Cognitive function dynamics in comorbid patients after angioreconstructive interventions

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Angioreconstructive interventions are generally known to be of prophylactic value for cerebrovascular diseases (CVD). At the same time, their prognosis in comorbid patients, particularly in those with type 2 diabetes (T2D), have been insufficiently covered.
Objective: *to study the impact of T2D on cognitive functions after carotid angioplasty with stenting (CAS)*
Patients and methods. *CAS was performed in 99 patients with chronic CVD. Group 1 consisted of 51 patients (median age, 64.5 years) without carbohydrate metabolism disorders. Group 2 included 48 patients (median age, 64 years) with T2D. Over time, all the patients underwent clinical, neurological, and neuropsychological examinations, general clinical and biochemical blood tests, duplex scanning of the brachiocephalic arteries, and magnetic resonance imaging (MRI) of the brain. Blood flow in the middle cerebral artery was monitored to assess the embolic and hemodynamic situation during a CAS procedure.*
Results and discussion. *The baseline frequency of neurocognitive impairment was almost the same (75%) in both groups; however, the impairment was more obvious in patients with T2D. Re-examination in Group 1 patients immediately after intervention revealed slight positive cognitive changes, while the patients with T2D showed a decrease in the indicators of mental functions. The improved ability to abstract and increase the level of generalization of functions appeared in T2D patients only 2 months after intervention. Post-CAS MRI revealed ipsilateral acute ischemic foci (AIF) in the brain substance in 11 (22%) patients of Group 1 and in 24 (50%) with concomitant T2D. Comparison of neuroimaging data with cognitive function assessments for the entire group of the examinees established deterioration in the cognitive status in patients with new ischemic brain changes detected after intervention.*
Conclusion. *CVD concurrent with T2D usually contributes to deterioration in the cognitive status. Angioreconstructive interventions, in particular CAS, are frequently accompanied by the identification of AIF (including «silent» ones) that can cause a transient deterioration in cognitive functions. When planning angioreconstructive interventions in patients with T2D, the question arises of predicting such risks and possible neuroprotective methods.*

Keywords: *cerebrovascular diseases; cognitive impairment; carotid angioplasty with stenting; type 2 diabetes mellitus.*
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Cerebrovascular diseases are still an important medical problem with an explicit socio-economic resonance [1]. Considerable progress has been achieved in the field of treatment of urgent cerebrovascular conditions that along with demographic changes associated with increased global life expectancy have contributed to the growing number of individuals with different manifestations of chronic cerebrovascular diseases (CCDs) in general population.

Type 2 diabetes mellitus (T2D) remains an equally important problem, associated not only with a considerable increased risk of ischemic disorders of cerebral circulation (DCC) in every age category but also with a more severe course and poor outcomes [2]. At the present time the negative influence of T2D and chronic hyperglycemia on the brain white matter through both direct brain damage and as a result of cerebral vessels damage, including the impact of progressive atherosclerosis, has been confirmed [3–6]. This poses the question of the necessity of proactive measures for primary prevention of CCDs as well as for prevention of their recurrences.

Angioreconstructive interventions such as carotid angioplasty with stenting (CAS) and carotid endarterectomy (CE) proved their high efficiency and safety in ischemic stroke prevention in patients with carotid artery atherosclerotic stenosis [7, 8]. The results of prospective trials indicate that the rate of neurological complications of CAS and CE do not differ significantly, however our previous observations showed a greater risk of perioperative acute ischemic lesions (AILs) seen on magnetic resonance imaging (MRI) scans as a result of microembolism in CAS – 54% of cases versus 17% after CE [9].

Microembolism associated with CAS in the early postoperative phase is a predictor of cognitive impairment that can persist for 6 months after the intervention [10, 11]. Our own results, as well as data from other sources, allow us to assume that the severity of perioperative brain damage in the presence of T2D correlates with long-term cognitive alterations [12].

It should be noted that the state of cognitive functions after operative treatment of carotid artery stenosis remains under-explored, and the impact of T2D on cognitive function in this setting has not been clarified. Thus, the goal of our study is to explore T2D influence on the cognitive functions after CAS.

