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The role of cardiovascular diseases in the development of Alzheimer's disease and cognitive impairment, including COVID-19

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Abstract

Alzheimer's disease (AD) is a complex neurological disease with a long latency period, which belongs to the group of neurodegenerative diseases. It is the most common neurogeriatric pathology that is characterized by the accumulation of beta-amyloid protein in the form of amyloid plaques and Tau protein (pTau) forming neurofibrillary glomeruli (NFG) in the neuronal bodies due to genetic factors.

However, cardiovascular diseases (CVD), including arterial hypertension (AH), has been found to be a significant risk factor. Early manifestations of AD include cognitive impairment (CI), which in real clinical practice is first encountered by primary care physicians: general practitioners, internists, cardiologists, neurologists. In addition, due to the COVID pandemic the number of patients with AD has significantly increased. CI is the most frequent neurological complication in the post-covid period, therefore, its timely diagnosis and correction will allow to slow down the progression of AD.

Key words: Alzheimer's disease, cognitive impairment, arterial hypertension, COVID-19, cholinesterase inhibitors, neuroprotective therapy.

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Alzheimer's disease (AD) is a neurological, incurable, degenerative (atrophic) disease of the brain that manifests itself as a rapidly progressive decline in a person's cognitive and intellectual abilities. The disease was first described in 1906 by Alois Alzheimer, a professor of neurology and psychiatry from Frankfurt. It was subsequently named after him.

As life expectancy increases, the number of people suffering from CI and dementia is rising. According to World Health Organization (WHO) experts, Alzheimer's disease is the most common cause of dementia in old age and accounting for 50 % of all dementia cases in people over the age of 80. The WHO recognises Alzheimer's disease as one of the 4 major medical and social problems of modern society. It is the 6th leading cause of death worldwide (3rd in economically developed countries), and the number of deaths is increasing. According to the WHO, 46.8 million people had dementia in 2015, and this number is expected to triple by 2050. Caring for people with Alzheimer's disease is economically very costly, with global expenditure on dementia-related interventions totalling $818 billion in 2015, of which 85 % was spent on social and family costs rather than medical care. AD could lead to a global health and social care crisis in the next 20 years [1, 2]. Therefore, the issues of early diagnosis of this pathology and the search for optimal and timely treatment are very relevant.

It has been established that hereditary cases of Alzheimer's account for about 1 %, the remaining cases are sporadic: 13 % — in people over 65 years of age; 50 % — over 80 years of age.

In Russia, 1.4 million (4.5 %) elderly patients suffer from Alzheimer's disease. In Moscow, every 21st person over the age of 60 suffers from this pathology. Professor V. Zakharov in his speech at the Fifth All-Russian Congress on Gerontology and Geriatrics stated that Alzheimer's disease is widespread, but little known and difficult to diagnose, not all patients are detected in the latent stage, so the real picture is even worse [3].

AD aethiology

The aetiology of AD is not fully understood. It is assumed that a number of risk factors (RFs), the presence of AroE-4 and inflammatory markers lead to a cascade of pathological reactions in the brain, and within a decade an Alzheimer's type neurodegenerative disease develops, up to dementia.

The pathogenesis of the disease remains unspecified, and the following hypotheses have been suggested:

- The cholinergic hypothesis. AD is caused by a decrease in the synthesis of the neurotransmitter acetylcholine.
- The amyloid hypothesis — an accumulation of beta-amyloid protein caused by genetic factors, with the formation of plaques between neurons. The gene encoding amyloid-precursor-protein (APP) from which beta-amyloid is formed is located on chromosome 21. Amyloid deposition in the walls of small vessels of the arachnoid mater and cerebral cortex is observed in all patients with AD (Fig.1).
- The glomerular or tau hypothesis, proposes that oxidative stress leads to a disruption of the tau protein structure (Fig. 2), its aggregation and transformation into neurofibrillary glomeruli (NFGs) through the formation of pathological bonds with oxidised proteins [3, 4].

Brain atrophy (temporal and parietal lobe hippocampus) occurs as a result of nerve cell death. Amyloid plaques compress the structures of neurons, disrupting their connections with other cells and leading to their death. These changes reduce the number of nerve cells by up to 30 % or more. When the number of nerve cells and the connections between them are critically reduced, the brain can no longer manage its functions.

