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Dynamics of the Markers to the Central Nervous System Damage in the Treatment of Patients with Autism

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Objectives. Studies to identify serologic markers of the nature of protein associated with the development of autism spectrum disorders are relevant for the improvement of diagnostic methods. The relationship between the quantitative content of phosphorylated tau protein and light chains of neurofilaments in the blood of children with autism and changes in the clinical picture of the disease during therapeutic interventions was revealed.
Methods. Children aged from 3 to 12 years with diagnoses: infantile autism — 23 children; impaired psycho-verbal development due to organic brain damage — 34; conditionally healthy children — 15 people were studied. Anamnestic data was collected, an objective examination was conducted, and medical records were analyzed. The study utilized: the Denver Developmental Screening Test, the Childhood Autism Rating Scale (CARS); Human Tau [pT181] phospho-ELISA Kit system test (KHO0631, USA), as well as the Human Neurofilament-Light Chain (NFL) ELISA Kit (EiAab, USA) for the quantitative determination of the phosphorylated isoform of tau protein and light chains of neurofilaments in blood samples by enzyme-linked immunoassay. The statistical processing of data was performed using the Mann-Whitney, Kruskal-Wallis, and Wilcoxon tests. Qualitative features were analyzed using Fisher's criterion.
Results. When studying the quantitative content of phosphorylated tau protein in the blood plasma and neurofilament light chains in the blood serum over time in 18 patients with autism, a significant decrease in the content of phosphorylated tau protein ($p < 0.001$, Wilcoxon test) and neurofilament light chains ($p = 0.007$, Wilcoxon test) was revealed when prescribing pathogenetic treatment with a positive effect from therapy. An example of a clinical case is presented.
Conclusions. It is shown that the determination of the quantitative content of markers of central nervous system damage in blood can be used to assess changes in the functional state of its neuronal and axonal apparatus under the influence of therapy in children with autism. It is possible to further develop the research using the results obtained in the comparison of clinical, neuropsychological and biochemical indicators in assessing the dynamics of the clinical picture of the disease.

***Keywords*:** autism; autistic spectrum disorders (ASD); markers of central nervous system damage; phosphorylated tau protein; neurofilament light chain; axonal apparatus; pathogenetic treatment; dynamics of the clinical picture

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Динамика уровня маркеров повреждения центральной нервной системы при лечении пациентов с аутизмом

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Актуальность и цель. Исследования с целью выявления серологических маркеров белковой природы, ассоциированных с развитием расстройств аутистического спектра, являются актуальными для совершенствования методов диагностики. Выявлялась взаимосвязь между количественным содержанием фосфорилированного тау-белка и легких цепей нейрофиламентов в крови у детей с аутизмом и изменением клинической картины заболевания при терапевтических вмешательствах.

Методы и методики. Исследовались дети в возрасте от 3-х до 12-ти лет с диагнозами: детский аутизм — 23 ребенка; нарушение психоречевого развития вследствие органического поражения головного мозга — 34; условно здоровые дети — 15 человек. Проведен сбор анамнестических сведений, объективный осмотр, анализ медицинской документации. При патопсихологическом исследовании использованы: Денверский скрининговый тест, Рейтинговая шкала аутизма у детей (CARS); тест системы Human Tau [pT181] phosphoELISA Kit (KHO0631, США), также Human Neurofilament-Light Chain (NFL) ELISA Kit (EiAab, США) для количественного определения фосфорилированной изоформы тау-белка и легких цепей нейрофиламентов в образцах крови методом иммунноферментного анализа. Статистическая обработка данных проводилась с применением критериев Манна-Уитни для двух несвязанных выборок, Крускала-Уоллиса для нескольких несвязанных выборок, Вилкоксона для двух связанных выборок. Анализ качественных признаков проводился с использованием критерия Фишера.

Результаты. При исследовании количественного содержания в плазме крови фосфорилированного тау-белка и легких цепей нейрофиламентов в сыворотке крови в динамике у 18 пациентов с аутизмом было выявлено достоверное снижение содержания фосфорилированного тау-белка ($p < 0,001$, Критерий Вилкоксона) и легких цепей нейрофиламентов ($p = 0,007$, Критерий Вилкоксона) при назначении патогенетического лечения с положительным эффектом от терапии. Результаты исследования продемонстрированы на реальном клиническом примере.

