

Role of Neurospecific Proteins and Indicators Magnetic Resonance Spectroscopy in Early Diagnostics of Cognitive Deficits in Children and Adolescents with Type 1 Diabetes

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Abstract This article contains our own results of analysis of neuropsychological, laboratory and neuroimaging examination methods related to the problem of cerebral complications in type 1 diabetes in children. Data from our own studies of psychological testing (MoCa test), Spielberger-Khanin methods for assessing situational (ST) and personal (PT) anxiety are presented. In addition, blood levels of S-100 protein and neuron-specific enolase (NSE) were demonstrated to study the pathogenetic and diagnostic roles of neuropeptides and major brain metabolites. Using proton magnetic resonance spectroscopy, the concentrations of brain metabolites N-acetylaspartate (NAA), choline (Cho) and creatine (Cr), and their ratios (NAA / Cr; Cho / Cr; Cho / NAA) were determined. According to the results obtained, we can say that the proposed set of diagnostic measures using modern methods of brain research in the early diagnosis of manifestations of cognitive and emotional disorders in this pathology is reasonable and appropriate, since it is possible to trace changes in brain tissue in the form of microstructural damage and visualize deviations in brain metabolism leading to cerebral dysfunction even at the preclinical stage.

Keywords Cognitive deficit, Children and adolescents, Diabetes mellitus, Neurospecific proteins, Proton magnetic resonance spectroscopy

1. Introduction

Diabetes mellitus (DM) is considered to be an endocrine autoimmune pathology that develops as a result of an absolute or relative deficiency of insulin caused by the destruction of beta cells of the pancreas. At the present stage, diabetes is a serious medical and social problem, as it remains one of the leading causes of the development of chronic complications with the occurrence of early disability in patients. Diabetes mellitus is characterized by persistent hyperglycemia, which is accompanied by abnormalities of various organs and systems [1]. Among the variety of complications of type 1 diabetes in children, a special place is given to changes in the brain, mainly manifested by cognitive impairment (CI). Close attention to cognitive activity in diabetes mellitus is associated not only with the normal daily functioning and social adaptation of the child, but also with regular adequate

self-monitoring of glycemia, which directly affects the overall course of the underlying disease [2]. Currently, the problem of early diagnosis of cognitive deficits in patients with diabetes occupies one of the leading places in modern neuropathology [3]. In the diagnosis of disorders of higher cortical activity, for example, such as deficits in memory, attention, and thinking, methods of neuropsychological testing have a dominant position. However, here we have to take into account that these methods still provide a subjective assessment with the presence of both false positive and false negative results and are not able to offer complete reliable information on all criteria of cognitive deficit of interest [4]. Therefore, the issue of adequate and at the same time early diagnosis of these disorders with objective criteria that most accurately indicate the localization of the pathological focus causing cognitive changes is considered quite relevant not only for neurologists, but also for specialists in other areas of medicine. According to this, the primary task today is to identify the risks of developing cognitive dysfunctions long before their occurrence. The development and implementation

of a clear algorithm for predicting cognitive deficit at the stage of the absence of its clinical signs can solve the problem and guide specialists in prescribing adequate preventive therapy, which in turn will contribute to the preservation of higher cortical functions at a satisfactory level for a sufficiently long time [5]. In this regard, in recent years, the interest of researchers in the biochemical components of cognitive impairment has increased significantly. Thus, much attention is paid to determining the content of various neurospecific proteins in the blood serum as markers of neurodegenerative and neuroinflammatory processes or, for example, using proton magnetic resonance spectroscopy to analyze the content of the main metabolites responsible for the structural and functional integrity of brain cells.

