Intracranial Atherosclerosis: Structure, Clinical Aspects and Risk Factors

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Abstract

Introduction. *Atherosclerosis is a complex pathophysiological process with a wide range of clinical manifestations. Active research is underway to determine the prevalence of intracranial atherosclerosis across different ethnic groups, the role of modifiable and non-modifiable risk factors in its pathogenesis, and the advances in diagnostic algorithms for patients with extra-/intracranial atherosclerosis.*

The ***aim*** *was to evaluate manifestations of intracranial atherosclerosis (patterns of intracranial artery lesions, including pathomorphological findings) and identify potential associations between known risk factors and intracranial atherosclerosis in patients with cerebrovascular disease.*

Materials and methods. *During the first phase, a retrospective analysis of autopsy protocols was conducted for 166 patients (66% men) hospitalized at the Research Center of Neurology between 1976 and 2007. The second phase involved clinical, laboratory, and imaging data from 120 patients (59% men) with atherosclerotic disease of the brachiocephalic arteries. These patients were divided into two subgroups: a main subgroup with intracranial artery involvement combined with extracranial atherosclerosis (n = 60) and a control subgroup with isolated extracranial artery involvement (n = 60).*

Results. *Pathomorphological assessment revealed a high rate of atherosclerotic lesions in the carotid artery system at both extra- and intracranial levels. One-third of patients had ⩾50% atherosclerotic stenosis in intracranial arteries without significant extracranial stenosis. Multivariate logistic regression analysis identified obesity (odds ratio [OR] 3.22), male sex (OR 6.17), and low-density lipoprotein levels (OR 2.5) as the most significant independent clinical laboratory factors associated with intracranial atherosclerosis.*

Conclusion. *The role of intracranial atherosclerosis in cerebrovascular events is underestimated. Overlapping neurological and generalized manifestations of isolated intra- and extracranial atherosclerosis may give a misleading impression of the true prevalence of intracranial atherosclerosis.*

Keywords: *intracranial atherosclerosis; risk factors; ischemic stroke*

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the Research Center of Neurology (protocol No. 9-5/22, October 19, 2022).

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Интракраниальный атеросклероз: структура, клинические аспекты и факторы риска

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Аннотация

Введение. *Атеросклероз – сложный патофизиологический процесс с огромным диапазоном клинических проявлений. Активно изучается распространённость интракраниального атеросклероза среди населения различных этнических групп, роль модифицируемых и немодифицируемых факторов риска в развитии данной патологии, совершенствуются алгоритмы обследования пациентов с экстра-/интракраниальным атеросклерозом.*

Цель *исследования – оценка проявлений интракраниального атеросклероза (характер поражения интракраниальных артерий, в том числе с учётом патоморфологических данных), а также выявление у пациентов с цереброваскулярными заболеваниями возможных ассоциаций известных факторов риска.*

Материалы и методы. *На первом этапе проведён ретроспективный анализ протоколов вскрытия 166 пациентов (66% – мужчины), находившихся на стационарном лечении в Научном центре неврологии в 1976–2007 гг. На втором этапе изучены клинико-лабораторно-инструментальные данные 120 пациентов (59% – мужчины) с атеросклеротическим процессом брахиоцефальных артерий, которые были разделены на две подгруппы: основную – с поражением интракраниальных артерий в сочетании с экстракраниальным атеросклерозом (n = 60) и группу контроля – с поражением исключительно экстракраниальных артерий (n = 60).*

Результаты. *В результате патоморфологического исследования установлена высокая частота атеросклеротического поражения артерий каротидной системы как на экстра-, так и на интракраниальном уровне. У трети пациентов атеростеноз ⩾ 50% определялся в интракраниальных артериях в отсутствие выраженного атеростеноза экстракраниальных артерий. Наиболее значимыми независимыми клинико-лабораторными факторами, ассоциированными с интракраниальным атеросклерозом, по данным многофакторной логистической регрессии, стали ожирение – отношение шансов (ОШ = 3,22), мужской пол (ОШ = 6,17) и уровень липопротеидов низкой плотности (ОШ = 2,5).*

