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Neuropsychiatric Manifestations of Amyotrophic Lateral Sclerosis

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Neuropsychiatric manifestations are observed in a significant proportion of patients with amyotrophic lateral sclerosis (ALS). Severe behavioral disorders develop when ALS is combined with frontotemporal dementia, and this is regarded as a single continuum. Mental disorders are less marked in ALS with predominantly motor manifestations and most frequently consist of apathy. Depending on etiology, mental disorders in ALS can be psychogenic, reflecting the patient's response to serious illness, or organic, developing as a result of degeneration and disconnection of fronto-subcortical and fronto-temporal connections. An important role in the development of mental disorders in ALS is played by various genetic factors, in particular, the occurrence of hexanucleotide expansion in the *C9orf72* gene. In ALS without dementia, especially in the first months after diagnosis, there is a high risk of developing depressive disorders, which in severe cases can lead to suicide. Further research is needed in this direction.

Keywords: amyotrophic lateral sclerosis, frontotemporal dementia, suicide, apathy, depression.

Amyotrophic lateral sclerosis (ALS) has long been regarded as a disease with exclusively motor manifestations [1]. However, studies in recent decades have shown that non-motor, in particular, mental disorders are common in this disease [1]. Some 13% of patients with ALS display signs of frontotemporal dementia (FTD), accompanied by severe cognitive and behavioral impairments [2]. The commonest situation is the combination of ALS and a behavioral variant of FTD. Symptoms of FTD may develop before the motor symptoms of ALS, simultaneously with them, or after their onset [2]. These two diseases are similar in pathogenesis and are regarded by many authors as a single ALS–FTD continuum [3].

Psychiatric disorders can be seen in ALS in the absence of dementia. These cases do not meet the criteria for diagnosis of ALS–FTD and are referred to as ALS with behavioral disorders [3]. The incidence of mental disorders in ALS without symptoms of dementia ranges from 14% to 40% [4]. Mild and moderate disorders are observed in 30% of patients, and severe in 13% [5]. The commonest symptom is apathy, as well as disinhibition, irritability, rigid thinking, and anxiety [6]. The frequency of affective disorders in ALS is high [1]. Empathy disorders, egocentric behavior, perverted and stereotyped behavior, and changes in food habits are less common [2].

Mental disorders in ALS and in the combination of ALS and FTD have a negative impact on the prognosis of the disease [7], reducing life expectancy by an average of 11 months compared to those who suffer from ALS without FTD. This trend comes from a decrease in treatment compliance, in particular in relation to the use of gastrostomy and non-invasive pulmonary ventilation [8]. At the same time, experts have noted that specialists pay little attention to the problem of mental disorders in ALS. Beswick et al. [9] found that of 216 large clinical trials of drugs for the treatment of ALS conducted over the past 25 years, only one evaluated drug effects on mental disorders and cognitive impairment as an efficacy indicator.

This review analyzes the clinical and pathogenetic aspects of the neuropsychiatric manifestations seen in patients with ALS.

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Molecular Genetic Mechanisms of the Development of Mental Disorders in ALS. The mechanisms of development of mental disorders in ALS are diverse [1]. Large-scale studies have demonstrated genetic similarities in patients with ALS and mental disorders [10]. The hexanucleotide expansion mutation in the *C9orf72* gene, which is seen in both ALS and FTD, is the most studied [11, 12]. The world literature indicates that this mutation is detected in 40% of patients with familial ALS, 30% of those with familial FTD, and 50–70% of those with combined familial ALS and FTD [13]. Its frequencies are lower in sporadic cases, at about 8% in ALS and 15–20% in combined ALS and FTD [14]. In the Russian Federation, the frequency of this mutation is 15% of familial cases of ALS and 2.5% of sporadic cases (according to a study of the population of Moscow and the Moscow region) [15].

