

COGNITIVE IMPAIRMENTS IN A RANGE OF SOMATIC DISEASES. DIAGNOSTICS, MODERN APPROACH TO THERAPY

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ABSTRACT

Cognitive impairments (CI) are the first clinical manifestations of the nervous system in certain diseases. In recent years, the perception of cognitive impairment has changed significantly. Previously, it was associated with the elderly and senile age, but now it is also relevant for people of young and middle age, which is a social and economic problem that arouses interest among doctors of various specialties. It is proved that arterial hypertension (AH) and diabetes mellitus (DM) are important predictors of the CI development and dementia, which, according to some authors, have a chance to become the main «epidemic» of the XXI century. According to the Russian Cardiology Society, the number of people suffering from AH will increase by 15-25% to more than 1.5 billion by 2025. And according to forecasts of the International Diabetes Federation, the total number of patients with diabetes will exceed 552 million by 2030, and to 642 million by 2045. That is why the article considers these somatic pathologies as the most important interdisciplinary medical and social health problems. However, despite the long existence of such terms as «hypertensive and diabetic encephalopathy», this topic has not been studied enough, which also determines its relevance.

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Introduction

Violation of higher brain (cognitive) functions is a frequent type of neurological disorders, which occurs both in the practice of a neurologist and other specialists. Humans interact with the world around them by perceiving, processing, and analyzing information, storing, exchanging, building and implementing action programs. These are the so-called stages of cognitive activity, each of which is associated with a specific cognitive function (CF): gnosis, praxis, memory, language, attention, executive functions, social intelligence [1, 2]. Recently, patients, including young people, are increasingly complaining of increased fatigue during mental work, memory loss, difficulties with concentration, and often it can remain unnoticed and only be detected during neuropsychological research [3, 4]. CF are considered as ones of the subtle markers of cerebral dysfunction, allowing to diagnose disorders at the preclinical stage, i.e. before the appearance of persistent «organic» symptoms [1, 5-7]. Thus, a violation of CF is understood as a decrease in cognitive abilities in a particular disease or condition compared to the baseline level in a particular individual. According to WHO data for 2010, more than 35 million people worldwide suffered from dementia and cognitive disorders (CD), and this figure will increase to more than 65 million people over the next ten years [8].

According to the severity degree, cognitive impairments are divided into mild, moderate, and severe [9]. Mild impairments are a subjective and/or objective decrease in cognitive abilities that do not disrupt daily activity and are primarily

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neurodynamic. Moderate (pre-dementia stage) ones are subjectively aware and/or visible to others, which do not violate the patient's independence, but there are difficulties in complex and unusual activities for them. Severe ones (dementia) are considered to be disorders of cognitive functions that restrict daily activities and lead to a partial or complete loss of independence and self-reliance [10-19].

We will examine cognitive sphere violations in such somatic pathologies as arterial hypertension and diabetes mellitus.

Results

Arterial hypertension and cognitive impairments

Arterial hypertension (AH) is one of the most common and socially significant diseases. According to the Russian Cardiology Society, AH prevalence among adults is 35-40% and this figure is growing. It is believed that the number of people suffering from AH will increase by 15-25% to more than 1.5 billion by 2025 [20].

The brain is one of the five leading target organs for arterial hypertension (along with the heart, blood vessels from the aorta to capillaries, kidneys, and eyes) and is often involved in the pathological process one of the first.

For the normal functioning of brain, appropriate cerebral blood flow is required to fulfill the organ's needs for oxygen and nutrients, despite changes in systemic and, consequently, perfusion pressures. When BP increases, the brain blood vessels narrow, thereby protecting the capillary bed from overload, and during arterial hypotension, on the contrary, they expand, preventing hypoperfusion of tissues and their ischemization.