Заключение. *Интракраниальный атеросклероз является потенциально недооценённой причиной развития нарушений мозгового кровообращения. Общность неврологических и общесоматических проявлений изолированных интра- и экстракраниального атеросклероза может создавать обманчивое впечатление об истинной распространённости интракраниального атеросклероза.*

Ключевые слова: *интракраниальный атеросклероз; факторы риска; ишемический инсульт*

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Introduction

Atherosclerosis (AS) is a complex pathophysiological process with a wide range of clinical manifestations. Decades of research on cerebral AS have provided robust evidence highlighting the significance of extracranial vascular lesions in the development and progression of a cerebrovascular event (CVE) [1, 2]. However, intracranial atherosclerosis (ICAS), which also represents a major global public health challenge due to the high risk of CVE [3], remains understudied. According to various studies, the rate of recurrent stroke in patients with ICAS ranges from 9.4% (short-term) to 15.1% (over 1 year) despite optimal preventive therapy [4], with a mortality rate of up to 13.2% within one year of a CVE [5]. Recent diagnostic advances have underscored the need for special attention to pharmacological treatment and prevention strategies, as well as the development of safe endovascular surgical techniques for intracranial artery stenosis. Current

research focuses on the variable prevalence of ICAS across different ethnic populations [6], the role of modifiable and non-modifiable risk factors, and the limitations of existing diagnostic protocols for patients with extracranial atherosclerosis (ECAS) and ICAS [7]. Multiple studies indicate that ECAS is predominantly associated with risk factors such as male sex, dyslipidemia, and diabetes, whereas ICAS is associated with hypertension and metabolic disorders, such as obesity and diabetes [8, 9].

The differential impact of risk factors on the development and progression of ICAS may be explained by morphological differences between intracranial and extracranial arteries [10]. Intracranial arteries have a stronger internal elastic lamina and sparse *vasa vasorum* (supporting the luminal diffusion theory and suggesting a more stable atherosclerotic plaque (AP) phenotype), absence of an external elastic lamina, and fewer smooth muscle cells. In addition, intracranial vessels have unique hemodynamics due to their tortuous anatomy, numerous perforating branches, and antioxidant defenses that provide long-term protection to the vessel wall. In contrast, extracranial arteries are elastic and musculoelastic vessels rich in collagen and elastin fibers in the medial layer and have an external elastic lamina [11].

Given the conflicting data on the prevalence of intracranial APs across different ethnic groups, we designed a two-phase study. The first phase involved morphological analysis, while the second phase focused on clinical and imaging comparisons in a cohort of patients with cerebral AS.

The **aim** was to evaluate manifestations of ICAS (patterns of intracranial artery lesions, including pathomorphological findings) and identify potential associations between known risk factors and ICAS in patients with cerebrovascular disease.

Materials and Methods

Phase 1

A retrospective analysis of autopsy protocols was conducted for 166 patients hospitalized at the Research Center of Neurology between 1976 and 2007. The study included 110 men and 56 women aged 38–89 years (mean age: 63.1 ± 11.0 years). The causes of death included cerebral infarction (n = 68), acute heart failure (n = 41), pulmonary embolism (n = 41), and other causes (n = 16). All evaluated cases revealed cerebral infarcts of varying size, location, and structure (1–15 infarcts per case, mean: 3.1 ± 2.4). Infarcts in the carotid artery system (CAS) or borderzone areas of the CAS and vertebrobasilar system were observed in 79.5% of cases (mean: 2.2 ± 1.6 infarcts per case): large/extensive infarcts (55 cases), medium infarcts (73), and small superficial/deep infarcts (51).

Cerebral artery macroscopy from autopsy reports was used to assess the prevalence of atherosclerotic lesions and the severity of stenosis in the CAS.

Statistica v. 13.0 (StatSoft) was used for statistical analysis. Student's t-test was used to evaluate differences. Results were considered statistically significant if $p < 0.05$.

