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CEREBROVASCULAR INSUFFICIENCY AND DIABETIC ENCEPHALOPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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The peculiarities of cognitive dysfunction structure in patients with type 2 diabetes mellitus and stage 2 diabetic encephalopathy characterized by disorders of memory, verbal fluency, attention and orientation, were revealed. Association of cognitive disorders with disease duration, glycosylated hemoglobin concentration, impaired brain activity, cerebral hemodynamics and cerebrovascular reactivity was established.

Key words: type 2 diabetes mellitus, diabetic encephalopathy, cognitive disorders, cerebrovascular insufficiency, cerebrovascular reserve.

Type 2 diabetes mellitus (DM) is one of the most common diseases revealed in 3–15% of the population of economically developed countries. Progress in glycemic control contributed to significant increase in life expectancy of patients with diabetes, increase of the number of individuals with long-term history of the disease and, consequently, increased incidence of its late complications. Leading complications of diabetes are disorders of the nervous system revealed in almost every patient.

Diabetic encephalopathy is resistant cerebral pathology that occurs in patients with type 2 DM as a result of chronic hyperglycemia, disturbances of signaling effects of insulin in the brain as well as metabolic disorders induced under these conditions. Chronic cerebrovascular accident plays a role in the development of encephalopathy in type 2 DM, the pathogenesis of which is due to formation of diabetic cerebral micro- and macroangiopathy. The changes in the small blood vessels (arterioles, capillaries, venules) are specific to DM nature; those in the large ones are regarded as early disseminated atherosclerosis [1–4].

The pathogenesis of microangiopathy in DM is associated with formation of autoantibodies against glycosylated proteins of the vascular walls, increased peroxidation processes with accumulation of excessive amounts of pro-oxidants, inhibition of synthesis prostacyclin and nitric oxide, producing antoaggregate and vasodilator effect. Diabetic macroangiopathy develops when hyperlipidemia and disorders of the vascular wall structure are combined with increase in its permeability, which leads to formation of atherosclerotic plaques, affecting the main vessels (macroangiopathy) [4, 5].

An important role in development of the brain disgemeny at DM is undoubtedly played by endothelial dysfunction, impaired autoregulation of cerebral blood flow, increase in blood viscosity and aggregation properties [1, 3–5]. It is known that the adequate function of the processes of cerebral flow autoregulation can compensate hemodynamic deficiency resulting from various causes owing to co-operation of anatomical and functional factors of compensation [6, 7]. Disturbance of autoregulation in type 2 DM is one of the mechanisms of forming cerebral dyscirculations, causing tissue hypoxia and energy metabolism disorders in the nervous tissue. As a result, neurons develop lactoacidosis and the energy deficiency promoting structural and functional abnormalities in the nerve cells and formation of the clinical picture of diabetic encephalopathy [2, 4, 5, 8].

The leading clinical syndrome of diabetic encephalopathy is cognitive dysfunction. Development of mild to moderate cognitive dysfunction significantly reduces the quality of life of the patients with DM, limits theirs ability to carry out effectively recommendations for the treatment of the disease and neurological complications, and is associated with significant risk of subsequent development of dementia and severe disability [3, 9–11]. Experimental and clinical data on relationship of diabetic macro- and microangiopathy with formation of small (lacunar) cerebral infarctions, which often develop without clinical stroke and/or leukoaraiosis has been accumulated. These structural changes in the brain substance are considered as the morphological substrate of cognitive dysfunction [12–15]. A certain role of insulin resistance, frequent hypoglycemic episodes, emotional disorders, as well as combination of type 2 DM and hypertension in development of cognitive disorders in DM has been established [3, 15–17]. However, despite the available literature data, the pathogenesis of cognitive dysfunction in type 2 DM is not fully understood.

