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Анализ роли нейроспецифических белков в диагностике когнитивной дисфункции у пациентов с сахарным диабетом 1 типа

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Одним из тяжелых прогрессирующих сосудистых осложнений сахарного диабета 1 типа (СД1) является поражение центральной нервной системы, проявляющееся когнитивными нарушениями вследствие метаболических или структурных изменений. Существенные трудности диагностики когнитивной дисфункции связаны с субъективизмом методов исследования.

Цель. *Определение роли нейроспецифических маркеров в диагностике когнитивной дисфункции у пациентов с СД1.*

Материалы и методы*. Было обследовано 58 пациентов с СД1 в возрасте 16-30 лет; группу контроля составили 29 здоровых молодых людей, сопоставимых по полу и возрасту. Комплекс обследования включал клинико-лабораторное обследование, психологическое тестирование и магнитно-резонансную томографию (МРТ) головного мозга. Для скрининга когнитивных нарушений использовалась Монреальская шкала (МоСа тест). Для идентификации ранних маркеров развития когнитивной дисфункции были определены нейроспецифические белки – протеин S100, глиальный фибриллярный кислый белок (GFAP), основной белок миелина (MBP). Для оценки структурных изменений центральной нервной системы была выполнена МРТ головного мозга на аппарате Siemens Magnetom 1,0 Тл.*

Результаты. *В результате проведенного исследования выявлен повышенный уровень всех нейроспецифических белков, который коррелировал с показателями гипергликемии и когнитивным дефицитом (МоСа тест менее 26 баллов). МРТ-картина головного мозга показала наличие признаков атрофии серого вещества, поражения белого вещества головного мозга, которые коррелировали с наличием хронической гипергликемии, когнитивными нарушениями, микрососудистыми осложнениями.*

Заключение. *Гипергликемия при сахарном диабете может быть частью патогенетического механизма развития патологии центральной нервной системы и формирования когнитивных нарушений. Взаимосвязь сахарного диабета и патологии центральной нервной системы требует дальнейшего изучения в проспективных контролируемых и наблюдательных исследованиях для разработки эффективных средств профилактики и лечения соответствующих расстройств.*

Ключевые слова: *сахарный диабет 1 типа; когнитивная дисфункция; нейроспецифические белки; магнитно-резонансная томография*

Analysis of the Role of Neurospecific Proteins in the Diagnosis of Cognitive Dysfunction in Patients with Type 1 Diabetes Mellitus

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Background. *Impairment of the central nervous system manifested as cognitive dysfunction caused by metabolic or structural changes is a severe progressive vascular complication of type 1 diabetes mellitus (T1DM). Significant difficulties in the diagnosis of cognitive dysfunction are associated with subjective diagnostic techniques.*

Objective. *To identify the role of neurospecific markers in the diagnosis of cognitive dysfunction in patients with T1DM.*

Materials and Methods*. A total of 58 patients with T1DM aged 16–30 years were included in this study. The control group included 29 healthy young adults matched by gender and age. The survey included clinical and laboratory examinations, psychological testing and magnetic resonance imaging (MRI) of the brain. The Montreal Cognitive Assessment (MoCA) was used to screen for cognitive impairment. The levels of neurospecific proteins (S100, glial fibrillary acidic protein and myelin basic protein) were determined to identify early markers of cognitive impairment. MRI of the brain was performed using a Siemens Magnetom 1.0 T system to assess structural changes in the central nervous system.*

Results. *The study revealed increased levels of all neurospecific proteins, which correlated with parameters of hyperglycaemia and cognitive deficit (MoCA scores of <26 points). MRI of the brain revealed signs of grey matter atrophy and involvement of white matter, which correlated with the presence of chronic hyperglycaemia, cognitive impairment and microvascular complications.*

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Conclusion. *Chronic hyperglycemia can be involved in the pathogenesis of cognitive dysfunction in T1DM patients. More studies (prospective controlled and observational trials) are needed to clarify the relationship of diabetes and central nervous system impairment.*
Keywords: *type 1 diabetes mellitus; cognitive dysfunction; neurospecific proteins; magnetic resonance imaging*