Phase 2

The study included 120 patients with atherosclerotic lesions of the brachiocephalic arteries (confirmed by computed tomography (CT)/magnetic resonance (MR) angiography). Patients were divided into two subgroups: the main group (intracranial artery lesions with ECAS, n = 60) and the control group (extracranial artery lesions only, n = 60). The main group had a mean age of 64.8 ± 9.7 years [58; 71.5]; 43 patients (72%) were male. The control group had a mean age of 68.7 ± 6.99 years [63; 73]; 32 patients (53%) were male. Extracranial atherosclerosis involved stenoses of varying severity in the internal carotid and vertebral arteries. Exclusion criteria were recent (<6 months) acute CVEs, severe cognitive impairment, major medical/malignant/infectious disease, or allergy to iodine/gadolinium-based contrast agents.

All patients underwent detailed clinical and neurological examination, ultrasound, and angiographic imaging of the brachiocephalic arteries (CT angiography at extra-/intracranial levels for both groups; high-resolution MRI of the vessel wall for the main group).

Extra-/intracranial CT angiography was performed using a Siemens SOMATOM Definition AS scanner with intravenous iodine-based contrast (Omnipaque 350, 1–2 mL/kg; injection rate: 5 mL/s). High-resolution MRI of the vessel wall was performed using a Siemens Magnetom Prisma 3T scanner with gadolinium-based contrast (0.1 mmol/kg; injection rate: 4 mL/s).

R v.4.2.1 was used for statistical analysis. Quantitative parameters were compared using the Mann–Whitney U test. Qualitative parameters were compared using Pearson's χ^2 or Fisher's exact test. Univariate and multivariate regression analyses were performed. The resulting regression model was evaluated using ROC curve analysis with area under the curve (AUC) calculation. The sensitivity and specificity of the model were also evaluated. The null hypothesis was rejected at $p < 0.05$.

Results

Histopathology showed high prevalence of atherosclerotic lesions of CAS at both extracranial and intracranial levels (Figure 1): APs were detected in 96.4% of cases, with higher prevalence in intracranial (88.6%) than extracranial arteries (80.1%). Severe AS was most common in the internal carotid artery (ICA) sinus and middle cerebral artery (MCA, predominantly M1 segment), with comparable AP prevalence and the severity of stenosis (p = 0.66). APs were present in >75% of these arteries ($p < 0.0001$). Based on the incidence of APs and the severity of atherosclerotic stenosis, the intracranial ICA (the cerebral part and the carotid siphon) ranked second with APs detected in 68.7% of cases ($p < 0.0001$). Anterior cerebral artery atherosclerosis was less frequent (39.2% with APs).

Multiple atherosclerotic lesions were observed with 2–13 APs in 97.5% of CAS atherosclerosis (mean: 6.13 ± 2.84). Most patients (75%) had APs in both extracranial and intracranial arteries, predominantly (55.6% of cases) at three CAS system levels: common carotid artery/ICA sinus, intracranial ICA,