The purpose of the work was to establish the association between impaired cerebral hemodynamics and formation of cognitive disorders in type 2 DM

The study involved 87 patients (61 females and 26 males) with type 2 DM and stage 2 diabetic encephalopathy, aged 56,3±5,9 with mean disease duration of 9,3±4,5 years (main group). Diabetes severity was defined as medium in 64,4 % of patients and severe in 35,6 % of cases. Glycosylated hemoglobin (HbA1c) level in the group of the patients ranged from 7,2 to 8,8 %. Insulin was administered as basic hypoglycemic therapy in 54 % of patients, tablet formulations were administered to 46%. Among diabetes complications distal diabetic polyneuropathy was present in 72,4 % of patients, 91,9 % patients had diabetic angiopathy in the fundus, 27,6 % signs of diabetic nephropathy. Stage I or II hypertension was noted in 89,7 % of patients with DM, 86,2 % of patients had lipid metabolism disorders demonstrated by biochemical blood analysis. The patients with the history of heart attacks and strokes who had severe or unstable concomitant somatic pathology were excluded from the study. The controls were 30 age-matched apparently healthy individuals.

Cognitive function was determined using a brief mental status evaluation scale Mini-mental State Examination (MMSE) and the scale of cognitive abilities Addenbrooke's Cognitive Examination-R (ACE-R) [18–20]. The latter is a questionnaire including 26 tasks, divided into five domains: attention and orientation, memory, speech fluency, language, visual and spatial skills. Maximum total score is 100.

The study of blood flow in the large arteries of the head and intracranial arteries was performed using extra- and intracranial Doppler study according to standard techniques using 2, 4, 8 MHz transducers with Spectromed-300 unit (Russia). Vasodilatator reserve and reserves of collateral circulation were assessed by compression test and evaluation of Overshoot coefficient [21].

The state of spontaneous bioelectrogenesis was assessed according to electroencephalography findings obtained with computer electroencephalograph DX-NT32; bioelectric activity of the brain was studied by recording the endogenous evoked potentials (EP) of the brain with computer myograph Neuro – MEP (Neurosoft, RF); the structural state of the brain substance was objectified by brain MRI.

The obtained data were statistically processed using statistical software application package Statistica-6. Mean values and average error were calculated. To determine the significance of differences in the samples parametric and nonparametric Wilcoxon and Student's criteria were used. The differences were considered significant at $p < 0,05$. To perform correlation analysis, Spearman rank correlation coefficient (r) was calculated.

The main complaints of the patients with type 2 DM and stage 2 diabetic encephalopathy were impaired memory of current events, decreased performance, headache (98,2 % of cases), dizziness (85,5 %), unsteady gait (74,6 %), emotional lability (63,6 %), asthenia (38,2 %), sleep disorders (69,1 %). Neurological examination revealed cephalgic syndrome (96,5 % of cases), cognitive dysfunction (94,3 %); static-coordination disorders (86,1 %), psychoemotional disorders ranging from emotional lability to depressive syndromes (89,5 %); intracranial hypertension (84,2 %), pyramidal insufficiency of central type (49,1 %); polyneuropathy syndrome (96.5 %), sleep disorders (66.7 %), etc.

Leading neurological syndrome in patients with stage 2 diabetic encephalopathy was mild cognitive disorder (27–26 points), moderate (25–24 points) severity by MMSE scale. Evaluation of the intellectual functions using ACE-R scale showed that total score decreased to 73–79 (lower limit of the normal values for this age group is 85–86 points [20]), which corresponded to moderate cognitive dysfunction. The memory was deteriorated most significantly, by 36,8 %, $p < 0,01$ (9–14 points by ACE-R scale at age norm over 19 points), speech fluency by 25,6 %, $p < 0,01$ (6–8 points by ACE-R scale at the age norm over 10 points), attention and orientation by 11,8 %, $p < 0,05$ (13–16 points by ACE-R scale at age over 17 points). Linguistic functions and visiospatial abilities had a tendency to reduction (by 5,6 and 8,4 %, respectively, $p > 0.05$), in the majority of cases they remained on the lower limit of age norm. This character of cognitive deficiency reflects disorders of fronosubcortical regions of the brain and neurodynamic of brainstem and subcortical structures [11].

