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Features of Autoimmune Disorders in Cerebral Paralysis in Children

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Annotation: Cerebral palsy (CCP) is a group of persistent movement and posture developmental disorders that cause activity limitations associated with non-progressive damage to the developing brain of the fetus or infant. The prevalence of cerebral palsy is 2-3 cases per 1000 live births, making this disease one of the leading causes of childhood disability worldwide. In recent years, researchers' interest in studying the immunological aspects of cerebral palsy pathogenesis has significantly increased. The accumulated data indicate that immune system dysfunction can play a significant role in both the development and progression of neurological disorders in this disease. Special attention is paid to the study of autoimmune mechanisms that can contribute to the maintenance of the chronic inflammatory process in the nervous tissue and exacerbate existing neurological deficits.

Keywords: Cerebral palsy in children, autoimmune disorders, neural inflammation, autoantibodies, cytokines, immune system, perinatal CNS damage, microglia, blood-brain barrier, neuroimmune interactions, inflammatory mediators, regulatory T-cells, molecular mimicry, oxidative stress, neurodegeneration.

Relevance. Autoimmune disorders in cerebral palsy can manifest as the production of autoantibodies to various components of the nervous tissue, disruption of the balance of pro- and anti-inflammatory cytokines, as well as dysfunction of the regulatory mechanisms of the immune system. Identifying and understanding these mechanisms is of fundamental importance for developing new approaches to diagnosis, predicting disease progression, and optimizing therapeutic strategies.

Perinatal hypoxia, intrauterine infections, and other factors leading to cerebral palsy can cause not only direct damage to brain tissue but also trigger a cascade of immunological reactions, including microglia activation, neural inflammation, and the formation of an autoimmune response. These processes can persist for a long time after primary damage, contributing to the progression of neurological disorders.

Despite the growing interest in this problem, many aspects of autoimmune disorders in cerebral palsy remain insufficiently studied. Further research into the mechanisms of autoimmune reactions development, their relationship with the clinical manifestations of the disease, and the development of methods for their correction are required. Understanding the characteristics of autoimmune disorders in cerebral palsy can open up new possibilities for a personalized approach to treating patients and improving their quality of life.

Physiological autoimmune reactions are not pathological in nature, but perform important regulatory functions under normal conditions. Their difference from pathological forms of autoimmunity lies not in qualitative, but in quantitative and contextual characteristics - the severity, duration, and spectrum of involved cells and mediators [5,6]. From this point of view, the detection of autoantibodies in blood serum should not be automatically interpreted as a marker of the pathological process. On the contrary, there is a significant amount of data indicating the constant presence of various natural autoantibodies in the body of healthy people, where they perform the functions of molecular clearance, recognition of aging or transformed cells, regulation of apoptosis, and modification of cellular signaling.

An important and promising area for the development of modern medicine is the identification of early markers of pathological processes to create new technological approaches for early diagnosis,

prevention, and treatment [3]. A number of researchers support the autoimmune theory of cerebral palsy - one of the most severe disabling diseases of childhood.

The aim of the study was to analyze the level of natural autoantibodies to neurospecific proteins in patients with cerebral palsy.

Materials and methods. The study included patients with cerebral palsy (DSP; n = 110) and a practically healthy control group comparable in age-sex characteristics (n = 30). Venous blood collection from patients was carried out upon initial admission to the hospital before the start of drug therapy, which excluded the influence of treatment on the studied indicators.

Quantitative assessment of serum immunoreactivity of natural neurotropic autoantibodies (NAAT) of the IgG class was carried out by solid-phase enzyme-linked immunosorbent assay using certified ELI-N-Test and ELI-N-Complex-12 kits (OOO "Immunculus," Moscow) according to the method of A. B. Poletaev [8, 9]. The antigen panel included: structural components of neurons - NF200 protein; glial markers - GFAP; myelin proteins of nerve fibers - OBM; Ca-binding protein S100; voltage-dependent Ca2+ channel; β-endorphin; neurotransmitter receptors: cholinoreceptor (nAChR), GABA receptors, glutamate NMDA and AMPA receptors, dopamine, serotonin, and μ-opioid receptors.

Primary results were entered into individual observation maps and an electronic database (Microsoft Excel 2010). The normality of the distribution was checked using the Shapiro-Wilk criterion. With a normal distribution, the data were presented in the format M ± m (mean ± error of the mean) or μ ± SD (mean ± standard deviation) and the group indicators were compared using the two-way Student's t-test. In all cases, the critical significance level was taken as $p < 0.05$.

The concentration of autoantibodies was expressed in conditional units, reflecting the percentage deviation of the sample's optical density from the standard serum immunoreactivity.

Results and discussion. After the conducted immunological studies, the level of the natural neurospecific autoantibody profile in patients with cerebral palsy was determined (Table 1). The obtained results - simultaneous and significant increase in autoantibody titers to NF-200, total myelin protein (TMP), GFAP, S100, voltage-dependent Ca2+-channel, β-endorphin, and a whole range of neurotransmitter receptors - convincingly confirm polyantigenic autoimmune reactivity in cerebral palsy in children. Below are the main conclusions and their clinical significance.