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There has been a steady increase in the worldwide incidence of diabetes mellitus (DM), reaching the proportions of a noninfectious epidemic. Analysis of the data from the Russian State Diabetes Mellitus Registry shows that the incidence of type 1 diabetes mellitus (T1DM) has increased over the past 10 years by 35.7% in children (from 59.4 to 80.6 per 100,000), 68.9% in adolescents (from 108.5 to 183.5 per 100,000) and 2.36% in adults (from 224.5 to 229.8 per 100) [1]. The central nervous system is adversely affected by hyperglycaemia even in the early stage of the disease. The clinical implications of this process include cognitive dysfunction, which, in turn, reduces patients' compliance with physician's recommendations and their quality of life [2]. Although changes in higher brain functions in patients with DM have been documented, no general concept describing these dysfunctions has been accepted. Thus, no data on brain disorders associated with DM are available in the International Classification of Diseases. However, attempts have been made to describe these changes using medical terminology. For example, DeJong RN introduced the term 'diabetic encephalopathy' (DE) in 1950 [3]. According to Trudeau F et al., DE represents persistent cerebral pathology caused by acute, subacute and chronic diabetic metabolic and vascular disorders that manifest clinically as neurosis-like and psychosis-like disorders and organic neurological and autonomic symptoms, including characteristic biochemical, electrophysiological and morphological changes [4].

The Montreal Cognitive Assessment (MoCA), which was developed as a tool for rapid assessment of various cognitive dysfunctions, is currently widely used by researchers to assess the overall severity of cognitive dysfunction in different nosological entities. However, bias introduced through human factors and the possibility of generating false-positive and false-negative results cannot be excluded when evaluating the results of this test [5]. Because neuropsychological testing may be subject to bias, researchers are focusing on identifying neurospecific markers of brain damage. For example, the levels of neurospecific proteins vary quantitatively in various traumatic, oncological and metabolic diseases and can serve as markers for ketoacidosis-related brain oedema and hypoglycaemia [6, 7, 8]. The levels of glial fibrillary acidic protein (GFAP) and S100 serve as markers of astrocyte death and those of myelin basic protein (MBP) indicate damage to oligodendrocytes [9, 10, 11].

Increased blood levels of neurospecific proteins indicate damage to the nervous tissue and allow clinicians and researchers to make intravital assessment of the status of the central nervous system and to study the dynamics of neurodegenerative processes. The morphological substrates of cognitive impairment can include cerebral atrophy, single and multiple low-density foci in the cerebral cortex and subcortical substances combined with expanded cerebrospinal fluid (CSF) transport pathways [12, 13].

OBJECTIVES

Therefore, the objective of our study was to determine the utility of neurospecific markers of brain damage for diagnosing cognitive dysfunction in patients with T1DM.

MATERIALS AND METHODS

We studied 58 patients with T1DM aged 22.45 ± 4.62 years, including 29 males and 29 females. The mean disease duration was 6.6 ± 3.95 years. The control group comprised 29 healthy individuals matched by age (22.37 ± 4.72 years), including 14 males and 15 females without chronic or acute diseases (Table 1). The group of patients with T1DM comprised high school or college students (56.9%) and employed individuals (43.1%). The Ethics Committee of the Siberian State Medical University, Ministry of Health of the Russian Federation, approved the study protocol. All patients provided voluntary informed consent to participate in the study.

The inclusion criteria were as follows: signed informed consent to participate in the study, T1DM and age between 16 to 30 years. The study included only patients without hypoglycaemic or ketoacidotic coma during the previous 2 months and without neurological infections, perinatal damage to the central nervous system or hematologic, oncological, severe infectious or traumatic diseases (Table 1).

