CLINICAL AND LABOATORY CHARACTERISTICS OF PSYCHOEMOTIONAL DISORDERS IN CHILDREN WITH DIABETES MELLITUS

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Abstract.
This review article attempts to analyze and systematize the existing data in contemporary scientific literature on the etiology, pathogenesis, and clinical manifestations of cognitive and emotional deficits in children and adolescents with type 1 diabetes mellitus (T1DM). The publication is aimed at neurologists and pediatricians. Currently, type 1 diabetes in children and adolescents remains one of the most significant medical and social problems of modern society, requiring comprehensive and thorough study, followed by maximum optimization of therapeutic and rehabilitation measures. Chronic hyperglycemia underlies the development of cognitive and psycho-emotional disturbances in T1DM. The prevalence of neurological disorders in T1DM, according to some authors, varies widely—from 10% to 74%—and often depends on factors such as age at disease onset, disease duration, baseline glycemic levels, diagnostic criteria used, and others. Nervous system pathology in diabetes is observed in approximately 50% of pediatric patients with disease duration of 3 years or more, while up to 25-30% of children with recently diagnosed diabetes already exhibit established neurological changes.

Keywords: diabetes mellitus, children, adolescents, cognitive functions, emotions, glycemia, insulin.

Objective: To succinctly present markers of cognitive and emotional disorders in children with type 1 diabetes mellitus.

Diabetes mellitus (DM) is commonly understood as a group of endocrine disorders characterized by persistently elevated blood glucose levels.

As of early 2018, according to the International Diabetes Federation (IDF), diabetes was diagnosed in more than 424.9 million people worldwide, with projections estimating an increase to 628.6 million by 2045. Many countries report

a documented rise in the incidence of T1DM in the pediatric population. In children and adolescents, type 1 diabetes (T1DM), characterized by autoimmune destruction of pancreatic β-cells leading to absolute insulin deficiency, is the most prevalent form. It is noteworthy that, according to many researchers and recent statistical data, there is a steady increase in other types of diabetes among children and adolescents, with type 2 diabetes accounting for up to 15-17%, monogenic diabetes (MODY) for 2-6%, and others [1]. However, these figures should be considered tentative due to varying research capabilities and diagnostic challenges in this patient group [2].

At the 61st session of the United Nations General Assembly, the global significance of diabetes, both in adults and children, was emphasized. Delegates also highlighted the absence of optimal national-level algorithms in some countries for prevention, early diagnosis, and treatment of diabetes [3].

In 1989, according to the long-term goals of the St. Vincent Declaration, comprehensive support was decided for the development and implementation of constructive and effective preventive measures, as well as promotion of research aimed at reducing the number of severe diabetes complications [4].

In the Republic of Uzbekistan, as in other developed countries, there is a steady increase in pediatric and adolescent T1DM. According to statistics from the Republican Medical Scientific Center of Endocrinology of Uzbekistan, over 277,000 patients with diabetes were registered by 2020, including 3,280 under the age of 18.

As noted earlier, the persistently elevated glycemic levels characteristic of diabetes lead to functional and structural abnormalities in various organs and systems. Most notably and severely affected are the eyes, cardiovascular system, kidneys, and especially the nervous system. The impact of hyperglycemia on the formation, frequency, and severity of diabetes complications was identified and confirmed by researchers as early as the mid-20th century.

Previous studies involving repeated systematic assessments of glycemic control repeatedly demonstrated its critical role in reducing the risk of complications at early stages of the disease. For this reason, many authors recommend close monitoring of patients during the early disease stages, since early signs of complications due to inadequate glycemic control tend to progress and do not regress even if glycemic management improves later [5,6].

In recent decades, growing attention has been paid, rightly so, to the adverse effects of diabetes on the central nervous system (CNS). Earlier research highlighted that CNS pathologies stand apart among diabetes complications due to the complexity of innervation, resulting in heterogeneous clinical manifestations, diagnostic difficulties, and challenges in therapeutic and rehabilitative decisions [7].

