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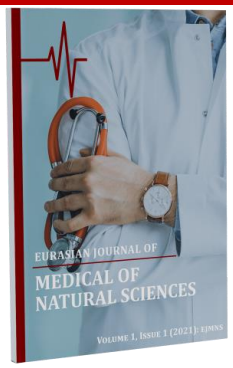

MORPHOFUNCTIONAL BRAIN CHANGES IN THE CONTEXT OF NEUROCIRCULATORY AND NEUROTROPHIC CONCEPTS OF DEPRESSIVE DISORDERS

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ABSTRACT

Emotional disorders, and in particular depression, are one of the most pressing problems of modern medicine. According to the World Health Organization, depression affects more than 280 million people worldwide, which determines the high socio-economic importance of this pathology. Modern research has significantly expanded the understanding of the neurobiological foundations of emotional disorders, revealing the key role of structural and functional changes in the brain in their pathogenesis.

Introduction. The development of neuroimaging techniques has revealed that depressive disorders cause significant changes in various areas of the brain, including the prefrontal cortex, hippocampus, amygdala, and other structures of the limbic system. These changes affect both the morphological characteristics of the nervous tissue and the functional connections between different parts of the brain.

The neurocirculatory hypothesis of depression suggests that the pathogenesis is based on disorders of cerebral hemodynamics and microcirculation. Changes in cerebral blood flow affect the metabolism of nervous tissue, which leads to impaired functioning of neural networks and, as a result, to the development of emotional disorders. Particular importance is attached to changes in the system of neurovascular units and regulation of cerebral blood flow. At the same time, the neurotrophic hypothesis focuses on the role of growth factors, especially BDNF (brain neurotrophic factor), in the development and maintenance of depressive states. A decrease in the level of neurotrophic factors leads to impaired neurogenesis, synaptic plasticity and interneuronal connections, which is reflected in structural and functional changes in the brain.

The integration of the neurocirculatory and neurotrophic hypotheses allows for a more complete understanding of the pathophysiological mechanisms of emotional disorders. There is a close relationship between cerebral hemodynamics and the production of neurotrophic factors: blood supply disorders can lead to a decrease in the synthesis of neurotrophins, while a deficiency of the latter can affect the state of the vascular system of the brain. Understanding these mechanisms is of great clinical importance, as it opens up new perspectives for therapeutic effects. Modern methods of treating depression are increasingly focused on

correcting the identified disorders, including the use of drugs that affect both neurocirculatory and neurotrophic mechanisms.

The relevance of this study is determined by the need for a deeper understanding of the relationship between structural and functional changes in the brain and the pathophysiological mechanisms of emotional disorders. This will make it possible to develop more effective diagnostic and treatment strategies based on a personalized approach, taking into account the individual characteristics of the disease pathogenesis in a particular patient.

Depression is one of the most common mental illnesses that doctors of various profiles have to deal with. This also applies to major depressive disorder (MDD). According to WHO, its relative prevalence during life is 16.2%, during the year – 6.6%.

The diagnosis of MDD according to the criteria of the American classification DSM-IV, designated major depressive disorder (MDD), requires the development of major depressive episodes (MDE) to have at least 5 symptoms for at least 2 weeks: low mood, feeling of insignificance / guilt, thoughts of death or suicidal, loss of interest feelings about others, impaired appetite, sleep disorders, psychomotor changes, hypo- or anergy, impaired concentration, and indecision.

Despite the fact that BDD is often characterized as an episodic disease, promising studies in recent years have shown that it is more prone to recurrent course. Thus, a 15-year study of 380 patients showed that 73% of patients with BDE had a recurrent course of the disease. At the same time, the development of each BDE increased the risk of developing a subsequent one. Similar results were obtained in the framework of the international project STARD (Sequenced Treatment Alternatives to Relieve Depression), which examined 1,500 patients with BDE, of whom 74% had more than one BDE.

It is assumed that the recurrent course of BDE is triggered by the development of a number of neurobiological disorders that increase the body's vulnerability to the development of a new BDE.

In this review, we present the criteria for depression according to the DSM-IV, since most of the studies discussed are focused on this classification. In accordance with this, the "kindling hypothesis" was put forward, according to which each BDE becomes a trigger for a new depressive episode and this phenomenon increases over time. As the number of BDES increases, their further development becomes more and more related to their previous number, rather than to stressful factors in the patient's life. S. Monroe and K. The harkness swing of the disease with an increase in the duration of the disease is explained by a decrease in the protective threshold (sensitization of the body to stress) and/or an increase in spontaneous dysregulation of the neurobiological systems responsible for the development of MDR. K. Kendler et al. When analyzing the risk of recurrent seizures in a cohort of twins, a large contribution of the genetic factor to the development of the phenomenon of "rocking" was shown. This study also found a decrease in the magnitude of the association between stress factors and the onset of recurrent MDR in patients with a high genetic risk.

