NEW MARKERS FOR DIAGNOSIS AND PROGNOSIS OF COGNITIVE IMPAIRMENT IN PATIENTS WITH MULTIPLE SCLEROSIS (review)

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Abstract

The article presents modern approaches to the diagnosis of brain damage and development of cognitive impairment in patients with multiple sclerosis. Neurodegenerative changes, which take place in the early stages of the disease and play an important role in the formation of irreversible neurological deficits, are considered. Cognitive impairment in patients with multiple sclerosis is quite common, but they are not always noticed, but they significantly reduce patients' quality of life. The article describes the possibilities of neuroimaging methods to identify structural changes in the parts of the brain responsible for cognitive functions. The importance of brain neurotrophic factor (BDNF) as a promising biomarker of multiple sclerosis is presented. Further study of BDNF remains interesting, which will allow to develop algorithms for early diagnosis and prediction of disease progression, that will provide an opportunity to deepen the understanding of the place of BDNF in the pathomorphological chain of nervous system damage in multiple sclerosis.

Keywords: *multiple sclerosis, cognitive impairment, brain neurotrophic factor (BDNF), neurodegeneration, neuroimaging.*

INTRODUCTION

Multiple sclerosis (MS) is the most common of the demyelinating diseases, characterized by formation of multifocal foci of demyelination in the brain and spinal cord, optic nerves associated with inflammatory cell infiltrates, reactive gliosis and axonal damage [1, 2].

The prevalence of multiple sclerosis in the world has recently tended to increase. This is due not only to the increase in morbidity, but also in improving the diagnosis of this pathology in the early stages [3, 4].

Researches of recent years have shown the presence, along with demyelinating processes, neurodegenerative changes in the substance of the brain in MS. It was found that neurodegeneration occurs in the early stages of MS, and plays an important role in the formation of the irreversible neurological deficit. Neurodegenerative changes are the main factor that leads to atrophy of the brain and exacerbates the severity of the neurological deficit [5].

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The peculiarity of development of MS is the simultaneous involvement of several different parts of the nervous system, which leads to the appearance of various neurological symptoms depending on the location of the pathological process. Visual, oculomotor, cerebellar, motor disorders, pelvic dysfunction, sensitivity disorders are most often observed in multiple sclerosis.

In recent years, researchers and clinicians have paid special attention to the study of psycho-emotional and cognitive disorders in patients with MS, given the significant impact of these disorders on the patients' quality of life and the necessity for their therapeutic correction. It has been found that depression and anxiety occur in 62% of cases, which is associated with demyelination in the temporal lobes. The occurrence of "constant fatigue" in patients (60–80%) is associated with rapid exhaustion of mental processes and causes drowsiness, difficulty in performing repeated actions, etc. [6, 7]. The prevalence of cognitive dysfunction ranges from 43% to 70% and it is observed at all stages and clinical types of MS [8].

The most vulnerable cognitive domains in MS are the domains of information processing speed, memory and attention [9, 10]. Thus, the typical picture of cognitive impairments in patients with MS includes decreased information processing

speed, speech impairment, lack of verbal and visual episodic memory, impaired attention, executive functions and visual-spatial skills [11, 12]. Speech disorders are usually associated with impaired speech fluency and poor word memorization (phonological and semantic fluency) [13]. The severity of cognitive impairments, which progresses over time, may be one of the determining factors in the deterioration of patients' quality of life [14, 15].

Cognitive impairments in patients with MS may occur in the early stages of the disease in addition to motor disorders or even precede them. This is due to the fact that at the beginning of the disease there is a loss of brain tissue in the structures responsible for cognitive functions, which reduces the social and psychological patients' quality of life, even after monitoring the severity and duration of the disease [16–18].

However, the peculiarities of formation of cognitive disorders, their early diagnosis need further study, especially given the fact that patients with MS in the presence of cognitive dysfunction are more disabled and socially maladapted than patients with MS without cognitive impairment.

In recent years, there has been a growing interest in identifying the possibilities of neuroimaging techniques to detect structural changes in the parts of the brain that are responsible for cognitive functions. Magnetic resonance imaging (MRI) is the most informative method of studying the structure of the substance of the brain and serves as the main neuroradiological marker for the diagnosis of MS. With the help of MRI it is possible to identify both old and new foci of demyelination, their total number and location in the brain and make a differential diagnosis of MS with other diseases. Gadolinium-based contrast agent is additionally used to determine the activity of the pathological process [19–21]. MRI is important for clinical monitoring of MS patients in facilitating the process of relapse and disease progression. MRI criteria for the damage of the brain is strategically important for cognitive functioning areas, but they still need to be further determined.