Arterial hypertension is a powerful risk factor for both acute cerebral circulatory disorders (an independent predictor of ischemic and hemorrhagic stroke) and chronic ones. Persistent and prolonged BP increase leads to the endothelium damage of the vascular wall and, as a result, endothelial dysfunction. As a result of a cascading reaction series, the autoregulation of cerebral blood flow is derailed. And initially, it is the small-caliber vessels that bear the brunt, especially the penetrating, blood-supplying subcortical grey nodes and deep sections of the white substance, contributing to changes in its density and microstructure. These changes are especially frequent in frontal lobes [21]. It is connected with the fact that subcortical grey nodes (thalamus, striatum, etc.) are in close connection with the frontal lobes, their defeat, therefore, entails the development of secondary dysfunction of the anterior parts of the brain. According to Leukoaraiosis And Disability in the Elderly (LADIS), arterial hypertension is the second most important factor (after age) contributing to the development of leukoaraiosis, which is non-specific damage to the white matter of the brain, manifested by a decrease in the density of nerve tissue, a violation of its function up to dementia. Also, chronic progressive vascular damage to the brain is the basis of the so-called «disconnection» phenomenon - a connection violation between the cortical and cortical-subcortical divisions. This also leads to the dysfunction of the frontal lobes, which play a key role in the cognitive process and emotion formation [22].

Thus, long-term AH, especially in the absence of appropriate therapy, in most cases leads to the brain secondary damage, which is based on a combination of impaired blood supply of the brain and diffusion of damage to white matter. As a result, cognitive and/or emotional-behavioral disorders are also observed in the clinical picture at an early stage, among young people [22, 23].

Since the middle of the last century, dozens of papers have been written and published indicating the correlation between arterial hypertension and cognitive impairment.

During the thirty-year follow-up of the Honolulu-Asia Aging Study, 3,735 people aged 45-50 years were shown to have a directly proportional relationship. High systolic pressure (>160 mmHg) in middle age increases the risk of developing cognitive impairments in old age and senility, while «an increase of average blood pressure for every 10 mmHg increased the risk of developing moderate CI by 7%, and severe CNS by 9%, respectively» [5, 8, 24, 25]. In Sweden, as a 15-year follow-up result, it was found that an increase of BP in middle age significantly increases the risk of developing severe CI in the elderly and senile ages. During the 7-year monitoring of more than 10,000 women aged 65 years and older, arterial hypertension was found to be an independent predictor of the development of the cognitive disorders (decreased concentration, speed of neuropsychological tests, speech production, spatial orientation disorders were noted) [26, 27]. And in the forty-year population study of Uppsala Longitudinal Study of Adult Men, which involved more than 2,200 young people with some degree of increased BP, 15% of cases revealed an extreme degree of cognitive impairment – dementia [12, 28].

According to the clinical recommendations of the Russian Medical Society on arterial hypertension, population studies have proven the correlation of hypertension with the developing cognitive dysfunction and/or dementia risk, and have shown that antihypertensive therapy (AHT) can delay their development [29]. In a four-year study that involved more than 1,000 patients with elevated blood pressure over 160/95 mmHg at the age from 59 to 71 years, it was found that the risk of developing cognitive impairment was significantly higher among those patients who did not receive AHT [8].

Also, it was revealed that the risk of developing cognitive impairments is higher among patients who, upon the background of increased BP, have had a particular form of stroke. According to Vladimir Parfenov and Yulia Starchina studies [8], sharp cerebral circulatory disorders were associated with greater severity of cognitive disorders, while mild or moderate forms of CI were more common outside of stroke in 46.7 and 26.7%, respectively. Also, a direct correlation was found between the presence of cognitive disorders and left ventricular hypertrophy (LVH) on the background of a prolonged blood pressure increase. It can be assumed that LVH is a predictor of brain damage in AH.

From the above, we can conclude that there is a fairly clear connection between the risk of developing or having cognitive impairments, their degree of severity and stage, age of AH onset, and the degree of increase in BP.

Diabetes and cognitive impairments

Cognitive impairments are not always associated with structural damage to the brain. They are often associated with severe somatic, including endocrine, diseases, or a combination of several pathological factors.

As defined by the WHO, diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia, which is the result of defects in insulin secretion, the action of insulin, or both of these factors. The prevalence of diabetes is steadily increasing. According to forecasts of the International Diabetes Federation, the number of patients will exceed 552 million by 2030, and 642 million by 2045 [6, 18, 24].

Both domestic and foreign literature actively raise the issue of the emergence and dynamics of DM cognitive disorders. But despite a large number of publications describing the cognitive status of diabetic patients, no consensus has been formed, except for one: CI is the most frequent expression of brain dysfunction during DM. They become a factor of reduced performance and violations of domestic adaptation.

