

SYMPTOMATIC AND SILENT CEREBRAL ISCHEMIA (DETECTED ON MRI) IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AFTER CAROTID REVASCLARIZATION PROCEDURES

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BACKGROUND: Type 2 diabetes mellitus (T2DM) is a significant independent risk factor for ischaemic stroke. Carotid revascularisation procedures are an effective method of primary and secondary stroke prevention. However, patients developed postoperative acute ischaemic lesions (AILs), which were identified via magnetic resonance imaging (MRI) of the brains. Most of the patients with these AILs lack clinically overt symptoms.

AIMS: To assess the risk of ischaemic brain damage in patients with T2DM in the setting of carotid angioplasty with stenting (CAS) or carotid endarterectomy (CAE).

MATERIALS AND METHODS: This open prospective study comprised of 164 patients with carotid atherosclerosis, who have undergone either CAS or CAE. Patients with T2DM were included in Group 1: 38 patients and 28 patients with CAE. Group 2 included patients without T2DM: 62 patients with CAS and 36 patients with CAE. All patients underwent a thorough neurological examination and diffusion-weighted brain MRI. In patients with T2DM, plasma glucose levels and glycated haemoglobin (HbA_{1c}) were determined and their relationships to brain damage were evaluated.

RESULTS: In CAS, there were no statistically significant differences in the AIL frequency in patients with and without T2DM. AILs were found in 15 patients with T2DM (39.8%) and 29 patients without T2DM (46.8%, $p = 0.24$); three patients without T2DM were diagnosed with stroke. Of the 28 patients with T2DM who underwent CAE, 13 had AIL (46.4%); three had stroke (10.7%). In patients without T2DM, AILs were less prevalent in seven cases (19.4%, $p = 0.012$) and appeared asymptomatic. Following CAS, the baseline HbA_{1c} levels were higher in patients with T2DM who developed AILs compared to those who did not develop AIL, $7.8\% \pm 1.4\%$ vs $7.1 \pm 1.1\%$ ($p = 0.0469$). Negative impact of hyperglycaemia on the risk of cerebral ischaemia was observed in patients who underwent CAE, the baseline fasting plasma glucose level was 8.5 ± 1.9 mmol/l vs 7.0 ± 1.5 mmol/l in patients without AIL ($p = 0.014$). The baseline HbA_{1c} levels in patients with and without AILs were $8.0\% \pm 1.7\%$ and $6.9\% \pm 0.9\%$ respectively ($p = 0.023$).

CONCLUSIONS: Carotid revascularisation procedure for patients with carotid atherosclerosis may be associated with risk of stroke and asymptomatic acute cerebral ischaemic lesions, which are more prevalent in patients with T2DM. Also, increased HbA_{1c} levels is a risk factor for AIL.

KEYWORDS: diabetes mellitus type 2; stroke; carotid angioplasty and stenting; carotid endarterectomy; brain ischemia

СИМПТОМНАЯ И АСИМПТОМНАЯ ИШЕМИЯ ГОЛОВНОГО МОЗГА (ПО ДАННЫМ МРТ) У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА ПОСЛЕ КАРОТИДНОЙ РЕВАСКУЛЯРИЗАЦИИ

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ОБОСНОВАНИЕ. Сахарный диабет 2 типа (СД2) – важнейший независимый фактор риска ишемического инсульта. Ангиореconstructивные операции на сонных артериях являются эффективным методом первичной и вторичной профилактики инсульта. У ряда пациентов, перенесших каротидную реваскуляризацию по поводу стенозирующего атеросклероза сонных артерий, при магнитно-резонансной томографии (МРТ) выявляются острые очаги ишемии мозга (ООИ), в том числе не сопровождающиеся неврологической симптоматикой.

ЦЕЛЬ. Оценка риска ишемического повреждения головного мозга у пациентов с СД2 при проведении хирургического лечения атеросклеротического стеноза внутренней сонной артерии (ВСА).

МЕТОДЫ. В открытое проспективное исследование включены 164 пациента со стенозирующим атеросклерозом ВСА, перенесшие операции каротидной ангиопластики со стентированием (КАС) либо каротидной эндартерэктомии (КЭАЭ). Первую группу составили пациенты с СД2: подгруппа КАС – 38 пациентов, подгруппа КЭАЭ – 28 больных.

Во 2-ю группу вошли больные без СД: подгруппа КАС – 62 пациента, подгруппа КЭАЭ – 36 пациентов. Всем больным в динамике проводилась оценка неврологического статуса и диффузионно-взвешенная МРТ головного мозга. У больных СД2 определяли показатели глюкозы плазмы и гликированного гемоглобина (HbA_{1c}), оценивали их связь с повреждением вещества головного мозга.

РЕЗУЛЬТАТЫ. При проведении КАС статистически значимых отличий по частоте развития ООИ у больных СД2 и без такового не получено. ООИ выявлены у 15 (39,8%) пациентов группы СД2 и у 29 (46,8%) больных без СД ($p=0,24$), при этом в 3 случаях у больных без СД диагностирован ишемический инсульт. Среди 28 пациентов с СД2, перенесших КЭАЭ, у 13 (46,4%) в веществе головного мозга выявлены ООИ; в 3 (10,7%) случаях – инсульт. ООИ у пациентов без СД2 выявлялись реже – в 7 (19,4%) случаях ($p=0,012$) и были только асимптомными. Исходный HbA_{1c} был выше у больных СД2, имевших ООИ после выполнения КАС: $7,8 \pm 1,4\%$ vs $7,1 \pm 1,1\%$ ($p=0,0469$) – без очагов. Негативное влияние гипергликемии на риск ишемических изменений мозга выявлено и в группе пациентов, перенесших КЭАЭ: исходно гликемия натощак составила $8,5 \pm 1,9$ ммоль/л vs $7,0 \pm 1,5$ ммоль/л у больных без ишемических очагов ($p=0,014$). Исходный HbA_{1c} у больных, имевших ООИ, составил $8,0 \pm 1,7\%$ vs $6,9 \pm 0,9\%$ у пациентов без повреждения мозга ($p=0,023$).