Family depression, early separation of the child from the mother (deprivation), and inadequate treatment in the initial stages of the disease are also risk factors for the development of recurrent MD. Some researchers believe that any aggravating events in the

patient's life from birth to the manifestation of the disease increase the risk of developing repeated bouts of MDR.

Chronification of the course of MDR suggests the presence of slowly increasing neurobiological consequences leading to the "rocking" of the disease. This makes it less and less likely that MD patients will recover in practice, especially in the late stages of the disease. If for patients with a disease duration of less than 1 year, the probability of recovery is 16%, then for patients suffering from BDD for more than 5 years, it is less than 1%. The longer the period between the previous and subsequent BDEs, the higher the probability of recovery. If it exceeds 1 year in the early stages of the disease, then the probability of non-recurrence of a new episode reaches 20%.

The recurrence and chronification of BDD reduce the prospects for treating the disease, while its goal is not to reduce or completely eliminate all the main symptoms of the disease, but to lengthen the periods between attacks.

Functional and structural changes of the brain in MD

Currently, a number of neurobiological abnormalities associated with BDD have been identified. They are especially pronounced in limbic structures and their connections, which are related to the regulation of affect. These neuroanatomic zones include the medial, orbitofrontal, and dorsolateral zones of the prefrontal cortex, the anterior cingulate cortex, and the ventral striatum, which includes the nucleus accumbens, amygdala, and hippocampus. It is assumed that the anomalies found in these structures in patients with MDR form the basis for its formation.

As an integrative circuit, the prefrontal cortex, cingulate cortex, amygdala, and hippocampus provide not only mood regulation, but also learning ability and contextual memory. In addition, the corresponding areas of the prefrontal cortex are related to pain, aggression, sexual functioning and eating behavior, the development of affective disorders, support for executive functions, attention and working memory. The individual parts inside the anterior cingulate cortex have different functions: the dorsal part of the anterior cingulate cortex provides some cognitive and executive functions, the ventral part of the anterior cingulate cortex processes emotional and motivational information, and the anterior cingulate cortex monitors behavior and cognitive functions.

Hyperactivation of the ventromedial and orbitofrontal zones of the prefrontal cortex, as well as decreased activity of the dorsolateral prefrontal cortex, was found in patients with BDD. Based on the functions of these brain regions, it has been suggested that these disorders are responsible for the manifestation of symptoms associated with MDR. Hyperactivity of the ventromedial and prefrontal cortex is associated with increased sensitivity to pain, increased anxiety, depressive rumination, and tension. Hypoactivity of the dorsolateral region of the prefrontal cortex can cause psychomotor retardation, apathy, attention deficit and working memory. When using magnetic resonance imaging (MRI), a decrease in "communication" between the amygdala and the anterior cingulate cortex was found. Due to the loss of these connections, the anterior cingulate cortex loses its inhibitory ability to be an emotional regulator, which leads to the development of a motivational and affective gap.

Being at the intersection of limbic, cognitive, executive, and neuroendocrine regulatory pathways, including the hypothalamic-pituitary-adrenal axis, the hippocampus should be

particularly vulnerable in MDR. P. Videbech and B. Ravnkilde, summarizing 12 studies using a meta-analysis, found that the volume of the hippocampus is significantly reduced in MDR compared to the norm, this decrease is observed bilaterally with a slight predominance on the right side. A number of other studies have shown that a decrease in hippocampal volume is directly proportional to the number of BDEs and the duration of BDR. Even in the period of remission after BDE, patients continue to experience a slow decrease in the already reduced volume of the hippocampus.

The difference in hippocampal volume between BDD patients and controls is not always related solely to the disease. Studies have shown that the genetic contribution to a reduced hippocampal volume is 54%. Studies of the autopsy brain tissue of patients with BDD showed a decrease in the size of the hippocampus due to an increase in the density of neurons and a decrease in the volume of the neuropile (due to a decrease in the branching of dendrites).

The generalized results of genetic, neuroanatomic, and clinical studies suggest that a decrease in the size of the hippocampus is a predisposing factor for the occurrence of BDD. During treatment, the volume of the hippocampus does not return to normal, which makes it impossible for the patient to fully recover.

Molecular processes mediating neurobiological changes in MD

Disturbances in the hippocampus by the feedback mechanism can lead to dysregulation of the function of the structures involved. At the same time, a high level of the main stress hormone cortisol, which affects neuroplasticity and cellular resistance, plays an important role. The disturbed balance between the hormones of the glucocorticoid and mineralocorticoid groups, as well as the high density of glucocorticoid receptors (GR) in the brain during BDR lead to the vulnerability of hippocampal neurons. As a result, atrophy of hippocampal cells develops, which leads to even greater neuroendocrine dysfunction and loss of control of hippocampal-mediated brain systems. As a result of increased levels of glucocorticoids (in particular, cortisol) and a decrease in the functional activity of the hippocampus, there is a decrease in the sensitivity of GH. In conditions of chronic stress (with an increased cortisol content), a decrease in GH sensitivity can have negative consequences, since insufficient GH signaling "turns off" the feedback mechanism of stress protection. As a result, hypothalamic-pituitary-adrenal hyperactivation occurs, which, combined with activation of the brain's amygdala function, increases sympathetic tone, which in turn causes increased release of pro-inflammatory cytokines from macrophages. Increased secretion of pro—inflammatory cytokines (interleukins 1 and 6 and tumor necrosis factor - TNF-α) reduces insulin levels and GH sensitivity, which exacerbates metabolic and neuroendocrine disorders. Clinically, such disorders are manifested by symptoms of fatigue, loss of appetite and libido, as well as hypersensitivity to pain.