All patients underwent physical examination and detailed analysis of their medical history. The diagnosis of T1DM was verified on the basis of the algorithms of specialized medical care for diabetic patients (2013), which recommend age-specific assessment of the target values of carbohydrate metabolism [14]. Therefore, the patients were divided into a group that included 12 adolescents aged 16–18

Table 1

Characteristics of patients

Groups	T1DM patients		Control group	
Sex	Males	Females	Males	Females
n/%	29 (50)	29 (50)	14 (48,3)	15 (51,7)
Age, years	22,45±4,627		22,37±4,727	
Glycated haemoglobin (HbA_{1c}), %	8,5±1,83*		5,0±0,64*	
Fasting glucose, mmol/l	10,0±4,95*		5,0±0,725*	

* $p < 0.001$ indicates a significant difference between control subjects and patients with T1DM.

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Table 2

Age-specific target values of HbA_{1c}			
The level of carbohydrate metabolism compensation (HbA_{1c})	Patients aged 16–18 years, n = 12	HbA_{1c} levels taking into account the individual selection of treatment targets	Patients aged 19–30 years (young), n = 46
Compensation stage (HbA_{1c} <7.5%)	3 (25%)	No severe complications/risk of severe hypoglycaemia HbA_{1c} <6.5%	0
Subcompensation stage (HbA_{1c} 7.5%–9%)	3 (25%)	Severe complications/risk of severe hypoglycaemia HbA_{1c} <7%	4 (9%)
Decompensation stage (HbA_{1c} >9%)	6 (50%)	No severe complications/risk of severe hypoglycaemia HbA_{1c} >6.5%	34 (74%)
		Severe complications/risk of severe hypoglycaemia HbA_{1c} >7%	8 (17%)

years and a group that included 46 adults aged 19–30 years. Analysis of glycated haemoglobin (HbA_{1c}) levels showed that 50% adolescents and 94.6% adults did not reach the target values of carbohydrate metabolism (Table 2).

Blood glucose levels were determined using a Hitachi 912 biochemical analyser (Hoffmann La Roche Ltd./ Roche Diagnostics GmbH). HbA_{1c} levels were evaluated using high-pressure liquid chromatography with a DS5 Glycomat glycated haemoglobin analyser (Drew Scientific Company, Netherlands). Continuous monitoring of blood glucose levels was performed using iPro®2 (Medtronic) and CGM System Gold (Medtronic) systems with Paradigm Veo and Paradigm REAL-Time MMT-722 insulin pumps (Medtronic). ComLink software was used.

Patients underwent neurological consultation. Neurological testing was performed using MoCA that rapidly screens for mild to moderate cognitive impairment and evaluates different cognitive functions as follows: visual–spatial perception (clock and cube drawing tests), executive functions (creating alternative pathways and testing ability to think in abstract terms), attention, concentration and short-term memory (serial subtraction of 7 and reproducing a numerical series in forward and reverse orders). Verbal function was assessed according to a subject's ability to identify depicted animals, repeat two syntactically complex sentences as well as speech fluency, which also evaluated executive functions [15].

S100 levels were quantitated using the COBAS test (Roche Elecsys 1010). GFAP levels were determined using an enzyme-linked immunosorbent assay (ELISA) and a reagent kit provided by the manufacturer (Human Fas ELISA, Bender MedSystems GmbH, Vienna, Austria) according to the manufacturer's protocols. MBP levels were determined using a Roche kit (USA).

The combination of obligatory diagnostic methods included MRI of the brain using a Siemens Magnetom 1.0 T system (Diagnostic and Treatment Center, International Institute of Biological Systems) that was routinely conducted in the axial, sagittal and coronal projections (T2- and T1-weighted images) using FLAIR software.

The data were processed using Microsoft Excel 2010 and IBM SPSS Statistics 21.0 software. The arithmetic mean (m) and standard deviation (SD) were calculated for quantitative parameters. The significance of the differences between the independent data samples with abnormal distribution of data was assessed using the Mann–Whitney and Kolmogorov–Smirnov tests, including determination of Z (Kolmogorov–Smirnov) and U (Mann–Whitney) values. For normally distributed data (MoCA), a t-test for independent samples was used, including calculation of the p-value for the Spearman correlation coefficient (r). When conducting correlation analysis, correlation between the data was considered to be strong at an absolute r value of >0.70, average at the r value of 0.69–0.30 and weak at the r value of <0.29. When testing statistical hypotheses, the statistical significance was defined as $p < 0.05$ [16].

