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Biochemical Markers for Predicting Cognitive and Autonomous Disorders in Adolescence

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Abstract: Adolescence is characterized by intensive neural development, including active myelination, synaptic reorganization, and prefrontal cortex maturation, making this age stage particularly vulnerable to the development of neuropsychiatric disorders. According to the WHO, up to 20% of adolescents experience mental health problems, including cognitive disorders and autonomic regulation disorders.

Keywords: adolescents, biochemical markers, cognitive impairments, autonomic disorders, neurotransmitters, neurotrophic factors, oxidative stress, predictors.

Introduction. Modern research demonstrates a close relationship between neurometabolic processes and the functional state of the central nervous system during adolescence. Neurotransmitter imbalance, impaired brain energy metabolism, and changes in the neurotrophic factor system can serve as early predictors of cognitive and autonomic disorders.

Biochemical markers reflecting the state of dopaminergic, serotonergic, and GABAergic systems, which play a key role in the regulation of cognitive processes and vegetative homeostasis, are particularly noteworthy. Disorders in these systems can manifest as a decrease in attention concentration, memory impairment, emotional lability, and autonomic nervous system dysfunction.

Furthermore, current data indicate the significance of oxidative stress and neuroinflammatory processes in the pathogenesis of neuropsychiatric disorders in adolescence. An increase in the level of pro-inflammatory cytokines, a change in the activity of antioxidant enzymes, and the accumulation of lipid peroxidation products can serve as early biomarkers of cognitive dysfunction. The relevance of the problem is due to the need for early diagnosis and prevention of neuropsychiatric disorders in adolescence, when therapeutic interventions are most effective due to the high neuroplasticity of the developing brain. Identifying reliable biochemical predictors will optimize approaches to screening, monitoring, and personalized therapy for cognitive and autonomic disorders in adolescents.

Metabolic disorders in children and adolescents have only recently been considered one of the most significant medical and social problems in modern healthcare, due to the steady increase in their prevalence and the pronounced impact on the formation of somatic, cognitive, and autonomic disorders. According to foreign studies, the frequency of metabolic disorders, including obesity, insulin resistance, and metabolic syndrome, among the child and adolescent population shows a steady trend towards an increase, reaching 20-30% in individual regions. At the same time, it is emphasized that

nervous system damage in metabolic disorders begins as early as childhood and is often subclinical, forming the basis for further cognitive and vegetative dysfunctions.

A significant amount of data has been accumulated in world literature indicating the relationship between metabolic disorders and disorders of higher mental functions, decreased attention, memory, and cognitive processing of information with disregulation of the autonomic nervous system. A number of authors note that chronic low-intensity inflammation, insulin resistance, endothelial dysfunction, and cerebral circulation disorders are considered the main pathogenetic mechanisms for the formation of cognitive and autonomic disorders in metabolic disorders in children and adolescents. At the same time, most studies are focused on adult populations, while childhood and adolescence remain insufficiently studied.

The purpose of the study is to study and identify the clinical and functional features of cognitive and autonomic disorders in children and adolescents with metabolic disorders to substantiate early diagnosis and a comprehensive approach to patient management.

Research material and methods. The study involved adolescents with clinical manifestations of metabolic disorders, who had an excess body weight in their medical history and nervous system disorders, primarily in the form of decreased cognitive functions and autonomic dysfunction. All patients were observed in outpatient and inpatient settings at the Multidisciplinary Clinic of Samarkand State Medical University (Pediatrics Department, Children's Neurology Department), Samarkand City Endocrinology Hospital (Children's Department), and Samarkand City Multidisciplinary Children's Hospital (Endocrinology and Children's Neurology Department). The total number of examined individuals was n=79 adolescents aged 13 to 15 years, who constituted the main study group. The study group consisted of patients of both sexes: boys in the amount of 41 (51.9%), girls in turn, respectively, 38 (48.1%).

The inclusion criteria in the study were: the presence of metabolic disorders (excess body weight and/or obesity), cognitive complaints (decreased memory, attention, school performance), signs of autonomic dysfunction, as well as established diagnoses according to ICD-10: E66 (obesity), E11-E14 (diabetes mellitus), G90.8 (other disorders of the autonomic nervous system), F06.7 (mild cognitive impairment). The criteria for exclusion were: organic brain lesions, epilepsy, congenital malformations of the central nervous system, severe mental disorders, genetic syndromes.

Depending on the severity of central nervous system disorders, patients in the main group were distributed as follows: mild cognitive-vegetative disorders were noted in 29 adolescents (36.7%), moderate in 32 adolescents (40.5%), severe in 18 adolescents (22.8%).