The clinical manifestations of the hexanucleotide expansion in the *C9orf72* gene are extremely diverse and include the phenomena of parkinsonism, corticobasal degeneration, psychotic disorders, suicidal behavior, etc. [14]. The presence of this mutation probably determines the increased risk of developing mental disorders in blood relatives of patients with ALS [16].

The normal number of GGGGCC repeats in this gene varies from 2 to 25, while there can be from 100 to 1000 repeats in patients with ALS and FTD [12]. The clinical manifestations of a moderate increase in hexanucleotide repeats – up to 30 – are currently unclear, though the belief is that in such cases, patients with FTD and combined ALS and FTD, as well as atypical parkinsonism, have an increased risk of developing mental disorders [17]. The physiological role of the proteins encoded by the *C9orf72* gene is not known with confidence. It is of note that the length of the expansion can vary in different tissues, which suggests instability of the mutation and, possibly, a role for epigenetic phenomena in its development [18]. From the clinical standpoint, mutations in the *C9orf72* gene are characterized by different penetrance and the phenomenon of anticipation [19].

A number of biomarkers of *C9orf72* gene carriership have been described. MRI studies have demonstrated atrophy of the left caudate nucleus, putamen, thalamus, and certain areas of the temporal, parietal, and occipital lobes [20], as well as signs of damage to the white matter tracts of the brain [21, 22] in patients with this mutation. However, studies reported by Floeter et al. [21] found no signs of cerebral atrophy in asymptomatic carriers of the *C9orf72* gene. The hypothesis that mental disorders appear in *C9orf72* carriers before the development of structural changes in the brain has also not been confirmed [22]. Indicators such as the levels of poly(GP) protein and neurofilament light and heavy chains in biological fluids can be used as biomarkers of the *C9orf72* mutation [23, 24].

A relationship between ALS and mental disorders is seen even after exclusion of patients with expansion in the *C9orf72* from the analysis [25]. The development of mental disorders in patients with ALS-FTD is likely also to be associated with mutations in the TBK1, PGRN, CHCHD10, TUB4A, and VCP loci, with molecular mechanisms similar to those in mutations in the *C9orf72* gene [26].

Pathomorphological Aspects of the Development of Mental Disorders in ALS. Pathological studies of the brain in patients with ALS during their lifetime generally reveal intraneuronal inclusions containing the pathological TDP-43 protein [27]. Similar changes have been found in about half of patients with FTD [28]. It is of note that of the four known types of TDP-43 protein, type B occurs in patients with ALS and combined ALS and FTD [29].

The distribution of TDP-43 protein in brain structures depends on the stage of the disease. While it is detected only in neurons of the granular layer of the motor cortex, α-motoneurons in the anterior horns of the spinal cord, and neurons in the motor nuclei of the cranial nerves in the brainstem at the early stages of ALS, it is present at the later stages in neurons in the reticular formation, prefrontal cortex, and basal ganglia, as well as the anteromedial parts of the temporal lobes and the hippocampus [30].

TDP-43 propagates in the behavioral variant of FTD on the same principle but in the opposite direction. At the initial stages, pathological protein is detected in the structures of the prefrontal cortex and amygdala and it subsequently spreads to neurons in the basal ganglia, red nuclei, and thalamus. In the advanced stage of the disease, TDP-43 is detected in neurons in the motor cortex, anterior horns of the spinal cord, and brainstem nuclei, as well as in the visual cortex [30].

Microglia play an important role in the neurodegenerative process. Microglial activation is observed in ALS, with switching from the neuroprotective M1 phenotype to the neurotoxic M2 phenotype, leading to the development of aseptic inflammation and aggravating the process of neuron death [31].

Some authors have tried to find a link between pathomorphological changes in ALS-FTD and schizophrenia. In general, schizophrenia is not characterized by such obvious degenerative processes as in the case of ALS, though autopsy studies of schizophrenia patients have demonstrated atrophic changes in the hippocampus, prefrontal cortex, and thalamus, as well as signs of microglial activation [32].