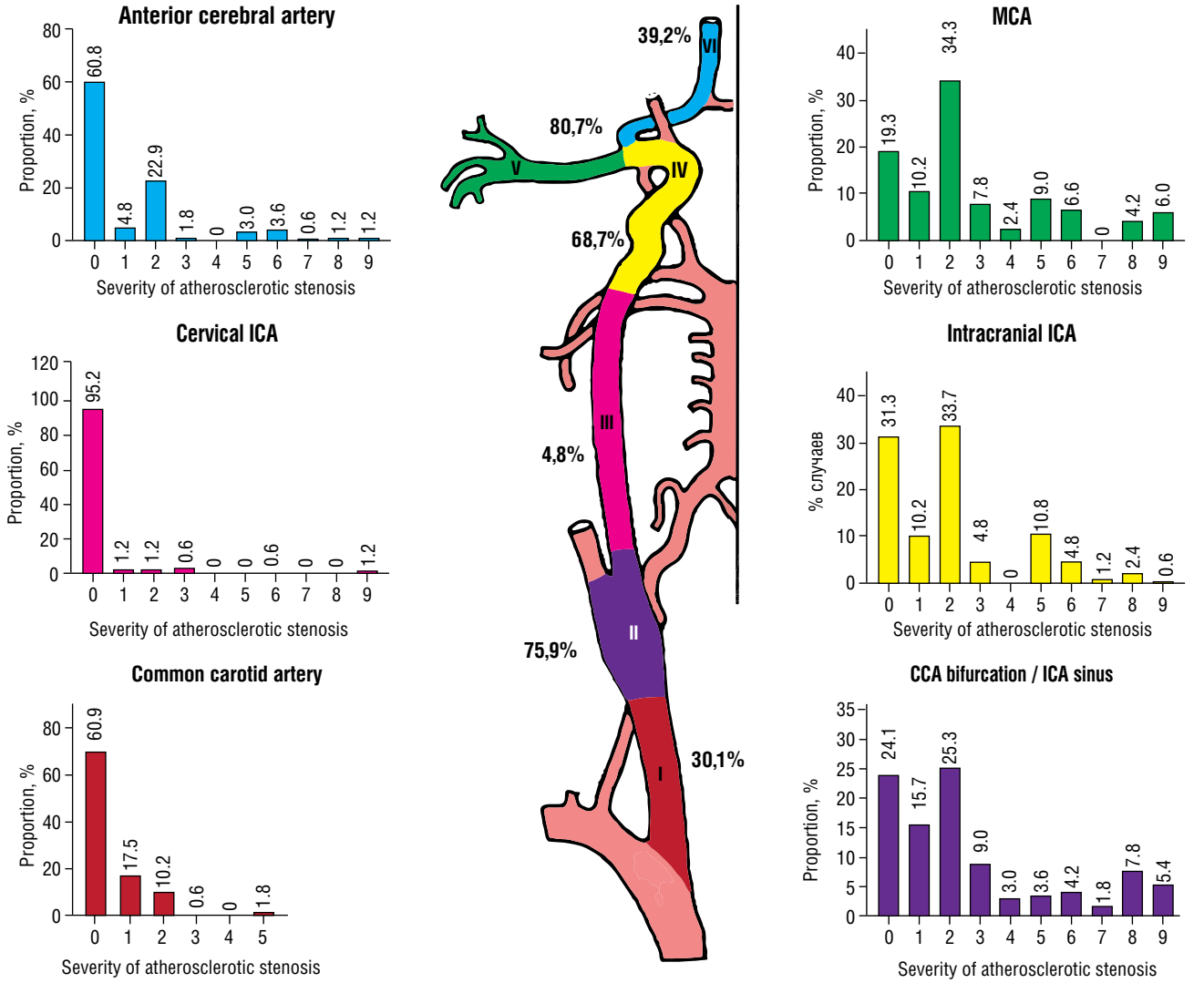

Fig. 1. Incidence of APs in the carotid system arteries (bilateral APs were considered; in the case of bilateral lesions, the most severe atherosclerotic stenosis was considered).
I – common carotid artery before bifurcation; II – CCA bifurcation with the ICA sinus; III – cervical ICA; IV – intracranial ICA; V – MCA; VI – anterior cerebral artery.
Severity of atherosclerosis: 0 – no APs; 1 – flat plaques; 2 – atherosclerotic stenosis < 20%; 3 – atherosclerotic stenosis ⩾ 20% and < 30%; 4 – atherosclerotic stenosis ⩾ 30% and < 40%; 5 – atherosclerotic stenosis ⩾ 40% and < 50%; 6 – atherosclerotic stenosis ⩾ 50% and < 60%; 7 – atherosclerotic stenosis ⩾ 60% and < 70%; 8 – atherosclerotic stenosis ⩾ 70% and < 80%; 9 – atherosclerotic stenosis ⩾ 80%.

and cerebral arteries (anterior cerebral artery and/or MCA). Multiple APs in intracranial arteries without extracranial lesions were observed in 14.4%, whereas isolated APs in extracranial arteries were rare.

APs were bilateral in 91% of cases, with 50% showing symmetrical CAS involvement. Bilateral lesions most frequently affected the ICA sinus/siphon and MCA (74–75% of cases). Multiple APs in the system of only one ICA (unilateral atherosclerotic lesion of the CAS) were rare (2.4%).