The control group consisted of 32 relatively healthy adolescents, comparable in age and gender, who underwent a preventive outpatient examination; participation was carried out with the written informed consent of the parents. Additionally, patients in the main group were distributed according to the level of glycemia: adolescents with normal blood sugar levels - 47 adolescents (59.5%), with impaired glucose tolerance - 19 adolescents (24.1%), with diabetes mellitus - 13 adolescents (16.4%). By the degree of excess body weight and obesity, the following subgroups were identified: 28 adolescents (35.4%) with excess body weight, 31 (39.2%) with I-degree obesity, and 20 (25.4%) with II-III-degree obesity.

Taking into account etiological factors, it was established that the most frequent causes of metabolic disorders were: family predisposition to obesity and metabolic diseases in 27 cases (34.2%), the presence of diabetes mellitus in the mother in 18 (22.8%), complicated course of pregnancy and childbirth in 14 (17.7%), intrauterine infections in 9 (11.4%), combination of several factors in 11 (13.9%). In addition, the entire main group was divided into subgroups depending on the nature of metabolic disorders: adolescents with diabetes mellitus 13 people (16.4%) and adolescents with normal glycemia levels, but with obesity and pronounced cognitive impairment 66 people (83.6%), which allowed for a comparative analysis of clinical, neurological, and vegetative features depending on the metabolic profile.

All adolescents in the main and control groups underwent a comprehensive clinical-neurological and psychophysiological examination aimed at identifying cognitive and autonomic disorders against the background of metabolic disorders. Clinical and neurological assessment included an analysis of complaints, medical history data, objective neurological status with an emphasis on signs of autonomic dysfunction, asthenic syndrome, emotional lability, and disorders of adaptive reactions. The obtained indicators were analyzed depending on the severity of cognitive-vegetative disorders and compared with the data of the control group. To assess cognitive functions, validated age-specific scales and tests were used: Montreal Cognitive Assessment (MoCA) in adolescent adaptation for screening cognitive status assessment, the Digit Span test for assessment of working memory and attention concentration, as well as the HADS anxiety and depression scale, which allows for the identification of affective components affecting cognitive productivity. The results of cognitive testing were analyzed quantitatively and qualitatively with subsequent comparison between groups of varying severity of impairments.

Assessment of the state of the autonomic nervous system was carried out using the Vein questionnaire, analysis of autonomic tone and reactivity, as well as functional tests (ortostatic test, clinical test). Additionally, indicators of heart rate, blood pressure, and their variability were recorded, which made it possible to assess the balance of the sympathetic and parasympathetic parts of the autonomic nervous system. The severity of vegetative disorders was compared with the level of glycemia, the degree of obesity, and cognitive function indicators. As an innovative component of the study, an integrative index of cognitive-vegetative dysfunction was used, based on a combined assessment of three parameters: (1) the total score on the MoCA scale, (2) the severity of vegetative disorders according to the Wayne questionnaire and functional test results, (3) the metabolic profile (glycemia level and obesity level). This index allowed for the identification of high-risk groups for the early formation of cognitive impairments and persistent vegetative dysfunction in adolescents with metabolic disorders. The obtained values of the integrative index were used for a comparative analysis between the groups and were considered as an early prognostic marker of an unfavorable neurometabolic profile.

Statistical processing of the obtained data was carried out using Statistica and SPSS application software packages on an individual computer. Quantitative indicators are presented as average values and standard deviation. Intergroup differences were assessed using the Mann-Whitney U-criterion, the Kraskel-Wallis criterion, and Pearson's χ^2 criterion. Correlation analysis was conducted using Spearman and Kramer (V) coefficients. Differences were considered statistically significant at a level of $p < 0.05$.

Research results. Analysis of the results of clinical-cognitive and autonomic examination showed that cognitive and autonomic disorders were significantly more frequently detected in adolescents with metabolic disorders compared to the control group, while the degree of their severity depended on the severity of disorders in the central nervous system and the characteristics of the metabolic profile. Thus, in the group with mild cognitive-vegetative impairments, moderate attention deficit, decreased concentration, and increased fatigue prevailed, which were noted in 65.5% of adolescents. The average total score on the MoCA scale in this group was 25.6±1.9, which corresponded to the lower limit of the age norm. Vegetative disorders were of a functional nature and manifested mainly as blood pressure lability, tachycardia episodes, and sleep disturbances, which were detected in 58.6% of patients. In the control group, cognitive indicators corresponded to the age norm (MoCA 28.9±1.4), and no clinically significant vegetative disorders were detected. At the same time, in the group with moderate severity of disorders, combined cognitive impairments in the form of a decrease in short-term and working memory, a slowdown in the pace of mental activity, and a decrease in learning were registered significantly more often, which were noted in 78.1% of adolescents. The average level of the MoCA indicator was 23.1±2.2 (p<0.05 compared to the control). Autonomic dysfunction was characterized by the predominance of sympathicotonia, dizziness, and episodes of heart palpitations, which were detected in 71.9% of patients in this group. According to the Vein questionnaire, the average values corresponded to moderately pronounced vegetative dysfunction.

