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An analysis of cognitive functioning of children and youth with type 1 diabetes (T1DM) in the context of glycaemic control

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Abstract. – OBJECTIVE: The aim of the study was to evaluate the cognitive functioning of children and youth with type 1 diabetes (T1DM).

PATIENTS AND METHODS: The study included 68 children with type 1 diabetes, aged 6-17 years, divided into 3 groups according to the level of glycated hemoglobin (HbA1c): group 1: HbA1c ≤ 6.0-7.5%; group 2: HbA1c 7.6-8.5%; group 3: HbA1c over 8.6%. Wechsler's intelligence scale (WISC-R), the Trail of 10 words and Brickenkamp's and Zillmer's d2 Test of Attention were used to assess cognitive functioning.

RESULTS: The research demonstrated a significant influence of low, medium or high glycaemic control on lowering the general level of functioning in verbal intelligence, and in WISC-R subtests: information, vocabulary, comprehension, number sequencing and block design.

CONCLUSIONS: Children with type 1 diabetes mellitus can experience difficulties in cognitive functioning, as a consequence of high HbA1c. Additional research, involving a larger group of patients and a wider age range when the disease was diagnosed, will enable further findings on the occurrence of cognitive impairment in T1DM.

Key Words
Diabetes, Cognitive functioning, Children, Adolescents, Glycated haemoglobin.

Introduction

Disorders of the central nervous system's development and its functional organization in people with diabetes mellitus are the subject of research more frequently[1-7]. The need for such studies emerges from scientific reports that neuronal connections between given brain parts develop differently, due to diabetes. It can be the cause of different functional organization of the brain and consequently it can affect cognitive functions. The image of cognitive dysfunctions can change along with the progress and the disease, as well as in connection to the applied treatment. A detailed analysis of functioning of children and youth with diabetes enables us to determine which cognitive functions are indeed decreasing. Furthermore, it helps to determine potential consequences of treatment.

The fact that cognitive functions decrease in relation to the duration of the disease is indicated by literature on the subject. According to Northam et al[8] and Kodl et al[9], disorders of cognitive functions can manifest very early. It can happen just after 2 years after the onset of diabetes in a child[8]. The patients in the cited research achieved lower results in the following areas: intelligence, vocabulary, visual motor coordination, speed of mental and learning processes[9]. After 6 years elapsed from the diagnosis, the results of subtests demonstrated that functions deteriorated progressively. In comparison with the control group, the following also worsened: general intelligence, attention, speed of mental processes, long-term memory and executive functions[10]. Northam et al[11,12] suggest that the disease influences the development of cognitive functions which determine motivation, anticipation and planning tasks – the processes dependent on the prefrontal cortex. These processes not only include health-focused behavior and help retain such goals in memory, but they also impede self-destructive behavior.

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Furthermore, they enable the patients to better adjust to therapeutic recommendations. Executive functions enable individuals to initiate and complete tasks. They are of particular importance when the required behavior is complex and connected with multitasking[13].

Patients and Methods

Patients

68 children between of 6 and 17 years of age (average age 11.8 (±2.83) years) took part in the research. They had all experienced type 1 diabetes for more than two years. All of the patients were under constant care of the Diabetes Clinic for Children (Poznan, Poland). Moreover, they were periodically hospitalized in the course of the research at the Diabetes and Obesity in the Developmental Age Clinic at Poznan University of Medical Sciences (Poznan, Poland). Both the parents of the patients, as well as the patients themselves, expressed informed consent for their participation in the research, in accordance with the Declaration of Helsinki.

The hospitalization was carried out as part of the scheduled medical routine. Except for type 1 diabetes, patients qualified for the study did not experience additional disorders, such as thyroiditis, absorption disorders, epilepsy, etc., which could have influenced the results of the research. Participation in the research did not interfere with therapeutic procedures at the hospital. In order to assess glycaemic control in the blood of children and youth with type 1 diabetes, glycated hemoglobin concentration (HbA1c) was marked. On the first day of the hospital stay, as a part of the standard admission and diagnostic testing, blood was taken from the median cubital vein (*vena mediana cubiti*). The patients were fasting at that time. HbA1c concentration was tested at the Laboratory of the Teaching Hospital of Poznan University of Medical Sciences (Poznan, Poland) utilizing AxSYM HbA1c test (Abbott Laboratories, Abbott Park, IL, USA).