Neurospecific proteins are tissue-specific for the nervous system and are histogenetically found in neurons and glial cells. In blood serum, the normal content of these proteins is considered to be low concentrations; this occurs due to the death of neurons, for natural reasons, as well as as a result of pathological changes. In this connection, an increase in the level of neurospecific proteins is considered in the format of markers of various pathological processes in the brain of adults and children, the most studied of which are epilepsy, head injury, diabetes mellitus, consequences of hypoxia, autism, Parkinson's disease. [6,7]. Of the total number of known neurospecific proteins, the most studied are protein S-100 and neuron-specific enolase (NSE), which, according to scientists, are more informative about the state of the pathological process and can be useful in studying the pathogenesis of neurological dysfunction, including in children and adolescents with type 1 diabetes [8].

The use in clinical practice of a method such as proton magnetic resonance spectroscopy (PMRS) has made it possible to intravitaly and non-invasively assess metabolic changes occurring in the brain in various neurological pathologies. This neuroimaging technique is based on the so-called "chemical shift" of the resonant frequencies of various chemical compounds. To date, two methods of magnetic resonance (MR) spectroscopy have been developed, these are single-voxel and multivoxel spectroscopy. The first spectroscopy technique provides rapid analysis of the biochemical profile of a localized volume within a brain region of interest. The second method of MR spectroscopy is based on the use of so-called color mapping, which covers a fairly large area of the brain with a multi-voxel volume, allowing localization from 16 to 64 voxels simultaneously, including not only the area of the altered brain matter, but even the opposite hemisphere, and at different anatomical levels [9]. The main metabolites studied by MR spectroscopy are N-acetylaspartate (NAA), choline (Cho) and creatine (Cr), and in addition to assessing their absolute concentration, their ratios are also determined, namely N-acetylaspartate to creatine (NAA/Cr); choline to creatine (Cho/Cr) and choline to N-acetylaspartate (Cho/NAA) [10]. According to the statements of specialists dealing with cognitive disorders in various nosological units, the sensitivity, specificity, and positive predictive value for identifying cognitive deficits

using MR spectroscopy are 89.8%, 88.2%, 95.3%, respectively [11]. There are many scientific works confirming the high importance of the above methods in the study of cognitive deviations associated with various diseases in both adults and children. However, despite this, quite a few questions remain that require more specific definitions and clarifications. This circumstance primarily concerns childhood and adolescence, when the problem of early diagnosis of cognitive deviations is especially acute and is of vital importance [12].

Purpose of the study. Determining the role of biomarkers in the early diagnosis of cognitive deficits in children and adolescents with type 1 diabetes.

2. Material and Methods

A survey was conducted of 205 children aged 7 to 18 years suffering from diabetes mellitus (type 1 diabetes), 92 (45%) patients were boys, 113 (55%) patients were girls. Children from 7 to 11 years old (average age - 9.0 ± 1.6 years) made up 81 patients (39.5%), patients from 12 to 18 years old, 124 patients were examined (average age - 14.7 ± 1.8 years) – (60.5%) (Table 1).

Table 1. Distribution of examined patients by age (according to classification N.P. Gundobin modified by A.V. Mazurin and I.M. Vorontsova, 1985) and gender

Age gender	Boys		Girls	
	N =	%	N =	%
7–11 лет – n = 81 (39.5 %)	37	40,2%	44	38,9%
12–18 лет – n = 124 (60,5%)	55	59,8%	69	61,1%
Total	92		113	

As part of the study, all patients underwent an objective clinical and neurological examination with a detailed analysis of the medical history. Cognitive impairment was determined using the Montreal Cognitive Assessment Scale (MoCAtest) [13]. The study of the emotional sphere was carried out using the methodology for assessing situational (ST) and personal (PT) anxiety by Ch.D. Spielberger – Yu.L. Hanina. Using the glucose oxidase method on a Hitachi 912 biochemical analyzer (Hoffmann-La Roch Ltd /Roche Diagnostics GmbH, Germany), the level of glucose in the blood was determined. Using liquid chromatography on a DS5 Glycomat analyzer (DrewScientific, the Netherlands), the content of glycated hemoglobin (HbA1c) in capillary blood was detected. Serum levels of S-100 protein and neuron-specific enolase were assessed by collecting fasting blood from the cubital vein into Vacutaner vacuum tubes. Concentrations in the blood serum of the subjects were determined by enzyme immunoassay using kits from CanAg S 100 EIA (Sweden) for protein S-100 and kits from CanAg Diagnostics (Sweden) for neuron-specific enolase (NSE).