Forms of Alzheimer's disease (according to ICD-10)

F00.0. Dementia in Alzheimer disease with early onset

Dementia in Alzheimer disease with onset before the age of 65, presenile dementia, type 2

F00.1. Dementia in Alzheimer disease with late onset

Dementia in Alzheimer disease with onset after the age of 65, senile dementia, type 1

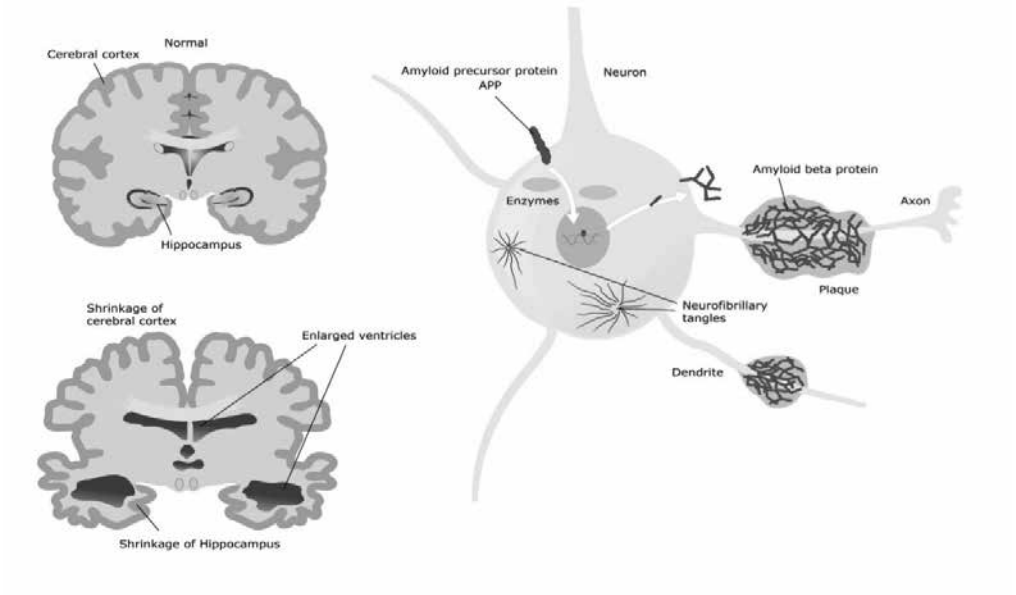

Fig. 1. Pathogenetic patterns of AD development

F00.2. Dementia in Alzheimer disease, atypical or mixed type

— The presenile type is characterised by a rapid progression with the development of aphasia, apraxia, agnosia, alexia. Often has a family history of AD or Down syndrome. Homogeneous structure of the syndrome: aphasic-apraxic-agnostic dementia.

— Senile type develops after the age of 65, slowly progressive. Memory impairment, confabulations predominate, usually sporadic. Different clinical forms of dementia.

Alzheimer's disease risk factors:

• Older age, family history of the disease, especially with early onset of dementia before the age of 60;

• CVD, uncontrolled AH in the middle and old age, atherosclerosis of the main vessels of the head, dyslipoproteinaemia (DLP); AH during pregnancy (associated with an increased risk of developing RFs even decades after delivery);

• Carbohydrate metabolism disorders, obesity (metabolic syndrome), head injury, hypodynamia, smoking, chronic hypoxia, hyperhomocysteinemia, sleep disorders, deficiency of B vitamins, folic acid;

• Female gender;

• Low educational level and low intellectual activity during life, episodes of depression in young and middle age [5–7].

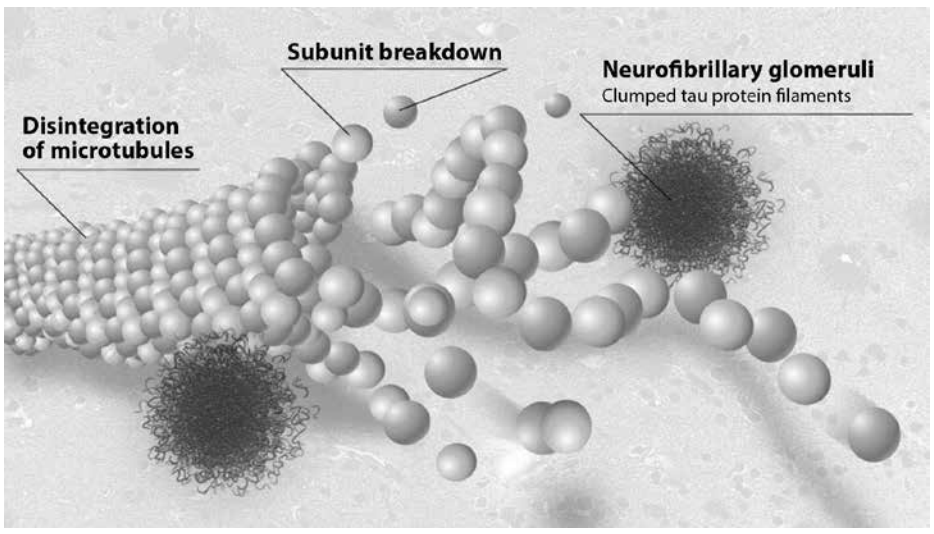

Fig. 2. Scheme of Tau-protein formation

Clinical course of AD, stages of the disease

An American psychiatrist Neil Buchholz explained the difference between ordinary forgetfulness and what happens in Alzheimer's: "If you forget where you put your keys, that's not a disease yet, but if you don't know what to do with the keys, what they're for, that's a problem".