The normative value was assumed on the basis of the available literature[14]. Psychological testing was carried out during a patient's stay at the ward. Neuropsychological tests were used in order to assess cognitive functioning. The tests enabled an objective evaluation of the efficiency of various cognitive areas, such as verbal and executive functions, memory, attention and learning processes. The tests were carried out by qualified personnel according to standardization principles. In order to minimize the patient's fear of evaluation, and also to enable solving tasks at the highest possible level, the neuropsychologist's responsibility was also to create an optimal emotional environment. Glucose level in the capillary blood was routinely monitored directly before testing, in order to exclude the potential for hypoglycemia or hyperglycemia during the tests.

Wechsler's Intelligence Scale was used to measure the general level of intelligence[15,16]. A modified version of the test was employed to evaluate children's intelligence level (WISC-R)[16]. The test includes verbal and nonverbal subtests. It engages various cognitive and executive functions, thus enabling a complete diagnosis of intellect. Scales used are: information, picture completion, similarities, picture concepts, arithmetic, block design, vocabulary, puzzles, comprehension, coding and number sequencing[17]. IQ of the verbal scale (IW) measures verbal skills. It is also an indicator of the generally understood language skills. A set of language skills depends on the child's experience, because it is based on the ability to recall the previously acquired knowledge. IQ of the nonverbal scale (IN) measures the level of nonverbal capabilities and it is based on the child's ability to solve new problems.

Brickenkamp's and Zillmer's d2 test of attention was used in order to evaluate attention[18,19]. It is a nonverbal test, which measures several attention characteristics, such as noticing speed, number of mistakes, as well as general attention and concentration ability. The d2 test is independent of the results of the intelligence level. It consists of a form with 14 lines, each of them includes 47 characters. After the task is completed, the number of correctly marked letters is counted, together with the number of mistakes (omissions and incorrectly marked letters). The next stage was an analysis of attention characteristics, such as: speed that the tested person works with, assessed by the total number of reviewed letters; accuracy, general noticing ability and the ability to concentrate. The patients obtained results, which are normal for their age group. Raw scores were cross-referenced in order to quantitatively compare the attention characteristics of the 3 tested groups.

The trial of 10 words was used to evaluate memory function in children and youth with type 1 diabetes[20-22]. The trial enables evaluating auditory memory, both direct and deferred, as well as the effectiveness of learning process. The tested subjects are given a list of 10 words, which they memorize during 5 consecutive attempts. The examiner reads the words from the list out loud and afterwards, the examined subjects repeat all the

words they managed to remember after each of the learning attempts. The score is the number of words reproduced by the tested person correctly at the first attempt (which is an indicator of effectiveness of the direct auditory memory) and after the next five attempts. In order to compare the results of each group, the raw scores were analyzed.

Average testing time of each person amounted to roughly 1.5 hours. The patients and their guardians were all given feedback about the results from each of the cognitive tests.

Statistical Analysis

The database and all calculations performed during the study were created in SPSS Statistica PL.17.0 statistical software package (SPSS Inc., Chicago, IL, USA). Test results were also interpreted via descriptive statistics. The parameters of the measured characteristics were presented as the arithmetic mean and standard deviation (SD). Statistical significance of the intergroup differences was assessed by using the Student's parametric *t*-test, after a verification of normal distribution was carried out. A nonparametric χ^2-test was used to define the differences in the distribution of the tested population. A statistical significance of $p<0.05$ was accepted as the base. The scope and plan of the research received a positive opinion from the Bioethics Committee of Poznan University of Medical Sciences (Poznan, Poland (Resolution number 871/10).

Results

The researched HbA1c variable was presented in Table I, which was divided into three groups according to literature on the subject. The groups were: a) low HbA1c control ≤ 6.0-7.5; b) medium HbA1c control between 7.6 and 8.5%; c) high HbA1c control over 8.6%. The characteristic of the tested group was presented in Table I due to glycaemic control. Most children (38) were in the group with the worst glycaemic control. Low glycaemic control was present in 29 cases, while medium glycaemic control was found in 9 patients.

Table I. Division and comparison of groups according to glycaemic control for each WISC-R subtest.