On average, in the Russian Federation, the average number of patients with type 1 diabetes is 5.6%, type 2 is 92.2%, and others is 2.2%. Among people of 60 years and older, DM is detected in an average of 18-20% of cases, cognitive impairment in about 25%, including 16-19% for moderate and 6-8% for dementia [23, 26]. During neuropsychological testing, patients with DM, especially with the second type, have lower results than normoglycemic individuals of the same age. The prevalence of CI for the second type of diabetes among young patients is 20-40%, which is higher than people without diabetes have. It was found that only 36% of patients with type 2 diabetes do not have cognitive and emotional disorders [18].

The pathogenesis is not completely clear, but it is obvious that the violation of cognitive functions is a multifactorial phenomenon. The type 1 and type 2 diabetes have significant metabolic, micro- and macrovascular disorders, which are the basis for the development of complications from the nervous system: violation of microcirculation in the system of vessels that carry blood to the peripheral nerves (*vasae nervorum*), diabetic axonopathy, segmental demyelination, etc. [16, 17]. The morphological substrate of CI can also be leukoaraiosis, which, as previously written, is based on microangiopathy, pathognomonic for DM [16]. Violation of all metabolic processes in the body, including the lipid one, leads to the formation of large and medium-sized arteries atherosclerosis, which contributes to the development of hypoxic-ischemic changes in the brain.

The relationship with hypo- and hyperglycemic states of the body is noted. In some studies of patients with insulin-dependent diabetes mellitus and frequent hypoglycemia, cognitive disorders of varying severity were detected with a debut at the age of 26-35 years [16]. In other cases, on the contrary, they were observed among older people, while in younger patients they were not noticed even after long-term follow-up [23]. Most often, it was the decline of attention and psychomotor processes associated with the fact that a decrease in blood glucose levels contributes to a decrease in brain regional perfusion and thereby a violation of osmotic balance in the cerebral neurons, as well as their death, especially the most sensitive areas, such as the hippocampus. It was noted that the hypoglycemic condition, which required calling an emergency medical team, increases the risk of developing extreme CI by 1.4 times. And if these episodes were repeated, it increases the risk by 2.4 times. Frequent hypoglycemic episodes associated with antidiabetic therapy may affect cognitive decline. Thus, cognitive dysfunction can be an indicator of inadequate DM treatment [23].

Acute hyperglycemia, i.e. a rapid rise in glucose levels, for example, after a meal, for patients with type 2 diabetes is directly associated with an attention deficit. Chronic hyperglycemia, in turn, has a negative and damaging effect on brain neurons, accelerates neurodegenerative processes, which has been proven in a number of experiments [16, 23]. One of the reasons is the development of an inflammatory reaction in the brain, accompanied by elevated production of pro-inflammatory cytokines: IL-6 and TNF- α . It is also believed that hyperglycemia leads to increased formation of a special glycosylation product named Advanced Glycation End-products (AGEs), which is potentially toxic to neurons. The randomized clinical trial ACCORD-MIND (the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes), as well as the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions Complications (EDIC), revealed a direct correlation between the level of glycated hemoglobin and the severity of cognitive disorders. And according to the United Kingdom Prospective Diabetes Study, a 1% increase in the level of HbA1c is accompanied by a 17% increase in the frequency of stroke [6, 18, 22, 23].

A separate role is assigned to the violation of insulin secretion. The point is that insulin, penetrating the blood-brain barrier, can have different effects, depending on the initial state of the body. I.e., in acute hyperglycemia, the insulin injection improves the cognitive sphere, not only by normalizing blood glucose levels, but also by direct action on the insulin receptors of neurons and cerebral cortex and limbic structures astrocytes. Type 2 diabetes is characterized by insulin resistance and, as a result, chronic hyperinsulinemia, that is attended by an increased risk of microvascular disorders, which leads to a natural decrease of cognitive functions [18, 23]. An imbalance of glucose in the blood and insulin resistance affect the acetylcholine synthesis, a regulatory pathways cognitive neurotransmitter, what leads to rapid depletion and decreased attention concentration and, as a result, the development of CD among patients with type 2 diabetes [6, 13].

Metabolic disorders in DM contribute to brain damage regardless of other factors. But if a patient has, for example, such risk factors as smoking and alcohol abuse, sedentary lifestyle, and obesity, the likelihood of developing cognitive decline increases significantly. The severity of small-caliber vascular lesions that determine cognitive disorders in diabetes mellitus is aggravated when it is combined with arterial hypertension. According to the Framingham study, the highest risk of developing dementia is in patients with a combination of DM and AH, then in patients with isolated DM and then in patients with isolated AH [18, 23, 25].