At the 1st stage of the disease (initial stage): gradual development of CI — mild subjective and objective disorders of short-term memory, attention, difficulties in spatial orientation, errors in professional activity. Depression may occur. Normal functioning. The first symptoms are often confused with manifestations of ageing or stress response and can be detected by a detailed neurovegetative testing. Such cognitive impairment tends to appear within 8 years prior to diagnosing.

Stage 2 of mild dementia (MMSE 19-26): mild memory impairment; difficulty in learning new information, performing complex household tasks, spatial orientation; limited interests, decreased initiative, lasting up to 1 year.

Stage 3 moderate dementia (MMSE 10-18): progressive cognitive deficits (apraxia, aphasia, agnosia, alexia, acalculia, agraphia), loss of long-term memory, impaired acquisition of current information and functioning in daily life.

Stage 4 dementia (MMSE 0-9): Total loss of intellect. Agitation, sleep rhythm disturbance, total inability to perform daily activities, hygiene skills, cachexia, epilepsy [5]. The final loss of function leads to death, mainly from CVDs.

When diagnosing Alzheimer's, it is important to bear in mind Rebo's Law, which states that "Recently acquired knowledge and skills are lost, and long-standing ones are lost in the opposite order to that acquired during life (i.e. a patient at the onset of the disease remembers the distant past, but not what happened yesterday or in the recent past).

Modern methods of diagnostics

Modern diagnostic methods include:

1) Neuroimaging techniques: CT, MRI. PET-CT most clearly visualises the pathological signs of Alzheimer's disease in the form of amyloid plaques and tau proteins in neurons.

2) Cerebrospinal fluid biomarkers: decreased beta-amyloid and increased tau protein. The study is carried out at a mild and moderate stage of the disease, when dementia has not yet developed.

3) Neuropsychological tests to determine the severity of the disease and assess the effectiveness of the therapy.

MMSE test — a short scale for assessing mental status, which allows you to determine the severity of the disease (mild, moderate, severe) by scores. Clock "drawing" test, clock copying, delayed reproduction test, etc. [1, 5, 6].

AD treatment

It should be noted that there is no drug for the treatment and prevention of Alzheimer's disease. The aim of treatment is to prevent the progression of CI and dementia.

The "gold standard" for overcoming cholinergic deficiency and improving cognitive function is the administration of anticholinesterase inhibitors (donepezil, velaxin) and acetylcholine donors (choline alphoscerate, gliatilin, cereton). Velaxin is an antidepressant, but indirectly affects cholinergic receptors as a pharmacological side effect. The therapeutic efficacy and safety of this group of drugs has been demonstrated in numerous national and international clinical trials in mild and moderate stages of the disease, and they may be able to prevent or delay dementia [8]. The 2-year, double-blind, multicentre ASCOMALVA study was conducted to evaluate the efficacy of combined therapy with donepezil and gliatilin in patients with chronic cerebral ischaemia and Alzheimer's disease. In the group of patients with AD, significant positive results were obtained according to the CI scales (MMSE and ADAS-cog).

Neuroprotective therapy to preserve neuronal viability: glutamate receptor blockers: acatinol memantine, nootropics, divase, antioxidants, neurotransmitters — cerebrolysine. The use of these drugs has been well documented. A relatively new drug is Divase — an innovative drug consisting of antibodies targeting the brain protein S-100 and antibodies against endothelial NO synthase.

To improve the neurotransmission, it is necessary to improve blood flow in the narrowest segment of blood flow — the microcirculatory vessels. To deliver cholinergic drugs, nootropics, oxygen, glucose and other metabolic agents, it is necessary to improve the microcirculation in the cerebral arteries, to increase the elasticity and deformability of erythrocytes, their ability to pass in the narrowest segments of capillaries. An example of such a drug is naphthidrofu-

ryl, which affects the microcirculation with a proven positive effect on cognitive functions (vasodilatory effect, improves blood rheology and platelet haemostasis, increases ATP concentration, reduces oxidative stress, increases resistance of brain cells to hypoxia). From the cardiologist's point of view, prescribing a choline supplier and other drugs in combination with microcirculation-improving drugs is important in the management of patients with Alzheimer's disease. An analysis of 9 randomised, blinded, placebo-controlled trials involving 847 patients with Alzheimer's disease, vascular dementia and mixed dementia showed improvement in behavioural and cognitive functions; improvement in patients' functional activity; good tolerability of naftidrofuryl [8].

It is recommended to correct the risk factors for the development of AD, especially CVD, metabolic risk factors for the development of CVD (obesity, AH, impaired carbohydrate and lipid metabolism). Medications that worsen cognitive function (benzodiazepines, anticonvulsants, antipsychotics, central cholinolytics, digitalis drugs) should be avoided unless necessary [9].