Patients and methods: This study enrolled 99 patients with CCD. Group 1 included patients with CCD (n=51) without glucometabolic disorders, median age – 64.5 [58; 72] years. Group 2

Table 1. **Main clinical and laboratory values**

Value	Group 1 – CAS without T2D (n=51)	Group 2 – CAS + T2D (n=48)	p
Age 65 or more	27 (52)	25 (52)	
«Asymptomatic» patients	35 (69)	20 (43)	
Stroke history	16 (31)	27 (57)	
IHD	22 (44)	23 (48)	
Angina	13 (27)	13 (29)	
Myocardial infarction history	4 (17)	10 (19)	
Hypertension	49 (96)	48 (100)	
Cardiac arrhythmias	13 (27)	0 (22)	
Congestive heart failure	17 (34)	22 (46)	
Body mass index, kg/m^2	27.9 [26.5; 31.2]	31 [28; 35]	**0.0001**
TC, mmol/L	5.4 [3.7; 7.8]	5.0 [4.1; 5.8]	0.0619
LDL, mmol/L	2.1 [1.5; 2.6]	2 [1.7; 2.9]	0.4485
TG, mmol/L	2.1 [1.3;2.9]	1.8 [1.4; 2.9]	0.0505
HbA1c, %	–	7.8 [6.4; 8.7]	
Glucose, mmol/L	5.3 [4.5; 6.1]	8.1 [6.9; 9.0]	**0,0000**

Note. These data are presented in the form of n (%) or median [25; 75 percentile].
Abbreviations: IHD – ischemic heart disease; TC – total cholesterol; LDL – low-density lipoproteins; TG – triglycerides; HbA1c – glycated hemoglobin.

included patients with CCD with concomitant T2D (n=48), median age – 64 [59; 70] years.

T2D was established based on the diagnostic criteria of diabetes and other glycemic disorders (2013).

Carotid atherosclerosis was verified via ultrasound examination on the Viamo (Toshiba, Japan) device with the use of NASCET algorithm; stenosis severity and atherosclerotic plaque echogenicity causing aforementioned stenosis were calculated.

According to 2014 international guidelines of the American Heart Association/American Stroke Association (AHA/ASA) and 2012 national TClinical guidelines for the management of vascular arterial disordersУ, CAS procedure was performed for:

– patients after stroke with carotid stenosis i60%;

– asymptomatic patients with critical stenosis (>80%) and non-stable atherosclerotic plaques for the purpose of stroke prevention.

In intraoperative middle cerebral artery (MCA) blood flow monitoring (Aspen, Siemens, Germany), the ipsilateral proximal segment of the MCA was investigated. The main criteria for blood flow evaluation were reference values of systolic linear blood flow speed (LBFS), peripheral resistance index and changes of these parameters during the procedure. The presence, amount and type of microembolic signals were also evaluated.

Every patient underwent clinical, neurological and neuropsychological evaluation; complete blood count and blood glucose level (by hexokinase method), total cholesterol (TC), low-density lipoproteins (LDL), triglycerides (TG), glycated hemoglobin (HbA1c; by immunoturbidimetric method) were assessed using autonomic biochemical analyzer Konelab 30i (Thermo Fisher Scientific, USA).

One day before the intervention and 24 hours after the intervention every patient underwent MRI on Magneton Symphony tomograph (Siemens, Germany, 1.5 T). Due to the prevalence of small size lesions, brain damage was evaluated with diffusion-weighted imaging (DWI) with diffusion coefficient b=1000. Any new hyperintense lesions in the brain that were not present before the intervention were regarded as AILs related to CAS emboli. The number of lesions, their size and location were taken into consideration.

Cognitive impairment (CI) was defined in accordance with N. Yakhno and V. Zakharov criteria (2005) [13]. To evaluate the cognitive profile, the total score of the following neuropsychological tests was used: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Controlled Oral Word Association Test, Clock Drawing Test, Digit Symbol Substitution Test, The Adjusting-Paced Serial Addition Test and The 12-Word Philadelphia Verbal Learning Test. Both MMSE and MoCA tests were used due to the fact that MMSE reliably distinguishes dementia from mild CI (which cannot be done with MoCA), while MoCA is more sensitive to the changes in the state of patients with mild CI.

After CAS, two stages of complex neurological, laboratory and neuropsychological examination were conducted: immediately after the operation and 2 months later in an out-patient setting.