RESULTS

Analysis of carbohydrate metabolism revealed that the average HbA_{1c} levels of patients with T1DM were 8.84% ± 1.833%, and their fasting glucose levels were 11.52 ± 4.957 mmol/l. Therefore, the patients had unsatisfactory metabolic control and did not reach the target values of carbohydrate metabolism, which were <7.5% for adolescents, <6.5% for patients aged 19–30 years in the absence of severe complications and risk of severe hypoglycaemia and <7% in the presence of these factors. The most frequent complication of T1DM was diabetic retinopathy, which occurred in 82.8% (48) patients [nonproliferative in 74.1% (43) patients, preproliferative in 6.9% (4) patients and proliferative in 1.7 % (1) patients]. Diabetic neuropathy was detected in 72.4% (42) patients [sensorimotor in 55.2% (32) patients and autonomous, akin to asymptomatic hypoglycaemia, in 17.2% (10) patients]. Diabetic nephropathy was identified in 37.9% (22) patients [microalbuminuria in 34.5% (20) patients and proteinuria in 3.4% (2) patients].

The present study reveals a significant increase in the levels of S100, MBP and GFAP in patients with T1DM compared with control subjects ($p < 0.001$) (Table 4). Furthermore, the levels of GFAP were much lower in females than in males ($U = 643.000$, $Z = -2.418$, $p < 0.05$).

MRI of the brain revealed indirect signs of grey matter atrophy in the frontal lobes and partially in the parietal lobes, indicated by the presence of arachnoid cysts containing CSF in 93.1% patients and widening of the convexital spaces containing CSF in 72.4% patients. White matter atrophy

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Table 3

MoCA results								
	Patients with T1DM (n = 58)		Females (n = 29)		Males (n = 29)		Control group (n = 29)	
	m	SD	m	SD	m	SD	m	SD
Alternative pathway	1,00	0,45	1,0	0,46	1,00	0,47	1,00	0,00
Cube	1,00	0,42	1,0	0,46	1,00	0,39	1,00	0,00
Clock	3,00	0,41	3,00	0,28	3,00	0,47	3,00	0,00
Naming	3,00	0,84	3,00	0,20	3,00	0,17	3,00	0,00
Memory	3,00*	1,29	3,00*	1,17	3,00*	1,36	5,00*	0,00
Numerical series	2,00*	0,63	1,00**	0,65	2,00*	0,62	2,0*	0,00
Letter A	1,00	0,87	1,00	0,20	1,00	0,17	1,00	0,00
Serial subtraction	2,00*	0,82	2,00*	0,81	2,00*	0,78	3,00*	0,00
Repeating sentences	2,00	0,38	2,00	0,29	2,00	0,46	1,83	0,37
Fluency of speech	1,00	0,78	1,00	0,82	1,00	0,76	0,87	0,34
Abstraction	2,00	0,43	2,00	0,5	2,00	0,36	2,00	0,00
Orientation	6,00	0,23	6,00	0,00	6,00	0,29	6,0	0,00
Total score	25,00*	0,81	25,00*	1,82	25,00*	2,27	30*	0,43

*p < 0.001, **p < 0.01 indicate significant differences between controls and patients with T1DM; m - median; SD - standard deviation

was not detectable. However, areas of gliosis and lesions of leukoaraiosis were observed in 15.5% and 19% patients, respectively.