Discussing the CVD-Alzheimer's relationship

Genetic-based CVDs play an important role in developing AD. Many genetic polymorphisms have now been shown to be associated with developing CVD. At this stage, it has already been established that chronic non-communicable diseases (CNCDs), which have reached epidemic scales, cause 71 % of deaths, mainly due to CVD, oncology, COPD and diabetes. The development of these diseases is caused by modifiable risk factors, among which AH, diabetes, obesity, smoking and hypodynamia play the most important role. It has been shown that the development of CVD is possible with a certain combination of behavioural and genetic RFs Thus, there is a certain correlation between AD and CVD at the level of the individual genome with gene expression in different cells of the organism. There is no doubt that the role of macro- and microcirculation plays an important role in brain homeostasis. It is through the bloodstream that not only the metabolites necessary for normal neuronal function are delivered, but also various free oxygen radicasl, pro-inflammatory cytokines, vasoconstrictors in the case of endothelial dysfunction (ED). This leads to the development of the cardio-cerebral continuum (CCC) and ultimately to neurodegenerative changes in the brain ending with neuronal death.

Therefore, there is a certain link between CVDs and beta-amyloid accumulation, which leads to inflammatory responses and neuronal death. The question remains as to why the beta-protein is not cleared from the brain, and what causes it to accumulate. Why does the tau-protein accumulate in the neuron? Perhaps there is a deficiency of cerebral autoregulation due to the developed AH, which is the trigger for the development of hypertensive encephalopathy through to dementia. The simplified scheme presented here begins to claim that Alzheimer's disease is a new cardiovascular pathology.

Research is being carried out around the world to understand the pathogenetic mechanisms and to develop effective drugs for Alzheimer's disease. Our task is to draw the attention of primary health care to the existing very serious problem of cardio-cerebral relationships and to consider any cardiac pathology as a marker of brain pathology, including Alzheimer's disease. It is necessary to carry out large-scale studies to determine the extent of the relationship and to further clarify the mechanisms for preventing the development of AD.

Age is a non-modifiable risk factor for the development of CVD and AD, particularly in older age groups. The main mechanism of cellular ageing is oxidative stress, which leads to progressive ageing and shortening of DNA telomere ends. The measurement of telomeres in patients with CVD, and possibly AD, has prognostic value and may help to identify individuals in need of preventive measures. A number of epigenetic studies have also demonstrated the importance of microRNAs in the pathogenesis of myocardial infarction, stroke and chronic heart failure (CHF). The role of the metagenome, the genetic material of the microbiota, which is involved in the homeostasis of the whole organism and is an important factor in biochemical interactions, should also be considered. The metagenome has already been linked (it was sequenced in 2010) to the development of AH, lipid disorders, obesity and other diseases. The mechanisms by which the metagenome interacts with the human body are still under investigation and have not been fully elucidated. Perhaps more precise targets indicating the possible development of CVD and AD will be revealed by further epigenetic studies taking into account the metagenomic status. Therefore, a per-

sonalised approach to the diagnosis and treatment of CNCDs is highly relevant [10]. The idea of personalised medicine is already being researched, and steps are being taken in Russia to introduce genetic panels into clinical practice to assess the effectiveness of drugs. In order to develop programmes to prevent the development of CNCDs, including CVD and AD, the development of an individual genetic passport is underway.

The development of CI as a complication of COVID 19

Negative effects of SARS-CoV-2 on the development of CI, independent of the severity of the disease course, were revealed during the pandemic. Advanced age, co-morbidities (AH, DM, obesity, COPD) are factors for the development of CI. There is a significant amount of cognitive and psychoemotional disorders developing after COVID-19. Dementia was the third most common neurological complication, accounting for 0.7%, which is 1.7 times the average population risk [11, 12]. The adverse effects are mediated by the direct neurotoxic effect of the virus on brain cells. SARS-COV-2, after proteolytic cleavage of its protein by S-serine protease, binds to the transmembrane ACE-2 and enters type 2 pneumocytes, macrophages, cardiomyocytes, pericytes (perivascular cells located on capillaries), causing endothelitis with thrombosis of small and large vessels. Pericytes are particularly abundant in the brain and the blood-brain barrier system, its permeability increases. Fibrinogen, viral particles, immunocompetent cells enter the brain parenchyma, which induces the inflammatory process, vasogenic oedema develops, oxidative stress, activation of microglia (macrophages) of the CNS.

Another factor is social isolation. It has been found that 50% of patients with mild CI and AD have a marked decline in cognitive function, and one in six patients have delirium. Walking difficulties and depressive disorders have also been reported. Following coronavirus infection, Alzheimer's disease manifests rapidly (1-6 months) [3]. Thus, a new coronavirus infection may lead to the development of clinical symptoms of AD. Therefore, physicians need to be vigilant in recognising these symptoms in order to promptly prescribe basic therapy with drugs that improve cerebral microcirculation. Additional therapy of post-covid syndrome includes prescription of: vitamins (including vitamin D), trace elements (selenium, magnesium, zinc, iron), antiplatelet drugs for cardiovascular and cerebrovascular risks, antihypoxants and antioxidants, nootrops, statins (for cardiovascular and cerebrovascular risks), anxiolytics.