Diverse nervous system dysfunctions in children and adolescents with T1DM have been repeatedly confirmed by epidemiological studies, emerging as early as 2 to 8 years after disease onset, or even sooner in some patients. The reported prevalence of neurological disorders varies widely from 10% to 74%, often depending on age at diagnosis, disease duration, baseline glycemia, diagnostic criteria, etc. [8,9]. Nervous system pathology in diabetes is noted in approximately 50% of pediatric patients with disease duration of 3 years or more, while up to 25-30% of children with more recent diagnoses already show established neurological changes. It should be emphasized that these figures mainly relate to diabetic neuropathy (DN), as for many years DN—specifically diabetic peripheral neuropathy—was considered the sole and most common nervous system complication in diabetes [10,11]. However, over recent decades, this view has been challenged by research demonstrating both direct and indirect effects of diabetes on structural and functional brain changes, primarily manifesting as cognitive impairments (CI). Furthermore, CI have been identified as the most common nervous system abnormalities in diabetes [12].

In 2002, N.N. Yakhno proposed the following definition of cognitive impairment: "Cognitive impairments are subjective or objective deviations in higher cortical functions, which may be organic or functional brain disorders of various origins, affecting optimal learning processes and the efficiency of professional, social, and daily functioning" [13].

Unfortunately, even with modern advanced medical technology, medicine cannot yet prevent the development of various diabetes complications. Most researchers attribute this to the late detection of brain abnormalities, caused primarily by (1) a blurred subjective clinical picture and (2) the subclinical and hidden nature of the pathology. Compared to peripheral nervous system damage, brain-related complications in diabetes remain a poorly studied aspect of neurodiabetology [14]. Moreover, fundamental questions about the mechanisms underlying cognitive impairments in children and adolescents with T1DM remain insufficiently explored, despite previous studies demonstrating various pathogenetic components of CI in this condition [15].

In summary, complications of diabetes, especially those affecting the brain, are highly prevalent and, moreover, represent an inevitable and predictable phenomenon requiring special monitoring.

Clinical Components of Cognitive and Emotional Impairments in Type 1 Diabetes

The so-called higher cortical or higher brain functions, or cognitive functions, are considered the most complex brain processes that play a key role in the meaningful perception and understanding of the world, as well as in purposeful interaction with it. These complex functions include:
– **Gnosis**, whose mission is the perception of information received from the sensory organs (vision, hearing, smell, touch, taste, and tactile sense);
– **Thinking**, which involves processing and analyzing incoming information, including the ability to synthesize, identify similarities and differences, produce logical conclusions, and form associative connections;
– **Memory**, which is responsible for storing and recalling acquired information;
– **Speech**, which enables the exchange of information;
– **Praxis**, meaning purposeful motor activity.

In children, the most important, or basic, cognitive components are formed by the age of 6–7 years, while the more complex ones develop between ages 12 and 15, continuing to improve throughout life. However, it is essential to take into account individual characteristics and capabilities of each person. It is also important to remember that the ability for social and everyday adaptation in today's rapidly changing world, especially in individuals with diabetes, directly depends on the state of their cognitive abilities.

Cognitive impairments, along with other neurological disorders, are among the most significant and, in many cases, the leading or sole manifestations of organic brain pathology with varying degrees of severity.

Another current issue is that a large number of patients with diabetes continue to live unaware (often due to medical staff's lack of professionalism) and, consequently, with untreated cognitive impairments. This persists despite many studies demonstrating the inevitable presence of cognitive deficits in patients with type 1 diabetes and all related consequences. This pathology's formation is even more significant when it occurs in childhood with type 1 diabetes.

One such study was conducted in 2015 by Duarte J.M.N., showing the consistent presence of cognitive pathology in diabetes, with manifestations in children and adolescents usually mild or moderate, but tending to worsen with age, disease duration, and poor glycemic control.

As noted earlier, cognitive deficit means deterioration compared to individual norms in one or more brain functions such as memory, attention, thinking, etc. In children, these can be caused by intellectual disability, brain underdevelopment, or injury around the time of birth or early postnatal period. In adults, cognitive impairments may develop due to a wide range of neurological diseases. This is

explained by studies showing that approximately 90% of the brain cortex area belongs to secondary and tertiary cortical centers responsible for regulating higher brain functions.

