mild or moderate cognitive impairment.

Pathogenetically, the relationship between hypertension and HF consists in damage to both large cerebral arteries (due to accelerated atherosclerosis due to high blood pressure) and small vessels, where lipohyalinosis develops. This leads to a narrowing of the vascular lumen, a decrease in their elasticity and deterioration of cerebral circulation.

Diffuse damage to the small cerebral arteries feeding the deep structures of the brain is associated with widespread changes in the periventricular and subcortical white matter of the major hemispheres, which is called "leukoareosis". In Russian clinical practice, this condition is traditionally considered as part of the diagnosis of dyscirculatory encephalopathy or chronic cerebral ischemia (CIG). In addition, brain hypoperfusion plays a key role in disrupting the metabolism of cerebral b-amyloid, which can

trigger the neurodegenerative process characteristic of Alzheimer's disease, especially in people with a genetic predisposition to this disease. Studies have shown that arterial hypertension (AH) is a risk factor for both vascular dementia and Alzheimer's disease, as well as their combination — dementia of the mixed type.

Among the well-known forms of cardiovascular diseases (CVD) associated with the development of cognitive impairment (CD) are coronary heart disease (CHD), atrial fibrillation (AF) and chronic heart failure (CHF). An increased risk of heart failure in these diseases may be associated not only with ischemic brain damage, but also with the development of Alzheimer's disease. This association remains statistically significant even after taking into account other common risk factors such as age, hypertension, or type 2 diabetes mellitus (T2DM). In some studies, it has been observed that patients with AF perform worse on neuropsychological tests for memory, thinking, and visual-spatial functions compared to patients with sinus rhythm. Moreover, the presence of AF is associated with a higher risk of developing dementia. According to the Rotterdam study, vascular dementia and Alzheimer's disease in patients with AF develop twice as often as in the general population, and in patients with pre-segment CN, the presence of AF increases the risk of their rapid transformation into dementia. The development of HF in AF may be associated with decreased cardiac output, decreased cerebral blood flow, and an increased risk of thromboembolic complications. It has been found that even a short-term delay or arrest of blood circulation caused by severe rhythm disturbances in AF can accelerate pathological processes in the brain, such as b-amyloid deposition and neurodegeneration.

Another disease that should alert a doctor about the risk of developing heart failure is coronary artery disease, including acute coronary syndrome (ACS). Cognitive impairments, including dementia, develop five times more frequently in patients with ACS than in the general population. At the same time, patients with a history of pre-existing coronary artery disease are more likely to have acute coronary syndrome. Experimental studies have shown that after suffering ACS, pathological changes in neurons in the frontal cortex and hypothalamus occur more often, which are traditionally associated with various cognitive functions.

Acute coronary syndrome most often develops against the background of atherosclerosis, which can affect both the coronary and cerebral arteries. Atherosclerosis of cerebral vessels is associated not only with the development of vascular dementia, but also with Alzheimer's disease (AD), in which there are also more pronounced atherosclerotic changes in large cerebral vessels compared with people without dementia. In addition, it was found that the polymorphic allele of the APOE4 gene, which encodes a protein involved in cholesterol transport, is associated with both the development of asthma and coronary artery atherosclerosis and acute coronary syndrome.

There is a close relationship between cognitive impairment (CI) and chronic heart failure (CHF): even taking into account factors such as age, hypertension, and cerebrovascular diseases, neuropsychological scales in patients with CHF are on average 1 point lower than in elderly people with heart disease but without CHF. Patients with severe CHF show worse results on tests for attention and regulatory functions compared to patients with milder CHF. Cognitive impairments become noticeable even to a layman when the left ventricular ejection fraction drops below 30%. In patients with severe CHF who have undergone successful heart transplantation, there is a significant improvement in cognitive functions. With long-term follow-up (more than 9 years), the incidence of dementia in patients with CHF reaches 80%. It is also worth noting that heart failure is more common in patients with HF than in cognitively healthy people. The development of subclinical myocardial dysfunction, both systolic and diastolic, is also associated with the risk of heart failure. The risk of HF is especially high when CHF is combined with hypertension, with cognitive functions such as memory, attention, and regulatory processes primarily affected. All these data confirm the important role of hypoperfusion in the development of HF, which is also confirmed by the close relationship between HF and the left ventricular ejection fraction.