Diabetes mellitus causes both a decrease in the overall assessment of cognitive functions and a violation of certain cognitive spheres. In particular, the clinical picture is dominated by neurodynamic and regulatory disorders, which are associated with the predominant dysfunction of the frontal lobes [16, 23, 26]. Reduced concentration, speed of psychomotor reactions, speech activity, ability to switch, as well as emotional lability, increased anxiety, symptoms of depression, etc. are the most common types of neurological disorders, especially among elderly patients with DM [24]. The memory is changed in this case a second time, which leads to reproduction problems during the saved process of remembering new information. But sometimes there are changes that go beyond the described disorders and are associated, for example, with a primary disorder of memory or visual-spatial functions [23, 30]. Thus, according to the results of the observation of Veronika Sosina *et al.* [18], 68% of the examined patients noted a violation of memory for current events. A number of studies have confirmed that the early onset of type 1 diabetes has a more distinct cognitive deficit, which may be associated with a greater susceptibility of the young people's brain to significant glucose levels [16, 22]. A direct correlation between the duration of DM and the severity of CD is also shown [18]. There was a decrease in all cognitive functions in patients with diabetic retinopathy, which (given the common embryogenesis and anatomy of retinal and brain vessels) may be associated with microcirculatory disorders [22].

Thus, we see a link between a diabetic background and the development of cognitive deficits. In the majority of cases, CD remains mild or moderate, but in any case, they negatively affect the quality of patients' life [16, 23].

Taking into account the progressive nature of CNS lesions in arterial hypertension and diabetes mellitus, an important role is assigned to the early diagnosis of CI, the algorithm of which can be represented as follows. The first is a subjective examination of the patient. Patients can clearly indicate the fact of a cognitive functions violation by making complaints, for example, increased fatigue during mental work, forgetfulness, decreased concentration, or, conversely, do not make complaints at all, for example, due to anosognosia – the lack of a critical assessment of the patient's condition. In some cases, the patient with developing CI focuses not on their own, for example, absentmindedness, but on headaches, dizziness, and other somatic complaints that they consider more significant. In these cases, it is necessary to contact their relatives or representatives and remember that the absence of cognitive complaints does not mean that there is no objective cognitive deficit, and their presence does not always mean the opposite. Sometimes complaints are veiled: "heavy" or "dull", "foreign" head – which prevents a person from performing their usual actions. Many authors agree that active complaints without leading questions should be considered in the first place, especially among young patients. It is necessary to assess the anamnesis of life, including daily activity, and the underlying disease to determine the duration of AH or DM, the patient's compliance, i.e. their adherence to antihypertensive and antidiabetic therapy.

The second is an objective examination, which uses neuropsychological research methods. In clinical practice, the Short mental status assessment scale (Mini-Mental State Examination, MMSE), the Montreal cognitive assessment (MoCa-test), the visual-motor coordination test (Trail Making Test, TMT), as well as tests for attention, speed of psychomotor reactions, speech activity, verbal associations, ability to switch, conceptual thinking, ten-word memory test, drawing watches, etc. are used. Thus, in the doctors' arsenal, there are a number of psychometric instruments for screening the CI. It is noted that in elderly patients with type 2 diabetes, the MMSE score is 1-2 points lower than in healthy individuals of the same age, and in the 2-year perspective, the score for this test on average decreases by 0.5 points faster than in people without diabetes [16, 23, 26]. The use of these methods makes it possible to detect cognitive disorders already at the stage of subclinical brain damage, and the MoCa test has the highest sensitivity and contributes to the detection of CD in the early stages in 90% of cases against 18% of MMSE [11].

If these tests do not reveal violations, then it is said about subjective CI. They are sensed by the patient and cause him to consult a specialist, but they are not confirmed during neuropsychological research. If tests reveal a decrease in cognitive abilities, i.e. there are objective CI, then they determine their severity together with the assessment of the patient's daily activity: light, moderate, or severe.

Laboratory methods of research: clinical analysis of blood, urine, general therapeutic biochemical blood analysis are more necessary not for the diagnosis of cognitive disorders, but for the detection of an etiological factor, i.e. the underlying disease.