ЗАКЛЮЧЕНИЕ. Проведение ангиореconstructивных операций у больных со стенозирующим атеросклерозом ВСА может сопровождаться формированием очагов ишемии мозга. Риск возникновения бессимптомных ООИ увеличивается при повышении HbA_{1c} и выполнении КАС.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет 2 типа; инсульт; каротидная ангиопластика со стентированием; каротидная эндартерэктомия; очаги ишемии головного мозга

Acute disorders of cerebral circulation (DCC) represent a significant medical and social problem, often leading in the rate of morbidity and mortality. In Russia, acute DCC is the second most common cause of death among patients with both type 1 and type 2 diabetes mellitus (DM) [1]. Moreover, 90% of strokes are potentially preventable with timely and efficient intervention [2]. It is known that DM is the most significant independent risk factor for ischaemic stroke (IS) [3]. Measures taken by the medical community to eliminate risk factors for vascular diseases over the past decades have led to a significant decrease in IS frequency. However, along with important progress in the normalisation of systolic blood pressure and reduction in the prevalence of smoking, the incidence of DM is increasing progressively, playing a negative role in this positive tendency. The prevalence of DM among stroke patients doubled from 1995 to 2012, and the current trend is that it will continue to increase [4].

In the vast spectrum of etiopathogenetic mechanisms of the onset of IS, the pathology of extracranial arteries (mainly of atherosclerotic genesis) plays a large role [5]. The data of contemporary studies indicate that significant stenoses are recorded in 37% of patients with IS along with DM type 2 (DM2) [6]. This raises a question about the need for active measures for primary prevention of DCC and for the prevention of their recurrence. Treatment of patients with DM involves complex cross-disciplinary interventions aimed at reducing the risk of vascular events and death, with some cases requiring surgery for carotid arteries. Carotid revascularisation has proven to be an effective method of treatment for carotid artery stenosis, with the aim of both primary and secondary prevention of stroke and reduction of the risk of death [7]. Currently, carotid endarterectomy (CEAE) is the gold standard for treatment of hemodynamically-significant carotid artery stenosis. Carotid angioplasty with stenting (CAS) is an alternative to endarterectomy in patients with higher risk for open intervention [8]. Angioreconstructive surgery is a procedure that not only prevents the development of stroke, but it also

improves the patient's health and subsequent quality of life. The benefits of the outcome generally outweigh the surgical risk. However, in some cases (4.1%–6.17%), a perioperative stroke may develop, which is an increased risk in patients with a history of DCC [9, 10]. Even transient may lead to white matter damage, which is a substrate for increasing the risk of chronic cerebral ischaemia with subsequent development of cognitive impairment [11]. However, there are reports that the influence of CAS and CEAE on the cognitive functions of patients after surgery is not significantly different [12]. Performing angioreconstructive surgery not only contributes to the prevention of acute DCC but also has a kind of neuroprotective effect, characterised by improvement in speech functions, attention and praxis [13].

Contemporary neurology has convincing information confirming the contribution of DM to the development of perioperative complications such as IS, haemorrhagic stroke, myocardial infarction and death from all causes [14]. In recent years, due to the widespread use of neuroimaging methods with various magnetic resonance imaging (MRI) techniques, information has been obtained on the possibility of the appearance of brain lesion nodules [15] in patients with carotid revascularisation in their history, without the concomitant development of neurological symptoms. The role of DM in the occurrence of brain lesion that is 'silent' in its course has not been adequately studied.

AIM

This study aimed to assess the risk of ischaemic brain lesion in patients with DM2 during the surgical treatment of atherosclerotic stenosis of the internal carotid artery (ICA).

METHODS

Study design

The study design was an open prospective study. It included 164 patients observed in the Research

Center of Neurology from 2015 to 2017 with atherosclerotic steno-occlusive lesion of the ICA, including 66 patients with DM2.

Depending on the type of surgical treatment performed within the groups, the patients were divided into subgroups of open (CEAE) and endovascular (CAS) intervention. A general clinical and neurological examination, assessment of the neurological status and neuroimaging of the brain (MRI) were performed before the surgery and 24 h after surgery.

Inclusion criteria

Patients who met the following two criteria were included in the study: 1) Atherosclerotic lesions of the carotid arteries could have clinical manifestations, in which case 'symptomatic' stenosis was diagnosed. Less commonly, this pathology did not have specific symptoms of a carotid system lesion ('asymptomatic' stenosis). In our study, stenosis was regarded as symptomatic if the patient had a cerebral circulation disorder in the system of hemodynamically-significant stenosis during the last six months. It was considered asymptomatic if there were no clinical symptoms of cerebral or retinal ischaemia on the ipsilateral (in relation to stenosis) side of the brain.

2) CEAE and CAS were recommended as surgical interventions for the prevention of stroke for patients who were symptomatic with stenosis of the ICA lumen of more than 50% or who were asymptomatic with stenosis of more than 70% [16]. The choice of revascularisation method was based on the experience of previous studies, considering clinical data and ultrasound examination results showing the degree of steno-occlusive lesion, structure and extent of atherosclerotic plaque in the ICA [17, 18, 19].