Glycemic control		≤ 7.5[%] HbA1cHbA1c	7.6-8.5[%] HbA1c	8.6[%]
N		**21 9**	**38**	
Age		**11.39±2.66a**	**11.50±3.29b**	**13.79±1.81ab**
Sex % girls		55 38	60	
T1DM duration (years)		**4.50±2.99c**	**3.44±1.29d**	**6.36±2.98cd**
Age at T1DM diagnosis (years)		6.89±3.48	8.06±4.19	7.42±3.20
WISC-R test	IQ Full-scale intelligence quotient (IQ)	116.06 ±11.64	**119.12 ±12.27e**	**110.27 ±11.09e**
	Verbal intelligence	115.00 ±10.92	**120.87 ±12.36f**	**106.70 ±11.09f**
	Non-verbal intelligence	113.56 ±13.24	114.62 ±16.03	112.09 ±12.98
	Information	**11.11 ±2.69g**	**12.25 ±2.91h**	**8.97 ±2.43gh**
	Similarities	13.17 ±2.35	14.50 ±3.33	12.03 ±2.21
	Arithmetic	11.78 ±3.47	11.12 ±3.35	11.45 ±2.69
	Vocabulary	**12.22 ±1.89i**	**13.12 ±2.16j**	**10.21 ±2.39ij**
	Comprehension	**13.61 ±2.06k**	**14.37 ±2.19l**	**12.27 ±2.45kl**
	Number Sequencing	**12.00 ±3.53m**	**9.12 ±2.53m**	11.06 ±3.08
	Picture completion	10.06 ±2.95	10.87 ±2.29	9.97 ±2.31
	Picture concepts	12.67 ±3.34	13.37 ±3.50	13.15 ±3.36
	Block design	**13.11 ±3.10n**	**12.25 ±2.81**	11.09 ±2.56n
	Puzzles			
	Matrix Reasoning	12.00 ±3.30	11.62 ±3.96	11.91 ±3.22
	Coding	11.89 ±3.12	12.25 ±4.49	12.33 ±3.16
d2 test	Speed of work (WZ)	378 ±59.36	399 ±35.71	392 ±57.83
	Accuracy of work (B)	133 ±16.86	153 ±27.78	136 ±21.04
	General noticing ability (WZ-B)	257 ±52.20	243 ±47.87	253 ±96.28
	Abilityt o concentrate (ZK)	140 ±18.52	136 ±35.77	143 ±24.20
10 word test	9 ±0.64	8 ±1.568 ±0.48		

SD: Standard Deviation. a, b, c – statistically significant differences at <0.05. a p=0.049; b p=0.003; c p=0.006, d p=0.002; e p=0.003; f p=0.006; g p=0.05; h p= 0.033; i p= 0.049; j p=0.016; k p=0.038; l p=0.0001; m p=0.0001; n p=0.01.

Table I presents the results of the mean of the intelligence quotient, verbal and executive functions. The results of the cognitive functions included within intelligence, together with glycaemic control, are also shown in Table I. A certain influence of the specific HbA1c values on a number of cognitive functions was demonstrated. Making a comparison between the group with HbA1c under 7.5%, and the group with HbA1c over 8.6%, significantly lower results in verbal functioning were found in the population with higher values of glycaemic control (p=0.003). The result of the verbal intelligence quotient in the group with HbA1c lower 7.5% was 115, while in the group with HbA1c over 8.6% was 107.

Further analysis (the Student's t-test) demonstrated a statistically significant difference (p=0.006) in the Information subtest of the WISC-R test, between the groups with HbA1c under 7.5% and 7.6-8.5% (result equal to 11 and 12 respectively), as well as the group with HbA1c over 8.6% (result equal to 9) (p=0.002).

A similar correlation was detected in the vocabulary subtest. The lowest results were achieved by the group with the worst control. The results in respective groups equalled were: 12 points – for HbA1c under 7.5%; 13 points – for HbA1c between 7.6 and 8.5% (p=0.003); 10 points – for HbA1c over 8.6% (p=0.006).

The analysis (the Student's t-test) demonstrated a statistically significant difference in the Comprehension subtest of the WISC-R test, between the group with HbA1c 7.6-8.5% (p=0.05) and the group with HbA1c over 8.6% (p=0.033). The lowest results were achieved by the group with the worst metabolic control.

A statistically significant difference (p=0.016) was also found in the Block design subtest of the WISC-R test, between the group with HbA1c under 7.5% and the group with HbA1c over 8.6%. These results were 13 and 11, respectively.

The analysis (the Student's t-test) also demonstrated a statistically significant difference (p=0.049) in the Number sequencing subtest of the WISC-R test, between the group with HbA1c under 7.5% and the group with HbA1c from the 7.6-8.5% range (mean values were 12 and 9.12, respectively).

The next aspect analyzed was the attention and memory test, taking into consideration the glycated hemoglobin concentration. The Student's t-test did not demonstrate statistically significant differences in the d2 and 10 word tests between the respective tested groups with different HbA1c control.

A statistically significant correlation was also observed with the duration of diabetes in the respective tested groups. Children who had type 1 diabetes on average for 6.36±2.98 years achieved significantly higher results in glycated hemoglobin concentration. Children and youth in this group were aged 13.79 (±1.81 years).