According to the literature, impairments of memory functions are among the earliest and most persistent symptoms of cerebral pathology developed in diabetes; accurate assessment of their nature and severity allows conclusions about the localization and extent of pathological processes in the brain.

Currently, classifications of cognitive deficits in diabetes are based on the severity of their manifestations. According to the most commonly used classifications — DSM-5 and the classification by N.N. Yakhno — cognitive changes can be divided into severe, moderate, and mild.

- **Severe cognitive impairments** are transient or persistent deviations characterized by high severity, significantly interfering with the patient's social, professional, and everyday life. These include intellectual disability, oligophrenia, dementia, as well as pathologies predominantly caused by genetic factors and brain developmental anomalies.
- **Moderate cognitive impairments** are acquired deviations in one or several areas of higher cortical function. Compared to severe impairments, these are less pronounced and do not cause loss of independence in daily life, although they exceed age norms. Difficulties arise only during the performance of the most complex and unfamiliar tasks.
- **Mild cognitive impairments** are neurodynamic manifestations involving impaired rapid switching between tasks, slower information processing, and working memory. Patients with mild impairments do not experience difficulties in professional, social, or daily activities. Such impairments may only be detected through subjective patient reports and detailed neuropsychological testing.

Many authors believe that cognitive dysfunctions as complications of diabetes mainly occur in mild and moderate forms, with severe impairments being rare. The most common manifestations include slowed information processing speed, memory and attention disorders, and executive dysfunction. Additionally, psychomotor response slows, intellectual flexibility decreases, and visual perception is impaired. It should be noted that hyperglycemia and hypoglycemia can have different impacts on cognitive deficit manifestations; for example, elevated glucose levels often affect verbal memory, whereas lowered glucose impairs visual memory.

Cognitive dysfunction in type 1 diabetes, especially in children and adolescents, can be detected at early stages of the disease. Opinions on this matter vary among authors, but there is consensus that cognitive deficit formation in type 1

diabetes is a 100% certainty and that deficits persist and progressively worsen with patient aging and longer disease duration.

In this study, we concluded that cognitive deficit in children and adolescents with type 1 diabetes begins to develop almost simultaneously with the onset of the main disease. This is caused by changes in brain metabolism and energy-producing processes, which in turn lead to impaired oxygen and glucose utilization by brain tissues—both essential for optimal brain function.

In addition to cognitive deficits, significant changes can also develop in the psycho-emotional and behavioral spheres of patients with type 1 diabetes. Clinical manifestations of these disturbances tend to emerge in two phases: the disease debut and the onset of possible complications. Most children exhibit moderately expressed emotional reactions upon diagnosis.

In other cases, reactions to the news of the disease are more pronounced, and examinations reveal initial changes in the psycho-emotional background [31]. Subsequently, approximately within nine months from the onset of the disease, the level of psychological activity returns to baseline [27].

There are quite a few publications on this issue in the literature. For example, some researchers who had the opportunity to observe children with type 1 diabetes almost from the first days of the disease concluded that the onset of type 1 diabetes itself does not have a significant impact on the psycho-emotional functioning of patients [32].

In 2019, it was established that a distinctive feature of the initial period of type 1 diabetes is the activation of pre-morbid personality traits, which are a determining factor in the reaction to the disease. Such reactions include: anxious suspicion; hyperbolic exaggeration of the treatment, or conversely, the formation of a frivolous attitude toward the disease. According to other authors, in individuals suffering from diabetes, the level of personal psycho-emotional changes at the early stages of the disease is much higher than in those who have been ill for a long time; this fact is explained by the organism's adaptive capacity to the disease. This leads to the formation of pathological personality changes — the emergence of asthenic and obsessive-compulsive disorders, increased irritability, and lack of restraint; in some cases, manifestations of depression with dysphoria may also appear.

Regarding the problem of psycho-emotional disorders in type 1 diabetes, it is worth noting that recently, more and more scientific works have been published devoted to the increasing risk among pediatric patients (especially adolescents) of developing psycho-endocrinological syndrome as described by Manfred Bleuler,

which in turn is considered the first stage of the manifestation of psycho-organic syndrome [33].

