МЕДИЦИНА, ПЕДАГОГИКА И ТЕХНОЛОГИЯ: ТЕОРИЯ И ПРАКТИКА
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# MORPHOFUNCTIONAL CHANGES IN THE NEURAL ENVIRONMENT IN SUICIDE

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## ANNOTATION

The presented analytical review of literature addresses the state of the study of the morphology of microglia, astrocytes, oligodendrocytes, and the blood-brain barrier in suicide. According to the generalized data, the most characteristic localization of changes in the development of suicidal behavior was determined by the suture nucleus, prefrontal and anterior cingulate cortex. There is evidence of a correlation between the development of suicidal behavior and an increase in inflammatory cytokines in the prefrontal cortex, disruption of the connection between astrocytes and oligodendrocytes in the anterior cingulate cortex, as well as indication of involvement in the process of forming suicidal behavior of the cortex, striatum, preclinium and cuneiform, orbitofrontal cortex.

**Keywords:** microglia; astrocytes; oligodendrocytes; suicide; morphology.

**Management** Suicide — death resulting from a certain behavior aimed at causing harm to oneself. Every year, about 703 thousand people in the world commit suicide. According to the World Health Organization, the main risk group for the development of suicidal behavior is young people under 49 years old, and in the 14-19 age group, this reason is fourth in importance. The most significant risk factor is the presence of previous unfinished attempts in the medical history. The main reason for the development of suicidal behavior is considered to be major depressive disorder, but not every depressive episode leads to incomplete suicide attempts or suicide.

The pathophysiology of depression, and consequently, suicide, still remains the focus of specialists' attention due to the diversity of forms, etiological factors, and comorbidity with other psychopathological syndromes. However, the results of recent studies demonstrate functional and morphological changes in certain areas of the brain leading to the development of depressive disorder, including the issues of changes and influences of the microenvironment on the functional activity of neurons and their relationship with the development of certain mental disorders.

In this review, we examined the main changes identified in astrocytes, oligodendrocytes, microglia, and the blood-brain barrier in completed suicide at this time. The listed cells are of particular interest, as they perform numerous functions responsible for the normal functioning and vital activity of neurons, and consequently, for a person's cognitive abilities and emotional state. These are primary immune cells of the central nervous system, having certain similarities with macrophages in their functions. Despite this, microglia cells do not have a monocytic origin, but are secreted from the yolk sac during embryogenesis, and in adulthood, their population is maintained through self-renewal. There are studies demonstrating different immunohistochemical expressions of CD39 and CD45 by microglia and monocytic macrophages. Specific immunohistochemical markers for microglia are HAM-56 and CD68.

Under the influence of external (trauma, infectious diseases) or internal (stress) factors, the microglia can be activated, thereby promoting the release of pro-inflammatory cytokines and neurotransmitters, triggering the processes of damage and premature death of neurons. As a result of activation, there is also an increase in the production of quinoline acid (QUIN) — a toxic product and agonist of N-methyl-D-aspartic acid (NMDA) receptors, the level of which increases and correlates with the development of suicidal behavior. QUIN formation occurs through the kinurenin pathway of tryptophan metabolism, which, in turn, leads to a decrease in serotonin production and its deficiency. In addition to serotonin, there is a decrease in kinurenic acid (KYNA) - NMDA antagonist, which suppresses glutamate neurotransmission. On the other hand, activation leads to an increase in the content of interleukins, which causes the loss of inhibition in glutamatergic neurons and an increase in the release of glutamate. In studies, microglia activation was detected in the postmortem brain material of patients with psychiatric illnesses who committed suicide and in the control group of people who died non-violent death. Larger and rounder cells with branched processes were identified using the immunohistochemical marker — HLA-DR-antigen — in the suture nucleus. In other studies, microglia activation in the prefrontal and anterior cingulate cortex in the brain material of people suffering from major depressive syndrome with completed suicide was detected, compared to the control group with sudden death, where no such changes were found. Astrocytes are multifunctional glial cells whose role is to maintain and regulate the nutrition and metabolism of neurons, as well as to synthesize growth factors and maintain the blood-

