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Neuroimaging methods for assessing the brain in diabetes mellitus (literature review)

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ABSTRACT

Diabetes mellitus (DM) is associated with changes in the structure of the brain and deterioration of cognitive functions from mild to moderate according to neuropsychological testing. With the growing DM epidemic and the increasing number of people living to old age, cognitive dysfunctions associated with DM can have serious consequences for the future of public and practical health. Chronic hyperglycemia, severe episodes of hypoglycemia, and microvascular complications are important risk factors common for type 1 and type 2 diabetes. DM is also associated with structural and functional changes in the brain, which can be diagnosed by various types of magnetic resonance imaging (MRI) of the brain.

In this review, we investigate studies conducted over the past two decades to improve the understanding of how DM effects the brain function and structure. We also describe the changes characteristic of type 1 and type 2 diabetes during standard MRI, functional MRI and proton magnetic-resonance spectroscopy (proton MRS) as well as their features.

Key words: diabetes mellitus, cognitive impairment, neuroimaging techniques.

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Нейровизуализационные методики оценки головного мозга при сахарном диабете (литературный обзор)

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РЕЗЮМЕ

Сахарный диабет (СД) связан с изменениями в структуре головного мозга и ухудшением когнитивных функций от легкой до умеренной степени по данным нейропсихологического тестирования. В условиях растущей эпидемии СД и увеличения числа людей, доживающих до старости, когнитивная дисфункция,

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ассоциированная с СД, может иметь серьезные последствия для будущего общественного и практического здравоохранения. Хроническая гипергликемия, тяжелые эпизоды гипогликемии и микрососудистые осложнения являются важными факторами риска, общими для СД 1- и 2-го типа. Также СД связан со структурными и функциональными изменениями в головном мозге, которые возможно диагностировать посредством различных вариантов магнитно-резонансной томографии (МРТ) головного мозга.

В представленном обзоре рассмотрены исследования, проведенные за последние два десятилетия, чтобы улучшить понимание того, как СД влияет на функцию и структуру головного мозга. Также опишем изменения, характерные для СД 1- и 2-го типа при проведении стандартной, функциональной МРТ и протонной магнитно-резонансной спектроскопии, и их особенности.

Ключевые слова: сахарный диабет, когнитивные нарушения, нейровизуализационные методики.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder that is characterized by absolute insulin deficiency in type 1 diabetes or its relative insufficiency or resistance in type 2 diabetes [1]. This is a serious problem that leads to development of complications in the peripheral and central nervous system [2]. In DM, there is a 20–70% decrease in cognitive abilities compared to healthy people, and the risk of dementia is 5% higher than in healthy people [3]. Cells and their extracellular matrix have a dynamic and reciprocal relationship. Modular components upon activation of the glycation process lead to altered neurogenesis, hyperphosphorylation of intracellular signal molecules, and expression of extracellular protein matrix. All these cellular changes can contribute to cognitive dysfunction in DM [4]. There are various methods for assessing cognitive dysfunction, such as neurocognitive testing, evoked potentials, electroencephalic research, MRI, and positron emission tomography [5].

For the most accurate diagnosis of cognitive impairment in diabetes, the method of standard brain MRI was used in practice, which allows to detect mainly macrostructural changes associated with cerebrovascular diseases, such as hyper-intensive activity of white substances and indirect signs of atrophy of brain substances [6]. The functional MRI focuses on changes in activation models, functional connectivity and signal fluctuations, as well as on interconnected cognitive impairment and activation domain names, default networks, and functional conjunctivity [7]. Proton magnetic resonance spectroscopy (PMRS) is an analytical method that allows scientists to identify and quantify metabolites in various areas of the brain and to determine energy metabolism and processes in brain tissue non-invasively [8].

FEATURES OF COGNITIVE IMPAIRMENT IN TYPE 1 DIABETES

In patients with type 1 diabetes, frequent variability of glycaemia, hyper/hypoglycemia, and cumulative chronic hyperglycemic exposure lead to such microvascular damages to organs as retinopathy and nephropathy [9]. In addition to microvascular complications, type 1 diabetes is associated with an increased risk of cognitive impairment, which primarily represents a decrease in the processing speed of information, attention, and executive function [10–12]. Cognitive dysfunction can be observed quite early (already two years after diagnosis) and persists in adulthood and at a later age [13, 14]. However, the exact neuropathological mechanism of cognitive impairment caused by type 1 diabetes is still largely unclear.

NEUROIMAGING TECHNIQUES FOR BRAIN NEUROPLASTICITY EVALUATION IN TYPE 1 DIABETES

Neuroimaging methods were used to study the anatomical and functional changes in the brain of patients with type 1 diabetes. A standard MRI scan reveals atrophy of the gray matter and lesions of the white matter, which are common structural abnormalities observed in

the studies and associated with a cognitive decline in patients with type 1 diabetes [15–17]. The decrease in the volume of the brain in the cortical and subcortical areas, including the occipital, lower frontal and parahippocampal regions, is mainly determined [18, 19]. There are no significant differences in the volume of gray or white matter of the brain compared with the control group in the article of Perantie et al. on analyzing MRI scans in children with type 1 diabetes [20]. It was shown that medical history of severe hypoglycemia is associated with a smaller volume of gray matter in the upper left temporal region, while chronic hyperglycemia is associated with a change in the volume of the gray matter in the right posterior parietal region and right prefrontal region [21]. In addition, there is evidence that these changes are noted within a few years from the start of manifestations and associated with cognitive functions [22].