Proton magnetic resonance spectroscopy of the brain was performed immediately after MRI of the brain, without changing either the apparatus or the position of the child's body, with a relaxation time $TE = 135$ ms, the volume of one

voxel was 1.5 cm³. During the PMRS procedure, resonance spectra corresponding to certain metabolites are created in a system of two axes: the vertical axis is the signal intensity, the horizontal axis is the position of the signal on a frequency scale. The spectra were measured in “parts per million” (ppm) [14]. This examination was performed in a multivoxel mode, allowing 64 voxels to be placed on one slice at a time. In the areas of interest, the main spectra of N-acetylaspartate, choline, creatine, as well as their ratios were recorded. The choice of mathematical methods was determined by the formulation of problems in each specific case and the requirements for processing medical data [15].

3. Results and Discussion

In a comparative assessment of HbA1c values taking into account the duration of the disease, we found that in the

first 1.5-2 years from the onset of diabetes mellitus, glycated hemoglobin levels were significantly lower and averaged 8.5%. In the group with an experience of 3 to 6 years, more precisely, by the middle of the third year of diabetes duration, carbohydrate metabolism indicators worsened and their average values were significantly higher than in children with a duration of up to 3 years - 9.4% ($p < 0.001$). In patients with longer durations of diabetes, the trend towards worsening HbA1c levels did not decrease and on average was significantly higher - 10.4% ($p < 0.001$) than in groups with shorter durations of the disease.

During the analysis of individual tasks for the MoCA test, it was determined that patients with type 1 diabetes performed significantly worse on the tasks “clock” ($p < 0.001$), “attention” ($p < 0.001$), and “repetition of a phrase” ($p < 0.001$) and “delayed reproduction” ($p < 0.001$) in relation to the control group (Figure 1.).