brain barrier. From an anatomical point of view, they are classified into protoplasmic (found in the gray matter and having many branching processes, the ends of which enclose the synapses) and fibrillar (located in the white matter and having long, thin, unbranched processes). There are also subtypes such as "pilocytic" astrocytes located in the periventricular region, cerebellum, and spinal cord; Bergman's astrocytes located between Purkinje cells in the cerebellum. The main immunohistochemical markers of these cells are glial-fibrillate acid protein (GFAP), glutamate transporter GLT-1, Ca+-binding protein, S100, glutamine synthase (GS), connexin, aquaporin receptor (AQP4), and aldehyde dehydrogenase 1L1 (ALDH1L1).

Studies in groups of people who have committed suicide revealed both morphological and immunohistochemical changes in astrocytes in various brain structures. Thus, the study of S.G. Torres-Platas et al. demonstrated the presence of changes in fibrillar astrocytes in the anterior cingulate gyrus (in the part adjacent to the dorsal part of the knee of the мозole body), which were larger and had longer and branched processes, unlike the cells in the control group. At the same time, protoplasmic astrocytes did not have significant differences in the comparison groups. Areas of fibrillar astrocytes changes in living patients may appear as areas of white matter hyperintensity on magnetic resonance imaging, which, in turn, has a correlation with the development of apathy, depression, and an increased risk of suicidal behavior. On the other hand, studies on animal models show a decrease in the number of astrocytic processes in the cerebral cortex. Morphological changes may not always be clear and unambiguous, therefore, immunohistochemical examination for GFAP can serve as an additional diagnostic method. It was noted that with a major depressive disorder, a decrease in the density of this protein is observed in areas such as the basolateral tonsil nucleus, orbitofrontal cortex, white matter of the ventral prefrontal cortex, compared to the control group. In the hippocampus, black substance, dorsolateral prefrontal, orbitofrontal, entorine, and anterior cingulate cortex, the immunoreactivity of astrocytes was similar both in individuals with depressive disorder and completed suicide, and in the control group who died from non-violent causes. The results of studies of postmortem material taken from people who have committed suicide and suffered from major depressive disorder indicate a decrease in vimentin-immunoreactive and GFAP-immunoreactive astrocytes in the prefrontal cortex and caudate nucleus compared to the control group. Oligodendrocytes These are small glial cells responsible for the formation and maintenance of the myelin sheath of

neuronal processes. In white matter, they are oriented along the fibers of the pathways, while in gray matter, they occur as two or three small dark nuclei pressed against the bodies of larger neurons. Immunohistochemically, oligodendrocytes are positive for protein S100 and transcription factor Olig2. Oligodendroglia plays a role in the neurocirculation of various substances necessary for maintaining cognitive functions. In a number of studies, a decrease in myelination of the prefrontal and occipital cortex in patients with severe depressive disorders has been identified. A decrease in the expression of antioxidant genes is also observed in groups with depression and suicidal behavior compared to the control group. Studies have shown that oligodendrocytes are extremely sensitive to oxidative damage due to their lipid membrane structure, high iron content, and metabolic activity. A few studies on postmortem material demonstrate a decrease in the density of oligodendrocytes in the tonsils during the development of depressive disorder, which is confirmed by the observed changes in neurotrophic factor signaling secreted by mature oligodendrocytes in suicidal individuals with depression in another study.

Hemoencephalic barrier The blood-brain barrier is formed by the endothelial cells of capillaries, the terminal stalks of astrocytes that encircle the capillary, and pericytes located in the basal membrane of the capillary. There are several studies that have determined the increase in the permeability of the blood-brain barrier in the development of suicidal behavior, however, changes in its structure are most likely the outcome of neural inflammation, and not an independent cause of suicidal behavior. Evidence base for the development of Suicide factors in assessing the causes of death: analytical review of literature Determining the characteristic morphology of death due to suicide is quite relevant from the perspective of understanding the pathophysiology of the development of suicidal behavior and the possibility of its prevention. On the other hand, in the development of this area, histological and immunohistochemical methods can potentially serve as an evidence base for confirming or excluding suicide development factors when assessing the causes of death.