Most APs were flat or mildly stenotic (82%). APs with ⩾ 50% luminal stenosis were identified in 53.1% of cases (1.1 ± 1.6 APs per case). In 75% of these cases, 1 or 2 hemodynamically significant APs were detected. Severe stenoses (⩾ 50%) were primarily intracranial (40.6% of cases), predominantly isolated (30.6%), without significant extracranial atherosclerotic stenosis. Combined extra-/intracranial atherosclerotic stenosis ⩾ 50% was found in 6.3%. Multiple hemodynamically significant APs in intracranial arteries without ECAS were observed in 3.1%.

In patients with ICAS and ECAS (Table 1), hypertension was the major risk factor (100%), followed by male sex (73%), obesity (43%), and smoking (38%).

Most patients with ICAS had anterior circulation involvement: APs were most frequent in intracranial ICA segments (39%), followed by the MCA (23%) and anterior cerebral artery (4%).

Table 1. Characteristics of patients with ICAS and ECAS

Parameter	ICAS (*n* = 60)	ECAS (*n* = 60)	*p*
Age, years, Me [Q_1; Q_3]	66 [58; 72]	70 [63; 73]	0.027
Male, *n* (%)	44 (73%)	31 (52%)	0.014
Female, *n* (%)	16 (27%)	29 (48%)	0.014
Hypertension, *n* (%)	60 (100%)	55 (92%)	0.057
Systolic blood pressure, mm Hg, Me [Q_1; Q_3]	190 [180; 200]	180 [160; 190]	< 0.001
Diastolic blood pressure, mm Hg, Me [Q_1; Q_3]	100 [90; 110]	90 [90; 100]	0.005
Diabetes, *n* (%)	28 (47%)	19 (32%)	0.092
BMI, Me [Q_1; Q_3]	29.2 [27.4; 32.5]	27.6 [24.9; 29.0]	0.020
Obesity, *n* (%)	26 (43%)	12 (20%)	0.006
Smoking, *n* (%)	23 (38%)	38 (63%)	0.006
Cholesterol, Me [Q_1; Q_3]	4.40 [3.75; 5.80]	5.40 [4.55; 7.05]	0.002
Low-density lipoprotein, Me [Q_1; Q_3]	1.97 [1.42; 2.48]	1.88 [1.14; 2.49]	0.3
Family history, *n* (%)	27 (45%)	26 (43%)	0.9
Ischemic heart disease, *n* (%)	28 (47%)	25 (42%)	0.6
Lower limb atherosclerosis, *n* (%)	19 (32%)	24 (40%)	0.3
CVE, *n* (%)	41 (68%)	28 (47%)	0.016

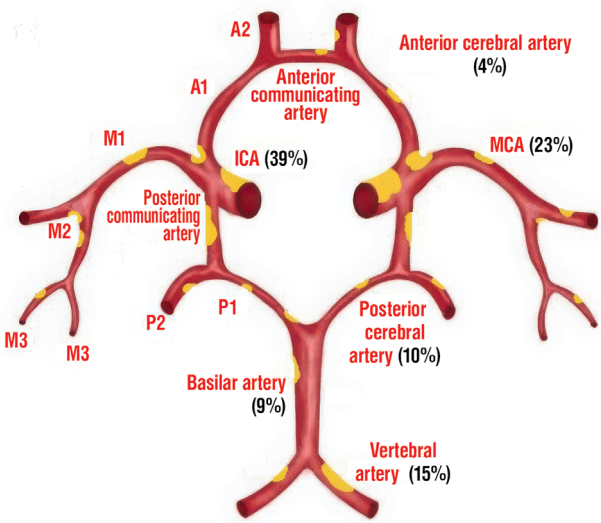

Fig. 2. Atherosclerotic burden on intracranial arteries.
M1–M3 – segments of the MCA; A1, A2 – segments of the ICA; P1, P2 – segments of the posterior cerebral artery.

Posterior circulation plaques were most commonly found in the V4 segments of the vertebral arteries (15%), followed by the posterior cerebral (10%) and basilar (9%) arteries. Figure 2 shows the atherosclerotic burden distribution across intracranial arteries (according to angiography data).

