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Cognitive Impairment in Patients with Type 2 Diabetes Mellitus

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Abstract: The nervous system is one of the main targets for diabetes mellitus. The pathology of the peripheral nervous system in diabetic neuropathies is well studied, which cannot be said about lesions of the central nervous system and, first of all, the brain. The most common manifestation of brain dysfunction in diabetes is cognitive impairment. This article is devoted to the relationship between cognitive impairment and type 2 diabetes.

Keywords: Diabetes, cognitive impairment, MMSE, FAB - test, cognitive status, diabetic encephalopathy, meantime hydrochloride, cerebrolysin.

Introduction. Type 2 diabetes and cognitive impairment are the two most common chronic conditions diagnosed in people 60 years of age and older. In this age period, diabetes is detected in approximately 18–20% of individuals, and cognitive impairment in approximately 25% of individuals, including 6% with dementia, and 19% with moderate cognitive impairment [16]. In recent years, the prevalence and, accordingly, the social significance of both conditions has been growing due to an increase in the proportion of elderly people in the population. Studying the relationship between cognitive impairment and diabetes can help find one of the ways to prevent the growth of the incidence of dementia, which, according to some experts, has a chance of becoming the main “epidemic” of the 21st century (4).

Cognitive status in patients with diabetes

Cognitive decline in diabetes patients has been known for a long time, since the classical work of WR Miles and HF Root (1922). Since then, more than a dozen studies have been conducted that have shown that neuropsychological testing in patients with diabetes, especially type 2 diabetes, has lower results than normoglycemicindividuals of the same age [16]. At the same time, both a decrease in the overall assessment of cognitive functions and impairments in individual cognitive areas are detected. A feature of the neuropsychological profile in patients with diabetes is the predominance of aerodynamic and regulatory disorders detected in tests for attention, speed of psychomotor reactions, speech activity, ability to switch, conceptual thinking, etc. At the same time, the sphere of memory often remains more intact or suffers secondary to attention and regulation of mental activity, resulting in problems of reproduction with a relatively intact process of memorization, as evidenced by the relative safety of recognition and the effectiveness of mediated memorization and reproduction techniques. However, some studies have noted a defect that goes beyond aerodynamic and regulatory cognitive impairment and is associated, for example, with a primary disorder of memory or visuospatial functions (24). In general, deviations from the age norm are found in 20-40% of patients with type 2 diabetes and in most cases it remains mild or moderate, although it can negatively affect the quality of life of patients [14]. A more accurate assessment of cognitive deficit in diabetes can be provided by tests for aerodynamic

and regulatory cognitive functions (attention, speed of psychomotor reactions, abstract thinking, switch ability, planning). Although the sensitivity of the Mini-Mental State Examination - MMSE), often used for general assessment of cognitive status in the elderly, in relation to the cognitive deficit inherent in patients with diabetes, is suboptimal , in elderly patients with type 2 diabetes, on average, a score is 1-2 points lower than in persons of the same age without diabetes, and in a 2-year perspective, the MMSE score in patients with diabetes decreases on average by 0.5 points faster than in the absence of diabetes [5,14,16]. The older age of patients, the duration of the disease increase the likelihood detection of cognitive decline. It has been shown that the level of glycosylated hemoglobin correlates with the severity of cognitive dysfunction. Moreover, with successful control of hyperglycemia, the severity of cognitive impairment may decrease, at least partially [16]. Thus, the development of cognitive dysfunction may be an indicator of inadequate diabetes therapy and, in turn, contribute to low adherence to treatment. Considering the association of cognitive deficit with metabolic disorders directly caused by diabetes, it is often considered within the framework of a specific diabetic encephalopathy, the existence and status of which continues to cause controversy [10].

Diabetic encephalopathy is usually understood as a cerebral complication of diabetes(most often type 1), characterized by progressive cognitive decline. Conventionally, primary diabetic encephalopathy (presumably associated with impaired insulin action and hyperglycemia) and secondary encephalopathy (resulting from vascular complications) are conventionally distinguished. At the same time, the substrate of encephalopathy remains unclear, and therefore, in recent years, this term has been used much less frequently [8].

