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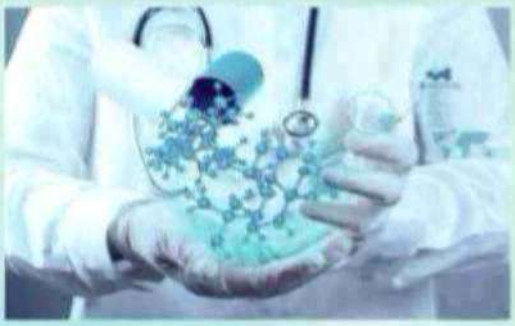

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NEW DAY IN MEDICINE

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НАРУШЕНИЯ АУТОИММУНИТЕТА ПРИ ДЕТСКОМ ЦЕРЕБРАЛЬНОМ ПАРАЛИЧЕ

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✓ ***Резюме***

Были изучены уровни естественных аутоантител к нейроспецифическим белкам у 110 больных с детским церебральным параличом (основная группа) сравнительно с контрольной группой практически здоровых детей соответствующего возраста. Дети с ДЦП демонстрируют значимое (×1,6–2,7) и клинически значимое повышение спектра нейроспецифических аутоантител, отражающее комбинированное аксонально-глиальное повреждение, демиелинизацию и нарушение работы ключевых нейромедиаторных систем. Эти данные усиливают концепцию аутоиммунного вклада в хронизацию и гетерогенность клинических проявлений ДЦП и обосновывают целесообразность включения данные аутоАТ в комплексный биомаркерный панельный скрининг для стратификации пациентов по риску тяжёлых двигательных и когнитивных исходов и для ранней селекции кандидатов на иммунотерапию (в/в иммуноглобулин, плазмаферез, анти-В-клеточные препараты)

Ключевые слова: детский церебральный паралич, аутоантитела, нейроспецифические белки, иммунореактивность

BOLALAR SEREBRAL FALAJIDA AUTOIMMUNITETDAGI BUZULISHLAR

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✓ ***Rezyume***

Neyrospesifik oqsillarga tabiiy autoantilelalar darajasi bolalar serebral falaji bo'lgan 110 bemorda (asosiy guruh) tegishli yoshdagi deyarli sog'lom bolalarning nazorat guruhiga nisbatan o'rganildi. serebral falaji bilan og'rigan bolalarda neyrospesifik autoantilelalar spektrida sezilarli (x1,6-2,7) va klinik jihatdan sezilarli o'sish kuzatiladi, bu aksonal-glial shikastlanish, demyelinatsiya va asosiy neyrotransmitter tizimlarining disfunktsiyasini aks ettiradi. Ushbu ma'lumotlar bolalar serebral falaji klinik ko'rinishlarining surunkaliligi va geterogengligi va autoantitelalar haqidagi ma'lumotlar kontseptsiyasini mustahkamlaydi va bemorlarni og'ir motor va kognitiv natijalar xavfi bo'yicha stratifikatsiya qilish va immunoterapiya uchun nomzodlarni erta tanlash uchun biomarkerlar panelini keng qamrovli skriningga kiritish maqsadga muvofiqligini asoslaydi. (immunoglobulin, plazmaforez, B hujayralariga qarshi dorilar)

Kalit so'zlar: serebral falaj, autoantitelalar, neyrospesifik oqsillar, immunoreaktivlik

AUTOIMMUNITY DISORDERS IN INFANTILE CEREBRAL PARALYSIS

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✓ ***Resume***

The levels of natural autoantibodies to neurospecific proteins were studied in 110 patients with cerebral palsy (main group) compared with a control group of practically healthy children of the corresponding age. Children with cerebral palsy demonstrate a significant (×1.6–2.7) and clinically significant increase in the spectrum of neurospecific autoantibodies, reflecting combined axonal-glial damage, demyelination and disruption of key neurotransmitter systems. These data reinforce the concept of an autoimmune contribution to the chronicity and heterogeneity of clinical manifestations of cerebral palsy and substantiate the feasibility of including these auto-ABs in a comprehensive biomarker panel screening for stratification of patients by risk of severe motor and cognitive outcomes and for early selection of candidates for immunotherapy (i.v. immunoglobulin, plasmapheresis, anti-B-cell drugs)

Key words: cerebral paralysis, autoantibodies, neurospecific proteins, immunoreactivity

Relevance

Physiological autoimmune reactions are not pathological in nature, but perform important regulatory functions under normal conditions. They differ from pathological forms of autoimmunity not in qualitative, but in quantitative and contextual characteristics - severity, duration and spectrum of involved cells and mediators (1,3,5,6). From this point of view, detection of autoantibodies in blood serum should not be automatically interpreted as a marker of a pathological process. On the contrary, there is a significant array 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 (2,4,8). An important and promising direction in the development of modern medicine is the determination of early markers of pathological processes to create new technological approaches for early diagnosis, prevention and treatment (3,7). A number of researchers speak out in favor of the autoimmune theory of cerebral palsy, one of the most severe disabling diseases of childhood**.**