Table 1. The level of neurospecific autoantibodies in the blood serum of the examined children with cerebral palsy (standard units)

Auto-AT	Main group (n=110)	Control group (n=30)	% increase
AT to NF200	84,23 ± 15,18	32,98 ± 9,34	+155%
AT to GFAP	104,57 ± 29,32	39,33 ± 16, 11	+166%
AT to S100	79,42 ± 17,23	48,05 ± 12,54	+65%
AT to CBM	117,76 ± 31,30	58,23 ± 17,01	+102%
AT to voltage-dependent Ca-channel	87,12 ± 12,43	43,08 ± 11,32	+104%
AT to H-cholinergic receptors	73,6 ± 14,1	29,56 ± 9,37	+149%
AT to glutamate receptors	91,38 ± 22,70	42,55 ± 21	+115%
AT to GABA receptors	75,30 ± 21,43	45,25 ± 13,22	+66%
ATP to dopamine receptors	81,30 ± 14,54	38,32 ± 10,9	+112%
AT to serotonin receptors	101,32 ± 21,49	51,32 ± 12,4	+97%

In all ten studied auto-AT sera concentrations in patients with cerebral palsy were statistically and clinically significantly higher than the control values. The most pronounced effects are observed for antibodies to NF200 (neurofilament of the heavy subunit) and Ca-dependent channels, N-cholinergic receptors, and dopamine receptors. These indicators indicate massive autoimmune sensitization to both structural proteins of the neuronal cytoskeleton and key receptor-ion complexes.

When examining the level of autoantibodies to structural antigens such as NF200, it was found to be 2.6 times higher than the control level, indicating damage to myelinated axons. A high titer correlates with the severity of axonal damage and can serve as an indicator of diffuse axonotomy, characteristic of hypoxic-ischemic and traumatic variants of cerebral palsy.

Autoantibodies to GFAP and S100 proteins - markers of astro- and microglial activation - were found to be 2.7 times and 1.65 times higher than the control values. Their increase reflects the phenomena of glial remodeling of the cortex and white matter; a moderate difference for S100 indicates a more variable contribution of the glio-vascular link. The processes we identified, characterized by increased autoantibody reactivity to glial proteins GFAP and S-100, indicate pronounced activation of the astrocytic link of neuroglia. This fact correlates with the pathomorphological data presented in Table 2 and emphasizes the morphofunctional significance of the identified immune shifts. A number of independent studies indicate that destructive changes in astrocytes in cerebral palsy have an immunocompromised nature - the obtained results fully confirm this concept. As is known, reactive astrocytopathy is triggered in brain tissue in response to neuronal damage of various origins, acting as a crucial component of the secondary neural inflammatory cascade. The double increase in anti-ABM (total myelin protein) confirms the demyelinating component of the pathogenesis, increasing the emphasis on the chronic autoimmune damage to oligodendrocytes, which partially explains the delayed myelination and impaired impulse conduction, reflecting active demyelinating processes, confirming the hypothesis of secondary myelinolysis due to perinatal hypoxic ischemic damage.

Simultaneous increase in antibodies to axonal, glial, myelin, and receptor antigens confirms polyantigenic autoimmune reactivity in children with cerebral palsy. High levels of autoantibodies to NF200, Ca-channels, nAChR, and DA-receptors allow these markers to be considered as priority for individual monitoring and assessment of the effectiveness of immunocorrective therapy.

Table 2. Increase in autoantibodies to membrane receptors and ion channels and their pathophysiological significance

Group	Growth	Pathophysiological significance
Voltage-dependent Ca-channels	+102 %	Disruption of Ca2+ entry leads to a disbalance of excitability and neurotransmission, exacerbating dystonic phenomena.
N-cholinery.	+149 %	Blockade/modulation of α7-nAChR reduces synapse plasticity and motor map reorganization potential.
Glutamate fish.	+115 %	Persistent excitation of NMDA/AMPA pathways increases exitotoxicity and forms hypertensive patterns.
GAMK-res.	+66 %	The weakening of inhibitory GABA potentials contributes to spasticity; a relatively small increase (d ≈ 1.5) can reflect the compensatory up-regulation of receptors.
Dopamine and serotonin receptors.	+112 % / +97 %	DA- and 5-HT signal suppression is associated with motor rigidity, mood disturbance, and sleep; the detected titers support multineuromediator dysfunction.

The combination of structural and functional (receptor) auto-AT indicates a two-phase lesion: primary hypoxic-ischemic/mechanical, followed by autoimmune neurotransmission modulation, which can explain both persistent motor impairments and cognitive-emotional disorders.

As is known, the main mediators of excitation and inhibition processes in the central nervous system are glutamate (Glutamate) and γ-aminobutyric acid (GABA). These amino acids form a dynamic link that ensures a "liquid" (humoral) connection between the immune, neuroendocrine systems, and the brain [1, 12]. Glutamothergic and GAMK-ergic neurotransmission are crucial for the formation of a stress response, the transmission of pain impulses, the regulation of breathing, and the processes of memory and learning [1, 9].

Immunoenzymatic analysis showed a significant increase in the titers of autoantibodies to glutamate (Glu-R) and GABA-R receptors in patients with initial stroke (II) compared to the control group (Table. 1). An increase in the serum concentration of these autoantibodies reflects the imbalance of excitation and inhibition in the nervous system, which potentiates the development of functional disorders characteristic of this pathology.

Conclusion.

Children with cerebral palsy demonstrate a significant (×1.6-2.7) and clinically significant increase in the spectrum of neurospecific autoantibodies, reflecting combined axonal-gliac damage, demyelination, and dysfunction of key neurotransmitter systems. These data reinforce the concept of autoimmune contribution to the chronicity and heterogeneity of cerebral palsy clinical manifestations and justify the feasibility of including auto-AT data in a comprehensive biomarker panel screening for stratification of patients based on the risk of severe motor and cognitive outcomes and for the early selection of candidates for immunotherapy (intravenous immunoglobulin, plasmapheresis, anti-B-cell drugs).

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