This study did not include patients admitted for the treatment of carotid stenoses caused by intimal hyperplasia or restenosis after previous surgeries.

The main contraindications to performing surgery were acute IS stage, the presence of severe neurological and cognitive impairments, tandem stenosis of the ICA greater than 50% at the level of the siphon or main trunk of the middle cerebral artery, multiple lesions of the extra- and intracranial arteries, severe somatic pathology, etc. For patients with DM2, hyperglycemia with acute metabolic decompensation and ketoacidosis were included.

Implementation conditions

The study was conducted from 2015 to 2017 in the neurosurgical department by a team of vascular and endovascular surgery of the Scientific Center of Neurology and the Department of General Angioneurology.

Description of medical intervention

All patients underwent angioreconstructive surgery on the carotid arteries. CEAE from the internal carotid artery or carotid angioplasty with stenting of the internal carotid artery (using a filter-type protective device) was performed. CEAE was performed in all patients according to the classical method. Angioplasty with stenting was performed on a biplane apparatus (Innova 3131, GE). Diagnostic X-ray contrast angiography was performed

by the standard method using Seldinger transfemoral access before and after stenting. The system of anti-embolic protection of the brain was used as filter traps made by Boston Scientific (USA) and Fibre-Net (Italy). For stenting of the carotid arteries, self-expanding conical nitinol stents (Invatec, Italy) without coating were used, with diameters of 6–9 × 40 mm and 7–10 × 40 mm. During carotid interventions, all patients received an intravenous bolus dosing of heparin to achieve a systemic anticoagulant effect. After endovascular intervention, double antiplatelet therapy was prescribed, namely aspirin (long-lasting) and clopidogrel (for three months). The surgeries were performed in the absence of contraindications, which included control of blood pressure. Intraoperatively, anaesthetic support ensured that the selected target level of blood pressure was maintained, and close monitoring was performed with the maintenance of central hemodynamics at all stages of the surgery.

All patients were examined to determine the presence of a neurologic impairment on the National Institutes of Health Stroke Scale (NIHSS) [20], and brain matter was also examined using diffusion-weighted (DW)-MRI using a 3-T magnetic field strength (Magnetom Verio 3-T, Siemens) before the surgery and 24 h after surgery.

Plasma glucose and glycated haemoglobin (HbA_{1c}) levels were determined in patients with DM2, and their potential association with brain matter lesion was also assessed.

Patients received antihyperglycemic therapy in the perioperative period in accordance with the algorithms for providing medical care to patients with DM [21].

Primary outcome of the study

The main indicators evaluated during the study were the development of stroke and/or the formation of acute ischaemic nodules (AIN) in the brain matter (according to DW-MRI).

Analysis in subgroups

The total sample of 164 patients who underwent angioreconstructive surgery was divided into two groups, patients with DM2 (n = 66) and patients without DM2 (n = 98). The division into subgroups was performed depending on the type of surgical intervention (CAS and CEAE). Group 1 consisted of patients with DM2; 38 patients were included in the CAS subgroup, and 28 patients were in the CEAE subgroup. Group 2 consisted of patients without DM and comprised 62 patients in the CAS subgroup and 36 patients in the CEAE subgroup.

Methods of registration of outcomes

All patients underwent clinical neurological examination, general clinical and biochemical studies with the following indicators: glucose (using the hexokinase method), lipid pattern (total cholesterol, low density lipoprotein cholesterol (LDL), triglycerides (TG)). For patients with DM2, the HbA_{1c} level was evaluated (by immunoturbidimetric technique) using an automatic biochemical analyser (Konelab 30i). For diagnosis of atherosclerotic lesion of the major arteries of the head, colour duplex ultrasonography was performed.

The state of the brain matter before the intervention and 24 h after was determined by the results of DW-MRI. To identify small nodules, the lesion of the brain matter was assessed using DW images (with a DW factor of $b = 1000$) [22].

Ethical expertise

The study was approved by the local ethical committee of the Research Center of Neurology (Minutes No. 11/14 of 19 November 2014). At hospitalisation, patients were informed about the possible use of their data for scientific purposes. Prior to cerebral revascularisation, written informed consent was obtained from all patients. Patients remained anonymous in subsequent data analysis.

Statistical analysis

The study was exploratory in nature, and the sample size was not calculated previously. Statistical analysis was performed on an Intel-compatible personal computer using Microsoft Excel 2000, Statistica 6.0 for Windows. According to the study design, the Kolmogorov-Smirnov criterion was used to test the hypothesis of normal

distribution. With normal distribution of signs, the results were described as mean \pm standard deviation. When the distribution of a sign was other than normal, data were presented as a median of values [value of upper and lower quartiles]. To test the difference hypothesis, Mann-Whitney, U-test, Wilcoxon and matched pairs test were used. To compare the proportions in the two independent groups, Fisher's ratio test and chi-square were used. Results were considered statistically significant with differences between the compared indicators with a significance level of at least $p < 0.05$, unless otherwise specified. To construct a model explaining the dependence of AIN occurrence on several cofactors, the logistic regression method was used.

RESULTS

Participants of the study

Table 1 presents characteristics of the study participants.