Выводы. Показано, что определение количественного содержания маркеров повреждения центральной нервной системы в крови может применяться при оценке изменения функционального состояния ее нейронального и аксонального аппарата под влиянием проводимой терапии у детей с аутизмом. Возможно дальнейшее развитие исследований с использованием полученных результатов при сопоставлении клинических, нейропсихологических и биохимических показателей при оценке динамики клинической картины заболевания.

Ключевые слова: аутизм; расстройства аутистического спектра (РАС); маркеры повреждения центральной нервной системы; фосфорилированный тау-белок; легкие цепи нейрофиламентов; аксональный аппарат; патогенетическое лечение; динамика клинической картины

Финансирование: Исследование выполнено при финансовой поддержке Белорусского республиканского фонда фундаментальных исследований (проект № М21-087).

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Introduction

Autism is among the most severe, disabling and socially significant mental disorders. The causes of autism are still unclear. According to modern ideas, it is one of the idiopathic diseases, the etiologic prerequisites of which are the joint action of genetic and exogenous (environmental) factors [20; 22; 23; 25]. Autism is a disorder arising from a disorder of brain development. It is characterized by a severe and comprehensive deficit of social interaction and communication, as well as limited interests and repetitive stereotyped actions [1; 10].

For a long time, early childhood autism, in the classifiers of ICD-10 (International Classification of Diseases, 10th revision) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders), belonged to the group of disorders of psychological development which is quite diverse in composition. In 2013, the concept of autism changed. In DSM-V, the term "autism spectrum disorders" appeared, including autism (Kanner's syndrome), Asperger's syndrome, childhood disintegrative disorder, and nonspecific pervasive developmental disorder [10].

Epidemiologic studies show that the prevalence of autism spectrum disorders (ASD) is increasing worldwide every year. This problem and the issues of helping people with autism are the focus of UN materials on the occasion of World Autism Awareness Day in 2018 [7]. The increase in the prevalence of autism from the 60s to the 90s of the XX century — from 4 to 40 per 10 thousand children, has attracted the attention of researchers around the world. There is an opinion that this dramatic increase is not due to a true increase in the number of cases of this disease. The high prevalence of ASD in children born between 1980 and 1991 is obviously due to the expansion of diagnostic criteria and the improvement of diagnostic tools [17]. According to official statistical data, the number of children with autism spectrum disorders under dispensary supervision in the Republic of Belarus at the end of 2022 amounted to 3383 [2].

The emergence of autism is associated with a disorder of brain development. There is a need to implement methods of the early detection of ASD in order to timely include children with this pathology and their parents in support programs to mitigate the depth of mental and behavioral disorders. Recent research work on the etiology of autism spectrum disorders focuses on the mechanisms of the development of symptoms of this condition. Neurophysiologic studies suggest the impaired function of mirror neurons, the structure of the cerebellum and neurotransmitter connections in its region, impaired synaptic connections, and the impaired differentiation of neurons of different brain regions [4]. Understanding the mechanisms of ASD development will help to explain the comorbidity of autistic disorders and other diseases (epilepsy, psoriasis, autoimmune diseases). It is relevant to conduct studies to identify the serological markers of the protein nature associated with the development of autism spectrum disorders.

Tau protein forms the cellular cytoskeleton, but if tau protein is excessively phosphorylated, it stops performing its functions and gathers into neurofibrillary tangles, which leads to neuronal damage [18]. Light chains of neurofilaments are normally considered as an intracellular structural part of nerve outgrowths, however, during the processes of axonal damage and neurodegeneration they penetrate into the intercellular space [19].

Data from scientific publications have shown increased levels of Serum 100 Beta Protein (S100B), tau, Neuron-specific Enolase (NSE), active caspase-3, M30 and M65 proteins, and NfL in blood in children with ASD [9; 12; 13; 19]. In addition, a positive correlation was determined between the S100B and tau levels, M30 and M65 levels, between the tau and NSE levels, and between NSE and M65 levels. An inverse correlation was determined between patient age and M65 levels. These results suggest the presence of neuronal, axonal and glial cell damage in children diagnosed with ASD, and that apoptosis and necrosis are enhanced and may be more intense, especially in younger children [11; 14; 15; 21]. This also confirms the importance of the effective early diagnosis and intervention in autism for a timely and effective compensation of the identified disorders.