DISCUSSION

Neurospecific proteins were investigated as possible objective diagnostic biomarkers of cognitive impairment. Their levels were high in patients with T1DM, which is indicative of microstructural brain damage. Further, patients with unsatisfactory control of carbohydrate metabolism had higher S100 levels. The positive correlation of S100 levels with HbA_{1c} levels and fasting glucose levels is shown in Figs. 1, 2 ($p < 0.05$), demonstrating the role of chronic hyperglycaemia in the apoptosis of neural tissue cells. In contrast with these observations , Strachan MWJ et al. reported that S100 levels were significantly higher in patients who died of hypoglycaemia. [17]. Nevertheless, these processes mediate the destruction of brain tissue to greater or lesser extents.

No studies are published that focus on the relationship between MPB levels and carbohydrate metabolism parameters in patients with T1DM. Here we show a positive correlation of MBP levels with HbA_{1c} levels and fasting glucose levels ($p < 0.05$) (Figs. 3, 4).

Table 4

Levels of neurospecific proteins				
Neurospecific proteins	T1DM (n = 58)		Control group (n = 29)	
	m	SD	m	SD
Myelin basic protein, ng/ml	0,13*	0,043	0,10*	0,036
Glial fibrillary acidic protein, ng/ml	0,11*	0,041	0,08*	0,033
S100, ng/ml	121,65*	66,39	62,85*	19,66

*p < 0.01 indicates a significant difference between control subjects and patients with T1DM.

The present study demonstrates a positive correlation between the parameters of carbohydrate metabolism and the levels of GFAP ($p < 0.05$), which indicates that hyperglycaemia affects the mechanism of astrocyte apoptosis (Figs. 5, 6). There is no unanimous opinion regarding the relationship between the levels of GFAP and the parameters of carbohydrate metabolism. For example, Coleman E et al. demonstrated that there is a significant increase in GFAP levels in the hippocampus, cerebellum and white matter of rats with experimentally induced T1DM [18].

By themselves, the high levels of neurospecific proteins in patients with T1DM do not support the conclusion that they serve as markers of cognitive impairment. Therefore, the relationship between protein levels and the MoCA score was analysed. We observed that S100 levels correlated negatively with MoCA parameters such as memory ($r = -0.617$, $p < 0.05$). Thus, S100 levels may indicate impaired memory (Fig. 7).

Brain MRI results revealed signs of cerebral atrophy such as arachnoid CSF-containing cysts and widened convexital spaces containing CSF. These findings are in agreement with published data. For example, one study described grey matter atrophy in patients with decompensated ketoacidosis with high HbA_{1c} levels, which were mainly detected in the frontal lobes and the central portions of the parietal lobes and were associated with cognitive impairment [19]. Our present results are consistent with these data, because widening of the convexital spaces was significantly more pronounced in patients with high HbA_{1c} levels ($\chi 2 = 16.276$, $p = 0.039$) and fasting glucose levels ($\chi 2 = 27.620$, $p = 0.024$). Correlation analysis of the results of examining the same patients revealed cognitive impairment and memory ($\chi 2 = 12.872$, $p = 0.025$) and attention loss ($\chi 2 = 6.820$, $p = 0.033$) as assessed by

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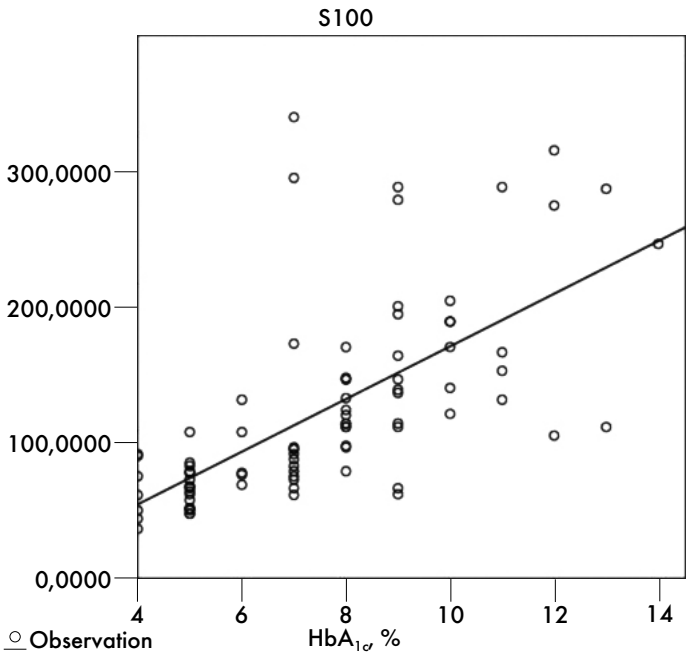