Among 60 patients with ICAS, stratification into subgroups based on the severity of ECAS revealed the following distribution: the largest subgroup comprised patients with ICAS without significant ECAS (stenosis < 50%), *n* = 30 (50%); subgroup with combined ICAS and hemodynamically significant ECAS (stenosis ⩾ 50%), *n* = 25 (42%); isolated ICAS (no ECAS): *n* = 5 (8%).

Comparative risk factor analysis between ICAS and ECAS groups demonstrated statistically significant differences:

- non-modifiable risk factors: younger age in ICAS group (66 years [58; 72] *vs* 70 years [63; 73]; *p* = 0.027); male predominance in ICAS group (73% [44/60] *vs* 52% [31/60]; *p* = 0.014);
- modifiable risk factors: higher systolic BP in ICAS group (190 mm Hg [180; 200] *vs* 180 mm Hg [160; 190]; *p* < 0.001); elevated diastolic BP in ICAS group (100 mm Hg [90; 110] *vs* 90 mm Hg [90; 100]; *p* = 0.005). Patients with ICAS more often had metabolic disorders and were characterized by higher body mass index (29.2 [27.4; 32.5] *vs* 27.6 [24.9; 29.0]; *p* = 0.020) and consequently greater prevalence of obesity (26 (43%) *vs* 12 (20%); *p* = 0.006). Conversely, prevalence of smoking (23 [38%] *vs* 38 [63%]; *p* = 0.006) and elevated total cholesterol levels (4.40 [3.75–5.80] *vs* 5.40 [4.55–7.05] mmol/L; *p* = 0.002) were significantly higher in controls.

No significant intergroup differences in type 2 diabetes rates were observed. However, ICAS patients with diabetes demonstrated higher rates of multifocal intracranial arterial involvement.

Univariate and multivariate analysis models were used to determine the significance of each risk factor in differentiating the level of atherosclerotic lesions of the cerebral arteries (Table 2). The multivariate logistic regression model identified independent predictors of ICAS such as age, sex, systolic blood pressure, lower total cholesterol levels, smoking, high low-density lipoprotein levels, and obesity.

Table 2. Univariate and multivariate logistic regression models of association of clinical and laboratory factors with ICAS

Risk factor	Univariate logistic regression model		
	odds ratio	95% CI	*p*
Age	0.95	0.90–0.99	0.015
Male	2.57	1.21–5.62	0.015
Systolic blood pressure, mm Hg	1.05	1.03–1.08	< 0.001
Diastolic blood pressure, mm Hg	1.05	1.02–1.10	0.007
Type 2 diabetes	1.89	0.90–4.02	0.094
Total cholesterol	0.68	0.52–0.86	0.002
Smoking	0.36	0.17–0.75	0.007
Chronic lower limb ischemia	0.70	0.33–1.47	0.3
Family history	1.07	0.52–2.21	0.9
Ischemic heart disease	1.23	0.60–2.53	0.6
Low-density lipoprotein	1.21	0.79–1.86	0.4
Obesity	3.06	1.38–7.09	0.007
BMI	1.10	1.00–1.22	0.053
History of stroke	2.47	1.18–5.26	0.017

Table 3. Characteristics of post-stroke patients with ICAS and ECAS, *n* (%)

Characteristic		ICAS (*n* = 60)	ECAS (*n* = 60)	*p*
CVE		41 (68%)	28 (47%)	0.016
Recurrent CVE		23 (56%)	5 (18%)	0.0024
Localization of a symptomatic AP (circulation system)	anterior	29 (71%)	23 (82%)	0.395
	posterior	12 (29%)	5 (18%)	0.395
Clinical presentation of the stroke	motor deficit	30 (73%)	21 (75%)	0.167
	sensory deficit	21 (51%)	14 (50%)	0.098
	vestibular ataxia	34 (83%)	23 (82%)	0.086
	cognitive dysfunction	28 (68%)	22 (79%)	0.954
	speech disorders	16 (39%)	19 (68%)	0.027
Severity of stroke, Me [Q_1; Q_3]	Rankin score	3 [2; 3]	2 [2; 3]	0.036
	Rivermead Mobility Index	11 [11; 13]	12 [10; 12]	0.043

ROC analysis evaluated the potential of this model as a predictor for verifying ICAS. Optimal threshold values were selected using the maximum Youden's index. The AUC was 0.882 (95% CI 0.826–0.939), indicating excellent predictive value. Sensitivity and specificity were 78 and 80%, respectively.