Diffuse tensor MRI reveals fractional anisotropy in the upper parietal lobe and a decrease in average diffusion in the thalamus [19]. In addition, there is a decrease in fractional anisotropy in the posterior parts of the brain, which is associated with a longer duration of the disease, as well as a decrease in a number of cognitive functions, such as speed of information processing and executive functioning [23]. Using only functional MRI of the brain, van Duinkerken et al. demonstrated impaired functional conjunctivity and network changes in patients with type 1 diabetes [24]. In addition, abnormal functional conjunctivity was found in the subgenual cingulate gyrus, which was associated with cognitive dysfunction in patients with type 1 diabetes [25]. Moreover, using an analysis of independent components, it was found that type 1 diabetes is associated with a violation in several networks, including attention, working memory, hearing, language, and processing [26–28]. Since the effect of hyperglycemia on the brain can be global, an analysis of the neural function of the entire brain is likely to reveal other deficits in the central nervous system associated with type 1 diabetes.

In the studies by Mangia and Heikkilä et al., a decrease in N-acetylaspratate metabolites was shown in the gray matter (occipital lobe, frontal lobe), white matter, and thalamic regions of patients with type 1 diabetes compared with the control group [29, 30]. Besides, it was shown that patients with high glycated hemoglobin have a decrease in glucose in the brain by almost 10%. This neurochemical process can explain the loss of neurons associated with cognitive impairment [31]. In addition, there is a change in the ratio of metabolites N-acetyl aspartate/creatine, choline/creatine and N-acetyl aspartate/creatine in the left posterior parietal region of the white matter in type 1 diabetes [32].

FEATURES OF COGNITIVE IMPAIRMENT IN TYPE 2 DIABETES

Several studies have shown that type 2 diabetes (at least 90%) is a risk factor for dementia [33, 34]. Typically, patients with type 2 diabetes have a moderate decrease in cognitive functions, and the metabolic syndrome is believed to make a significant contribution to their decline [35]. Type 2 diabetes is usually diagnosed at an older age and is usually associated with obesity, insulin resistance, hypertension, and dyslipidemia, which can have a negative effect on the brain [36].

NEUROIMAGING TECHNIQUES FOR BRAIN NEUROPLASTICITY EVALUATION IN TYPE 2 DIABETES

Type 2 diabetes is associated with diffuse atrophy of the brain [37]. A decrease in the average total brain volume is more pronounced in type 2 diabetes, which is comparable with 3–5 years of normal aging [38]. Brain atrophy associated with type 2 diabetes is most pronounced in areas which are surrounding the ventricles, such as the subcortical region of the gray or white matter [39].

In patients with type 2 diabetes, there is a decrease in the functional relationship between the areas including the medial frontal gyrus, precuneus and medial temporal gyrus, which are associated with cognitive functions [40].

When performing proton MRS in patients with type 2 diabetes, a low level of N-acetyl aspartate was recorded in the right frontal and parietal–temporal regions, and glucose levels were elevated in all areas of the brain [41]. Besides, reduced levels of choline and creatine in the lenticular nuclei and areas of the thalamus and decreased N-acetyl aspartate/creatine and choline/creatine ratios were identified. These changes had a negative correlation with the level of glycaemia and glycated hemoglobin [42].

CONCLUSION

Typical signs of brain atrophy which can be detected during standard MRI are to a larger extent associated with metabolic disorders, but give no evidence of a connection with cognitive impairment and do not provide a further diagnostic algorithm [43].

In diabetes, there is a change in the spontaneous activity of the brain, especially in the visual zones, as well as a change in the functional connection in various default networks. However, the plasticity of the nervous system at a young age is possible, and the functional relationships are improved after rehabilitation measures [44].

A change in the level of N-acetyl aspartate is associated with the density, function or viability of neurons that can be found when conducting PMRS [45]. Choline concentration changes with damage to the cell membrane [46]. Creatine is involved in energy metabolism, and its increased level means increased oxidative stress and mitochondrial dysfunction, both in neurons and in glial cells [47].

Structural and metabolic changes which were described in this article lead to impaired neurotransmission, accelerated neurodegeneration and demyelination, as well as cause brain atrophy in diabetes. However, further studies should confirm the above stated results in larger clinical trials.

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Authors contribution

Matveeva M.V. – literature search, patient recruitment, research, drafting of the manuscript. Samoilova Yu.G. – research design, manuscript editing. Zhukova N.G. – research design, manuscript editing. Tolmachov I.V. – literature search, consultation on the statistical processing of neuroimaging findings. Brazovskiy K.S. – research design, manuscript editing. Leiman O.P. – literature search on type 2 diabetes, patient recruitment. Fimushkina N.Yu. – literature search on type 1 diabetes, patient recruitment. Rotkank M.A. – literature search on type 1 diabetes, patient recruitment. Tonkikh O.S. – manuscript editing.

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