Risk of dementia in patients with diabetes

It has already been mentioned that cognitive impairment in patients with type 2 diabetes is most often mild or moderate, but patients with type 2 diabetes often also have dementia, in which a general decrease in cognitive functions limits daily activity [4]. A number of large-scale prospective studies have shown that patients with DIABETES have an increased risk of developing dementia. According to a meta-analysis , the risk of developing dementia in patients with diabetes increases on average by 1.6 times, while the risk of developing vascular dementia increases by 2-2.6 times, and the risk of developing Alzheimer's disease by about 1.5 times, regardless of age of onset of diabetes[2,8]. Thus, dementia that develops in a patient with diabetes can be associated with both cerebrovascular pathology and a primary degenerative process, or have a mixed character [2, 6].

Pathogenesis of cognitive impairment in diabetes

The pathogenesis of cognitive decline in diabetes remains largely unclear [7]. The correlation between cognitive dysfunction and the degree of hyperglycemia, obtained in a number of studies, may indicate that it is this main metabolic abnormality in patients with diabetes that can be the cause of cognitive impairment. It has been shown that a rapid rise in glucose levels (including after a meal) is directly associated in patients with type 2 diabetes with a decrease in attention and other neurodynamic functions [1, 2]. Acute hypoglycemia can reduce regional perfusion of the brain and disturb the osmotic balance in cerebral neurons [15]. The effect of chronic hyperglycemia may be more pronounced. It can be mediated by the formation of glycation end products (AGEs), activation of alternative polyol and hexose metabolic pathways, activation of protein kinase C, and inflammatory processes in the brain (proven by increased production of pro- inflammatory cytokines, such as interleukin-6 or tumor necrosis factor α) [14]. In general, hyperglycemia certainly plays a role in the development of cognitive dysfunction, but only a moderate, predominantly aerodynamic cognitive deficit can be directly associated with it [13]. Apparently, cerebrovascular or

neurodegenerative pathology, accelerated by metabolic disorders characteristic of diabetes, as well as hypoglycemic episodes, can play a great role in the development of cognitive decline [11, 12]. It is well known that diabetes increases the risk of developing cerebral atherosclerosis and the risk of heart attacks. Brain [9,10]. Thus, one of the substrates of dementia in diabetes can be a multi-infarction state [6, 7]. However, according to a number of studies, damage to small cerebral vessels is of great importance in the development of dementia in diabetes, which causes diffuse pathology of the white matter of the cerebral hemispheres, multiple lacunar foci and micro infarctions [16]. In a recent study by JA Sonnenet al. (2009), which performed an autopsy of 196 patients with dementia, showed that the number of micro infarctions in the brain in patients with diabetes was 2 times higher than in individuals without diabetes [9]. A more important role in the development of cognitive decline was played by micro vascular lesions in the deep parts of the brain, supplied with blood by penetrating arteries. The role of micro vascular pathology in the genesis of dementia is evidenced by the correlation between cognitive decline and some changes in MRI (leukoaraiosis , lacunar infarcts, micro hemorrhages , cerebral atrophy, etc.), as well as its connection with retinal vascular pathology [5,6]. The cause of damage to small cerebral vessels in diabetes is not completely clear. It is assumed that the formation of AGEs, as well as the activation of alternative pathways of carbohydrate metabolism, contribute to the development of oxidative stress, which leads to damage to the vascular endothelium and the development of cerebral ischemia. However, in a study by JA Sonnenet al. (2009), the molecular marker of oxidative stress F2-isoprostane in patients with diabetes was, on the contrary, lower than in patients with dementia who did not have diabetes [4]. In recent years, it has been shown that changes in the production of angioneurins(for example, vascular endothelial growth factor) can mediate damage to small vessels and neuronal death [9]. The connection between DIABETES and the degenerative process characteristic of Alzheimer's disease is more complex and controversial (see the next section). It can be assumed that vascular and degenerative mechanisms interact during the development of dementia [2]. A common link between neurodegeneration and cerebrovascular pathology can be an inflammatory process associated with increased production of pro- inflammatory cytokines in the brain and activation of microglia [1]. In a study by JA Sonnenet al. (2009) one of the differences in patients with dementia suffering from diabetes was an increased level of interleukin-6 [16]. Activation of the hypothalamic -pituitary-adrenal axis, leading to an increase in the level of cortisol in the blood, may also play a certain role in cognitive decline [16]. Hypoglycemia associated with an overdose of exogenous insulin and oral hypoglycemic agents is one of the most important factors contributing to a decrease in attention and speed of psychomotor processes. During a hypoglycemic episode, brain cells are deprived of essential nutrients. The presence of episodes of severe hypoglycemia, requiring hospitalization or emergency care, significantly increases the risk of developing dementia: with a single episode, the risk increases by 1.4 times, and with multiple episodes - by 2.4 times. The absolute risk of dementia after a severe episode of hypoglycemia increases by 2.4% per year [16]. Whether milder episodes of hypoglycemia have an impact on the risk of developing dementia remains unclear. The adverse effects of hypoglycemia may be associated with neuronal death, especially in several of the most vulnerable areas of the brain, such as the hippocampus, as well as activation of blood coagulation systems (due to increased platelet aggregation and fibrinogen formation) and ischemia. The damaging effect of hypoglycemia seems to be predominantly affecting elderly patients, who, due to a lower cognitive (brain) reserve and low plasticity, are less able to level the consequences of damage. In young patients with type 1 diabetes, despite the high frequency of hypoglycemic episodes, no significant cognitive decline was noted, even after many years of follow-up [3,5].