Recently, researchers have focused on identifying biological markers for the diagnosis of various diseases. Some biomarkers have been proposed for MS [22]. However, there are currently no confirmed biomarkers for diagnosing of the disease, monitoring it, predicting the rate of disease progression and assessing its consequences.

In foreign and domestic literature there is more and more data of the importance of brain-derived neurotrophic factor (BDNF) as a promising biomarker of MS.

Brain-derived neurotrophic factor (BDNF) is a protein from the class of cytokines, the family of growth factors and the subfamily of neurotrophins, which is found in glial and mainly in neuronal cells. BDNF is synthesized as a precursor protein with a molecular weight of 32–35 kDa (pro-BDNF), which is subsequently converted in the Golgi complex to biologically active mature BDNF (mBDNF) with a molecular weight of 13 kDa. Mature BDNF contacts the tyrosine kinase B receptor (TrkB), which induces phosphorylation cascades and leads to protein synthesis, axon growth, dendritic maturation, and increased synaptic plasticity. TrkB and BDNF induce intracellular cascades that control neuronal development and plasticity, cell cycle, and apoptosis [24].

From the pathogenetic point of view, formation of cognitive impairment in neurodegenerative diseases is closely related to such processes as neurogenesis and neuroplasticity [25].

It is known that BDNF affects the mechanisms of neuroplasticity, regulating the formation of new synapses and their plasticity, stimulating the survival, migration, proliferation and regeneration of neurons. Neuroplasticity is the basis of human development, learning and the formation of memory [26]. In addition, BDNF affects the processes of myelination and remyelination, regulating the rate and severity of apoptosis, controlling development and survival of cholinergic and GABAergic neurons in the brain, which play an important role in learning and memory. It was found that the content of BDNF in serum shows its concentration in brain tissue [27], which can be used in practice.

One of the main processes of neuroplasticity is neuronogenesis – the constant generation of nerve cells in the dentate gyrus of the hippocampus, olfactory bulb and striatum. About 700 nerve cells are formed daily in the human hippocampus (which is 1.75% of the total number of cells in the hippocampus). There are some factors that lead to the activation of neurogenesis, including physical activity, continuing education, diet, the formation of certain substances (GABA, glutamate, neurotrophic factors) [26].

Thus, the search of biomarkers for the diagnosis, prediction and evaluation of the effectiveness of MS therapy is a very promising area of research. In this regard, a promising marker may be a brain-derived neurotrophic factor (BDNF), which shows the condition of neuroplasticity [22]. Disorders of neuroplastic processes can be an im-

portant part of the pathogenesis of cognitive impairments.

There are few literature data of the possibility of using BDNF as a marker of MS. Sarchielli P. and co-authors examined 35 patients with relapsing-remitting and secondary-progressive MS. An increased BDNF's level in the supernatant of stimulated mononuclear cells of peripheral blood (MCPB) during relapse in relapsing-remitting type of MS compared with during the phase of clinical stability was found. Also, the authors obtained data about decreased concentration of BDNF in stimulated MCPB in the secondary-progressive type of MS, compared with the control group [28, 29].

Azoulay D. and co-authors found reduced serum and cerebrospinal fluid BDNFs' levels in patients with relapsing-remitting MS. The authors noted that BDNF may have a neuroprotective effect in MS, and immunomodulatory therapy may increase the effect of this mechanism [30].

Yoshimura S. and co-authors measured serum BDNFs' levels in 74 patients with MS and 86 patients with other neurological diseases. Evidence of a significant increase in BDNF's production in MS patients compared with control group and patients with other neurological diseases was found. Young people with MS had the highest level of BDNF. Based on the data obtained on the high concentration of BDNF in patients with a large number of relapses of MS, the authors suggested the correlation between BDNFs' levels and disease severity [31].

Comini-Frota E.R. and co-authors determined the serum BDNF's level of 28 patients with MS and 28 healthy people. A relationship was found between serum BDNFs' levels in patients with relapsing-remitting MS and the number of foci in the brain that accumulates gadolinium during T2 / FLAIR MRI. Based on these data, the authors suggest that the concentration of BDNF in serum can be considered a promising biomarker in patients with multiple sclerosis, which indicates severity of CNS damage [22, 23].

Thus, the clinical picture of MS has a very wide variety and in addition to motor, sensory and cerebellar disorders is often accompanied by cognitive impairment. Detection of cognitive dysfunction in the early stages should be an important part of assessing the patient's clinical status.

Further research of biomarkers for the diagnosis and prognosis of MS can be interesting. A promising marker may be a brain-derived neurotrophic factor (BDNF). However, the possibility of using BDNF requires further study, which will allow to develop algorithms for early diagnosis and prediction of disease progression, that will provide an opportunity to deepen the understanding of the place of BDNF in the pathomorphological chain of nervous system damage in MS.

DECLARATIONS:

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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