Statistical analysis was done with Statistica 10.0 software (TIBCO Softcare Inc., USA). Descriptive statistics for categorical or ordinal variables was represented as frequency and proportion (%) of occurrence. Quantitative features were described with mean, standard deviation, median and quartile. To compare the groups by quantitative features non-parametric tests of Kruskal–Wallis and Mann–Whitney were used. In the case of binary dependent variable, logistic regression method was used with the presentation of the results in ROC-variable and counting the area under the curve (AUC) to evaluate the quality of the model.

Results. Both group of patients were comparable by age and presence of concomitant cardiac disease. (Table 1)

Primary neuropsychological assessment showed CI in 75% of patients in both groups; in 56% of patients it was mild, and in 19% CI met the criteria for moderate cognitive impairment; CI was more expressed in patients with the T2D. For instance, memory impairment (by MoCA, MMSE), lobar dysfunction, constructive praxis disruption (clock drawing test), episodic memory impairment (12-word test), intellectual flexibility failure (adjusting-paced serial addition test), a decrease in short-term memory, attention span and distraction immunity volume initially were different in both groups, with predominance in patients with T2D ($p<0.05$). At the same time, evaluation of general mental activity (Tliteral associationsУ test), nominative speech function, semantic memory and visual gnosis did not reveal significant differences between the two groups (p i0.05, Fig. 1).

The leading neuropsychological mechanism was the lack of voluntarily activity (71% of cases). Loss of general psychic activity (Tliteral associationsУ test) and episodic memory (12 words test) was noted, along with intellectual flexibility failure (adjust-

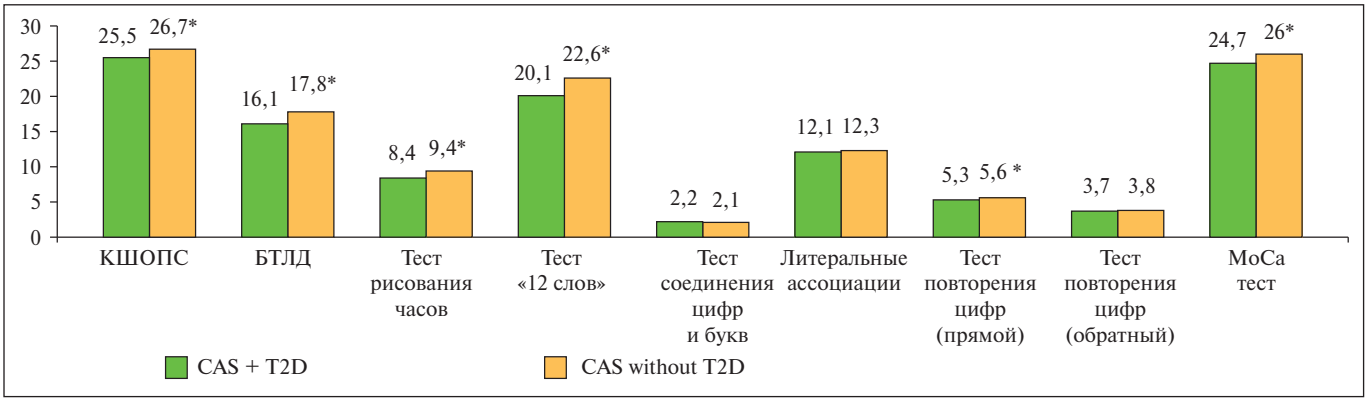

Fig.1. *Baseline indices of neuropsychological testing. * the achieved level of statistical significance p<0.05*