Cardiologist's perspective on CI in cardiac patients

It has been established that the development of CVD increases the risk of CI and psychoemotional disorders by 2–3 times compared to healthy individuals and increases up to 40%, leading to a worse prognosis due to cardiovascular events (including suicide). These patients die on average 20 years earlier than the general population (Lancet, 2018). The most important and best studied major RF of CVD development is AH. AH is a RF of AD development as well and also worsens the prognosis of coronavirus infection, especially in the postcovid period. CIs are found at all stages of AH and are well reported.

Cognitive functions (CF) — complex brain functions through which the process of rational perception of the world and purposeful interaction with it is carried out. Gnosis, praxis, intellect, memory and speech are the five basic functions.

- Gnosis — the perception of information, the ability to combine elementary sensations and holistic images. An agnostic patient sees an object, can describe it, but does not recognise it.
- Praxis is an arbitrary, purposeful motor action; patients with apraxia are unable to perform a particular action due to a loss of ability, despite the absence of a paresis.
- Intelligence — the ability to analyse information, to identify similarities and differences, general and specific, major and minor, the ability to abstract, solve a problem, make conclusions.
- Memory — the ability to capture, store and repeatedly reproduce the received information. Moreover, subjective complaints of patients about memory do not correspond to its true disorders, which are detected by special methods of research.
- Speech — the ability to understand spoken language and to express one's thoughts by using verbal means (words) [1, 11].

Neuropsychological testing is recommended for the assessment of CI, which makes it possible to identify and assess the cognitive disorder (CD). In outpatient practice it is convenient to use the most optimal test "Mini-Cog" (S. Borson, 2000). It is a

combination of the three-word memory test and the drawing of a clock: 1) repeat after the doctor and memorise 3 words (for example: apple, circle, chair); 2) draw a clock face with hands and write the time (for example, 10 minutes to noon); 3) name 3 words that were memorised at the beginning of the test. The interpretation of the test is as follows: if the patient has remembered 1 or 2 words, the drawing of the clock is analysed. If it is correct, there is no cognitive disorder (CD); if it is incorrect, there is a CD. The test has a sensitivity of 99 % and a specificity of 93 %. The test can be administered to patients with speech and language disorders.

CVDs, including myocardial infarction (MI) and stroke, are leading causes of all-cause mortality and account for a high proportion of disability in the able-bodied population. It is known that acute and chronic brain damage is caused by a number of CVDs, but the leading ones remain: CHD, AH, CHF, arrhythmia (more commonly atrial fibrillation), DLP, acquired heart defects and prosthetic heart valves.

Role of CVDs in the development of cerebrovascular disorders

In the last decade, an interdisciplinary field of medicine such as cardioneurology has emerged as a result of the recognition of the relationship between cardiac and cerebral pathology. One of the important directions of cardioneurology is the study of neurological disorders in patients with cardiac pathology [11]. In modern literature, the terms "cardiogenic encephalopathy", "cardiogenic dementia", CCC and others have emerged. Therefore, prevention and treatment of patients with these co-morbidities will be optimised by the early detection of chronic cardiac diseases leading to progression of cerebrovascular pathology and clarification of the pathogenetic mechanisms. It should be emphasised that this is not only a medical problem. It is also a very important social problem.

The development of cardio-cerebral diseases is based on common RFs: AH, DLP, DM, smoking, obesity, alcohol abuse, unbalanced diet, hypodynamia, prolonged psycho-emotional stress, etc., which cause general remodelling of CVDs, parallelism of pathological processes in heart and brain. Common in the pathogenesis of cardioneurological pathology is the development of active free radical oxidation (FRO). FRO is a process of direct transfer of oxygen to the substrate with formation of peroxides, ketones, aldehydes, inducing reactions of peroxidation with participation of reactive oxygen species — superoxidants, hydrogen peroxide, hydroxyl radical.

It is sometimes difficult to determine the true role of cardiac pathology in the development of chronic cerebrovascular disease [CVD]. However, the main cause of CVD is cardiovascular pathology, namely:

- CHD (myocardial infarction, arrhythmias, CHF with reduced LV ejection fraction);
- AH and hypertensive crises;
- cardiogenic cerebral emboli;
- cardiogenic syncope with development of post-ischaemic encephalopathy;
- DLP and hypercholesterolaemia;
- atherosclerosis of both extra- and intracranial vessels;
- neurological complications of infective endocarditis.

CVDs can lead to the development of dyscirculatory encephalopathy (DEP), which is based on the following pathogenetic aspects: impaired autoregulation of cerebral blood flow; impaired rheological properties of blood; DLP; intravascular activation of haemostatis.

In DEP, the unfolding 'ischaemic cascade' leads to biochemical disturbances, the steps of which are described as follows:

- decreased blood flow and oxygen content;
- cyclic nucleotide formation and oxygen utilisation;
- eicosanoid release, calcium accumulation, protease activation;
- development of oxidative stress and local inflammatory reactions;
- endotheliocyte dysfunction and development of microcirculation block.