Modern highly sensitive methods make it possible to determine the tau protein and light chains of neurofilaments not only in cerebrospinal fluid but also in blood serum, which opens up opportunities for their routine diagnosis in clinical practice.

A study was conducted to identify the relationship between the quantitative content of phosphorylated tau-protein and light chains of neurofilaments in the blood of

children with autism and changes in the clinical picture of the disease during therapeutic interventions.

Methods

The study included children aged 3 to 12 years with the following diagnoses: childhood autism (F 84.0 according to ICD-10) — 23 children; impaired psycho-speech development due to organic brain syndrome — 34 children; and 15 conditionally healthy children. Informed parental consent was obtained for the participation of the children in the study. The criteria for the exclusion of patients from the study: a severe concomitant somatic pathology.

The patients were divided into three groups: the main group and two comparison groups. The main group included patients diagnosed with childhood autism (F84.0 according to ICD 10). Comparison group 1 — patients diagnosed with impaired psycho-speech development due to organic brain syndrome. Comparison group 2 — healthy children.

Anamnestic data was collected, an objective examination was performed, and medical records were analyzed.

The pathopsychological study included the use of the following methods: Denver Developmental Screening Tests (DDST), Childhood Autism Rating Scale (CARS) [8].

The following commercial test systems were used to quantify the level of markers of the neurodegeneration and axonal damage of neuronal cells in clinical material (blood): Human Tau [pT181] phospho Elisa Kit (KHO0631, USA), Human neurofilament Light (NF-L) chain Elisa Kit (EiAab, USA). The quantitative content of phosphorylated tau protein in the blood plasma samples, the quantitative content of neurofilament light chains in the blood serum samples of children included in the study were determined.

A clinical case was selected and analyzed on the basis of medical record extracts, as well as a registration card specifically designed for the study. The recommendations of The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development were followed. The study was conducted in accordance with the World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects and the requirements of the Guideline of Good Clinical Practice (ICH GCP). Informed consent was obtained from the patient's mother for treatment, participation in the study and the subsequent publication of anonymized scientific data.

Methods of statistical data processing using nonparametric criteria were also used. The statistical processing of the data was performed using the IBM SPSS Statistics v. 23.0 (IBM Corporation, USA) software package.

Results and Discussion

A clinical pathopsychological study of the children in the formed groups was conducted (see Table 1).

The results of the Denver Developmental Screening Test in the main group showed statistically significant differences in the frequency of deviations in individual development ($p<0.05$, Fisher's ( ) criterion), in fine motor adaptive activity ($p<0.01$, Fisher's ( ) criterion), and in speech development ($p<0.05$, Fisher's ( ) criterion) between the main group 1 and comparison group 1. In comparison group 2, the indicators of this study corresponded to the age norm. According to the results of testing the children of the main group using the Child Autism Rating Scale (CARS), which takes into account the frequency and intensity of observed behavioral reactions, the difference in the total score between the main group 1 and comparison group 1 was statistically significant ($p<0.001$, Mann-Whitney test) (see Table 2)

According to the results of the quantification of the markers of neurodegeneration in the blood of children in the studied groups, there were no statistically significant differences between the groups in the quantitative content of phosphorylated tau protein in the blood plasma ($p=0.221$, Kruskal-Wallis test) and light chains of neurofilaments in the serum ($p=0.574$, Kruskal-Wallis test) (see Table 3).

Table 1

Results of complex clinical diagnostics

Index	Main group (n=23)	Group comparisons 1 (n=34)	Group comparisons 2 (n=15)
Average age	6±0,4	7±0,4	6±0,4
Gender (boys/girls)	20/3	26/8	13/2
History (burdened/no)	20/4	15/19	15/0
Family and living conditions (satisfactory/not)	23/0	34/0	15/0
Physical development (normal/not)	23/0	30/4	15/0
Concomitant diseases (yes/no)	23/0	34/0	15/0
Laboratory data (normal/no)	23/0	34/0	15/0