Patients in groups 1 and 2 did not have statistically significant differences in age, gender or concomitant

Table 1. Clinical characteristics of the examined patients

Characteristics	Group 1, DM2 (n = 66)			Group 2, without DM (n = 98)			p1h
Type of intervention	CAS n = 38 (57.6%)	CEAE n = 28 (42.4%)	p2	CAS n = 62 (63.3%)	CEAE n = 36 (36.7%)	p3	
Gender							
Male, n (%)		50 (75.8)			72 (73.5)		0.8
Female, n (%)		16 (24.2)			26 (26.5)		
Gender							
Male, n (%)	28 (74%)	22 (78%)		45 (72.6%)	25 (69.4%)		0.37
Female, n (%)	10 (26%)	6 (22%)	0.354	17 (27.4%)	11 (30.6%)	0.37	
Age, years	65.5 \pm 7.6 [59-71]			64 \pm 8.7 [58-70]			0.44
Age, years	65 \pm 8.1	64.9 \pm 8.6	0.31	64.2 \pm 6.8	62.7 \pm 8.9	0.27	
Age (60 years and older), n (%)	28 (74)	21 (75)	0.46	43 (69.4)	26 (72.2)	0.38	
DCC in history, n (%)	29 (43.9)			28 (28.6)			0.04
Asymptomatic stenosis, n (%)	17 (45)	20 (71)		41 (66.1)	28 (77.8)		0.11
Symptomatic stenosis, n (%)	21 (55)	8 (29)	0.02	21 (33.9)	8 (22.2)	0.11	
IHD, n (%)	29 (43.9)			42 (42.9)			0.9
	17 (45)	12 (43)	0.44	29 (46.8)	13 (36.1)	0.14	
Hypertensive disease, n (%)	38 (100)	28 (100)	0.5	60 (96.8)	35 (97.2)	0.46	
Cardiac rhythm disorder, n (%)	15 (22.7)			21 (21.4)			0.88
	10 (26%)	5 (18)	0.22	16 (25.8)	5 (13.9)	0.08	
BMI, kg/m ²	30.4 \pm 5.5			27.8 \pm 2.7			0.001
TC, mmol/L	4.9 \pm 1.4			5.75 \pm 2.3			0.004
LDL, mmol/L	1.9 \pm 1.1			1.8 \pm 0.8			0.5
TG, mmol/L	1.94 \pm 1.4			2.2 \pm 1.3			0.11
HbA _{1c} , %	7.5 \pm 1.7	7.4 \pm 1.6	0.4	-	-		
Fasting plasma glucose, mmol/L	7.8 \pm 1.9	7.7 \pm 2.0	0.41	5.3 \pm 0.7	5.5 \pm 0.6	0.08	0.00

Note: n—number of patients; %—percentage of patients; HbA_{1c}—glycated haemoglobin; BMI—body mass index; IHD—ischaeamic heart disease; DCC—disorder of cerebral circulation; TC—total cholesterol; LDL—low density lipoprotein; TG—triglycerides.

p1—level of significance of differences between the groups; p2—level of significance of differences between subgroups of patients with DM2;

p3—level of significance of differences between subgroups of patients without DM.

Table 2. Perioperative brain lesion

Characteristics	Group 1, with DM2 (n = 62)		Group 2, without DM2 (n = 98)	
	CAS (n = 38)	CEAE (n = 28)	CAS (n = 62)	CEAE (n = 36)
Distribution by type of intervention				
Perioperative stroke, n (%)	Not detected	In three (10.7%) patients,	In three (4.8%) patients	Not detected
score by the NIHSS scale		one patient had 3 points, two patients had more than 10 points	up to 6 points	
p1		p1=0.02		p1=0.09
p2			p2=0.09	
p3				p3=0.02
AIN in the brain matter (according to DW-MRI), n (%)	15 (39.8%)	10 (35.7%)	29 (46.8%)	7 (19.4%)
p1		p1=0.37		p1=0.004
p2			p2=0.24	
p3				p3=0.012

Note: n–number of patients; %–percentage of patients; NIHSS–National Institutes of Health Stroke Scale; AIN–acute ischaemic nodules; DW-MRI–diffusion-weighted magnetic resonance imaging.

p1–level of significance in the group between subgroups; p2–level of significance between patients with and without DM2 during CAS; p3–level of significance between patients with and without DM2 during CEAE.

cardiovascular diseases ($p > 0.05$). Angioreconstructive surgery in both groups was more frequently required for patients over 60 years old, and males prevailed (75.8% and 74.5%, respectively). Hypertension was diagnosed in almost all patients of both groups. Ischaemic heart disease (IHD) and cardiac rhythm disorders were found in patients with DM2 and without it with a comparable frequency of 29 (43.9%) vs 42 (42.9%), $p = 0.44$ and 15 (22.7%) vs 21 (21.4%), $p = 0.38$, respectively. The prevalence of DCC in the history in patients with DM2 was 29 (43.9%), which was significantly higher than in patients without DM (28 (28.6%), $p = 0.04$). Patients with DM who needed angioreconstructive surgery had higher BMI (30.4 ± 5.5 kg/m²) than patients without DM had (27.8 ± 2.7 kg/m², $p = 0.01$).

Separate lipid pattern, even in the absence of statistically significant differences between the groups, exceeded the reference values of atherogenic parameters among patients both with and without DM2. The level of total cholesterol (TC) in the group of patients with DM2 was 4.9 ± 1.4 mmol/L, while it was significantly higher (5.75 ± 2.3 , $p = 0.02$) in the group of patients without DM. The groups did not have significant differences in the level of low density lipoprotein (LDL) and triglycerides (TG), which was 1.9 ± 1.1 mmol/L vs 1.8 ± 0.8 mmol/L, $p = 0.5$ and 1.94 ± 1.4 mmol/L vs 2.2 ± 1.3 mmol/L, $p = 0.1$, respectively.