Neuroimaging study data have confirmed some similarity between the morphological substrates of combined ALS and FTD on the one hand and schizophrenia on the other. In both conditions, atrophic changes were observed in the medial frontal cortex, anterior cingulate gyrus, orbitofrontal cortex, insula, caudate nucleus, putamen, thalamic nuclei, the middle, inferior, and superior temporal gyri, the lateral temporoccipital gyrus, the lateral occipital cortex of both hemispheres, and the right hemisphere of the cerebellum [33]. Damage to the anterior cingulate gyrus and insula indicates involvement in the pathological process of the so-called salience network, which is responsible for identifying,

analyzing, and integrating emotionally significant stimuli. Disruption of the functioning of this network underlies the development of symptoms of FTD and schizophrenia [34].

The development of apathy in ALS correlates with decreases in the thickness of the orbitofrontal cortex of both hemispheres, as well as the left precentral gyrus, while the severity of disinhibition correlates with decreases in the thickness of the temporal and cingulate regions of the right hemisphere [35].

Clinical Correlates of Neuropsychiatric Manifestations of ALS. The frequent combination of FTD and ALS, as well as similar pathological changes in the CNS, makes it possible to address these two diseases as a single continuum [3]. However, clinical observations show that in some cases severe behavioral disorders are observed in the early stages of ALS, while in others they are absent even at the advanced stage of the disease [36].

Burke et al. [5] ran a cross-sectional population study and did not find any relationship between mental disorders in ALS or disease duration with the sex of patients. However, caregivers indicate that patients in the later stages of ALS had more marked behavioral disorders than patients in the early stages [5]. Chio et al. [36] ran a study with a similar design and showed that patients with ALS were more likely to experience FTD at the later stages than at the early stages (44.4% in stage IV and 16.5% in stage I, on the King system). The frequency of cognitive behavioral disorders in ALS patients without dementia increased as the disease progressed from stage I to stage III on the King system and decreased at subsequent stages [36]. These data indirectly confirm the pathomorphological and MRI data indicating gradual spread of pathological changes in different areas of the brain, which formed the basis of the corticoefferent spread model [37]. Behavioral disorders, particularly emotional lability [5], were more often detected in patients with bulbar onset of disease [36].

Lulé et al. obtained rather different results [38]: their study involved interviews with the caregivers of 762 ALS patients with predominantly motor manifestations and FTD with predominantly behavioral disorders. The results showed that cognitive and behavioral disorders developed at later stages of disease and did not reach a severe level in the first group of patients, while the second group first showed behavioral disorders, with subsequent addition of motor disorders. The data led to the conclusion that ALS and FTD, despite certain similarities, cannot be regarded as a single disease, and that the symptoms that any individual patient develops are determined at the very beginning of the disease by some factor (probably genetic, but not the *C9orf72* mutation), which is currently unknown.

Behavioral disorders are combined with cognitive decline in a quarter of patients with ALS [39]. Impairments to regulatory cognitive functions correlate with the severity of behavioral disorders [10]. The main clinical manifestation in ALS patients with cognitive and behavioral disorders is rigid thinking[35].

Association Between ALS and Psychotic Disorders. The relationship between ALS and psychotic disorders, in particular schizophrenia, has been confirmed by many clinical studies [40]. In particular, signs of dysfunction of both central and peripheral motoneurons have been demonstrated in patients with schizophrenia [40, 41]. Population studies have shown that patients with ALS have an increased risk of developing schizophrenia at five years (and especially at one year) before diagnosis [42]. On this basis, some authors regard mental disorders as a possible prodrome of ALS [42].

The first symptom of disease was psychosis in 38% of patients with ALS-FTD and a mutation in the *C9orf72* gene. Delusional-hallucinatory experiences were not associated with patients' premorbid background [43]. Patients with combined ALS-FTD and with the *C9orf72* mutation showed characteristic features of behavioral disorders and complex motor stereotypes.