Important factors contributing to ischemic brain damage in patients with CHF are decreased vascular reactivity, concomitant neurohumoral disorders, thromboembolism, and excessive lowering of blood

pressure during antihypertensive and vascular therapy [13]. The most severe form of brain damage that develops in patients with CHF is the so-called cardiac encephalopathy. The mechanism of development of cardiac encephalopathy is associated with impaired diastolic function of the heart, which leads to increased pressure in the venous system, fluid retention in the body and can contribute to overfilling of the intracranial venous sinuses and jugular veins, resulting in impaired absorption of cerebrospinal fluid and its accumulation in the subarachnoid space, cerebral cisterns and sometimes in the ventricles of the brain. This disrupts the perfusion of the brain, which is also facilitated by a decrease in cardiac output, and additional damaging factors may be hypoxia and pulmonary hypertension caused by circulatory disorders in the small circle.

The main signs	I stage	II stage	III stage
Complaints	+/++	+/++	+
Cognitive impairment	Lungs	Moderate, mild dementia	Significantly pronounced (dementia)
Motor disorders	Mild and moderate	Mild, moderate, or significant	Moderate or significant
Ability to work	Able to work	Partially able-bodied/disabled	Disabled
Household independence	Independent	May be partially dependent on others	We depend on others

Important risk factors for cognitive impairment (CI) include diabetes mellitus (DM), whose association with cardiovascular diseases (CVD) is well documented. According to the International Diabetes Federation, 463 million cases of diabetes were reported worldwide in 2019, and this number could reach 700 million by 2045. In Russia, as in many countries, there is a noticeable increase in the number of people with diabetes, mainly due to an increase in the number of patients with T2DM. At the beginning of 2019, their number in the country was 4.24 million, according to the national register. However, these data do not fully reflect the actual spread of DM2, since, according to the NATION epidemiological study, about 54% of cases remain undetected. Thus, the actual prevalence of T2DM in Russia may be twice as high as the number of reported cases.

Cardiovascular diseases are 2-5 times more common in patients with T2DM than in people without diabetes, with a particularly high risk of complications such as acute coronary syndrome (ACS) and stroke. Arterial hypertension (80%), atherosclerosis (70%), diastolic myocardial dysfunction (50-75%), chronic heart failure (12-22%) and atrial fibrillation (25%) are common among comorbid diseases in patients with DM2. One of the key factors in the development of CHF in patients with DM2 is insufficient compensation of glycemic levels, as well as frequent hypoglycemic episodes. It is known that the risk of hypoglycemia increases significantly with a disease duration of more than 6 years, and severe hypoglycemic conditions are associated with a high risk of sudden cardiovascular death, ACS, stroke, as well as the progression of heart failure, up to dementia.

The morphological substrate of HF in patients with CVD is dyscirculatory encephalopathy, or chronic cerebral ischemia (CCM). Chronic cerebral ischemia is one of the most common conditions in patients with CVD, which, unfortunately, is often not recognized at an early stage and continues to be the leading cause of social diseases such as stroke and dementia. In the early stages of HCG, patients are often under the supervision of general practitioners, internists, or cardiologists, who should be aware of the chronology of major events related to the development of vascular CNS on the background of CVD.

Cardiovascular diseases (CVD) without brain damage (approximately 1 year after the onset of CVD);

Clinically asymptomatic vascular lesions of the brain (the first 2-5 years after the onset of CVD);

Mild vascular cognitive impairment (CI) (approximately 5-8 years after the onset of CVD);

Moderate vascular CNS (from 8 to 10 years from the onset of CVD);

Vascular dementia (may develop immediately after the first stroke or 10-15 years after the onset of CVD).

Speaking about patients with a high probability of developing chronic cerebral ischemia (CCI) and CN on the background of CVD, the following groups can be distinguished:

- Patients with a diagnosis of chronic heart failure (CHF) at any stage;
- Patients with atrial fibrillation (AF) of any form – persistent or permanent;
- Patients who have undergone acute coronary syndrome (ACS) or myocardial revascularization surgery;
- Patients with multifocal atherosclerosis;
- Patients with type 2 diabetes mellitus (DM2);
- Patients with arterial hypertension (AH).

Chronic cerebral ischemia is a set of clinical manifestations that are associated with a progressive decrease in blood supply to the brain. This can lead to diffuse or focal changes in brain tissues. The diagnosis of HCG is based on the identification of significant risk factors and should be accompanied by recommendations for lifestyle changes and the appointment of necessary etiopathogenetic therapy, such as antihypertensive, hypoglycemic, hypolipidemic, and anticoagulant therapy. HCG, being the result of various CVD, significantly impairs the quality of life and can affect the daily activity and performance of patients, especially due to the development of heart failure.

In elderly patients, improper use of antihypertensive or hypoglycemic therapy may contribute to the progression of HCG, which in turn increases the risk of hypoglycemia or hypotension. Therefore, the treatment of such patients should be very careful. To solve this problem, protocols for the withdrawal of sugar-lowering drugs for people over 65 years of age have recently been developed, as well as new clinical guidelines for the treatment of hypertension and other CVD in elderly patients.