Table 2

Pathopsychological examination data

Group, statistical criterion	Denver screening test (there are deviations, people (%))				Children Autism Rating Scale (CARS) scores
	Individual development	Fine motor-adaptive activity	Speech development	Gross motor skills	
Main group (n=23)	17 (74%)	15 (65%)	17 (74%)	10 (44%)	35,1±0,9 Me=35,0 [33,3; 36,8]
Group comparisons 1 (n=34)	17 (50%)	9 (27%)	15 (44%)	9 (27%)	19,7±1,8 Me=17,0 [16,1; 23,3]
Group comparisons 2 (n=15)	0	0	0	0	0
Fisher's criterion (φ) Mann-Whitney test (U) group 1, group 2	φ=0,1,845 p<0,05	φ=2,956 p<0,01	φ=2,282 p<0,05	φ=1,326 p>0,05	U=93,5 p<0,001

Note: Me — median, [ ] — interquartile range, p — significance level.

Table 3

Quantitative content of phosphorylated tau protein in blood plasma samples, neurofilament light chains in blood serum samples of children included in the study

Group, statistical test	Phosphorylated tau protein, pg/ml	Neurofilament light chains, pg/ml
Main group (n=23)	53,85±9,65 Me=48,4 [20,7; 64,1]	25,29±3,07 Me=20,7 [14,1; 36,3]
Group comparisons 1 (n=34)	56,86±10,31 Me=38,1 [16,1; 81,7]	13,09±3,88 Me=0,3 [0,3; 19,35]
Group comparisons 2 (n=15)	26,31±3,42 Me=21,2 [16,4; 40,1]	3,29±0,88 Me=2,2 [0,3; 6,7]
Kruskal-Wallis test, groups 1–3	H=4,722 p=0,094	H=3,079 p=0,215

Note: Me — median, [ ] — interquartile range, p — significance level.

However, when studying the quantitative content of phosphorylated tau-protein and light chains of neurofilaments in the blood in dynamics, a significant decrease in the content of phosphorylated tau-protein ($p < 0.001$, Wilcoxon's test) and light chains of neurofilaments ($p = 0.007$, Wilcoxon's test) was revealed in 18 out of 23 patients of the main group, who had a positive effect of the therapy aimed at improving the functional state of the brain (see Table 4).

We demonstrate the results of the study on a clinical example.

Table 4

Quantitative content of phosphorylated tau protein in blood plasma samples, neurofilament light chains in blood serum samples of children included in the study over time

Group/ Treatment Effect	Phosphorylated tau protein, pg/ml		Wilcoxon test	Neurofilament light chains, pg/ml		Wilcoxon test
	before treatment	after treatment		before treatment	after treatment	
Main group / with improve-ment	58,7±11,9 Me=48,6 [20,0; 67,0]	22,0±2,7 Me=16,6 [13,7; 35,2]	W= –3,680 p < 0,001	26,5±4,5 Me=28,6 [5,8; 39,8]	12,7±2,9 Me=11,6 [2,5; 16,4]	W = –2,675 p = 0,007
Main group / without dynamics	36,2±9,0 Me=27,8 [19,5; 57,3]	37,2±10,4 Me=26,6 [20,8; 58,9]	W= –0,405 p = 0,686	37,0±10,4 Me=48,6 [14,0; 54,3]	29,4±7,1 Me=24,3 [16,5; 44,8]	W = –1,214 p = 0,225

Note: Me — median, [ ] — interquartile range, p — significance level.

Clinical Example

The child D.K. is 5 years and 10 months old, born from a first pregnancy. According to the mother, the pregnancy was without complications, and the labor was normal. Discharged from the hospital on the fifth day, the feeding is natural (breastfeeding). He was immunized in accordance with the established procedure. According to the mother, the child developed normally until the age of 1.5 years. Then the parents paid attention to peculiarities in his behavior: he did not look into the eyes, did not respond to his name, constantly repeated manipulations with a doorknob, lacked an index gesture. In the city clinical children's psychiatric clinic, a doctor-psychiatrist-narcologist diagnosed the child with autism. Speech therapy and psychological corrective measures were carried out, with no effect. The child's documents were submitted to the medical rehabilitation expert commission to identify a disability group. MREC conclusion: the child is with a disability, the degree of health loss is 3rd.

At the parents' request, the patient was referred to the Republican Scientific and Practical Center for Mental Health. The mother complained about the child's lack of speech, hyperactivity, inattentiveness, a lack of contact, constant manipulations with a door handle, a lag in the child's mental development.