Fig. 1. S100 levels vs HbA_{1c} levels

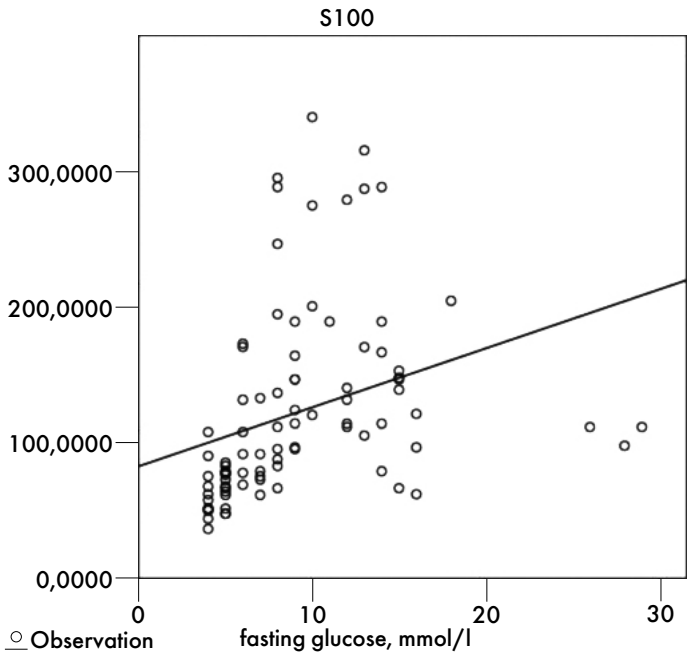

Fig. 2. S100 levels vs fasting glucose levels

Note: HbA_{1c}: glycated haemoglobin; S100: S100 neurospecific protein

S100: S100 neurospecific protein

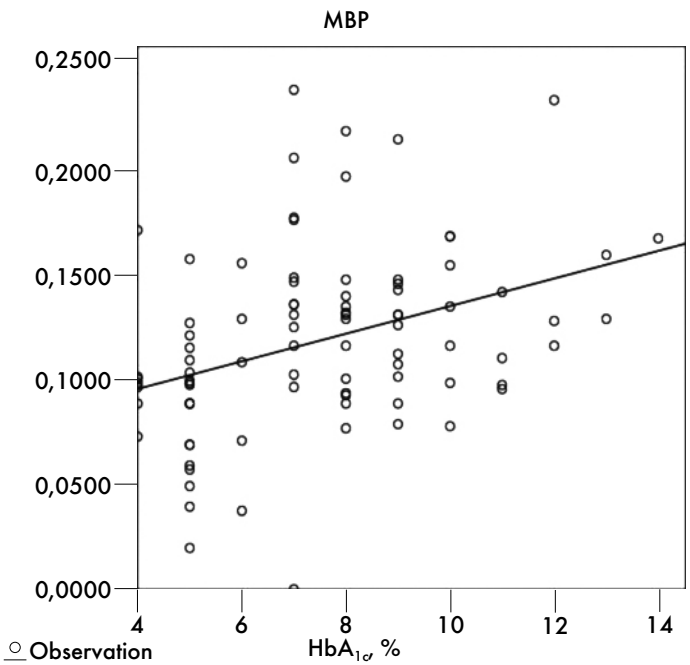

Fig. 3. MBP levels vs HbA_{1c} levels

HbA_{1c}: glycated haemoglobin; MBP: myelin basic protein

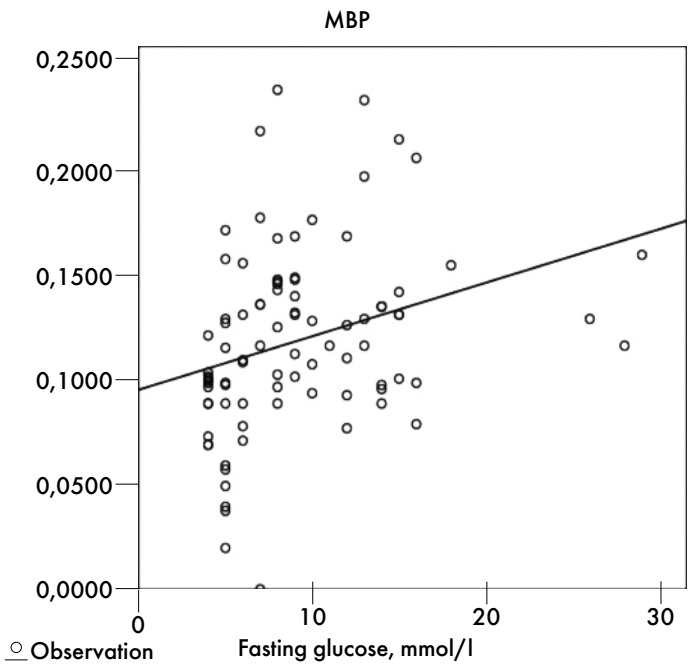

Fig. 4. MBP levels vs fasting glucose levels

MBP: myelin basic protein

MoCA. Brands AMA et al. revealed that cerebral atrophy is significantly less pronounced in patients who receive insulin pump therapy with satisfactory glycaemic control [12]. Such patterns were not detected in the present study.