These steps in the pathological "cascade" in the conditions of ischaemia/hypoxia that develop in DEP lead to CD, a progressive condition that will eventually turn into dementia. Thus, if a patient is diagnosed with moderate CD, 5–15 % of patients will develop dementia within one year and 100 % of patients will develop dementia within 5 years [1]. It is therefore very important to detect CI in patients with CVD at an early stage.

Possibilities of organ-protective therapy in the field of cardioneurology

Metabolic therapy, aimed at improving the efficiency of oxygen use by the heart muscle and brain in condi-

tions of developing ischaemia, has recently received special attention in cardioneurology. It is known that in physiological conditions FRO is necessary for normal functioning of the organism. In case of increased oxidative stress, DE develops, cells are damaged and processes of oxidative phosphorylation and tissue respiration are dissociated, enzymatic systems are inhibited, DNA is depolarised, cell membranes are damaged and their permeability is disturbed, loss of elastic properties is observed, up to rupture and cell death. Oxidative stress plays an important role in the pathogenesis of atherosclerosis, CHD, CHF, ischaemic and haemorrhagic stroke and other CVDs.

Thus, the underlying cause of the disorders caused by increased lipid peroxidation (LPO) activity in many CVDs is hypoxia; therefore, it is desirable to prescribe drugs with multi-organ and pleotropic properties in complex therapy. The use of renin-angiotensin-aldosterone system blockers (ACEi, sartans), long-acting dihydropyridine calcium channel blockers (DCCB), beta-adrenergic blockers of the II (bisoprolol, metoprolol succinate) and III (nebivolol, carvedilol) generations — in sympathicotonia; Mineral corticoid receptor antagonists (MCRAs) with the ability to exert antifibrotic effects in the heart and vasculature, inhibitors of glucose sodium cotransporter type 2 (iSGLT-2), imidazoline receptor agonists may have a beneficial effect on CI. Neuroprotective therapy should be added at all stages of CI, taking into account the correction of all CVD risk factors.

Neurologist's view of CDs and their correction

Depending on the severity of the CR, it is usually divided into the following categories:

- **Moderate (MCD, pre-dementia stage, DEP 1–2 stages):** obvious cognitive dysfunction, usually noticed by the patient, not very noticeable to others, interfering with professional activity (although our patients are more likely to be retired by this time), but practically not affecting daily activity and independence. Mild forgetfulness, often confused with natural age-related memory loss. The MCD stage lasts for several years.
- **Mild dementia:** occupational activities, complex household activities are impaired, but self-care skills are preserved. This is a fairly common and underrecognised stage of dementia, and it is at this stage that patients attend neurologists: Treatment is aimed at maintaining preserved functions. The patient needs outside help (often a little) to organise their life, hints, reminders.
- **Moderate dementia:** all household activities are affected (problems with cooking, personal hygiene, needing almost constant help from others). The impairment is quite obvious to others, but is still underestimated even at this stage. Moderate dementia is often associated with psychotic and affective disorders, which make life even more difficult for others.
- **Severe dementia:** the patient's activity is bedridden, constant nursing care is required.

It is important to note that dementia does not always mean irreversible cognitive impairment. It is very important not to overlook cases of pseudodementia (cognitive decline associated with depression, less often with other mental illnesses, regressing on therapy with antidepressants and other specific drugs). Another case is the potentially reversible dementia, in which identification of the cause and its elimination contribute to a significant improvement in cognitive status with a reduction in the severity or regression of the patient's maladaptation (e.g, correction of glycaemia, vitamin B12 and folic acid deficiency, surgical treatment of intracranial hemaetomas and hydrocephalus).

Thus, the most common cause of dementia in people over the age of 60 is Alzheimer's disease. In our country, especially among psychiatrists (these are purely personal observations), Alzheimer's disease is traditionally understood more as a presenile form of the disease (dementia with early onset, rapid progression, malignant course, and a clear clinical picture). At the same time, studies have shown the complete morphological identity of presenile and senile dementia, which justifies identical therapeutic approaches and leads us to reconsider the historically established classification.

The basis of Alzheimer's disease is a progressive central acetylcholinergic defect that spreads from the entorhinal cortex to the hippocampus and on to the temporal, parietal and occipital lobes. Memory problems are the first and foremost complaint of both patients and family members. However, it is worth noting that the early symptoms are much more likely to go unnoticed or ignored, as they are explained by the natural age-related decline in cognitive function of the CNS. As the disease progresses, problems with language, counting, visual-spatial orientation and

practical skills appear and increase. Emotional (behavioural) and psychotic disorders such as depression, agitation, delusions, hallucinations may occur at any time from the onset of the disease. Neurological examination findings, excluding mental status evaluation (testing), are often normal.