The cognitive impairments seen in ALS are associated with hyperactivation of the secondary somatosensory cortex and impaired integration of sensory information, which are also characteristic of schizophrenia [44]. Transcranial magnetic stimulation studies indicate that schizophrenia involves an increase in the excitability of the prefrontal cortex of the brain due to decreases in the inhibitory effects of subcortical structures on this area, resulting from decreased GABAergic neurotransmission activity. A similar impairment to fronto-subcortical relationships and an increase in the excitability of the cerebral cortex are also observed in ALS, manifesting as speech disorders and reductions in attention and regulatory functions [1, 2, 7].

Affective Disorders in ALS. The incidence of depression in ALS as found in different studies ranges from 0.9% to 75%, [1, 38]. This significant spread in the data is primarily due to study designs (methods for detecting affective disorders, longitudinal or cross-sectional type of study, exclusion of patients with cognitive disorders, etc.). It is possible that some studies mistook phenomena such as apathy, pseudobulbar syndrome with uncontrollable crying, asthenia, and behavioral disorders within FTD as depressive phenomena [6].

The risk of developing depression is significantly increased within the first year of diagnosis of ALS. These data are also supported by more frequent prescription of antidepressants in patients with ALS. However, prospective studies have shown that depression often develops a year before diagnosis of ALS. The risk of developing ALS is 3.6 times higher in patients with depression than in the general population [42, 45]. The same pattern is noted for anxiety and neuroticism, the risks of which are increased both in the prodromal phase of the disease and after diagnosis [7].

Apathy is one of the commonest mental disorders observed in ALS [46]. Caga et al. [47] found apathy in 67% of patients with this disease, of which 71% were mild and 29% were moderate to severe. The main components of

this phenomenon were identified with the aim of clarifying the psychological mechanisms of apathy: these were regulatory apathy (impaired motivation for organizing and planning actions, impaired attention), emotional apathy (impaired emotional motivation, indifference, and emotional neutrality), and initiation apathy (impaired motivation to self-generation in relation to motor or ideatory activity). Impairments of the latter were most marked in patients with ALS. Correlation analysis revealed a connection between decreased initiative and decreased verbal activity, which in turn reflects the ability to generate internal motivations, and emotional apathy, with impairment of emotional perception as part of a decrease in social-cognitive functions [48].

Pseudobulbar syndrome with uncontollable crying and laughter develops as a result of degeneration of central motoneurons. It is more frequently seen in ALS with bulbar onset and is associated with degeneration of the cortico-ponto-cerebellar pathways [49]. The development of affective disorders after diagnosis of ALS is in most cases associated with severe psychological stress reactions. The appearance of affective disorders before the onset of the main signs of disease probably has a more complex mechanism. It has been suggested that anxious-depressive disorders may be a manifestation of the prodromal phase of ALS. They may be based on genetic mechanisms, personality traits, and external factors, as well as patients' socio-economic vulnerability. One hypothesis holds that depression may be the first sign of frontal degeneration, indicating early involvement of the motor and prefrontal cortex in the pathological process in ALS. Another hypothesis is that early involvement of the frontal cortex may lead to cognitive and psychiatric impairments (e.g., apathic-abulic syndrome) which may be misinterpreted as depression. Degenerative mechanisms are likely to play an important role in the development of not only the motor symptoms of ALS, but also depression. This is partly supported by the fact of common risk factors for the development of both conditions. In particular, chronic lead poisoning can be manifest as depressive neuropsychological disorders and signs of ALS. Risk factors also include smoking, viral CNS diseases, and a history of traumatic brain injury. One candidate gene that may be associated with the development of depression in the prodromal phase of ALS is *C9orf72*, discussed above. On the other hand, the relationship between stress associated with the development of the first symptoms of motoneuron damage before the diagnosis of ALS and the development of depression is poorly understood [1, 7].