To further evaluate features of CVEs in patients with ICAS, we compared the characteristic localization of a symptomatic AP, clinical presentation of ischemic injury, and stroke severity between two patient groups (Table 3). The number of CVEs (41 (68%) *vs.* 28 (47%); $p = 0.016$) and recurrent ischemic events (23 (56%) *vs.* 5 (18%); $p = 0.0024$) was significantly higher in the ICAS group. Symptomatic APs in both ICAS and ECAS patients were more commonly located in the carotid (anterior) circulation (29 (71%) *vs.* 12 (29%); $p = 0.395$). Ischemic stroke severity, evaluated using the Modified Rankin Scale (3 [2; 3] *vs.* 2 [2; 3]; $p = 0.036$) and the Rivermead Mobility Index (11 [11; 13] *vs.* 12 [10; 12]; $p = 0.043$), differed significantly between ICAS and ECAS groups. No significant differences were observed in the clinical presentation of CVEs between two groups, except for speech disorders (16 (39%) *vs.* 19 (68%); $p = 0.027$).

Discussion

The presented analysis of morphological data demonstrates a high rate of atherosclerotic CAS involvement, with a slight predominance of intracranial lesions. This further highlights

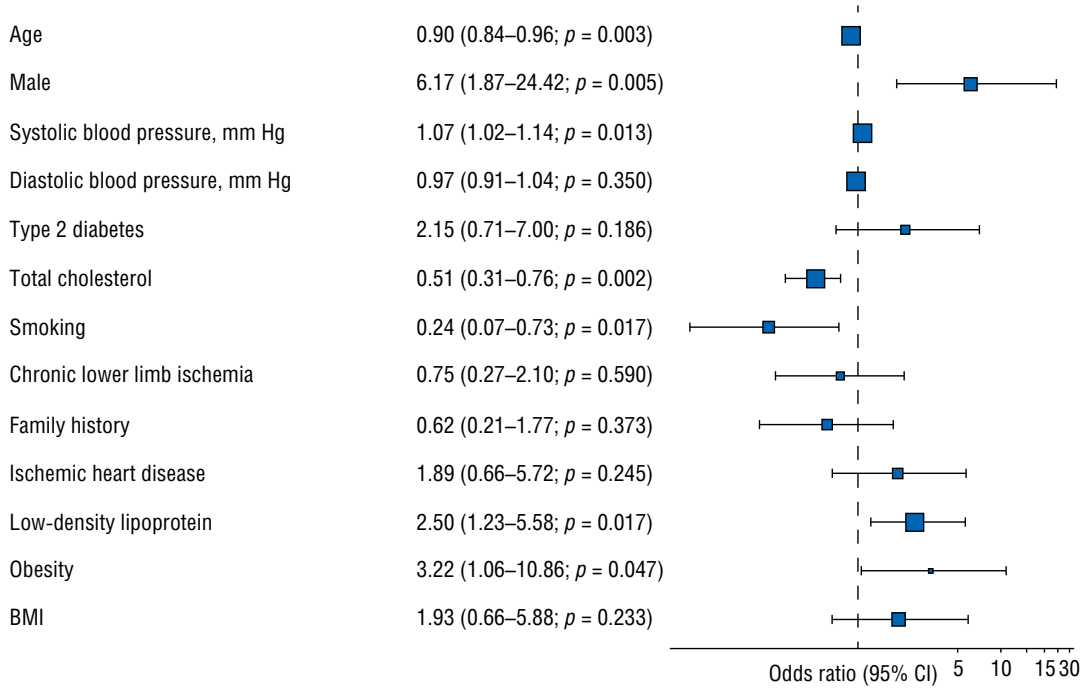

Fig. 3. Multivariate logistic regression models of association of clinical and laboratory factors with ICAS.

the clinical significance of ICAS and the need to improve conventional angiographic techniques, which currently fail to identify its true prevalence. It should be noted that 82% of APs were either flat or mildly stenotic, suggesting that lumen-oriented techniques such as digital subtraction angiography and CT angiography may overlook abnormalities in the intracranial arterial segments. This observation aligns with findings from H. Yan et al., who reported a higher prevalence of positive AP remodeling in the vertebrobasilar system and similarly cautioned against underestimation of such changes during angiographic evaluation [12].