According to several studies on the psychological adaptation processes in children with type 1 diabetes, there is a steady increase in personal (trait) anxiety and situational or reactive anxiety. Referring to statistical data, it is seen that the overall prevalence of anxiety in children and adolescents with type 1 diabetes ranges from 15 to 42%. High rates of anxiety disorders in children and adolescents are primarily associated with the specific characteristics of diabetes itself, such as the constant need for injections and self-monitoring. Additionally, a connection is observed with parental overprotection, where parents assume controlling functions [34].

According to many authors, and in our opinion as well, the neuropsychological status of pediatric patients with diabetes is of great importance in determining the course and outcomes of the disease. For this reason, parameters of neuropsychological status can be considered additional, auxiliary factors influencing the effectiveness of therapy [35].

Thus, in pediatric patients with type 1 diabetes, there is a high frequency of cognitive impairments, and a direct positive correlation exists between early manifestation and the risk of brain involvement in the pathological process. Moreover, cognitive dysfunctions against the background of concomitant anxiety-depressive disorders can not only negatively affect good and long-term glycemic control but also significantly impact social activity, work capacity, and patients' quality of life.

Neurospecificity Peptides as Markers of Cognitive and Psychoemotional Disorders

Currently, the pathogenesis of cognitive deficit in type 1 diabetes in children and adolescents remains not fully understood [36]. Several studies have found correlations between higher cortical function impairments and the degree of glycemia, leading to the assertion that this metabolic disturbance is the primary cause of cognitive deficit formation in diabetes [37].

It is well known that neuropsychological testing is primarily used to assess the severity of cognitive deficit; however, these test results are subjective and therefore cannot provide a complete picture of the changes occurring in higher cortical brain activity. Because of this, specialists worldwide are continuously searching for specific markers of cerebral disorders in diabetes [38].

More than 25 years ago, research began on biochemical markers with diagnostic significance for various brain changes, but to date, an ideal biomarker has

not been found. Among many studied biomarkers, special attention is given to determining the levels of neurospecific proteins, which can indicate damage occurring in brain tissues in various pathologies, including diabetes, both in adults and children [39].

Many scientists believe that the ideal marker of cerebral disorders should have the following characteristics: high specificity; high sensitivity; should be released during irreversible neuronal damage and provide information about the nature of the damage; detectable in blood and cerebrospinal fluid (CSF) shortly after injury; easy to measure in laboratory conditions; and naturally reflect the dynamics of pathology and treatment effectiveness [40].

In the pathogenesis of diabetic encephalopathy, the authors consider that the main role is played by pathological permeability of the blood-brain barrier (BBB). This fact, i.e., disruption of BBB structural integrity and normal function, has been demonstrated in several clinical and experimental studies. Impaired BBB permeability during cognitive deficit formation leads to the appearance in blood and CSF of certain neurospecific proteins, in particular neuron-specific enolase (NSE) and protein S-100 [41].

According to the authors, deviations found in protein concentrations in various neurological diseases can be detected earlier than any structural changes. The particular interest in analyzing brain-specific proteins lies in the fact that they are assumed to participate in key nervous tissue functions: generation and conduction of nerve impulses, synaptic transmission and cell interactions, and actively participate in learning and memory processes.

Neuron-specific enolase (NSE) is an informative neurospecific protein representing a glycolytic enzyme — 2-phospho-D-glycerate hydrolase. It belongs to the enolase group and participates directly in the terminal stage of glycolysis, catalyzing the conversion of 2-phospho-O-glyceric acid to 2-phosphoenolpyruvate. It was first isolated in the 1970s-1980s. Its isoenzyme is γγ-enolase, also called neuron-specific enolase, which is abundantly found in neurons and importantly in neuroendocrine cells. Normal NSE levels in blood are less than 15 μg/L [42].

From available literature sources, it follows that nowadays this brain-specific marker is widely used to diagnose acute conditions such as cerebral ischemia, brain hypoxia, and for studying the pathogenesis of neurological pathologies. Many authors emphasize its great importance in various nervous system diseases, such as epilepsy; Parkinson’s disease; senile dementia; Alzheimer’s disease; intrauterine brain damage; diabetes mellitus; brain tumors; traumatic brain injury (TBI).