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

Materials and methods

In the blood serum samples of all observed patients with cerebral palsy, as well as in the blood samples of the control group (n=30), the serum immunoreactivity of natural neurotropic autoantibodies in the blood serum was quantitatively determined using the ELI-N-Test reagent kit (Immunculus LLC). The kit is used to determine IgG autoantibodies interacting with antigens of neurons (NF200 protein), glial cells (GFAP), nerve fibers (MBP), Ca-dependent protein (S100), voltage-dependent Ca channel, β-endorphin and neurotransmitter receptors (cholinergic receptors, GABA receptors, glutamate NMDA and AMPA receptors, dopamine receptors, serotonin receptors, m-opiate receptors). The content of neurotropic autoantibodies (NAAT) was determined according to the method of A.B. Poletaev using the standard solid-phase enzyme immunoassay ELI-N-Test and the test kit of the same name from MIC Immunculus (Russia) [8, 9]. The level of serum concentration of e-AT for each neuroantigen was expressed in arbitrary units (i.e., percentage deviation from the standard serum IR).

The results were recorded in individual patient questionnaires and entered into an electronic database in Microsoft Excel 2010. Conventional methods of dispersion statistics were used. The results were presented as M (mean) ± m (error) and μ (mean) ± (standard deviation). After checking the normality of the data distribution, a quantitative analysis was performed using Student's t-test.

Immunological examination of children with cerebral palsy was carried out upon admission of patients to the hospital, before the start of treatment. The immunoreactivity profiles of natural regulatory auto-ABs, which most informatively reflect quantitative changes (content) of their individual variants [1], as well as the amplitude of fluctuations of the studied parameters were assessed in blood serum using the ELI-N-Complex-12 test kits (MIC Immunculus, Moscow), according to the manufacturer's instructions. In this case, using solid-phase ELISA, changes in the content of class G auto-ATs interacting with antigens of the microstructures of the nervous tissue and also reflecting the general reactivity of the immune system (a total of 12 auto-ATs) were determined.

Results and discussions

After conducting immunological studies, the levels of the profile of natural neurospecific autoantibodies in patients with cerebral palsy were determined. These data indicate multiple immunopathological processes in children with cerebral palsy, involving both axons and myelin, as well as astrocytic glia and neurotransmitter regulation systems.

In all ten studied auto-ATs, seroconcentrations in patients with cerebral palsy statistically and clinically significantly exceed the control values. The most pronounced effects are observed for antibodies to NF200 (neurofilament 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, a 2.6-fold excess of the control level was revealed, indicating damage to myelinated axons. A high titer correlates with the severity of axonal damage and can serve as an indicator of diffuse axonotmia, 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 exceed the control values by 2.7 and 1.65 times. 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 gliovascular link. The detected pathological processes associated with the activation of astrocytic glia (increased levels of auto-AB to GFAP and S-100 proteins) confirm the corresponding data on the pathomorphological significance of the detected changes. A number of studies have suggested that pathological processes in astrocytes in this disease are associated with immune changes, which is confirmed by the results of this study. As is known and noted earlier, the processes of astrocytic glia activation are triggered in brain tissues in response to damage to neurons of various origins.

A twofold increase in anti-MBP (total myelin protein) confirms the demyelinating component of pathogenesis, increasing the emphasis on chronic autoimmune damage to oligodendrocytes, which partly explains the delay in myelination and impaired impulse conduction, reflecting active demyelinating processes, confirming the hypothesis of secondary myelinolysis due to perinatal hypoxic ischemic injury. reflects demyelination characteristic of post-hypoxic and inflammatory damage to the white matter in cerebral palsy.

A 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, DA receptors allow us to consider these markers as a priority for individual monitoring and evaluation of the effectiveness of immunocorrective therapy. The combination of structural and functional (receptor) auto-AT indicates a biphasic injury: primary hypoxic-ischemic/mechanical, then autoimmune modulation of neurotransmission, which can explain both persistent motor disorders and cognitive-emotional disorders. Glutamate and γ-aminobutyric acid (GABA) are known to be mediators of physiological processes of excitation and inhibition. These amino acids provide a fluid connection between the immune and neuroendocrine systems and the brain. These biomolecules are most important in the formation of the body's stress response, transmission of pain impulses, and are also responsible for proper breathing, memory maintenance, learning ability, etc. Immunoassay showed that the levels of autoantibodies for Glu-R and GABA-R in patients with ischemic stroke were significantly increased compared to the values obtained in the control (Table 1). An increased level of autoantibodies against Glu-R and GABA-P indicates disturbances in excitation and inhibition processes in the nervous system.

Conclusion

1. Children with cerebral palsy demonstrate a significant (×1.6–2.7) and clinically significant increase in the spectrum of neurospecific autoantibodies, reflecting combined axonal-glial damage, demyelination, and disruption of key neurotransmitter systems.
2. The above data reinforce the concept of an autoimmune contribution to the chronicity and heterogeneity of clinical manifestations of cerebral palsy and substantiate the advisability of including these auto-ABs in a comprehensive biomarker panel screening for stratification of patients by risk of severe motor and cognitive outcomes and for early selection of candidates for immunotherapy (IV immunoglobulin, plasmapheresis, anti-B-cell drugs).

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