Discussion

Analyzing the influence of type 1 diabetes on cognitive processes seems significant because of two reasons: the first, appearing in reports from many scientific research, suggesting possible cognitive deficits hindering the young patients' ability to control the disease. The second one, an increasing number of type 1 diabetes cases appearing among younger children. Decreasing cognitive functions should be treated as a disturbing sign, because children are simultaneously endangered by the long-term effects of T1DM, which intensify along with age of the patient. The disease requires continuous calculations and analysis of the consumed food, physical activity and the child's own insulin demand. A decrease of cognitive functioning can negatively affect diabetes control. In this context, an early intervention and functional neuropsychological therapy could lower the risk of early complications.

In the studies, a lower level of cognitive functioning was detected in patients who did not control their blood sugar level well. Their lower scores in the verbal scale, as well as in the subtests (information, vocabulary, comprehension, block design and number sequencing) further prove it. The information subtest is comprised of 29 questions pertaining to general knowledge which children acquire at home and at school. Questions refer only to familiarity with specified facts, without requiring an ability to connect them, or finding a connection between them. This subtest measures verbal expression; ability to acquire, retain and retrieve knowledge; retrieving information from the area of general knowledge; persistence of verbal memory; ability to automatically remember memorized answers[17]. The vocabulary subtest measures the auditory perception of simple verbal stimuli, verbal expression, abstract thinking, creating concepts, knowledge resources, language skills (verbalization and defining), the ability to learn, as well as long-term memory and recall[17]. The analysis of the assembled research material showed a statistically significant

difference in the comprehension subtest of the WISC-R test between the groups of children with glycaemic control at the level ≤6.0-7.5; and the group of children whose glycated hemoglobin was over 8.6%. The first group (HbA1c between 6 and 7.5%) achieved higher results in the comprehension subtest. The subtest examines familiarity with conventional behavioural standards, common knowledge about the environment, as well as socially accepted judgments and rules of behaviour. It also refers to understanding of their origins and what purpose they serve[17].

The block design subtest requires the ability to visually synthesize and organize. It measures such functions as visual-motor integration, an ability to organize and synthesize observable data, comprehensive and simultaneous information processing, an ability to plan, speed of mental processes, learning by trial and error, creative thinking, and the ability to work under the pressure of time[17].

Significantly lower results were achieved by the patients with the highest HbA1c in the Number sequencing subtest. It measures auditory perception of simple stimuli, understanding commands, simple skills of naming, short-term auditory memory, direct remembering, sequential processing, information coding for later processing (backwards), and experience with numbers[17].

Regardless of the level of general intelligence, difficulties with using acquired knowledge (for example, solving new problems) are connected with a number of problems. They include difficulties with verbalizing and naming a problem (vocabulary), predicting and planning behaviours (comprehension), as well as assembling elements into a whole (block design). These can negatively influence one's ability to react in difficult circumstances (connected with hypoglycemia and with hyperglycemia), e.g. prolonged emotional strain (connected with uncontrolled glycaemia) and experiencing difficulties dealing with the disease. Observations lasting for 18 years, undertaken as a part of Diabetes Control and Complications Trail (DCCT) program, showed an interesting result: patients with type 1 diabetes, whose mean concentration of glycated hemoglobin (HbA1c) was lower than 7.4%, achieved significantly better results in the tests examining speed of thought processes and visual-motor integration, than people with mean HbA1c larger than 8.8%[23].

The higher the HbA1c value, the lower the results in the area of general cognitive functioning[24]. The latest research shows changes in microstructural integrity of white matter in the parietal lobe, the hippocampus and the thalamus[25]. It is believed that these changes are responsible for neurocognitive deficits, such as lower processing speed, weaker attention and smaller executive abilities[26]. However, it is unknown whether the structural changes of the white matter are directly connected with the course of diabetes[25,26].

The results of our research do not stand in opposition with the results achieved in previous testing of children with T1DM with mild cognitive impairment[6,27]. It is worth emphasizing the difference in our research and research studies conducted by other authors, leading to separate findings. Cognitive processes can be particularly susceptible to insulin level fluctuation during the period of intensive brain growth (in childhood). Even though mild cognitive differences can be detected early, more serious effects can become visible in later stages of life. The effects of the changes in brain functioning connected with age, are superimposed on long-term effects of T1DM and comorbidity, for example: hypertension or microangiopathy.