The main goals of the treatment of patients with chronic cerebral ischemia (CCB) include stroke prevention, which is achieved through the correction of all identified risk factors, as well as slowing the progression and reducing the severity of pre-existing cognitive impairments (CI). It is important to remember that cognitive deficits can go unnoticed for a long time. Therefore, patients with cardiovascular diseases (CVD) need to actively ask questions about possible cognitive problems, such as memory loss for current events, absent-mindedness, difficulties in choosing words, problems with performing simple calculation operations or orientation in an unfamiliar area. Patients with developing CH often pay attention not to their forgetfulness or absent-mindedness, but to symptoms such as headache, dizziness, tinnitus or ringing, weakness, which they consider more significant for their health.

Due to the high prevalence of CVD leading to the development of heart failure, doctors should be particularly wary of possible cognitive impairments. As already mentioned, cognitive deficits can go unnoticed if the doctor does not conduct a targeted survey and/or neuropsychological testing. The study of the cognitive sphere in all patients without exception is not always justified, but it is extremely useful for patients who seek help for CVD for the first time, especially among middle-aged and elderly people, if they have the following signs:

- Patient's complaints of memory impairment, absent-mindedness, or difficulty concentrating;
- Evidence from relatives about the recent deterioration of the patient's cognitive functions;
- Problems with self-presentation of medical history or with the correct implementation of doctor's recommendations;
- The symptom of a "turning head" is when a patient answers a doctor's question, asking his companion to answer for him.

Modern diagnosis of CN requires that the patient's complaints be supported by the results of a neuropsychological examination. Screening neuropsychological scales have been developed for practical use in the clinic, which are easy to apply and interpret. These scales are often sufficient for the diagnosis of CN and do not require special equipment. In addition, they allow for quantitative assessment, which makes it possible to use them for dynamic patient monitoring. One of the recommended screening tools is the Mini-Cohg scale, which is easy to use, takes little time, and is quite sensitive to CT. Patients with identified cognitive impairments require special attention and the appointment of therapy aimed at preventing further deterioration of cognitive functions.

Given the complexity and versatility of the pathogenesis of cognitive impairment (CD) in chronic cerebral ischemia (CVD) on the background of cardiovascular diseases (CVD), it is necessary to choose drugs with a complex effect. Such drugs should normalize the energy metabolism of neurons, protect against oxidative stress, stabilize the structure of cell membranes, eliminate neurotransmitter imbalance and have a neurotrophic effect. An important goal of drug therapy for HF is to restore the balance of neurotransmitter systems, especially cholinergic ones, which improves cognitive functions such as memory, attention, and learning ability. One of the leading drugs that improve the condition of HF through the activation of cholinergic processes is Cereton (choline alfoscerate). The use of Cereton in neurorehabilitation has opened up new perspectives for studying the processes of recovery in the central nervous system.

Uncorrectable (unmodifiable)	Correctable (modifiable)
Old age Paul Genetic factors	HYPERTENSION Atherosclerosis of diabetes Dyslipidemia Cardiac arrhythmia Violation of rheological properties of blood Lifestyle–related factors: - smoking; – excessive alcohol consumption; – overweight; – low physical activity; – irrational nutrition

Cereton, being a universal choline donor that easily overcomes the blood-brain barrier, contributes to the full-fledged correction of choline deficiency in the central nervous system. It is a substrate for the rapid synthesis of acetylcholine and stimulates its release from presynaptic terminals, which helps restore interneuronal connections and improve neurotransmission. The drug also activates the restoration of dendrite growth and branching, enhances the formation of dendritic spines, which improves conduction between neurons. An important feature of Cereton is its participation in the synthesis of phosphatidylcholine, a key component of membrane phospholipids. Additionally, Cereton increases the secretion of neurotrophic factors, including nerve growth factor and its receptors, which promotes axonal growth, the formation of new synapses, and cellular migration from subventricular zones to the injury zone.

Taking into account the neuroprotective effect of Cereton, its ability to restore the cholinergic system, maintain the membrane structures of neurons, improve synaptic transmission and have a neurotrophic effect, it can be argued that the drug actively affects the processes that support the normal functioning of the central nervous system. Data on the safety of Cereton have been obtained in numerous clinical trials and confirmed in real practice.

To begin treatment with Cereton, it is recommended to use the parenteral form of the drug (intravenous or intramuscular injections) at a dose of 1000 mg per day. The duration of parenteral therapy is 10-15 days, after which the patient switches to Cereton capsules of 400 mg (2 capsules in the morning and 1 capsule in the afternoon). The duration of the course of therapy depends on the stage of ADHD and the

severity of cognitive impairment, on average it is 6 months, while the course can be repeated after 3 months.

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