When considering the clinical characteristics in the subgroups, there was also the absence of statistically significant differences depending on the surgical intervention performed by gender, age, the presence of hypertension and IHD. Patients in both groups undergoing CAS tended to have a greater frequency of heart rhythm disorders (Table 1).

Primary results of the study

Based on the main aim of the study, an analysis was made of AIN frequency and perioperative stroke (according to DW-MRI) after CAS and CEAE interventions (Table 2).

In patients who underwent CAS, the immediate perioperative period was generally clinically favourable. However, acute nodules of ischaemia in the brain matter were detected in some cases by DW-MRI. AIN sizes ranged from 1 to 21 mm, in an amount from 1 to 6. In three patients (all patients in group 2 without DM), perioperative stroke occurred in the system of the operated artery, manifested in impaired motor functions of the limbs and reduced tactile sensitivity. It should be noted that perioperative stroke developed in patients who initially had a high risk of developing cardiovascular complications, a multifocal lesion of various vascular systems, as well as a history of ischaemic stroke. In these patients, the score for neurologic impairment on the NIHSS scale at the time of diagnosis was 6 points.

Among the 38 patients with DM2 who underwent CAS, asymptomatic lesion to the brain matter was diagnosed in 15 (39.8%). In the remaining 23 patients (60.2%), the presence of AIN after surgery was not identified.

Out of 62 patients who did not have DM2, brain matter lesion was detected in 29 patients (46.8%), which was almost one-half of the cases. There were no statistically significant differences in the incidence of AIN in patients with and without DM2 who underwent endovascular intervention ($p = 0.24$) (Fig. 1, 2).

Among patients who underwent open intervention (CEAE), three (10.7%) patients in the group with DM2 had clinical signs of acute focal neurological symptoms in the immediate postsurgical period, and IS was diagnosed.

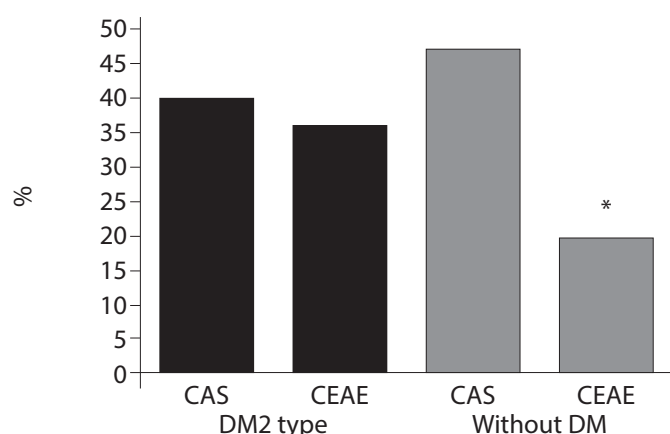


Fig. 1. The frequency of acute ischaemic nodules in patients, depending on the type of intervention.

Notes: * $p = 0.004$; CEAE—carotid endarterectomy; CAS—carotid angioplasty with stenting.

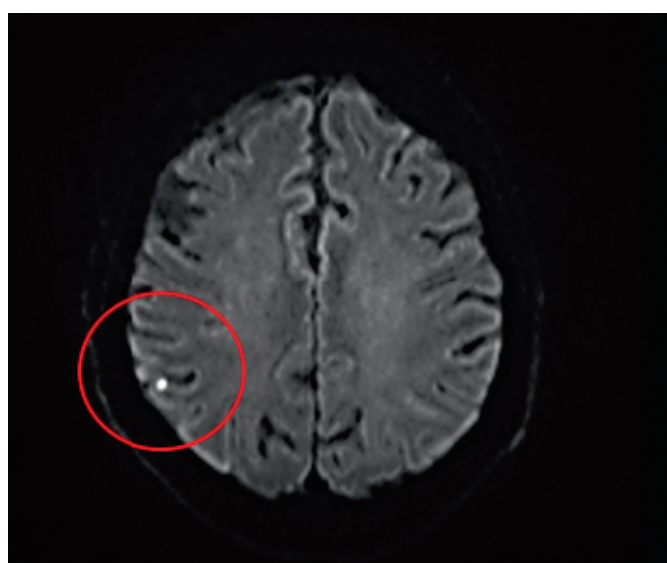


Fig. 2. Acute nodule of ischaemia in patient K., 66 years old, without diabetes mellitus, according to diffusion-weighted magnetic resonance imaging 24 h after angioplasty with stenting of the cortical substance in the parietal lobe of the right cerebral hemisphere.

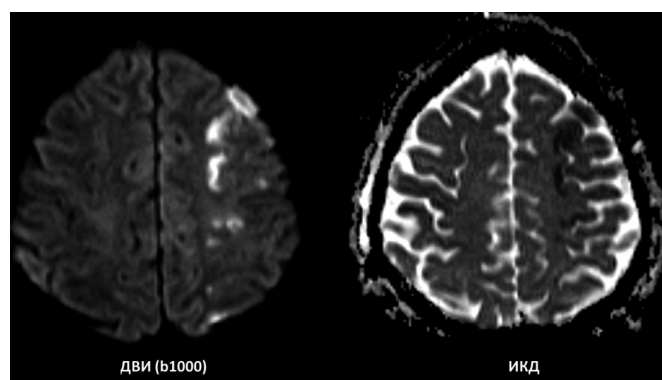


Fig. 3. Acute nodules of ischaemia in the cortical and subcortical substance of the frontal, parietal and temporal gyri (according to diffusion-weighted magnetic resonance imaging 24 h after carotid endarterectomy) in patient S. aged 64 years old with type 2 diabetes mellitus and perioperative stroke. Notes: DWI - diffuse-weighted image; ICD - measured diffusion coefficient during MRI.