The volume of white matter is significantly lower in patients with diabetic retinopathy, which is associated with impaired cognitive function that may be partially mediated by damage to small blood vessels [20]. The present study reveals a correlation between damage to white matter, such as the presence of dyscirculatory foci, and the development of proliferative retinopathy in patients with T1DM ($\chi 2 = 9.124$, $p = 0.028$). A reduction in the total score of MoCA was observed for all patients with focal changes in their white matter ($\chi^2 = 4.539$, $p = 0.033$).

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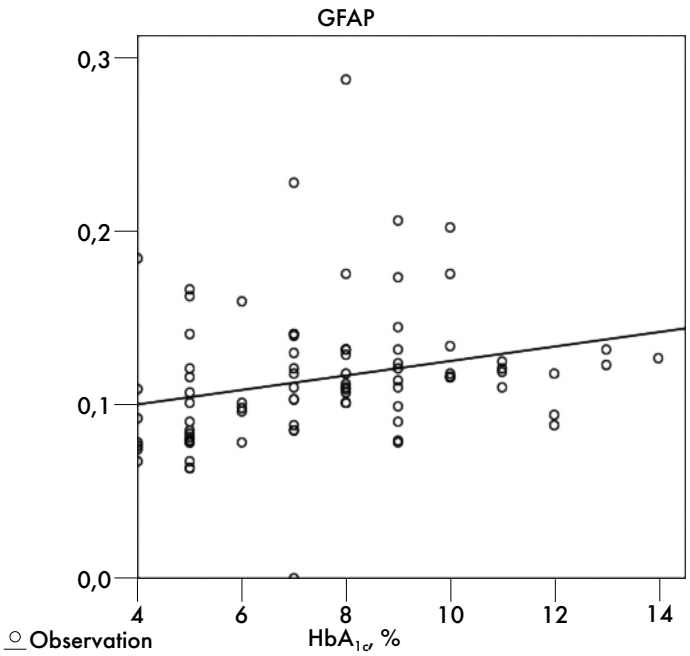