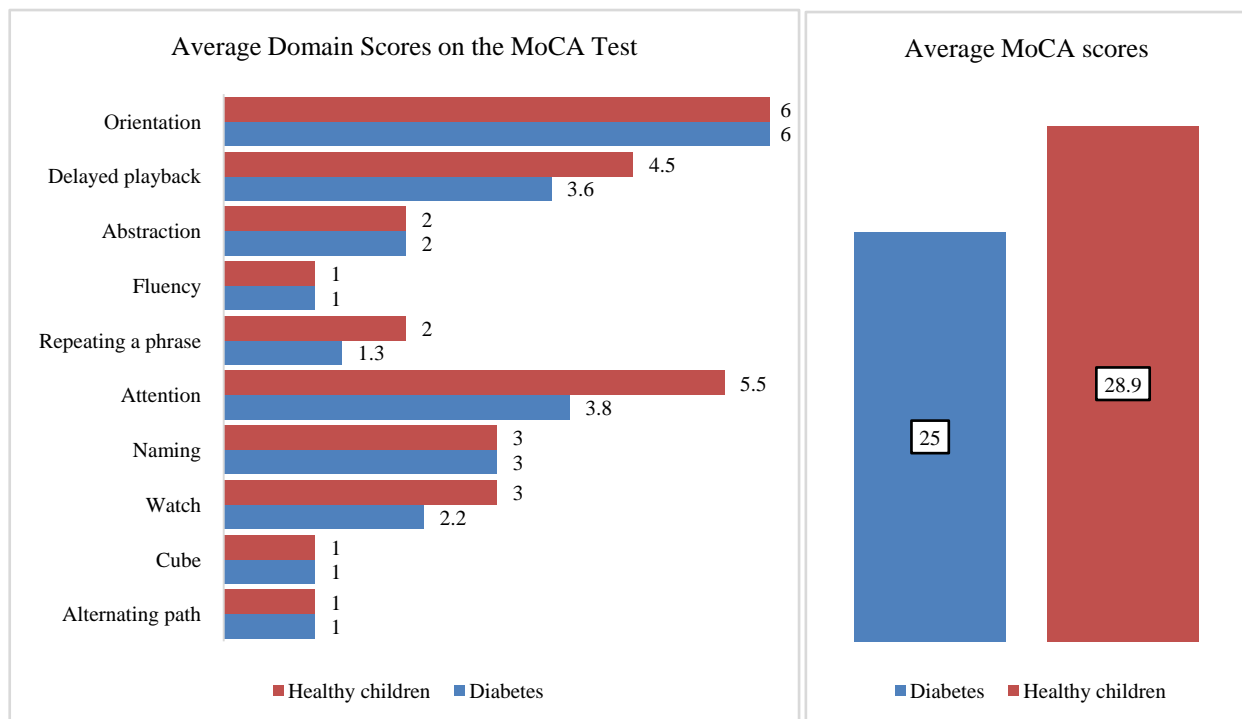


Figure 1. Average score across MoCA domains depending on presence of diabetes

The results of the test for the presence of anxiety demonstrated the presence of moderate degree of situational anxiety in 120 (58.5%) patients, high degree in 85 (41.4%) children. As for personal anxiety, it was detected to a low degree in 4 (2%) patients, moderate in 70 (34%) cases and high in 131 (64%) patients.

In order to study the pathogenetic and diagnostic role of neuropeptides in cognitive impairment in patients with type 1 diabetes, the levels of S-100 and NSE proteins were assessed. The control group in this case was children with type 1 diabetes, but without cognitive impairment. Thus, the content of S-100 protein in patients with cognitive manifestations was significantly higher - 0.696 µg/l, similar

indicators compared to patients without cognitive impairment - 0.284 µg/l, and with its reference values. A similar picture was observed when analyzing the results of neuron-specific enolase. Thus, in children in the group with cognitive deficits, the protein concentration was significantly higher - 53.9 µg/l, both in comparison with patients without cognitive disorders - 18.5 µg/l, and with reference values. According to the results of neuropsychological testing and a test for anxiety with indicators of enzyme immunoassay of proteins, noticeably close correlations were established - ($p < 0.001^*$) Thus, with an increase in S-100 by - 0.065, the expected decrease in scores on the MoCA test is - 1 point. With an increase in NSE by - 7.618, the expected decrease in MoCA

test scores is – 1 point. With an increase in S-100 by 0.017, one should expect an increase in the situational anxiety scale by 1 point. With an increase in NSE by 1.431, one should expect an increase in the situational anxiety scale by 1 point. With an increase in S-100 by 0.015, one should expect an increase in the personal anxiety scale by 1 point. With an increase in NSE by 1.223, one should expect an increase in the situational anxiety scale by 1 point.

For the purpose of early verification of the main

pathological changes occurring in the brain, the content of brain metabolites, as well as their ratios, were studied using the method of proton magnetic resonance spectroscopy. According to the results obtained, a significant significant decrease was visible in comparison with the control group in the content of N-acetylaspartate in the hippocampus on the left - 1.71 mmol/l., and in the gray matter on the right - 1.66 mmol/l., in addition, a significant increase in NAA in the white substance on both sides – 2.56 mmol/l. (Table 2.).

