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DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF GENETIC MARKERS OF MOTOR NEURON DISEASE.

LITERATURE REVIEW.

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Abstract: Genetic studies have significantly expanded the understanding of motor neuron disease and related motor neuron damage. Currently, the TARDBP, SOD1, and FUS genes are listed as the main genetic determinants most associated with the disease, and some sources include mutations in the IL-6 and TBK1 genes involved in the regulation of inflammatory processes among the important genes that cause severe neurodegenerative changes. The existence of interpopulation differences indicates the need to study genetic factors separately in different regions.

Key words: motor neuron disease, amyotrophic lateral sclerosis, TARDBP, SOD1, and FUS genes, cytokine (interleukin 1, 6, tumor necrosis factor α).

Motor neuron disease (MND) is a group of neurologic disorders with severe clinical course, early disability, and high socio-medical importance. Amyotrophic lateral sclerosis (ALS) is particularly prominent among this group of diseases, characterized by progressive neurodegeneration of central and peripheral motor neurons, rapid progression, and leading to disability and early death [Wolfson et al., 2023; Bradford et al., 2024].

According to recent data, although MND is a relatively rare disease, its clinical and social consequences are extremely severe, with most patients developing profound functional impairment within a few years of the onset of symptoms, and respiratory muscle damage is one of the main lethal factors [Bradford et al., 2024; Nijs et al., 2024].

The current literature interprets the etiopathogenesis of this disease as a multifactorial and complex process. In particular, genetic predisposition, protein aggregation, RNA metabolism disorders, oxidative stress, mitochondrial dysfunction, glutamate exotoxicity, axonal transport disorders, proteostasis disorders, neuroinflammation and immune mechanisms play an important role in the development of motor neuron damage [Bradford et al., 2024; Calma et al., 2024]. In this regard, studying the clinical course of the disease in relation to immunological and genetic markers is of great importance from a scientific and practical point of view.

Despite many years of research into the pathogenesis and etiology of NMDA, there is still insufficient information about the causes of the uncontrolled mechanisms of motor neuron death, as well as the trigger factors that trigger this process [8;86-88-p, 14;89-92-p].

Modern views on the pathogenesis of the disease indicate that NMDA belongs to the group of proteinopathies [29;162-164-p,63;9-15-p]. Aggregation of protein deposits in motor neurons is of great importance in the damage of motor neurons [3;12-18-p,117;203-208-p]. At the beginning of the disease, aggregation of mutant proteins that affect the normal structure and their accumulation in large quantities are observed. Later, healthy cellular proteins are involved in this pathological process. This deposit includes pathological proteins TDP-43, C9orf72, SOD-1, FUS, alsin, senataxin, etc. [82;7789-7801-b, 85;4152-b]. The death of motor neurons occurs with impaired immune reactions and the development of inflammation of the nervous tissue. This process is studied in two phases, in which in the initial (early developing) phase the immune system has neuroprotective properties, glial

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cells, macrophages and T-cells try to utilize the dead neurons, and also maintain the viability of cells by stimulating reparative processes. In the second (rapidly developing) phase, there is a deficiency of T-cells with neuroprotective properties, the immune response is weakened, and cytotoxic immune mechanisms are activated, and the process continues with the intensification of inflammatory mechanisms [9;72-79-p, 37;29-35-p].

This cytokine (interleukin 1, 6, tumor necrosis factor α), which causes neuronal destruction, the S3 component of the complement system, and neurotoxic molecules (chemokines, adhesion molecules, proteases) subsequently act as a factor enhancing the degradation of motor neurons [113;2489-2502-p, 115;2014-p,123].

In HNC, the neurotrophic factors of astrocytes: glial neurotrophic factor (glial cell-derived neurotrophic factor, GDNF), nerve growth factor (nerve growth factor, NGF), brain-derived neurotrophic factor, ciliary neurotrophic factor, neurotrophin and vascular endothelial growth factor are insufficient for metabolism, differentiation and function of neurons, and the process enters an irreversible stage [68;72-77-p, 132;2031-2041-p].

There is insufficient information about the systematic influence of these factors in the development of the pathological reaction [15;63-73-p, 134;168-173-p]. It is assumed that these factors act simultaneously or with different levels of activity [38, 42]. Optimization of new drugs that affect the pathogenetic process in the treatment of the disease, based on the results of ongoing molecular genetic research, will serve as the next stage of development [4;6-10-p, 5;145-146-p].

In recent years, the role of neuroinflammation in the pathogenesis of motor neuron disease has been increasingly recognized. In the central nervous system, activation of microglia and astrocytes, involvement of peripheral immune cells, cytokine imbalance, and chronic inflammation have been shown to exacerbate motor neuron damage [Calma et al., 2024; Stacchiotti et al., 2025]. In addition, some studies have identified autoantibodies, proinflammatory mediators, and immune dysregulation in the blood and cerebrospinal fluid of patients, indicating that immune mechanisms are one of the important pathogenetic components in these diseases [The presence and clinical significance of autoantibodies in ALS, 2024; Calma et al., 2024].

The relevance of motor neuron disease (MLD) is also determined by its clinical heterogeneity. In the early stages of the disease, the nonspecificity of clinical symptoms, similarity with other neuromuscular diseases, and phenotypic diversity delay diagnosis.

Current reviews have reported that the diagnostic delay can be around 12 months on average, limiting the possibility of early therapeutic intervention [Irwin et al., 2024]. Therefore, enriching clinical criteria with immunological, neuroimaging and genetic biomarkers remains an important scientific and practical task [Irwin et al., 2024; Khalil et al., 2024].

Biomarker research is one of the most promising areas in this direction. In particular, neurofilament light chain, phosphorylated neurofilament heavy chain and motoneuron and axonal injury are considered promising diagnostic and prognostic biomarkers [Irwin et al., 2024; Khalil et al., 2024; Obara et al., 2025]. This further reinforces the need to evaluate clinical indicators in an integrated manner with laboratory and genetic markers.

Thus, scientific research aimed at determining the diagnostic and prognostic significance of clinical, immunological, and genetic markers of motor neuron disease (MND) is relevant and necessary in terms of early diagnosis of diseases, comparative diagnosis, assessment of disease severity, early

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identification of the risk of disease development, and improvement of patient monitoring systems based on an individual approach [Nijs et al., 2024; Calma et al., 2024; Irwin et al., 2024].

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