Pro-inflammatory cytokines can also reduce neurotrophic cell support and monoamine neurotransmission, which in turn leads to apoptosis of neurons and impaired glial function and neuron-glial relationships in MDR. The importance of such relationships is determined by the fact that glial cells are involved in complex interactions with neurons, maintain homeostasis of the neuron and its environment by regulating the content of electrolytes, neurotransmitters, cytokines and neurotrophic factors. Recently, much attention has been paid not only to astro- but also to microglia, which are associated with immune dysregulation

and additional production of proinflammatory cytokines. The neurons, in turn, reciprocally support the functioning of the glia through the production of neurotrophin.

The brain-derived neurotrophic factor (BDNF) plays an integral role in maintaining normal neuron-glial interaction. Being involved in neurogenesis, BDNF is the main neurotrophin in the hippocampus. As a dimeric protein involved in cell maintenance, plasticity, growth, and death (apoptosis), BDNF is structurally related to nerve growth factor and is widely distributed in the brain. BDNF, interacting with tyrosine kinase receptors, determines cellular resistance to external factors and the effects of prolonged potentiation. However, the BDNF – pro-BDBF precursor, binding to the p75 receptor, can cause a forced reduction of such intercellular contact structures as dendritic spines and cell death. Depending on the amount of BDNF expression, this process can be expressed to varying degrees. This process is regulated by various neurotransmitters (glutamate, gamma-aminobutyric acid, serotonin, norepinephrine, acetylcholine, dopamine, and hormones).

Preclinical and clinical studies show that BDNF dysregulation occurs in chronic stress and depression. In animal models of depression, a decrease in the expression of BDNF synthesis in brain tissues was shown (similar results were obtained using models with acute or chronic pain stimulation in animals). Reduced serum BDNF levels were found in untreated patients with BDD compared to treated patients or healthy ones. Similar results were obtained on autopsy material of the brain of patients with BDD (after suicide): decreased levels of BDNF and NT-3 type neurotrophin compared to the material obtained from patients with BDD who did not die as a result of suicide).

The above data allowed the well-known Venezuelan scientist Fuad Lechin to formulate the so-called neurocirculatory and neurotrophic hypothesis of the pathogenesis of MDR. This hypothesis is based on the idea of the existence of connections between systems of neurotransmitters or neurotrophic factors in the periphery (blood, cerebrospinal fluid, etc.) and the systems of relationships between these same neurotransmitters or neurotrophic factors in the central nervous system in depression and other mental disorders. As part of the development of this hypothesis, it was shown that stress and genetic vulnerability through changes in the system of relationships between mediators, neurohumoral and neurotrophic factors in the periphery increase the production of central glucocorticoid steroids, which leads to a violation of cellular plasticity and a decrease in the system of growth factors and sensitivity of GH. At the same time, there is also a decrease in the synthesis of neurotrophic growth factors such as BDNF (in the blood and central nervous system). This causes negative structural and functional changes in the limbic system, especially the hippocampus. In chronic and recurrent forms of BDD, gradual atrophy of the hippocampus occurs, followed by dysregulation in the neural circuits of the limbic system. According to this hypothesis, the recovery or remission of BDD depends on the reversibility of these processes, especially on increased BDNF synthesis during treatment.

Within the framework of the neurocirculatory and neurotrophic hypotheses of MDR, monoamine theories (serotonin, norepinephrine) become complementary. Recall that according to monoamine theories, depression is associated with low levels of monoamine neurotransmitters, especially serotonin and norepinephrine. Recent MRI studies of patients with untreated depression have shown an increased protein density of the enzyme

monoamine oxidase A (MAO-A), which has non-specific enzymatic activity against both serotonin and norepinephrine.

Conclusions: Therefore, the modern version of the monoamine theory of depression postulates that a prolonged decrease in serotonin and norepinephrine levels due to the activation of MAO-A in various parts of the brain of patients leads to a malfunction of serotonin transporter proteins (SERT) and norepinephrine, and as a result, to an exacerbation of depression. Serotonin and noradrenergic ascending nerve fibers originate from the nuclei of the brainstem and innervate the limbic system and prefrontal cortex, which are associated with structures involved in mood regulation.; The descending pathways pass through the dorsolateral parts of the spinal cord and are associated with the regulation of the threshold of pain sensitivity. Therefore, depending on the magnitude of changes in the functional activity of SERT or the norepinephrine transporter protein, different clinical manifestations of depression may occur in the corresponding regions of the brain.

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