Table 2. Analysis of brain metabolites in children and adolescents depending on presence of type 1 diabetes

Indicators	Categories	Group of patients			p
		Me	Q ₁ – Q ₃	n	
NAA content in the left hippocampus	Diabetes	1,71	1,60 – 1,79	59	0,008*
	Control group	1,83	1,66 – 1,93	20	
NAA content in the Hippocampus on the right	Diabetes	1,93	1,79 – 2,04	59	0,088
	Control group	1,85	1,77 – 1,95	20	
NAA content in the White matter on the left	Diabetes	2,56	2,20 – 2,95	59	< 0,001*
	Control group	1,80	1,73 – 1,87	20	
NAA content in the White matter on the right	Diabetes	2,92	2,54 – 3,08	59	< 0,001*
	Control group	1,86	1,77 – 1,90	20	
NAA content in the Gray matter on the left	Diabetes	2,02	2,00 – 2,03	59	< 0,001*
	Control group	1,96	1,92 – 2,01	20	
NAA content in Gray matter on the right	Diabetes	1,66	1,56 – 1,73	59	< 0,001*
	Control group	2,64	2,49 – 2,72	20	
Choline content in the hippocampus on the left	Diabetes	3,11	3,00 – 3,25	59	0,016*
	Control group	3,04	3,01 – 3,06	20	
Choline content in the hippocampus on the right	Сахарный диабет	3,10	2,99 – 3,20	59	0,800
	Control group	3,04	2,98 – 3,21	20	
Choline content in the white matter on the left	Diabetes	3,00	2,58 – 3,17	59	0,304
	Control group	3,05	3,02 – 3,09	20	
Choline content in the white matter on the right	Diabetes	2,94	2,49 – 3,08	59	0,928
	Control group	2,91	2,88 – 2,95	20	
Choline content in the white matter on the right	Diabetes	3,20	3,10 – 3,30	59	0,735
	Control group	3,21	3,10 – 3,26	20	
Choline content in the gray matter on the right	Diabetes	3,10	3,05 – 3,17	59	0,003*
	Control group	3,00	2,89 – 3,10	20	
Creatine content in the Hippocampus on the left	Diabetes	4,25	4,14 – 4,52	59	< 0,001*
	Control group	2,92	2,81 – 2,98	20	
Creatine content in the Hippocampus on the right	Diabetes	3,34	3,01 – 3,70	59	0,004*
	Control group	3,00	2,99 – 3,07	20	
Content of Creatine in White matter on the left	Diabetes	3,09	2,98 – 3,35	59	0,198
	Control group	3,06	3,03 – 3,10	20	
Content of Creatine in White matter on the right	Diabetes	3,10	2,94 – 3,29	59	0,071
	Control group	3,04	2,99 – 3,09	20	
Creatine content in the gray matter on the left	Diabetes	3,28	3,08 – 3,48	59	< 0,001*
	Control group	3,09	3,05 – 3,20	20	
Creatine content in the gray matter on the right	Diabetes	2,40	2,24 – 2,66	59	< 0,001*
	Control group	3,07	3,04 – 3,11	20	

* – differences in statistically significant indicators (p < 0,05).

Table 3. Analysis of correlations in children and adolescents depending on presence of type 1 diabetes

Ratios		Diabetes	Healthy children	P
Hippocampus				
Cho/Cr	On right	0,92 (0,62–1,21)	1,14 (1,01–1,31)	< 0,001*
Cho/NAA	On right	0,54 (0,51–0,57)	0,66 (0,59–0,71)	0,088
NAA/Cr	On right	2,31 (1,37–3,10)	1,82 (1,76–1,86)	< 0,001*
Cho/Cr	On left	0,88 (0,60–1,19)	1,03 (0,98–1,12)	< 0,001*
Cho/NAA	On left	0,57 (0,50–0,79)	0,78 (0,70–0,81)	< 0,001*
NAA/Cr	On left	1,74 (0,88–2,05)	1,75 (1,69–1,81)	< 0,001*
White matter				
Cho/Cr	On right	0,89 (0,72–0,98)	0,85 (0,77–0,91)	0,016*
Cho/NAA	On right	0,5 (0,46–0,56)	0,46 (0,41–0,51)	0,800
NAA/Cr	On right	1,17 (0,69–1,71)	1,69 (1,65–1,75)	0,304
Cho/Cr	On left	1,31 (1,13–1,52)	0,92 (0,84–1,07)	0,928
Cho/NAA	On left	0,41 (0,38–0,48)	0,5 (0,46–0,56)	0,735
NAA/Cr	On left	0,78 (0,54–1,38)	1,68 (1,60–1,73)	0,003*
Gray matter				
Cho/Cr	On right	1,12 (0,99–1,40)	0,98 (0,90–1,06)	< 0,001*
Cho/NAA	On right	0,61 (0,58–0,64)	0,51 (0,47–0,53)	0,004*
NAA/Cr	On right	1,52 (1,19–2,27)	1,62 (1,57–1,70)	0,198
Cho/Cr	On left	1,05 (0,68–1,36)	0,96 (0,90–1,06)	0,071
Cho/NAA	On left	0,42 (0,39–0,45)	0,48 (0,47–0,51)	< 0,001*
NAA/Cr	On left	1,82 (0,91–2,69)	1,57 (1,51–1,62)	< 0,001*