Currently, the most studied biomarker is the neurospecific glial protein S-100. This protein is found in brain tissue complexed with calcium and consists of two subunits: α (10.4 kDa) and β (10.5 kDa). Its normal blood concentration is less than 0.2 μg/L. An important feature is that its content in the white matter is higher than in the gray matter, and in the cerebellum its concentration is greater than in all other brain structures [43].

Protein S-100 is found in cerebral cells such as astrocytes, oligodendrocytes, as well as ependymal, choroidal, endothelial, and lymphocytic cells of the brain.

Many authors consider, though presumably, that since this protein is widely present in various cell types, it serves as a marker of widespread blood-brain barrier damage rather than isolated glial damage [44]. When S-100 protein concentration is low, it exerts a neuroprotective effect, acting as a growth factor and differentiating neurons and glia, blocking NMDA receptors. If its concentration is elevated, it stimulates pro-inflammatory cytokines and leads to cell self-destruction (apoptosis or autolysis). At optimal concentrations, S-100 protein in the brain performs trophic functions, serves as a barrier protecting neurons from oxidative stress, and stimulates the growth of nerve processes. It also stimulates the NF-kappa B complex. Numerous studies focus on the clinic-pathogenetic role of S-100 protein and its significance in determining the severity and outcomes of neurological pathologies. For example, increased S-100 protein levels correlate with worsening auditory evoked potentials and unfavorable outcomes after aneurysm surgeries [45]. Also, moderate increases in S-100 concentrations in patients with depression are associated with delayed visual evoked potential peaks, which normalize during treatment, indicating the neurodegenerative significance of S-100.

In the study by Saleh A. et al. (2007), the clinical diagnostic significance of S-100 protein was demonstrated as an indicator of the severity of higher cortical dysfunction in patients with hepatic encephalopathy [46].

In the study by Novoselova M.V. et al. (2014), data were obtained showing statistically significant increases in the levels of the studied neurospecific proteins. Specifically, a positive correlation was demonstrated between these protein levels and glycated hemoglobin as well as fasting hyperglycemia, confirming the impact of carbohydrate metabolism decompensation in patients with type 1 diabetes mellitus [47].

As a result of all these identified disturbances related to the S-100 protein in various neurological pathologies, this protein has been included in the group of brain C-reactive proteins and is used as a neurospecific biomarker of central nervous system damage.

Conclusions. Thus, the development of complications in type 1 diabetes is inevitable, expected, and requires monitoring. The conducted analysis of domestic and foreign literature indicates the existence of various pathogenetic mechanisms underlying cerebral impairments in diabetes, leading to extensive and diverse neuropsychological, psychopathological, and neurological symptomatology.

There is no doubt that diabetes mellitus negatively affects cognitive function. However, the specific pathogenetic mechanisms contributing to the formation and progression of cognitive deficit in patients with diabetes, both adults and children, are not fully understood; the data are fragmented, limited, and sometimes contradictory. Most literature sources highlight the significant contribution of hyperglycemia; at the same time, many authors also point to the more significant influence of hypoglycemia. However, the role of major pathophysiological consequences of hyper/hypoglycemia, such as tissue (neuronal, glial) hypoxia, endothelial dysregulation, and activation of angiogenesis, remains insufficiently studied.

There is a lack of comprehensive studies elucidating the relationship between clinical, biochemical, and neuroimaging changes of the CNS in diabetes. The clinical and diagnostic significance of neuropeptides such as NSE and S-100 is not fully understood, despite their demonstrated informativeness in blood serum in many other CNS diseases. Objective diagnostic criteria for diabetic encephalopathy in childhood, including its earliest and preclinical stages, are absent.

Therefore, in addressing these problems, the issue of studying cerebral disorders in children and adolescents with type 1 diabetes using modern neuroimaging, psychometric, and biochemical methods that cover the main possible links in the pathogenesis of these disorders remains highly relevant. The obtained data could provide a basis for developing a set of measures for prevention, treatment, and rehabilitation of CNS disorders, which would contribute to optimizing current approaches to diabetes management and improving the quality of life for diabetic patients in the long term.

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