At the appointment: The child does not follow simple instructions. Responds to his name if persistently addressed by mother. Visual contact is difficult, stereotypical movements are present, restlessness. Speech is not developed: he pronounces separate sounds. The understanding of addressed speech is non-existent. Self-care skills are partially developed. The index gesture is absent. Play activity is not formed. He is not selective in eating.

The parents signed informed consent for participation in the study.

Pathopsychological testing was prescribed for the patient. Along with this, a blood analysis was performed to determine the levels of the markers of central nervous system damage.

The analysis of the pathopsychological testing data showed that the child was found to have signs of autism, a mild degree of severity. Child-parent relations in the family are respectful and trusting. Both parents are actively engaged in the upbringing and development of the child. There is an unstable emotional background in the mother, as she feels a sense of fear, anxiety in relation to her son, to his future independent life. Parents feel sympathy for the child and believe in his future.

The determination of the levels of the markers of central nervous system damage showed the following results:

Phosphorylated tau protein — 120.9 pg/ml ↑ (norm 0—10 pg/ml);

Neurofilament light chains — 36.5 pg/ml ↑ (norm 30—40 pg/ml).

The patient was prescribed a course of therapeutic rhythmic transcranial magnetic stimulation. The treatment protocol included exposure to a low-frequency (0.9 Hz) pulsed magnetic field for 20 minutes on the projection of the left dorsolateral prefrontal cortex daily, with a break on weekends according to the instructions for use approved by the Ministry of Health of the Republic of Belarus from 25.04.2019 № 047-0419 "Method of treatment of general developmental disorders, specific disorders of speech and language development by transcranial magnetic stimulation".

After the first procedures, the mother noted a noticeable change in the child's behavior: he began to look into his mother's eyes, showed interest in the objects of the home environment. During the following procedures the behavior became more orderly, new syllables appeared.

Twenty-four procedures of rhythmic transcranial magnetic stimulation were performed. The child tolerated the procedures well, no undesirable reactions were detected.

At the end of the course there is a stable emotional background, the child is assiduous, began to fulfill simple requests, responds to his name. During the follow up consultation he was calm and adequate. According to the data of psychological diagnostics, positive dynamics are noted. According to the mother: during lessons at preschool with a speech therapist, the child became more assiduous, he performs tasks without stimulus help.

The determination of the markers of central nervous system damage in the blood serum after the end of the course of therapeutic rhythmic transcranial magnetic stimulation showed the following results:

Phosphorylated tau protein — 36.3 ng/ml;

Light chains of neurofilaments — 4.5 ng/ml.

As can be seen from the data above, a clinical improvement of the child's condition was accompanied by a severe tendency towards the decrease of the level of phosphorylated tau-protein and light chains of neurofilaments. The latter indicates the normalization of the functional state of both the neuronal and axonal apparatus of the central nervous system. The increase in the level of phosphorylated tau-protein in the blood reflects the continuity and progression of the course of pathological process. Changes in the concentration of the light chains of neurofilaments reflect the degree of the degradation of brain neuronal axons, allowing us to predict how changes in brain tissue will develop and, accordingly, how the clinical picture of the disease will change.

Conclusion

The results obtained in the presented study of the assessment of the dynamics of the level of phosphorylated

tau-protein and the level of light chains of neurofilaments in the blood allow for the possibility of using these markers as indicators of changes in the functional state of the central nervous system under the influence of therapy in children with autism. The results of the present study are consistent with the works of Russian authors who have worked with this problem. Thus, in the work of G.V. Reva et al. an assumption was made about the role of epiphysis development disorders in this pathology in corpora arenacea dysgenesis. Therefore, it is necessary to create an archive of biopsy material of this pathology taking into account all the links of pathogenesis. The possibility of the treatment of autism not only with the help of pedagogical correction methods, but also with the use of physiotherapy is not excluded [6]. S.G. Nikitina et al. suggest assessing the severity of oxidative stress to predict the course of the disease in ASD [5]. Experimental models are actively used to search for effective methods of the treatment of this pathology [3; 16]. The search for diagnostic markers in autism spectrum disorders continues [24]. In the future, it is possible to further develop research in the field of developing new methods of medical care for patients with autism using the results obtained as additional diagnostic criteria in the comparison of clinical, neuropsychological and biochemical indicators in assessing the dynamics of the clinical picture of the disease.

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