The most pronounced changes were identified in adolescents with severe cognitive-vegetative impairments. In this group, 88.9% of patients experienced a significant decrease in cognitive productivity, including impairments in memory, attention, performance functions, and learning motivation. The average total score on the MoCA scale was 20.4 ± 2.6 ($p<0.01$ compared to the control group). Vegetative disorders were persistent and manifested as pronounced disregulation of vegetative tone, a combination of sympathetic and vagotonic reactions, ortostatic instability, and thermoregulation disorders, which were detected in 83.3% of adolescents.

Comparative analysis depending on the level of glycemia showed that cognitive and autonomic disorders were more pronounced in adolescents with diabetes mellitus than in patients with normal blood sugar levels but obesity. In the group with diabetes mellitus, the average MoCA score was 21.8 ± 2.4, while in adolescents with obesity without hyperglycemia, it was 24.9 ± 2.1 ($p<0.05$). A similar trend was noted in the indicators of autonomic dysfunction, which indicated a more pronounced adverse effect of hyperglycemia on the state of the central and autonomic nervous systems. Consequently, the research results demonstrate a clear dependence of the severity of cognitive and autonomic disorders in adolescents on the severity of metabolic disorders and the degree of involvement of the central nervous system, which confirms the feasibility of a comprehensive clinical-scale approach for early detection and risk stratification of adverse neurometabolic disorders.

The obtained correlations confirmed that the decrease in cognitive indicators (MoCA) and the increase in the severity of vegetative dysfunction (Vein questionnaire, ortostatic reactions) are closely associated with the severity of cognitive-vegetative disorders. The most significant predictors of severe course were low MoCA values, high severity of vegetative dysfunction, obesity of II-III degree, and carbohydrate metabolism disorders, which allows for the use of a comprehensive clinical-scale approach for early risk stratification and justification of individualized correction in adolescents with metabolic disorders.

Comparative analysis showed that cognitive impairments and autonomic dysfunction are more pronounced in adolescents with diabetes mellitus than in patients with obesity without hyperglycemia and conditionally healthy adolescents. The most significant differences were found in MoCA indicators, the severity of vegetative dysfunction according to the Vein questionnaire, and the frequency of positive ortostatic reactions ($p<0.05$), which indicates an additional adverse effect of hyperglycemia on the state of the central and autonomic nervous systems.

The obtained results confirm that in children and adolescents with metabolic disorders, combined damage to the cognitive and autonomic spheres is formed, the severity of which increases with the severity of the metabolic profile and the degree of involvement of the central nervous system. The identified cognitive impairments in the form of decreased attention, memory, and executive functions are consistent with data from foreign and domestic studies indicating the negative impact of insulin resistance, chronic low-intensity inflammation, and endothelial dysfunction on brain function.

The peculiarity of this study is the demonstration of a close relationship between cognitive impairments and autonomic nervous system dysfunction, which manifested as a high frequency of autonomic disorders, ortostatic instability, and lability of cardiovascular reactions in adolescents with metabolic disorders. These results confirm the concept of neurovegetative disadaptation as one of the main pathogenetic mechanisms of cognitive decline in metabolic disorders in adolescence. The novelty of the study lies in the use of an integrative clinical-scale approach that combines the assessment of cognitive functions, vegetative status, and metabolic indicators into a single prognostic framework. The use of the integrative index of cognitive-vegetative dysfunction allowed not only to objectify the degree of disorders but also to identify a group of adolescents with a high risk of adverse neurometabolic course, which has significant practical significance for early diagnosis and individualization of therapeutic and preventive measures.

Conclusions: Thus, the research results expand the understanding of the pathogenetic mechanisms of cognitive and autonomic disorders in children and adolescents with metabolic disorders and justify the

expediency of a comprehensive interdisciplinary approach, including clinical-scale and autonomic assessment in routine clinical practice.

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