* – differences in statistically significant indicators (p < 0,05).

Reduced levels of N-acetylaspartate in the hippocampus and gray matter may indicate changes in neuronal integrity with a decrease in the activity of nervous tissue; in addition, a decrease in NAA in the gray matter of the cerebral cortex on the right indicates the appearance of early signs of atrophy of this area.

Analysis of the content of choline, which is responsible for the optimal functioning of membrane processes, showed its significant increase in comparison with the control group in the hippocampus on the left - 3.11 mmol/l., and in the gray matter on the right - 3.10 mmol/l. Similar changes are possible with the occurrence of reactive gliosis followed by membrane necrosis, as well as the occurrence of excessive oxidative stress activity. The study of creatine content, which reflects energy processes and cell metabolism, demonstrated its significantly significant increase compared to the indicators of the control group in the hippocampi on the left and right - 4.25 mmol/l., and - 3.34 mmol/l. accordingly, a significant increase in the gray matter on the left is 3.28 mmol/l, and a statistically significant decrease in the gray matter on the right is 2.40 mmol/l. High levels of creatine in the bilateral hippocampi, as well as in the gray matter on the left, can be associated with compensatory reactions occurring in these areas of the brain. An increase in energy metabolic processes in cells indicates that for optimal activity the hippocampi require large energy expenditures, which subsequently can cause the formation of pathology at the anatomical level. As for the low creatine content in the gray matter of the cerebral cortex on the right, this indicates the appearance of initial

signs of atrophy in this area due to depletion of energy reserves.

To more accurately determine the content of metabolites, in most cases, the calculation of the ratio to several metabolites is used. As practice shows, creatine (Cr) plays the role of such a “reference” metabolite, since it is a relatively stable element of cellular energy metabolism of the brain, and it is often used to calculate metabolite ratios, for example, Cho / Cr, NAA / Cr, [16]. According to all of the above, we analyzed the relationships between the metabolites of interest in the indicated areas of the brain. Thus, the results of the study showed that in the cells of the hippocampus on the right, compared with the control group, a significantly significant (p < 0.001*) decrease in the ratio of choline to creatine (Cho/Cr) and a statistically significant (p < 0.001*) increase in the ratio of N –acetylaspartate to creatine (NAA/Cr) (Table 3.).

In the cells of the hippocampus on the left, compared with the indicators of the control group, there are significantly significant (p < 0.001*) decreases in the ratios of choline to creatine (Cho/Cr,) choline to N-acetylaspartate (Cho/NAA) and N-acetylaspartate to creatine (NAA /Cr). These changes demonstrate the formation of an energy imbalance with destruction of the integrity of neurons and disruption of their connections, which are in the early stages of formation.

Analysis of the ratios in the white matter of the brain determined statistically significant decreases in choline to creatine (p = 0.016*) on the right and N-acetylaspartate to creatine (p = 0.003*) on the left. For other indicators of

relationships, statistically significant results could not be established. The identified changes (Cho/Cr, NAA/Cr) may indicate energy depletion in white matter neurons and, due to changes in the myelin sheath, disruption of their connections.