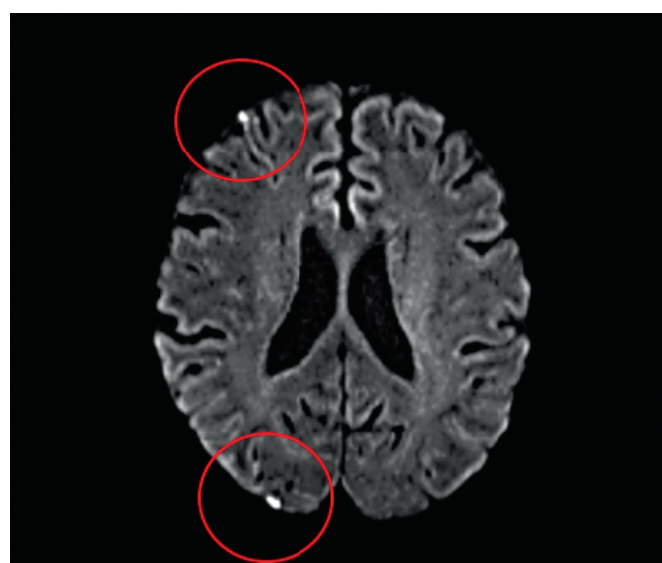


Fig. 4. Acute nodules of ischaemia in a patient with type 2 diabetes mellitus according to diffusion-weighted magnetic resonance imaging 24 h after carotid endarterectomy in the cortical substance of the frontal and parietal lobes of the right cerebral hemisphere.

The score on the NIHSS scale in one patient was 3 points, while the rest had more than 10 points (Fig. 3).

Out of 28 patients with DM2 who had CEAE, acute stroke and AIN in the brain matter were detected in a total of 13 (46.4%) cases (Fig. 3, 4). In patients without DM2, DCCs were not noted, and AIN was found in seven cases (19.4%), $p = 0.012$.

In patients with DM2, the incidence of AIN did not depend on the type of intervention (15 cases (39.8%) with CAS vs 10 cases (35.7%) with CEAE, $p = 0.37$). However, in patients without DM2, damage to the brain matter was observed 1.5 times more frequently during CAS with open intervention (29 cases (46.8%) vs seven cases (19.4%), $p = 0.004$).

To analyse the dependence of AIN development on several factors, a multiple logistic regression model was constructed (a similar model for only perioperative strokes could not be obtained due to the extremely low frequency, and the model for analysing at least one of the two specified outcomes coincided completely with the model for AIN. During all cases of perioperative strokes, AINs were also observed). The following

cofactors were chosen as predictors: gender, age, type of surgical intervention, DM, fasting glucose levels, HbA_{1c} level (in people without DM, the value of 5% was used), cholesterol level, symptomatic stenosis course, IHD and rhythm disorders. Because BP level was subject to active pharmacological correction both before and during intervention on the carotid arteries, this parameter was not included in the model.

Significant cofactors ($p < 0.1$ for Wald statistics) included the presence of DM, type of intervention and HbA_{1c} level. Table 3 presents the coefficients and odds ratios for the logistic regression model.

Based on the available data, a model was obtained with a rather low predictive capability; however, it was interesting to note that in this model a negative coefficient was obtained for the 'presence of DM' factor, which was not expected. However, a higher level HbA_{1c} led to an increase in the probability of occurrence of AIN. Additionally, a significant factor of the model was the type of surgical intervention (for $p < 0.1$), as CE was characterised by lower probability of AIN.

Table 3. Multiple logistic regression results for the development of acute ischaemic nodules

Independent variable	Coefficient of regression β	Standard error SE β	Wald Z-Value (H0: $\beta = 0$)	Wald p-Value (H0: $\beta = 0$)	Odds ratios	Lower limit of 95% CI for odds ratios	Upper limit of 95% CI for odds ratios
Intercept term	-4.81819	1.9644	-2.453	0.01418	0.00808	0.00017	0.37983
Presence of DM (reference: no DM)	-1.82679	0.69586	-2.625	0.00866	0.16093	0.04115	0.62944
CE2 (reference: CAS 1)	-0.64704	0.37657	-1.718	0.08575	0.52359	0.2503	1.09528
Cholesterol level	-0.11684	0.09884	-1.182	0.23715	0.88972	0.73303	1.07991
Age	0.0265	0.02482	1.068	0.28567	1.02685	0.9781	1.07804
Glucose level	0.138	0.1703	0.81	0.41774	1.14798	0.82219	1.60286
Female gender (reference: male gender)	0.30416	0.41042	0.741	0.45864	1.35548	0.60638	3.03003
Presence of cardiac rhythm disorders (reference: no cardiac rhythm disorders)	0.38271	0.42586	0.899	0.36883	1.46625	0.63637	3.37832
Presence of IHD (reference: no IHD)	0.42047	0.37762	1.113	0.26551	1.52268	0.7264	3.19186
Symptomatic course of stenosis (reference: asymptomatic course of stenosis)	0.5235	0.36866	1.42	0.1556	1.68792	0.8195	3.4766
HbA _{1c}	0.54699	0.25419	2.152	0.0314	1.72804	1.05	2.84392

Logistic regression model for AIN

Log likelihood = -96.57500, $R^2 = 0.89225$, AUC = 0.72887.

The percentage of cases classified correctly: 70.7%.

Additional results of the study

The initial indices of carbohydrate metabolism (prior to the surgery) compared with DW-MRI changes over time in patients with DM2 were of interest (Table 4, Fig. 5).