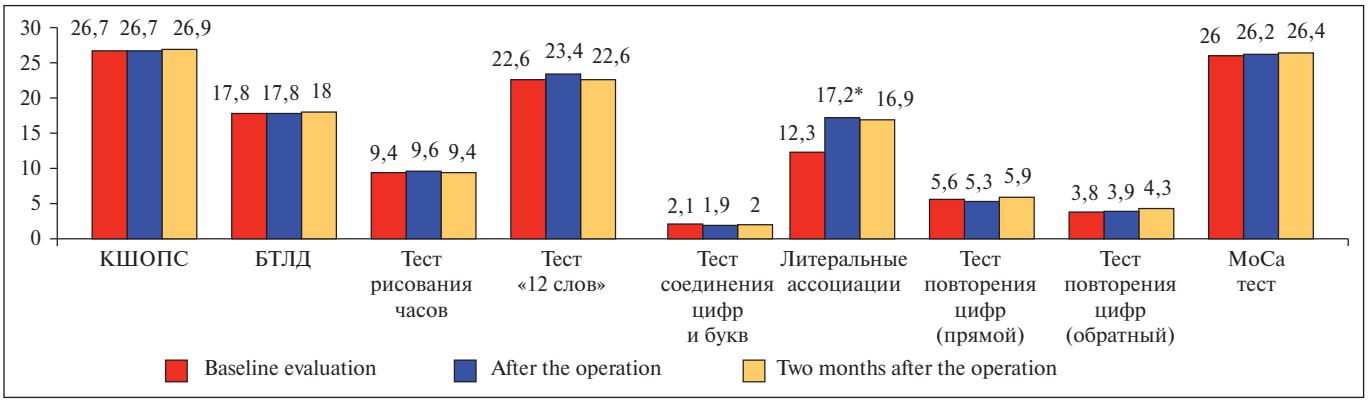

Fig. 2. *Results of neuropsychological testing in Group 1 (CCD without T2D)*

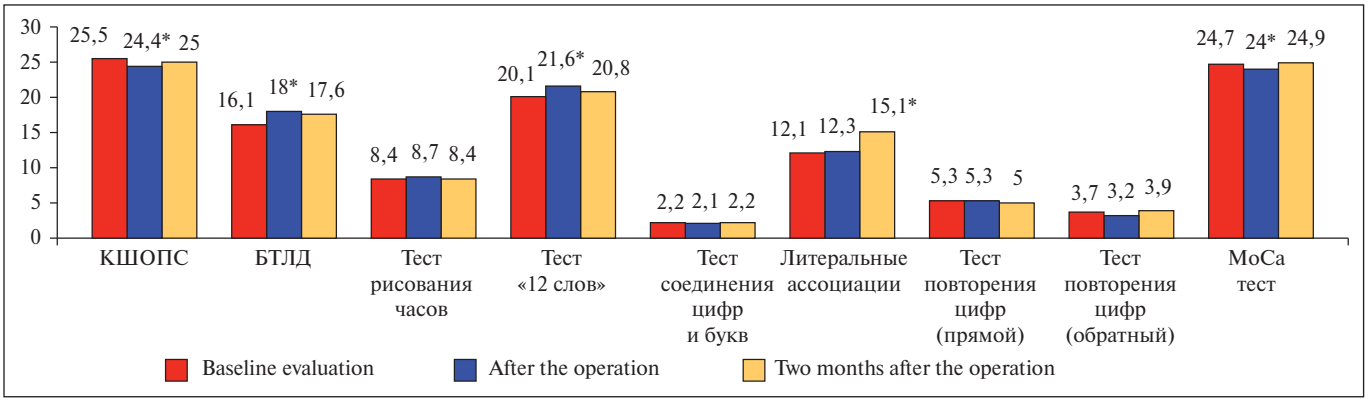

Fig. 3. *Results of neuropsychological testing in Group 2 patients (CCD with T2D)*

ing-paced serial addition test) and constructive praxis disruption (clock drawing test). We did not observe speech nominative function, semantic memory or visual gnosis disruptions.

Analysis of the data obtained demonstrated dorsolateral frontal cortex involvement, while concomitant T2D negatively affected cognitive functions, resulting in general cognitive impairment as well as lobar dysfunction and disruptive verbal associative productivity.

Conducting similar examination in the early postoperative period and comparison of its results with the baseline data showed minor improvement in the cognitive profile of the patients from Group 1 compared with the patients with T2D. PatientsX evaluation on the out-patient basis 2 months after CAS, allowed to systemize and summarize the obtained data to establish the level of CI significance (Fig. 2 and 3).

In patients with T2D transient declining of cognitive functions in the early postoperative period was registered from 24.7±1.7 points (MoCA) to 24.0±1.7 points (p=0.046). After 2 months of follow-up, cognitive functions restored almost to the baseline level – 24.9 ±1.8 points (the level of statistical significance between visits 2 and 3, p=0.013). Similar results were obtained in MMSE evaluation. «Literal associations» test results were unchanged in the early postoperative period (12.1±1.2 and 12.3±1.3 points respectively; p=0.240), however we identified significant improvement in the results of this test after 2 months of follow-up – to 15.1±1.2 points (p<0.001).