Neuroimaging methods: CT or MRI of the brain from instrumental studies are actively used. There is a direct correlation between cognitive decline and certain changes in MRI (leukoaraiosis, lacunar infarctions, microhemorrhages, cerebral atrophy, etc.). Single-photon emission computed tomography and positron emission computed tomography (PET) allow us to assess the level of brain metabolism and blood perfusion to reflect the brain function characteristic of vascular cognitive disorders [14]. However, they remain expensive and cannot be used as a screening test. An important task of these methods is to exclude diseases that threaten the patient's life: a tumor, brain abscess, hematoma, etc. – i.e., conducting differential diagnostics.

In recent years, an actual method is a neurophysiological examination using evoked P300 cognitive potentials. The advantage of this method is the objectification of the obtained data, as well as the ability to detect early violations of cognitive functions. This method is also relevant for differential diagnosis between mild and moderate CI, dementia, and functional disorders, including depression [12-14].

Given that CD is an interdisciplinary problem, a comprehensive approach to their treatment with the participation of cardiologists, therapists, endocrinologists, and neurologists is necessary. At the stage of subjective, as well as mild and moderate cognitive impairments, special attention should be paid to non-drug treatment methods, which are a physically active lifestyle, proper nutrition, exercises to train memory, attention – the so-called cognitive training, etc. A meta-analysis

by S. Guure *et al.* [11] showed that physical activity is associated with a 21-24% reduction in the risk of dementia, which may be associated with increased production of cerebral neurotrophic factors that slow down the progression of the neurodegenerative process. Nutrition optimization, the use of foods containing B and E vitamins, unsaturated fatty acids, and calorie restriction have a positive effect on cognitive functions. The Mediterranean diet, in particular, actively recommended for patients with AH, contributes to the improvement of cognitive functions by MMSE and the watch drawing test [11].

As for drug therapy, there are currently no drugs that cure or prevent the development of CI. Etiotropic treatment aimed at correcting the underlying disease is in the first place. In 6 large international randomized clinical trials (Syst-Eur, PROGRESS, SCOPE, SHEP, PRoFESS HYVET), it was shown that the risk of cognitive disorders was significantly reduced against the background of autologous blood therapy. In addition, it was noted that younger patients when prescribing therapy had a longer follow-up and significantly reduced risk of severe cognitive impairment [8, 11, 12, 30]. Blood pressure reduction should be rational, since hypotension can contribute to the development of cognitive deficits, especially among elderly patients. The control of the lipid profile is also important. However, in the Heart Protection Study and PROSPER studies, there was no significant effect of statins on CF with vascular risk factors. Similar results were observed for the disaggregants [11, 16]. As mentioned earlier, the level of HbA1c correlates with the severity of cognitive dysfunction, which indicates the appropriate antidiabetic therapy importance. Several open studies have shown that the application of hypoglycemic agents for several months leads to improving memory and other CF. But it is worth remembering that therapy leading to frequent hypoglycemic episodes can contribute to the progression of cognitive decline [23].

Unfortunately, adequate control of DM and AH does not completely exclude damage to the nervous system. Therefore, it is crucial to influence the pathogenetic mechanisms of damage to the CNS. In CD, the first-line therapy is neurometabolic drugs with a neuroprotective effect, which can not only improve CF but also delay or even prevent dementia. If it is already diagnosed, then acetylcholinesterase inhibitors (galantamine, donepezil, rivastigmine) and/or glutamate receptor blockers (acatinol, memantine) are prescribed [1, 11]. On the background of basic therapy, there is a significant improvement in cognitive functions, partial regression of behavioral and psychotic disorders, an increase in the time of relative independence of patients and, accordingly, reduced time and labor spent on caring for these patients.

Conclusions

Cognitive disorders are a socially significant complication of DM and HA, leading to a violation of everyday activity and a decrease in patients' ability to work. Unfortunately, the standard plan of patients' examination with these nosologies does not include a study of the brain, so in clinical practice, the doctor states its defeat more often at the complications development stage. Prompt and adequate etiotropic and pathogenetic therapy reduces the risk and acuteness of cognitive decline and helps to improve the intellectual state. In connection with the above, further researches are required, for early detection of CD, take measures to prevent further cognitive deficits and improve the quality of patients' life.

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