Insulin resistance as a factor in the development of cognitive impairment

In a significant number of people with type 2 diabetes, insulin resistance is detected, which is often accompanied by hyperinsulinemia, central obesity, hyperlipidemia, and arterial hypertension [1]. Insulin is able to penetrate the blood-brain barrier and have a multidirectional effect on cognitive functions. On the one hand, acute insulin adiabetesinistration can improve cognitive functions, possibly due to a direct action on specific insulin receptors found on neurons and astrocytes in the cortex and limbic structures (the brain normally produces some amount of insulin, which acts as a peptide neuromodulator) [7]. On the other hand, chronic hyperinsulinemia can have a fundamentally different effect, causing cognitive decline and an increased risk of micro vascular complications and Alzheimer's disease [8]. A constant excess of insulin in the periphery can negatively affect the energy metabolism of cells and persistently suppress the production of endogenous insulin in the brain (it has been shown, for example, that in patients with Alzheimer's disease, the concentration of insulin in the brain is lower than normal) [3,4]. On the other hand, hyperinsulinemia can affect the metabolism of β-amyloid and contribute to the development of Alzheimer's disease in its early phase [4,5]. Cerebral clearance of amyloid-beta occurs through microglial uptake mediated by low-density lipoprotein receptors or proteolytic degradation mediated by the insulin-degrading enzyme (IDF), which has a higher affinity for insulin than for amyloid-beta. Thus, by entering into a competitive relationship with β-amyloid, insulin can increase its level in the brain. Thus, hyperinsulinemia, especially accompanied by other metabolic disorders (for example, hyperlipidemia and obesity), may contribute to the initiation of the degenerative process [16]. This is also facilitated by glycation of β-amyloid, which enhances its ability to aggregate, as well as vascular complications of diabetes, leading to ischemia of the brain tissue [15]. The effect of hyperinsulinemia, especially in individuals with abdominal obesity, may also be mediated by an increase in the production of pro- inflammatory cytokines [13]. At the same time, a number of clinical and pathological studies have shown that Alzheimer's disease that has already occurred in patients with type 2 diabetes develops more slowly than in individuals without diabetes. So, according to M. Musiccoet al. (2009), the number of cases with rapid progression of Alzheimer's disease in patients with diabeteswas one third lower than in those without diabetes(18). According to a study by JA Sonnenet al . (2009), the degree of amyloid deposition in the brain parenchyma and cerebral vessels in diabetes patients with dementia was lower than in similar diabetes patients, although higher than in individuals without dementia [8,9]. The reasons for this paradoxical phenomenon remain unclear at the moment. It is suggested that at a certain stage in the development of type 2 diabetes, when there is a relative insufficiency of pancreatic islet cells and the level of insulin decreases, the degradation of β-amyloid may become more effective. It is also possible that it is not hyperinsulinemia itself that has a pathogenic effect, but metabolic disorders associated with it. Insulin itself at high concentrations can act on insulin-like growth factor 1 (IGF1) receptors, maintaining neuronal trophism and counteracting the degenerative process [7,8]. Thus, the role of insulin resistance and hyperinsulinemia in the development of dementia. Gets understudied.