Fig. 4. *Acute ischemic lesions (DWI MRI 24 hours post-surgery): a – subcortical white matter in the left parietal lobe; b – left occipital cortex*

Wide scoring variation in different tests 2 months after CAS represents multidirectional changes depending on the group. Tests of episodic memory and FAB in the early postoperative period showed statistically significant improvement. However, the results obtained 2 months after the intervention, did not differ significantly from the baseline level.

The detected cognitive profile alterations prompted us to search for the morphological substrate of these deteriorations.

Neuroimaging with diffusion-weighted MRI in the perioperative period demonstrated ipsilateral AILs in the brain of 11(22%) patients without T2D and 24 (50%) patients with comorbid T2D. The number of lesions in each patient varied from 1 to 9 with primary localization in the cortex on the intervention side and size up to 5 mm. It should be noted that no perioperative strokes were observed in the studied groups, and all detected changes in the brain were not accompanied by additional neurological symptoms.

It was found that AIL frequency in CAS interventions directly correlated with T2D (p=0.0383).

Transcranial monitoring of MCA in patients with TsilentУ AILs showed that in 81% of the patients at the moment of balloon dilation there was a local decrease in LBFS in MCA by more than 50% compared with the baseline value. In the analysis of embolic situation in patients with these lesions, in 70% of all cases microembolic signals were noted, suggesting that microembolism was the primary source of new lesions.

The informativity of preoperative ultrasound (US) test of US signals of high intensity associated with the presence or absence of postoperative AILs was determined with ROC-analysis. The test sensitivity was 75%, specificity – 100%, the area under the curve – 87% (p=0.01; Fig. 5).

The comparison of neuroimaging data with the evaluation of cognitive function on MoCA scale showed that in each group new AILs in the brain were associated with more prominent cognitive function deterioration, while the absence of new lesions was considered to be a prognostic sign of cognitive function stabilization (Fig. 6).

Discussion. The main method for stroke prevention in patients with explicit atherosclerotic damage to brachiocephalic arteries, along with antiplatelet therapy, are angiorecostructive interventions – CAS and CE. Usually postoperative evaluation of a patientXs condition consists of assessment of obvious neurological symptoms: motor, sensory and coordination status. Insufficient neuropsychological examination before and after such interventions determined the lack of knowledge about CI detection and its subsequent clinical significance. Revascularization can lead to cognitive deficit caused by intraoperative emboli, general anesthesia or temporal blood flow restriction (due to carotid arteries clamping in CE or balloon dilation in CAS) or, on the contrary, blood flow restoration in a stented vessel can improve cognitive function, which was impaired as a result of chronic hypoperfusion [14]. The percentage of cognitive function worsening (10–15%) and improvement (10%) after carotid interventions was approximately equal [15, 16]; moreover there was no difference in CI development regardless of stroke history or asymptomatic manifestations of carotid disease [17, 18].

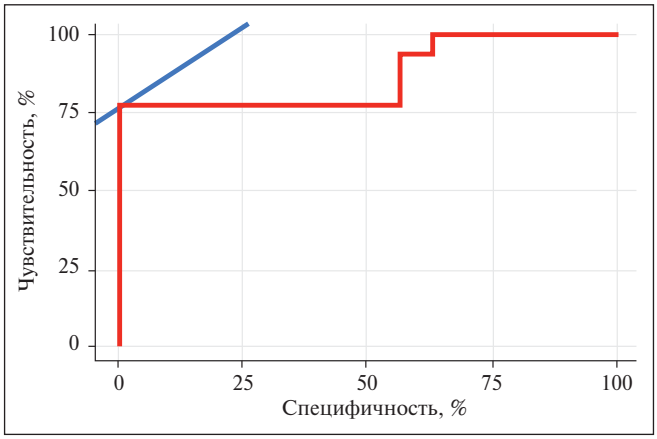

Fig. 5. *ROC-analysis of the pre-operative ultrasound test in AIL prognosis post-CAS*

The study showed that the leading neuropsychological mechanism of CI development in CCD patients was insufficient regulation of voluntarily activity on the background of general cognitive deterioration. These alterations are probably caused by more pronounced disruptions of non-specific activating brain structures in the environment of chronic ischemia (involuntary attention) and the continuing tendency to further reduction in the short-term memory, concentration and distraction immunity. This intervention was found to exert less influence on the temporal and parieto-occipital structures, leaving unaffected auditory and verbal (short-term) memory and constructive praxis.