In patients after CAS with AIN identified after the intervention, the mean fasting blood glucose value prior to surgery was 8.1 ± 1.7 mmol/L, while in patients without AIN, the fasting blood glucose value was lower, but the difference did not reach a statistically significant level (7.4 ± 1.5 mmol/L, $p = 0.09$). The baseline HbA_{1c} level was higher in patients with AIN identified after the surgery ($7.8 \pm 1.4\%$), and in patients without AIN, the HbA_{1c} level was $7.1 \pm 1.1\%$ ($p = 0.0469$).

Analysis of carbohydrate metabolism in patients who underwent CEAE demonstrated the relationship of preoperative increased blood glucose values in patients with DM2 with the development of subsequent ischaemic changes in the brain matter. Thus, AINs were detected with fasting glucose values of 8.5 ± 1.9 mmol/L, but in patients with DM2 without changes in the brain matter, the basal glycemia was lower (7.0 ± 1.5 mmol/L ($p = 0.014$)). The HbA_{1c} level in patients who had AIN was significantly higher and amounted to $8.0 \pm 1.7\%$ versus $6.9 \pm 0.9\%$ in patients without signs of postoperative brain matter damage ($p = 0.0232$).

Hypoglycaemic conditions in the perioperative period were not registered.

Adverse events

This study was devoted to describing an understudied adverse event, the formation of nodules of cerebral ischaemia during angioreconstructive intervention on the carotid arteries. Additionally, we focused on the possibility of analysing the factors contributing to their occurrence.

DISCUSSION

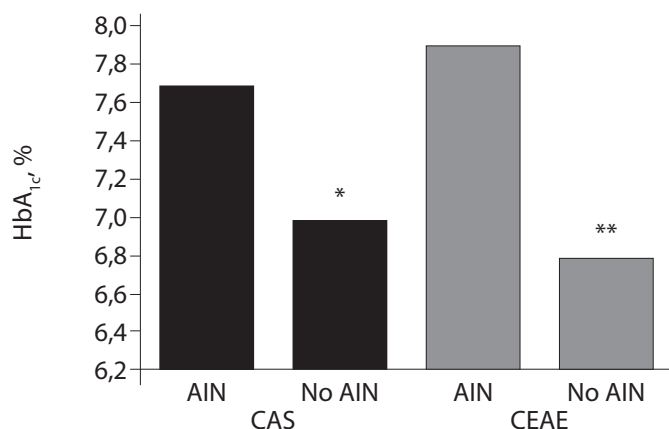
Summary of the main result of the study

Progress in the field of vascular surgery, the success of reconstructive surgery on the vessels of the head, contributes to the reduction of recurrent strokes and increases the life expectancy of patients. At the same time, angiosurgical intervention for atherosclerotic stenosis of the carotid arteries may be accompanied by the formation of acute nodules of ischaemia in the brain matter. In most cases of endovascular and open interventions, the revealed changes have a clinically asymptomatic ('silent') course. According to the results of our study, the occurrence of brain matter lesion was associated with the quality of glycemic control before the surgery and the type of intervention; the risk of AINs increased with increasing levels of HbA_{1c} and the implementation of CAS.

Table 4. Indicators of carbohydrate metabolism and data of diffusion-weighted magnetic resonance imaging of patients with type 2 diabetes mellitus who underwent carotid angioplasty with stenting and carotid endarterectomy

The presence of ischaemic nodules	Fasting plasma glucose, mmol/L			HbA _{1c} , %		
	AIN	No AIN	p	AIN	No AIN	p
CAS (n = 38)	8.1±1.7. n=15	7.4±1.5. n=23	p=0.09	7.8±1.4 n=15	7.1±1.1. n=23.	p=0.0469
CEAE (n = 28)	8.5±1.9. n=10	7.0±1.5. n=18	p=0.0147	8.0±1.7. n=10	6.9±0.9. n=18	p=0.0232

Note: n—number of patients; %—percentage of patients; p—level of significance; AIN—acute ischaemic nodules.

**Fig. 5.** Indices of glycated haemoglobin in subgroups by the type of intervention and the development of acute ischaemic nodules.

Notes: * p = 0.0469, ** p = 0.0232; AIN - acute ischaemic nodules; CAS—carotid angioplasty with stenting; CEAE—carotid endarterectomy.

Discussion of the main result of the study

In the course of this study, a high incidence of asymptomatic brain lesion during intervention on the carotid arteries was noted. AINs included nodules of increased intensity of the brain matter, identified for the first time after the surgery. In some cases, they were only neuroimaging findings not accompanied by neurological symptoms. These ischaemic nodules localised in the 'silent' areas of the brain. At the time of occurrence, there were no clinical manifestations; however, given the involvement of pathways, it was possible to develop disconnection syndrome. In this case, the manifestation of clinical symptoms may be delayed in time, including the development of cognitive disorders.

Due to insufficient coverage of neuroimaging studies before and after the surgery, the identification of 'silent' lesion in the brain matter in patients, including those with DM2, and their subsequent clinical significance has been understudied. Thus, currently, there are no indications of the attribution of an AIN to a number of well known complications [23]. The identification of such nodules of ischaemia was the result of an active search using high-resolution equipment.

As our results show, the development of such asymptomatic nodules occurs during both types of intervention.

The reference to DCC in the history was significantly noted more frequently in patients with DM2 (43.9% of cases) than in patients without DM (28.6% (p = 0.04)). Thus, our findings correlated with reports of a possible deterioration of the neurological status after surgery in patients who already had a neurologic impairment. It was in patients with DM that the symptomatic course of

precerebral arteries stenosing atherosclerosis and the development of damage to the brain matter after CEAE were more often noted, both in the form of the DCC development and 'silent' nodules of ischaemia.