Other Factors Contributing to Cognitive Decline in Patients with diabetes

Other complications of DIABETES, such as coronary heart disease, as well as concomitant risk factors, such as arterial hypertension, smoking, lack of physical activity, dyslipidemia, and obesity, can also contribute to the development of cognitive decline. With a combination of several vascular risk factors, the likelihood of cognitive decline increases. For example, the severity of damage to small cerebral vessels, which largely mediates cognitive decline in patients with diabetes, is aggravated when diabetes is combined with arterial hypertension

[14]. Genetic factors also play an important role: in patients with DIABETES who are carriers of the ε4 allele of the apolipoprotein E gene, the risk of developing dementia increases significantly by 4.6 times (for people with AD) and 3.9 times (for mixed dementia) [10]. The development of cognitive decline can also be promoted by depression, which is detected with an increased frequency in patients with diabetes, as well as the use of certain drugs, for example, sedatives or β-blockers [11]

Impact of ant diabetic therapy on cognitive status

A number of open studies have shown that adequate treatment of diabetes is associated with improved cognitive status. A number of studies have shown that the use of hypoglycemic agents for several months leads to an improvement in memory and other neuropsychological functions. Similar results were obtained in longer two-year studies showing that good glycemic control leads to improved cognitive functions, especially in individuals with longer duration of diabetes. In one study, the use of meglitinide(which specifically affects postprandial hyperglycemia) for 1 year was associated with a more beneficial effect on cognitive function than sulfonylurea treatment [10]. Thus, timely (started in the middle years of life) adequate therapy for diabetes and correction of other vascular risk factors (hyperlipidemia, arterial hypertension, obesity) can reduce the risk of developing dementia in the elderly, however, this provision should be verified in long-term controlled prospective studies [11]. However, overly aggressive therapy, accompanied by the development of hypoglycemic episodes, may contribute to the progression of cognitive decline. Moreover, recent path morphological studies have brought paradoxical results: it has been shown that against the background of ant diabetic therapy (a combination of insulin and oral hypoglycemic agents), the number of micro vascular infarctions in sub cortical structures increased, while the degree of accumulation of amyloid, both in the parenchyma and in the vessels, was lower. Than in untreated patients or those without diabetes [13]. However, it cannot be ruled out that this result is due to the greater severity of diabetes in treated individuals (as reflected in higher glucose and glycated hemoglobin levels). In recent years, there has been growing interest in new generation hypoglycemic drugs (eg, thiazolidinedionesrosiglitazone and pioglitazone): suggest that, unlike traditional ant diabetic agents, they lack the ability to enhance microvascular pathology [16]. In any case, additional prospective studies are needed to evaluate the impact of ant diabetic therapy on cognitive impairment. On the other hand, the presence of a pronounced cognitive deficit should be taken into account when planning antidiabetic therapy: treatment in this case should be simplified as much as possible and corrected in stages to ensure an optimal result. Developed cognitive deficits, treatment programs should include agents that enhance cognitive functions, in particular, in patients with dementia caused by Alzheimer's disease or cerebrovascular pathology, the use of cholinesterase inhibitors and memantine is indicated [4]. One of the promising areas for the treatment of cognitive impairment in patients with diabetes is the use of drugs with a neurotrophic effect (for example, Cerebrolysin). The effect on cognitive decline of antioxidants, in particular thiocticacid preparations, which have demonstrated efficacy in patients with diabetic polyneuropathy , remains unexplored [16] .

Conclusion

Type 2 diabetes is accompanied by the development of cognitive decline in a significant proportion of patients and is a risk factor for the development of both vascular dementia and Alzheimer's disease. The leading mechanism for the development of dementia in patients with type 2 diabetes seems to be cerebral microangiopathy, while the relationship between diabetes and neurodegenerative pathology seems to be more controversial. In general, the mechanisms of development of cognitive impairment in patients with diabetes remain largely

unclear, which makes it difficult to find effective strategies to prevent dementia. Nevertheless, efforts are already needed for the widest possible neuropsychological screening of elderly patients with type 2 diabetes for the early detection of cognitive impairments and the use of all available options for their correction.

Literature

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