Assessment of ratios in gray matter demonstrated significantly significant increases on the right in the ratios of choline to creatine ($p < 0.001^*$) and choline to N-acetylaspartate ($p = 0.004^*$), as well as significant increases ($p < 0.001^*$) in Cho/NAA and NAA/Cr on the left, which may also indicate a greater need for energy supply to the cells of the gray matter of the brain. When processing the obtained results of MR spectroscopy on the content of metabolites and their ratios, using the Chaddock scale, we established moderate and noticeable ($p < 0.001^*$) closeness of both direct and reverse correlations with the MoCa test and the Spielberger-Khanin anxiety test. The established connections proved the participation of persistent disturbances in the metabolism of nerve cells in the brain in the formation of complications in the form of cognitive and emotional disorders in type 1 diabetes.

4. Conclusions

Thus, a significant increase in the level of protein S-100 in the blood serum in children and adolescents with cerebral changes in type 1 diabetes and a noticeable correlation ($p < 0.001^*$) of this component with the MoCa test indicates an increased intensity of reactive gliosis with increasing the severity of brain disorders. In addition, an increase in the level of S-100 in the blood indicates a direct influence of reactive gliosis on the processes of pathogenesis of the development of cerebral disorders in type 1 diabetes in children and adolescents. An increase in the level of NSE in the blood serum in children and adolescents with type 1 diabetes with the presence of dysfunctions affecting the brain indicates activation of anaerobic glycolysis in the central nervous system and increased permeability of neuronal membranes during the formation of cognitive deficit, especially in the early stages of diabetes, which also has of particular importance in clinical and pathogenetic processes. When analyzing MR spectroscopy in children and adolescents with type 1 diabetes, the main changes in metabolites were determined in areas directly related to the processes of cognitive activity - this is the hippocampus area, gray and white matter (subcortical structures, thalamus) of the brain. Thus, a statistically significant decrease in NAA content in the left hippocampus was revealed ($p < 0.001^*$); increased NAA levels in the white matter on the left and right ($p < 0.001^*$); decreased NAA content in the gray matter on the right ($p < 0.001^*$); increased choline level in the left hippocampus ($p = 0.016^*$); increased choline in the gray matter on the right ($p = 0.003^*$); increase in creatine in the hippocampus on the left ($p < 0.001^*$); increase in creatine in the hippocampus on the right ($p = 0.004^*$); an increase in creatine in the gray matter on the left ($p < 0.001^*$) and a decrease in creatine in the gray matter on the right ($p < 0.001^*$). The results demonstrated,

as well as the observed heterogeneous changes in the Cho/Cr ratios; Cho/NAA; NAA/Cr in patients with cognitive deficits in type 1 diabetes, in addition, the presence of correlations between the studied components may indicate intracellular changes with energy deficiency, as well as due to energy imbalance, disorders of the integrity of neurons and optimal functioning of nervous tissue in these areas, this is important both in the pathogenetic and clinical processes of changes in cognitive activity in type 1 diabetes.

Conducting a PMRS study made it possible to localize the areas of the brain responsible for the decline in cognitive functions in children and adolescents with type 1 diabetes, in addition, to obtain more accurate information about metabolic changes in these areas of the brain. In general, this method makes it possible to determine the dynamics of the condition of patients with type 1 diabetes mellitus, the presence of cerebral changes in them, even at a stage when there are no clinical manifestations, in addition to monitoring the possible progression of the disease, as well as the adequacy of the selected therapy for correcting abnormalities higher cortical activity. Referring to the results obtained, we can conclude that the use of P-MRS of the brain in the early diagnosis of manifestations of cognitive and emotional disorders in this pathology is justified, since it is possible to trace changes in brain tissue in the form of microstructural damage and visualize deviations in brain metabolism leading to cerebral dysfunctions even at the preclinical stage.

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