In order to find information about structural changes in brain cells surrounding neurons in the development of suicidal behavior, we analyzed 72 articles from the PubMed database for the period from 2004 to 2022, of which 28 works, including research on the morphological features of the brain's cellular structure in postmortem material, generated the greatest interest.

Thus, the most studied are the cells of the microglia. Activation of this type of cell leads to dysregulation of the serotonergic system and depletion of serotonin and melatonin content. At the same time, there is an increase in aggressiveness and impulsiveness. The main changes in serotonergic neurons during the development of major depressive disorder and suicidal behavior are observed in the suture nucleus. The formation of serotonin occurs from tryptophan under the influence of 5-tryptophanhydroxylase. However, there is an alternative — kinurenin — pathway for its metabolism, which is triggered by pro-inflammatory cytokines. Its main product in the microglia is QUIN, which, as an NMDA receptor agonist, leads to the disregulation of the glutamine-glutamate cycle. The main site of synapse activity regulation is the astrocytes, where glutamate is reabsorbed. In astrocytes, NMDA receptor antagonist KYNA is also synthesized from tryptophan. Many studies note a decrease in kinurenic acid during the development of major depressive disorder. Failure in the glutamine-glutamate cycle system leads to impaired cognitive abilities and is also associated with the development of suicidal behavior.

It has been shown that the interaction between neurons and glial cells can be carried out using microvesicles. Due to this type of transport, changes in the microglia can spread to the surrounding tissue. There are data indicating a decrease in exosome release from microglia cells when serotonin levels decrease. Astrocyte vesicles also contribute to the activation of the microglia, thereby exacerbating the development of neural inflammation through the release of cytokines and chemokines. The vesicles of oligodendrocytes are released due to the activity of the glutamine-glutamate cycle via NMDA receptors. Their main function is to myelinate the fibers and protect oligodendrocytes from oxidative stress. It can be assumed that with the development of disorders in the glutamatergic system, the processes of oligodendroglia damage and demyelination will worsen, however, there is currently no data evaluating exosomes in the development of suicidal behavior.

The most characteristic localization of changes in the development of suicidal behavior was determined by the suture nucleus, prefrontal and anterior cingulate cortex. There is evidence of a correlation between the development of suicidal behavior and an increase in inflammatory cytokines in the prefrontal cortex, as well as a disruption in the relationship between astrocytes and oligodendrocytes in the anterior cingulate cortex. There are also studies indicating the involvement of the shell,

striatum, preclinium and cuneiform, and orbitofrontal cortex in the formation process of this behavior, however, morphological data on these areas are insufficient.

**Conclusion**: When analyzing the literature, the most significant are reports of microglia activation in the prefrontal cortex and suture nucleus, leading to disorders of the serotonergic and glutamatergic systems, both directly and indirectly through the production of pro-inflammatory cytokines. The development of neural inflammation is also associated with an increase in the size and number of fibrillar astrocytes in the anterior cingulate gyrus, a decrease in GFAP and vimentin-immunoreactive astroglia in the prefrontal cortex and caudate nucleus. The fibrillar astrocytes of the anterior cingulate gyrus become larger, with long and branched extensions. Data on oligodendroglial morphological changes indicate demyelination of the prefrontal and occipital cortex areas. Morphological studies on postmortem material demonstrate a decrease in the density of oligodendrocytes in the tonsils. Under the influence of inflammation, an increase in the permeability of the blood-brain barrier occurs, however, the pathophysiology of this process is unclear. At the same time, there is no data that only inflammation is involved in the development of the described changes. At this stage, there is insufficient research on autopsy material that combines and examines the totality of changes, linking them to specific localization. The immunohistochemical method is considered a potential method that can serve as a evidence base for understanding suicide factors. Further research is needed to form a clearer picture of pathomorphological changes in brain structures in relation to forensic medical examination practice. Additional funding source. The authors state that there is no external funding for the search and analytical work.

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