All observed patients had diffuse changes in brain bioelectrical activity in the form of disorganized basic rhythms, smoothed zone differences, elevated slow-wave activity index. The investigation of indicators of endogenous EP in patients with stage 2 diabetic encephalopathy at type 2 DM showed increased latency of peak P 300 to 359±13 ms ($p < 0.05$) vs. the controls (314±18 ms). In addition, the resultant wave of endogenous EP in the group of the investigated patients was often smoothed and peak P 300 amplitude was decreased. The revealed negativization of induced brain activity was neurophysiological correlate of cognitive decline in type 2 DM.

Doppler sonography revealed decrease in linear blood flow velocity (LBFV) in the internal carotid artery (ICA) by 33,9 %, in the middle cerebral artery (MCA) by 34,5 %, in the subclavicular artery (SA) by 44,7 %, in the common carotid artery (CCA) by 32,6 % in patients with stage 2 diabetic encephalopathy against a background of type 2 DM with respect to those of the controls and the signs of increased vascular tone in all investigated vessels according to increase of pulsatility index (PL) and circulatory resistance (RL) on average in 1,8 and 1,75 times (Table 1).

Disorders of cerebral vascular reactivity in the examined patients with stage 2 diabetic encephalopathy were characterized by decreased capacity of collateral flow (anatomical level of cerebral vascular reserve), which was confirmed by depression with respect to benchmarks of residual

Table 1

Hemodynamics of blood flow in the major arteries of the head and intracranial arteries at rest

Vessels	LBFV, cm/s		PL, conventional units		RL, conventional units	
	main group	controls	main group	controls	main group	controls
ICA d	35,4±5,8*	53,2±6,4	1,5±0,13*	0,83±0,21	0,97±0,20*	0,55±0,16
ICA s	34,9±6,1*	51,9±5,9	1,6±0,14*	0,82±0,19	0,99±0,20*	0,53±0,15
MCA d	40,9±5,7*	62,4±11,3	1,11±0,11*	0,56±0,14	0,77±0,15*	0,50±0,10
MCA s	41,8±6,9*	65,2±10,7	1,11±0,12*	0,57±0,14	0,80±0,11*	0,51±0,09
SA d	21,7±5,6*	37,6±7,8	1,12±0,13*	0,78±0,11	0,81±0,09*	0,52±0,08
SA s	209±5,9*	38,6±8,7	1,08±0,16*	0,74±0,10	0,89±0,15*	0,52±0,07
CCA	30,7±5,3*	46,4±5,6	0,99±0,19*	0,54±0,19	1,05±0,16*	0,56±0,09

* $p < 0,01$ with respect to the controls. The same in Table 2.

blood flow velocity in the MCA (V2) at the time of the ipsilateral CCA compression by 28,1% (Table 2). This reflected impaired patency of the perforating and connective arteries, possibly as a result of their secondary obliteration as a manifestation of diabetic microangiopathy. Reduction of Overshoot index in patients with stage 2 encephalopathy and type 2 DM vs. the controls by 26,9% indicated exertion of the functional cerebrovascular reactivity, in particular its myogenic component due to disorders of in the structure of the vascular wall and its tone in DM. 2.3-fold increase in the recovery time of blood flow velocity to the initial values reflected disturbance in the metabolic circuit of vascular reactivity as a manifestation of general dismetabolic processes developing in the organism at DM: disturbances of the polyol pathway of glucose oxidation, excessive accumulation of sorbitol and pro-oxidants, development of hyperlipidemia, deficiency of depressor factors, irreversible glycosylation of proteins, including those of vascular walls [1, 4, 5, 8].