The diagnosis of **AD** is confirmed by the following signs:

- The undetected onset and progression of dementia;
- The prevalence of memory disturbances (especially recollection and recall of new material) in the early stages of the disease (e.g. when the patient is ready to tell in great detail about their youth, but cannot remember what happened to them the day before);
- The onset after the age of 60;
- Absence of focal neurological symptoms and gait disturbances, especially in the early stages of the disease;
- The absence of any other cause of dementia.

Vascular dementia (the most common type of dementia) can result from diffuse damage in the deep white matter caused by changes in small vessels under the influence of various factors (AH, hyperlipidaemia, hyperglycaemia, hyperhomocysteinaemia) or from focal (more often multifocal) brain damage caused by stroke. Vascular dementia is characterised by a sudden onset of impairment in one or more cognitive domains; gradual progression of the process; the presence of focal neurological symptoms, including limb weakness, strong deep tendon reflexes, positive extensor plantar reflexes, and gait disturbance; and anamnestic or neuroimaging evidence of stroke. However, gradual progression and/or the presence of focal neurological symptoms are not found in all cases of vascular dementia. Affective disorders, psychotic symptoms and depression may occur in vascular dementia.

The combination of **vascular and neurodegenerative pathology** is particularly noteworthy. These processes can coexist in several ways. On the one hand, vascular RFs themselves potentiate the development of neurodegeneration, thus making it partially possible to prevent this from occurring. On the other hand, vascular and neurodegenerative processes may have different contributions to the clinical picture. In our country, the prevalence of different forms of dementia differs somewhat from that observed in Western countries. Thus, if purely neurodegenerative forms of dementia are more characteristic of Western Europe and America, in Russia the majority of patients with dementia have a mixed or vascular genesis, which is determined by the higher prevalence and poorer control of the corresponding RFs.

Delirium in patients with CD is a problem in its own right. Delirium can be caused by a variety of somatic conditions, such as latent pneumonia or other infection, CVD decompensation, etc., which, if corrected, will resolve and the patient will return to normal state. Delirium is characterised by a sudden onset and fluctuation of symptoms during the day (e.g. yesterday an elderly patient was alert and active, today he does not recognise anyone and sees enemies everywhere); short duration, change in activity level from drowsiness, stupor to agitation, psychomotor agitation, presence of hallucinations and distorted visual perception.

Recommendations for patient evaluation:

The examination of the patient should aim to identify factors that cause or worsen the course of dementia.

1) Assessing the cardiovascular system (presence of AH or hypotension, atherosclerosis of the main head arteries, CHF, arrhythmias). Ultrasound of the neck vessels, ECG (possibly Holter ECG, daily blood pressure monitoring), ECHO-CG are recommended among the instrumental methods.

2) Blood tests (general blood count, glycated hemoglobin (HbA1c), liver and kidney function, thyroid function, vitamin B12, homocysteine, vitamin D, blood lipids, coagulation indices) and urinalysis (urine may be tested for heavy metals, etc. if history relevant).

3) Neuroimaging. Neuroimaging is an important diagnostic tool, although it is by no means mandatory in typical cases. MRI is usually used to clarify the severity of diffuse and focal changes, to exclude damage in brain areas strategic for cognitive activity, and to assess the degree of atrophy (coronal slices through the hippocampus area may even suggest Alzheimer's disease).

When neuroimaging is mandatory: suspected tumour or trauma, especially if there is a dramatic deterioration in condition and an evidence of a previous fall or hit to the head (e.g. abrasions on the head, patient may have amnesia about the time of injury; CT scan to rule out intracranial haematoma is standard), suspected history of stroke, hydrocephalus, brain infection.

4) Assessment of medication history. Patients may be taking medications that contribute to the worsening of CF, a list of which and their pathogenetic mechanisms are presented in the literature [9]. In addition, patients may make medication errors due to poor memory (relatives should be made aware of the need for total control of what the patient is taking). In severe cases, a carer is needed; in mild cases, a timer and a pillbox with a metered dose are required).

5) Ideally, neuropsychological assessment of cognitive status is recommended. When in doubt, it is reasonable to administer brief cognitive scales: MMSE (Mini-mental State Examination, sensitivity 83–100 % for MCD, 94–100 % for AD, specificity 35–87 %) is not well suited to "vascular patients" as it is mainly focused on speech and memory impairment, which is more characteristic of AD.

The MoCA is a more modern questionnaire, but a little more time consuming. It is well suited to all types of dementia and has a standardised form in Russian. Clock Drawing Test — illustrates visual-spatial functions and regulatory disorders. Word List Memorisation Test (3 to 12) — very illustrative of Alzheimer's disease.

CD treatment

Thus, the treatment of cognitive and other neuropsychiatric disorders associated with dementia will depend to some extent on the aetiology, the associated RFs and the stage of the disease.