The results of our research motivate us to undertake further longitudinal studies of changes to cognitive functioning of people with T1DM in later phases of their development. In the course of DCCT research, covering a period of 18 years, no significant proof of a decrease in cognitive functions was found among patients with diabetes[23]. However, many participants of DCCT were diagnosed when they were already adults (average age in the DCCT research is 27.0 years and an average duration of diabetes is 5.7 years). This stands in contrast to our group, which included people up to 16 years of age who were diagnosed in their childhood. Moreover, two young adults with a relatively good metabolic control took part in the DCCT research. In another research, lasting 14 years and involving a group of people with T1DM with the mean HbA1c ≥7.5% (58 mmol/mol), it was demonstrated that the most prevalent disorders were distal symmetric polyneuropathy and proliferative retinopathy, and that they were associated with cognitive disorders[28,29]. Further testing of young adults with T1DM points to a relationship between the number of severe episodes of hypoglycemia and cognitive disorders. Chronic hyperglycemia, and the vascular and metabolic symptoms of it, can cause structural changes in the brain, which may disrupt cognitive functioning. A study of the relationship between cognitive disorders and type 1 diabetes do not always leads to unequivocal findings. For this

reason, it is necessary to consider more than just the form of the disease manifestation, but also its duration and the often-resulting high blood pressure[30-33]. These combined factors can certainly influence cognitive functioning of patients. Results of several neurocognitive tests used in our research (for instance D2, WISC-R subtests) depend on the visual acuity and motor-visual capabilities. Both can be weakened in people with T1DM with proliferative retinopathy and distal symmetric polyneuropathy. These symptoms can contribute to achieving lower scores in tasks that require psychomotor speed and executive function, especially for people experiencing T1DM for a long time. They also seem to influence cognitive functioning in children with T1DM well before microvascular complications appear[6,34]. Long-term T1DM causes impairment of microcirculation in the brain, which influences sight. This helps to understand why patients with proliferative retinopathy and distal symmetric polyneuropathy tend to meet clinical criteria for significant cognitive disorders more frequently [7]. As authors of the research, we are aware that the results achieved are not representative of the whole population of patients with T1DM. We have concentrated on observing whether a bad glycaemic control influences the cognitive functioning, and if it does, in what areas it occurs most frequently. Only people diagnosed with diabetes in childhood were included in our research. Consequently, functional cognitive effects of T1DM were determined in children at risk for chronic hypo- and hyperglycemia, during a period of critical brain and cognitive functions development[35]. Limitations of this research are connected with the fact that the group of patients with the highest HbA1c level was the largest, and patients in this group were also significantly older (13.8 years in comparison to 11.5 years). This means that the members of this group had experienced diabetes for a significantly longer period. It is common knowledge that glycemic control decreases during adolescence and also with a longer duration of diabetes. This in turn is connected with a higher probability of experiencing severe complications, such as diabetic ketoacidosis or severe hypoglycemia, that can affect cognitive functioning. The research results are significant and they accentuate the importance of glycemic control, both in relation to the disease duration and to its effective management. As for the relationship between quality of life (QoL) and metabolic control, it was observed that a higher number of daily glycaemic controls correlates with better psychological aspects of QoL[36].

One of strong points of our research is the choice of a well-defined group of patients with diabetes. It enabled us to identify risk factors and detrimental changes in cognitive functioning. Utilising a wide spectrum of neuropsychological tests, targeting a number of different cognitive areas, further contributed to the robust character of the achieveed results.

Selective deficits in anticipation and selecting an appropriate response can influence the ability to manage the disorder. The findings of our research can contribute to constructing neuropsychological methods, which help patient to cope with the disease. It is vital to adjust diabetes education to the level of intellectual functioning, as well as to the age of a patient. This will improve their ability to make independent decisions regarding therapy, e.g. analyze a meal's glycaemic value and the required dosage of insulin. Such changes in patients' understading of the disease are helpful in shaping and maintaining motivation to act in a manner to protect their own health[37,38].

Conclusions

A significant relationship between the high level of HbA1c and a decrease of the general level of cognitive functioning was noted. It was particularly visible with verbal intelligence; especially, in the results of the following subtests: information, vocabulary, comprehension, number sequencing, and block design. Even discrete cognitive changes may, as one of the factors, influence diabetes control, especially in situations connected with psychological stress. Difficulties with controlling diabetes may be connected with the need for frequent hospitalization. It also increases the risk of a disability occurring in adult life. There is a need to conduct further research, involving a larger sample and a wider age spectrum of patients, at the time of diagnosing the disease. This should be undertaken in order to get a better understanding of growth processes and the neurocognitive impairments that may be connected with T1DM.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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