In patients with comorbid T2D the improvement in abstracting and enhancing the level of generalization of functions was noted only 2 months after CAS, and in the group without T2D improvement could be seen immediately after the intervention.

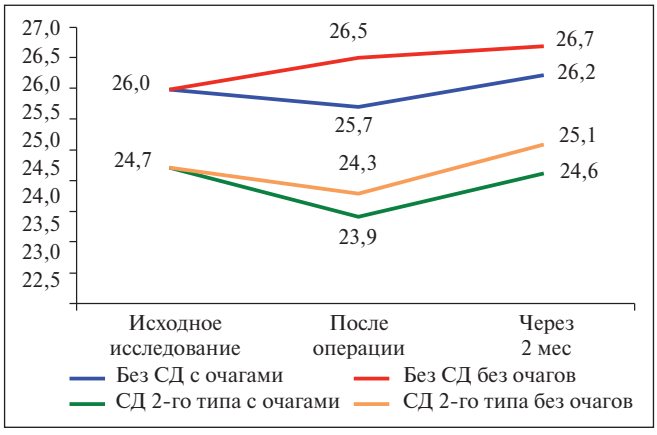

Fig. 6. *Cognitive function dynamics post-CAS in relation to AIL presence*

Another important and still unresolved problem is how the detected CAS-related ischemic lesions in the brain (in our study in half of the patients with T2D) affect brain functions, in particular cognitive function. Cognitive impairment in patients after brain revascularization was a subject of research with the different results. For instance, cognitive function improvement after CAS is related to changes in connectivity of the network of passive operation mode in the brain [19]. However, considering the conduction pathways involvement, we suggested the possibility of disconnection syndrome development. In this case, clinical symptoms of these lesions can be manifested mainly through cognitive impairment. In our earlier studies we noted that CI in patients after angioreconstructive operations on carotid arteries was associated not only with brain matter changes but also with clinical manifestations [20].

Similar discussions on the link between postoperative ischemic lesions and neurocognitive functions are given by other authors [21, 22]. Nevertheless, AIL development and cognitive profile worsening in patients after CAS require a thorough analysis in order to develop new algorithms for prevention of embolic complications.

The data from this study and few reports from other authors indicate a possible decline of cognitive functions after angioreconstructive interventions in patients with comorbid T2D. Thus, patients with T2D prevailed (56%) among the patients with microembolism after angioreconstruction [10]. In the study by C. Kraemer et al. published in 2020 [23], it was shown that older age, obesity and T2D independently predicted microinfarct volume associated with carotid interventions.

The role of glycemic control in acute ischemic lesions prognosis in T2D patients was shown in our previous work [12], though this factor currently appears to be less known in connection with postoperative neurocognitive alterations. According to the study of patients with T2D, HbA1c level correlates with cognitive tests results; HbA1c elevation by 1% resulted in significant deterioration of MMSE results. Furthermore, worse glycemic control accompanies volume reduction of both white and gray brain matter, while intensive glycemic control does not allow to achieve improvement of cognitive functions [24]. Chronic hyperglycemia nowadays is considered to be a major risk factor for CI development in T2D patients, which is reflected in our patientsX metabolic profile. For example, HbA1c median values were 7.8%, which, on the one hand, is an acceptable level for elderly patients with CDD and, on the other hand, indicates chronic hyperglycemia.

Conclusion. The association of CCD and T2D usually promotes worsening of cognitive profile. Despite the significant effect of brain perfusion enhancement in angioreconstructive interventions on stroke prevention, in some cases there is a possibility of postoperative brain ischemic lesion appearance. Comorbidity of T2D with vascular pathology leads to more frequent detection of the aforementioned neurovisual findings. Postoperative ischemic lesions, including TsilentУ ones, could be a possible risk factor for transient worsening of cognitive functions in the early postoperative period.

In planning angioreconstructive interventions in patients with T2D, preoperative assessment, and, if necessary, correction of sugar-lowering therapy is advisable to ensure long-term glycemic control. Predicting risk factors and possible neuroprotective methods requires additional studies.

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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Conflict of Interest Statement

The investigation has been conducted within the state assignment on researches and its conduct was approved by the Local Ethics Committee of the National Center of Neurology under No. 11-5/19 dated November 20, 2019.

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