Identification of predictors that enable the prediction of ischaemic nodules during surgical intervention is a difficult task. A correlation between the structural tissue characteristics of the plaque and the risk of ischaemic cerebral circulation was noted earlier. The presence of plaques containing nodules of atheromatosis and haemorrhage increases the risk of emboli during CAS [24], and when performing CEAE, this may be due to partial intraoperative destruction of the tectum areas, atheromatous masses, multiple calcifications located in the nodules of atheromatosis and superficial sections of the plaque with subsequent embolisation of the ICA branches.

An important aspect is the role of chronic hyperglycemia and increases in HbA_{1c} in DM, including in the context of preventing or minimising the possibility of developing AINs.

The data obtained about reducing the risk of AIN in the presence of DM2 and increasing this risk only with an increase in HbA_{1c} indicate that poor glycemic control rather than the presence of DM increases the risk of vascular events and aggravates the prognosis. Additionally, it should be noted that the treatment of patients with DM includes not only antihyperglycemic therapy to achieve individual treatment aims with recommendations for lifestyle changes, but also the elimination of other modifiable risk factors such as dyslipidemia and hypertension during regular visits to the doctor. In favour of this judgement, there is a statistically significant lower level of cholesterol and a tendency to lower TG values obtained in our work with patients with DM2. Moreover, this can be regarded as evidence of a greater commitment to treating patients with an established diagnosis of DM, which is generally the result of the active work of the entire medical community.

An increase in the risk of AIN development when performing CAS can be explained by the fact that this type of intervention is an alternative to endarterectomy and is performed in patients who have higher risk. The occurrence of AIN demonstrates the implementation of these risks. It should be noted that the effect of DM is differently directed depending on the type of surgery.

When both types of revascularisation were performed, an increase in the level of HbA_{1c} in patients with DM2 with the presence of AIN was noted (7.8 ± 1.4% in patients who underwent CAS and 8.0 ± 1.7% in those who underwent CEAE).

Thus, damage to the brain matter occurs in both types of intervention, but CE is accompanied by the formation of ischaemic nodules less frequently than endovascular intervention (26.5% vs 44%, $p = 0.01$). However, in patients with DM2, poor glycemic control can lead to an increase in the incidence of intraoperative ischaemia, the risk of which depends on HbA_{1c} before intervention when performing both types of carotid revascularisation. To develop algorithms for assessment and adjustment of carbohydrate metabolism to prevent ischaemic brain lesion, these data require a more thorough and weighted analysis. It should be emphasised that the presence of DM results in high surgical and anaesthetic risk, but it is not a contraindication to surgery.

Study limitations

The study is exploratory in nature, and the sample has not been calculated previously. Although statistical hypotheses are tested for all comparisons of interest, in the absence of statistical significance, a rather low power for all comparisons may be considered. Thus, even for the main groups (according to the presence of DM) by binary signs, to obtain statistical significance with $\alpha = 0.05$ with a power of 80%, the actual difference must be from 12% (with shares close to 0% or 100%) to 23% (with shares close to 50%), which is a large difference. For comparison of the subgroups by the frequency of AINs for detecting the minimum clinical difference of 10% with the available samples and $\alpha = 0.05$, the power ranges from 8% to 49%.

The type of intervention is determined by the clinical situation. This fact creates certain limitations in the standardisation of the groups under study. It follows from the model that the presence of DM and CE surgery reduce the risk of AIN, and a high level of HbA_{1c} increases it. The limitations of the analysis also include the imbalance of groups in the presence of DM and the type of intervention, which is due to the study design.

This study does not provide an assessment of cognitive status in patients prior to and after the intervention. Evaluation of the effect of revascularisation on the mental function of patients with DM2 requires further research. It is advisable to continue the prospective monitoring of the cognitive function of patients, because progression of disorders is possible. Additionally, the effect of preoperative adjustment of antihyperglycemic therapy

with the provision of long-term (at least three months) good glycemic control on the risk of intraoperative ischaemia, both symptomatic (stroke) and asymptomatic, should be studied.

CONCLUSION

Due to the undoubted success of modern angioreconstructive surgery, great opportunities have been implemented for the prevention of ischaemic DCC in patients with carotid atherosclerosis. However, the widespread use of high-resolution neuroimaging techniques has contributed to the accumulation of data about the possibility of perioperative ischaemic nodules of the brain, which are often asymptomatic. It is well known that such changes in the brain matter form the basis for the development and progression of cognitive impairment, making the medical problem of carotid revascularisation a medical-social problem. Considering the close concurrence of atherosclerosis and DM, we attempted to develop a personalised approach to patients with DM and cerebrovascular diseases. It must be clarified that an important predictor of the occurrence of asymptomatic nodules of cerebral ischaemia after these interventions may be an increase in HbA_{1c} levels. Such results require confirmation in a more extensive study to develop clear curation algorithms for such patients.

ADDITIONAL INFORMATION

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Contribution of authors. M.M. Tanashyan created the concept and design of the study, performed editing and final approval of the manuscript. K.V. Antonova performed collection and processing of materials, perioperative management of patients with diabetes, analysis of the data obtained and writing the text. R.B. Medvedev conducted enrollment of patients and performed clinical, neurological and ultrasound studies, as well as analysis of the data obtained and prepared the publication. S.I. Skrylev was involved in the selection and conduction of angioreconstructive surgeries. M.V. Krotchenkova organised and evaluated the neuroimaging studies. T.I. Romantsova edited the text.

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