Fig. 5. GFAP levels vs HbA_{1c} levels

HbA_{1c}: glycated haemoglobin;
GFAP: glial fibrillary acidic protein

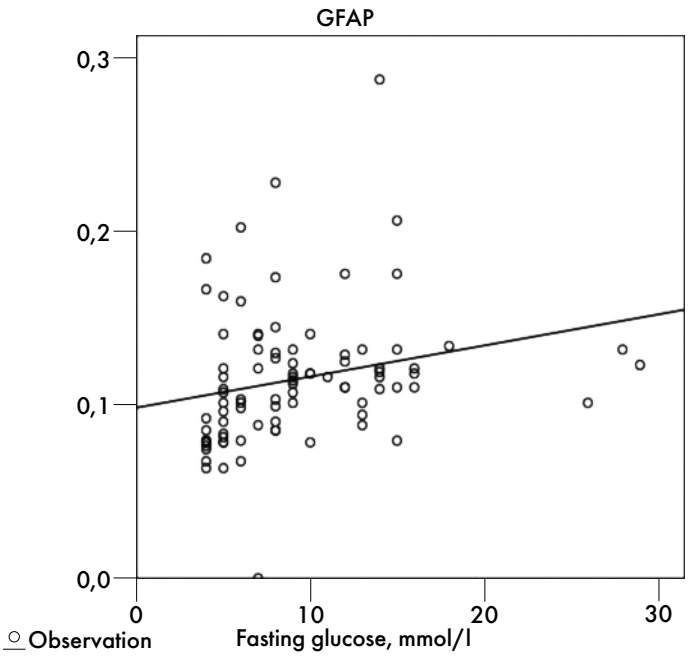

Fig. 6. GFAP levels vs fasting glucose levels

GFAP: glial fibrillary acidic protein

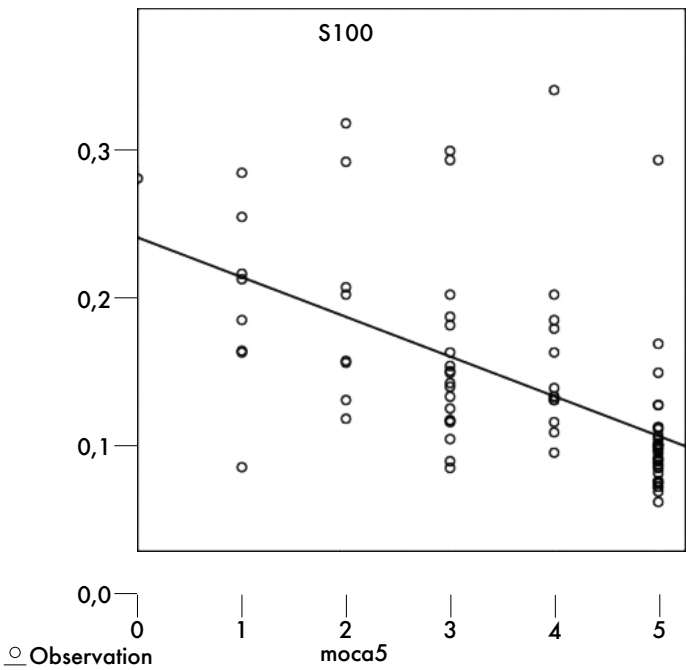

Fig. 7. S100 levels vs. MoCA scores

S100: S100 neurospecific protein; MoCA5: memory function according to the MoCA score

CONCLUSIONS

The present findings indicate that chronic hyperglycaemia is one of the major causes of cognitive impairment. Most MoCA test parameters that determine cognitive impairment were reduced in patients with T1DM, such as tasks to evaluate memory function and attention. Highly significant differences in the levels of neurospecific proteins that correlated with carbohydrate metabolism decompensation and the presence of cognitive deficits were detected in patients with T1DM. Changes in brain MRI results were detected in patients with short-duration T1DM accompanied by chronic hyperglycaemia. Signs of grey matter atrophy in the frontal and parietal lobes, which correlated with hyperglycaemia and cognitive impairment, were the most common morphological changes in the central nervous system. Further, analysis of brain MRI data revealed small dyscirculatory foci and mild leukoaraiosis in the white matter that was accompanied by cognitive impairment and microvascular changes.

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The authors declare no conflicts of interest in connection with the writing of this article.

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