Differences in risk factor profiles between ICAS and ECAS remain poorly understood. A 1995–2018 systematic review and meta-analysis of 31 risk factors for ICAS identified elderly age, metabolic syndrome, type 2 diabetes, and hypertension as the most significant contributors [13].

In our study, hypertension demonstrated a statistically significant role in both the initiation and progression of ICAS compared to ECAS. Most ICAS patients had grade 3 hypertension with hypertensive crises. These findings support previous hypotheses linking ethnic differences in ICAS prevalence (higher in Asian, Hispanic, and European populations) to differences in hypertension incidence, severity, and genetic risk factors in these groups [14]. In addition, metabolic disorders, such as obesity and diabetes, were also shown to contribute substantially to ICAS development and progression. While prior studies confirmed an association between diabetes and ICAS severity and progression [15], our analysis did not identify diabetes as an independent predictor of intracranial involvement. In contrast, obesity was a significant factor, more than tripling the potential for ICAS diagnosis. This difference may be attributed to the high prevalence of diabetes in both study groups.

As noted above, anatomical and physiological differences between extracranial and intracranial arteries tend to underlie differences in atherosclerotic lesion patterns. However, these processes are closely related: the presence of extracranial carotid APs independently predicts ICAS progression [16].

Our study found that patients with ICAS had recurrent CVEs more frequently than those with ECAS, aligning with global trends advocating aggressive management of ICAS [17]. Notably, strokes in the ICAS group predominantly localized to the anterior circulation, whereas Korean studies reported higher rates of posterior circulation stroke [18]. The lack of distinct clinical features between ICAS- and ECAS-related CVEs may contribute to underdiagnosis of ICAS in routine clinical practice. However, our findings suggest that a history of recurrent CVEs and increased stroke severity, both more common in ICAS, should prompt detailed angiographic and neuroimaging examinations.

Identifying associations between ICAS and established risk factors may increase neurologists' clinical alertness for this condition in patients with a history of CVE. To our knowledge, this is the first Russian study to identify independent risk factors for atherosclerosis at two anatomical levels (extra- and intracranial). Risk factors associated with ICAS should be considered when adjusting patient management strategies, given the high rate of recurrent CVE in this cohort. These findings may aid in developing personalized diagnostic and therapeutic algorithms and inform ICAS monitoring

programs. Further research and statistical analysis of these results may also allow the creation of specific scales for ICAS identification and risk stratification of recurrent CVE in ICAS patients.

A limitation of this study is its small sample size; larger cohort studies are needed to validate the significance of the identified ICAS risk factors.

Conclusion

ICAS represents a potentially underestimated cause of CVE. Isolated intracranial artery atherosclerotic stenosis (⩾ 50%) without significant extracranial atherosclerotic stenosis was observed in one-third of patients.

This study provides the first comprehensive clinical and pathological analysis of the structure, risk factors, and progression patterns of cerebral atherosclerosis. Our findings demonstrate that ICAS is not a part of extracranial vascular pathology but a distinct disease entity requiring personalized treatment and prevention strategies. The most significant independent clinical and laboratory factors associated with ICAS in our cohort were obesity, male sex, and elevated low-density lipoprotein levels.

Overlapping neurological and generalized manifestations of isolated ICAS and ECAS may obscure the true prevalence and etiological role of ICAS in cerebrovascular disease. We identified specific factors such as a history of recurrent CVE with severe symptoms, that may help clinicians suspect intracranial involvement during initial evaluation and prioritize advanced angioneuroimaging.

A deeper analysis of risk factors and improvement of diagnostic algorithms may lead to a better understanding of the ICAS pathophysiology and ultimately to optimal therapeutic and preventive strategies for this patient population.

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