MCD stage: correction of blood pressure, cholesterol, glucose, homocysteine (not clinically proven, but theoretically sufficiently justified), vitamin D, vitamin B12 and folic acid levels, normalisation of thyroid function, reduction of body weight, lifestyle modification including regular physical and mental exercise, promotion of life activity and socialisation, correction of depressive/anxiety disorders (if necessary, consultation with a psychotherapist). By western international standards, no other medication is required. Therefore, metabolic and vascular drugs, which are popular in our country, are justified only at this stage and only if all other factors are balanced. It is important to remember that all vascular and metabolic drugs have side effects (vinpocetine can have a negative effect on heart rhythm, ginkgo preparations can cause epileptic seizures in sensitive people, cinnarizine is associated with a risk of Parkinson's disease, etc.).

Dementia: treatment, taking into account the pathogenesis based on acetylcholinergic deficiency, consists in the use of drugs that improve acetylcholine transmission — acetylcholinesterase (AChE) inhibitors. Another type of disturbances observed in dementia are disturbances in the regulation of nervous activity and the speed of mental processes (patients poorly able to switch from one subject to another, often fragmentary in their perception, impulsive). It is thought that memantine, an NMDA receptor blocker, has an influence on this link in the pathogenesis. In fact, the mechanism of action of memantine is quite complex, ranging from a mild dopaminergic effect, which allows its use as an adjuvant in Parkinson's disease, to the effects of modulating glutamatergic transmission, similar to magnesia, by modifying the functional activity of NMDA receptors. Memantine is thought to negate the "white noise" of nerve impulses that disorganise the CNS in case of diffuse lesions of the deep white matter.

AChE inhibitors are indicated in all stages of dementia. In Russia, the most commonly used drugs are galantamine (Reminyl) or rivastigmine (Exelon). Among the problems — most often gastrointestinal disorders (to some extent facilitated by the use of transdermal system in the form of patches) and disorders of the cardiovascular system (conduction disorders, etc.). The dosage should be increased slowly, depending on the clinical effect and side effects. According to international standards, memantine is added at the stage of moderate dementia, when the effect of AChE inhibitors becomes insufficient. At the same time, in the last decade the hypothesis of neuroprotective effect of memantine has been discussed in the literature, which creates conditions for its prescription at any stage of cognitive disorders (almost from the stage of MCD, but this is only a hypothesis, not a guide to action). Memantine is much better tolerated than AChE inhibitors. The effect is not so obvious, but it is undoubtedly present in a significant proportion of patients.

Treatment for behavioural and affective disorders

Behavioural problems are often secondary to CD. For example, the "doppelganger" symptom, where patients mistake their reflection in a mirror for a stranger in the room, is not a true hallucination but a visual perception disorder. Anxiety and depression

have a very significant impact on the progression of behavioural and psychotic disorders. Therefore, first of all, such patients need non-drug measures consisting of a strict daily regime, no change of the usual environment. E.g., moving to a new place is often the trigger for a decompensation. Insults and harsh criticism are not allowed, because due to the impairment of speech understanding, patients are oriented not on the meaning of what is said, but on the intonation).

Now to antipsychotics. Studies have clearly shown that the use of traditional neuroleptics is associated with increased patient mortality. It is interesting to note that very often the prescription of basic anti-dementia therapy makes it possible to eliminate (or at least weaken) psychotic disorders. Therefore, if the situation allows, we start treatment with these drugs rather than with neuroleptics. The effectiveness of the initial treatment is assessed every 6–8 weeks. If the effect is sufficient, then every six months. If absolutely necessary, in case of delirium, hallucinations, aggression, psychomotor agitation, the drugs of choice are (in descending order): quetiapine, risperidone, olanzapine, aripiprazole.

In case of aggression, irritability, impulsiveness: valproic acid, followed by carbamazepine, propranolol.

In case of agitation, depression, anxiety: escitalopram, sertraline, fluoxetine, citalopram.

For insomnia and other sleeping disorders: first of all, non-pharmacological methods — restricting sleep during the daytime, exclude emotional events in the evening, add walks in the fresh air, introduce a daily regime, avoid stress. Medication: melatonin, trazadone, mirtazapine, correction of restless legs syndrome. All doses should be started at the lowest adult starting dose and titrated at the lowest interval, with no more than one dose increase per week.

In case of apathy/abulia: AChE inhibitors, memantine, dopaminergic agents, low-dose levodopa, low-dose stimulant antidepressants (fluoxetine).

Conclusion

The presented concepts of cognitive disorders and Alzheimer's disease with various manifestations have been formed within the framework of modern achievements on this problem, controversial and not fully understood mechanisms of developing cardio-cerebral interrelations, experience of treating such patients in real clinical practice.

COVID-19 causes marked deterioration in the course of CVDs and in various cognitive spheres, up to rapid, lightning-fast development of dementia. Timely administration of vasotropic, neurotropic, neurometabolic drugs, cholinesterase inhibitors, memantine, anticoagulant and antiplatelet therapy is necessary to prevent and treat cognitive impairment.

Obviously, further large-scale clinical trials are needed to determine the extent of the interrelationships and to further clarify the mechanisms in preventing the development of Alzheimer's disease, in early diagnosis and in optimising the treatment of cognitive impairment in patients with CVD, especially those associated with new coronavirus infections.

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