Table 2

Hemodynamics of blood flow in intracranial arteries during compression tests

Hemadynamic values	Main group	Controls
V1 MCA (cm/s)	40,9±5,7*	63,8±9,7
V2 MCA (cm/s)	22,3±1,6*	31,8±3,4
V3 CMA (cm/s)	46,7±4,9*	86,8±7,1
Overshoot coefficient (conventional units)	1,13±0,04*	1,36±0,09
Blood flow velocity recovery time T (c)	14±3*	6±2

Brain MRI in patients with stage 2 encephalopathy at type 2 DM demonstrated the signs of cortical hypotrophy in the area of the frontal and parietal lobes (78,4% of cases), lacunar defects (33,4%), signs of leukoaraiosis (21,6%). Thus, in type 2 DM the most common morphological type of brain lesion was cortical atrophy indicating more significant effect of chronic hyperglycemia on the corticoatrophic changes in the brain.

The performed correlation analysis revealed association of cognitive dysfunction (total point by ACE-R scale) with the duration of type 2 DM ($r = -0,34$; $p < 0,001$), concentration of glycosylated hemoglobin ($r = -0,39$; $p < 0,001$), δ-rhythm index increase ($r = -0,31$; $p < 0,01$), increase of peak P 300 latency ($r = -0,47$; $p < 0,01$), Overshoot coefficient reduction ($r = +0,41$; $p < 0,05$). The dependence of reduction of Overshoot coefficient on DM duration ($r = -0,37$; $p < 0,05$), glycosylated hemoglobin level ($r = -0,41$; $p < 0,01$) was determined. These figures reflect the associations of the revealed cognitive sand vascular disorders and carbohydrate metabolism disorders and DM duration, as well as indicate the presence of complex disorders of corticosubcortical connections that underlie development of cognitive disorders in patients with type 2 DM and can be a marker and predictor of their development.

Thus, the leading syndrome of diabetic encephalopathy in type 2 DM are cognitive disorders clinically characterized by the presence of symptoms of frontal dysfunction and participation of temporoparietal brain regions and pathogenetically associated with negative effects of disorders of metabolic processes and those of cerebral hemodynamics on the brain. An important role in development of cerebral discirculation in type 2 DM is played by disorders of cerebral vessels reactivity, and deterioration of collateral and vasodilator links of the vascular reserve. For screening and diagnosis of cognitive decline in type 2 DM Addenbrooke's Cognitive Examination demonstrated a good validity. In turn, early detection of cognitive decline and administration of adequate therapy considering the state of cerebrovascular reserve allowed preventing its decline in patients with diabetic encephalopathy in type 2 DM, to improve their quality of life and social adaptation.

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ЦЕРЕБРОВАСКУЛЯРНАЯ НЕДОСТАТОЧНОСТЬ И ДИАБЕТИЧЕСКАЯ ЭНЦЕФАЛОПАТИЯ У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2-го ТИПА

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Выявлены особенности структуры когнитивной дисфункции при сахарном диабете 2-го типа и диабетической энцефалопатии II стадии, которые характеризовались нарушением функции памяти, беглости речи, внимания и ориентации. Установлена связь когнитивных расстройств с длительностью заболевания, концентрацией гликозилированного гемоглобина, нарушением биоэлектрической активности мозга, церебральной гемодинамики и цереброваскулярной реактивности.

Ключевые слова: сахарный диабет 2-го типа, диабетическая энцефалопатия, когнитивные нарушения, цереброваскулярная недостаточность, цереброваскулярный резерв.

ЦЕРЕБРОВАСКУЛЯРНА НЕДОСТАТНІСТЬ І ДІАБЕТИЧНА ЕНЦЕФАЛОПАТІЯ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ 2-го ТИПУ

О. Л. ТОВАЖНЯНСЬКА, І. О. БЕЗУГЛОВА

Визначено особливості структури когнітивної дисфункції при цукровому діабеті 2-го типу і діабетичній енцефалопатії II стадії, що характеризувалися порушенням функції пам'яті, мовлення, уваги та орієнтації. Встановлено зв'язок когнітивних розладів із тривалістю захворювання, концентрацією глікозильованого гемоглобіну, порушенням біоелектричної активності мозку, церебральної гемодинаміки та цереброваскулярної реактивності.

Ключові слова: цукровий діабет 2-го типу, діабетична енцефалопатія, когнітивні порушення, цереброваскулярна недостатність, цереброваскулярний резерв.

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