The literature contains data on the relationship between ALS and other mental disorders – bipolar affective disorder and diseases on the neurosis spectrum, as well as histories of various forms of addictive behavior. Relatives of patients with combined ALS and FTD with the *C9orf72* mutation have an increased incidence of autism spectrum disorders [50]. The clinical picture of combined ALS and FTD often includes signs characteristic of autism: decreases in empathy and social cognitive functions (social intelligence), and particularly impairment to the theory of mind, as well as obsessions, stereotypies, and rigid thinking [6, 51]. Social-cognitive impairments, including impairments to the theory of mind, are detected in around 27% of patients with ALS [52].

The development of these autistic disorders is probably based in a degenerative process involving the medial and orbitofrontal areas of the prefrontal cortex, leading to dysfunction of the fronto-striatal-thalamo-cortical feedback loops [1, 53].

Suicidal Behavior in ALS. The lack of effective treatment and the rapidly progressive course of the disease often lead to feelings of hopelessness and despair in patients with ALS, the formation of suicidal thoughts, and in some cases, suicide attempts [54]. Individuals with ALS have an approximately 5–6 times higher risk of suicide than the general population [55]. The incidence of suicide and suicidal thoughts is higher in the early stages of the disease, in the first months after diagnosis [56]. Disease onset is dominated by the fear of facing the future complications of an incurable disease, and there is a relative preservation of physical capabilities for committing suicide [54].

Among the factors predisposing to the appearance of suicidal thoughts in ALS are financial problems, lack of support from relatives, and the feeling of being a "burden" on the family [57]. At the same time, religiosity and the availability of social support have positive impacts on the quality of life of patients with ALS and reduce the risk of suicide. It is of note that some authors have not found any correlation between ALS-associated cognitive or behavioral impairments and suicidal thoughts [58].

Major depressive disorder predisposes to suicidal behavior in ALS. The expression of thoughts about death by patients with ALS can be regarded as a sign of major depressive disorder [59]. Symptoms of depression are detected in more than a third of patients with ALS [57]. At the same time, not all ALS patients suffering from depression receive appropriate treatment. Timely treatment of depression in this category of patients can be regarded as an important preventive measure against suicidal behavior [57].

Conclusions. Thus, neuropsychiatric manifestations are widespread in patients with ALS. On the one hand, these can be psychogenic in nature, reflecting patients' responses to the incurability of the disease and its steadily progressive course. On the other hand, degeneration of the central motoneurons, leading to dissociation of the frontosubcortical and frontotemporal connections, can lead to the development of mental disorders of an organic nature. In the case of combined ALS and FTD, neuropsychiatric disorders reach a severe level and cause disability in patients. In ALS with predominantly motor manifestations, mental disorders do not reach the degree characteristic of dementia and mainly involve the affective domain.

In clinical practice, when establishing the diagnosis of ALS, it is important to screen for mental disorders in a time-

ly manner, in particular, using the ECAS questionnaire [60]. In patients with combined ALS and FTD, a comprehensive assessment of the behavioral domain and early psychiatric referral are necessary for correction of any impairments identified. In ALS without dementia, especially in the first months after diagnosis, there is a high risk of developing psychogenic affective disorders, which in severe cases can lead to suicide. In this regard, screening of patients for affective disorders and early administration of anxiolytics and antidepressants, if indicated, is justified. Patients with ALS, especially in the later stages, also often experience apathy, which can reduce patients' quality of life and make it difficult to care for them.

Future studies should clarify the molecular genetic and pathophysiological mechanisms of the development of mental disorders in ALS, as well as their place in the clinical picture of the disease. There is a need to elucidate factors other than the *C9orf72* mutation as causes of ALS with predominantly motor manifestations in some patients and ALS with FTD in others. Research evaluating new drugs for the treatment of ALS must address their impact on the mental domain.

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