ISCHEMIC STROKE WITH AND WITHOUT BRACHIOCEPHALIC ARTERY DISSECTIONS: RESULTS OF COMPREHENSIVE EXAMINATION OF PATIENTS

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Currently, there are no clearly defined optimal diagnostic strategies of detection of dissections. This study aimed to analyze and compare the results of comprehensive examinations of people who suffered an ischemic stroke (IS) with and without brachiocephalic artery (BCA) dissections. Dissections group, formed based on the results of multispiral computed tomography angiography that confirmed dissections, included 53 patients, and control group — patients without BCA dissections — comprised 1451 people; examination of all patients involved duplex scanning (DS) of BCA and transcranial part, transthoracic echocadiography (TTE), multispiral computed tomography angiography (msCTA) and/or magnetic resonance imaging (MRI). Patients with dissection were younger ($p < 0.0005$) and had a lower body mass index ($p < 0.0005$) than participants from the control group; according to echocadiography, they were less likely to have left ($p = 0.014$) and right ($p = 0.018$) atrial dilation and aortic stenosis ($p = 0.017$). Also, dissections were significantly less often associated with atherosclerotic plaques in the common carotid artery (CCA) ($p < 0.002$), and BCA deformations ($p < 0.05$). Duplex scanning of BCA revealed that in patients with dissections, differentiation of the intima-media complex in CCA was compromised significantly less often, and signs of thrombosis of the internal carotid artery were registered significantly more often ($p = 0.021$ and $p = 0.004$); according to MRI, such patients had less pronounced changes in the periventricular and deep white matter of the brain ($p < 0.0005$ and $p = 0.001$) and never suffered strategic infarcts affecting the thalamus area ($p < 0.0005$). Comparison of the results of examinations of IS patients with and without BCA dissections revealed differences that are probably conditioned by the younger age of those who had said dissections.

Keywords: dissection, duplex scanning, brachiocephalic arteries, CT angiography, ischemic stroke

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Compliance with ethical standards: the study was approved by the Ethics Committee of the Federal Center for Brain and Neurotechnology of FMBA of Russia (Minutes № 09/03-07-23 of July 03, 2023). All study participants signed the voluntary informed consent form.

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ИШЕМИЧЕСКИЙ ИНСУЛЬТ С НАЛИЧИЕМ И ОТСУТСТВИЕМ ДИССЕКЦИЙ БРАХИОЦЕФАЛЬНЫХ АРТЕРИЙ: РЕЗУЛЬТАТЫ КОМПЛЕКСНОГО ОБСЛЕДОВАНИЯ ПАЦИЕНТОВ

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Актуальность исследования обусловлена наличием неопределенности в оптимальных диагностических стратегиях при выявлении диссекций. Целью исследования были анализ и сопоставление результатов комплексного обследования лиц, перенесших ишемический инсульт (ИИ), с диссекциями брахиоцефальных артерий (БЦА) и без них. Основная группа пациентов с наличием диссекций по данным мультиспиральной компьютерно-томографической ангиографии включала 53 пациента, группа без диссекций — 1451 человек; все пациенты обследованы с проведением дуплексного сканирования (ДС) БЦА и транскраниального ДС, трансторакальной эхокадиографии (ЭхоКГ), мсКТА и/или магнитно-резонансной томографии (МРТ). Пациенты с диссекцией были моложе ($p < 0{,}0005$) и имели меньший индекс массы тела ($p < 0{,}0005$) в сравнении с контролем. По данным ЭхоКГ, у лиц с диссекциями реже встречались расширение левого ($p = 0{,}014$) и правого (p = 0,018) предсердий и аортальный стеноз ($p = 0{,}017$). При наличии диссекций достоверно реже наблюдали атеросклеротические бляшки в общей сонной артерии (ОСА) ($p < 0{,}002$) и деформации БЦА ($p < 0{,}05$). По данным ДС БЦА, у лиц с диссекциями достоверно реже ($p < 0{,}0001$) наблюдали нарушение дифференцировки комплекса интима-медиа в ОСА и достоверно чаще отмечали наличие признаков тромбоза внутренней сонной артерии ($p = 0{,}021$ и $p = 0{,}004$), а по данным МРТ, у них были менее выражены изменения перивентрикулярного и глубокого белого вещества головного мозга ($p < 0{,}0005$ и $p = 0{,}001$) и не встречались стратегические инфаркты, затрагивающие область таламуса ($p < 0{,}0005$). Сравнение результатов обследования перенесших ИИ пациентов с диссекциями и без них выявило различия, вероятно, связанные с более молодым возрастом лиц с диссекциями.

Ключевые слова: диссекция, дуплексное сканирование, брахиоцефальные артерии, КТ-ангиография, ишемический инсульт

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Effectiveness of secondary prevention of ischemic stroke (IS) largely depends on verification of the causes of its development, and their multifactorial nature and heterogeneity complicate the process and require application of a combination of various diagnostic techniques [1, 2].

The role of brachiocephalic artery dissections in IS pathogenesis has been established, but there are some issues that need to be clarified. Thus, there is no clear understanding of the exact mechanism of development of cerebral infarction with dissections in the background; the true prevalence of dissections remains unknown because in a significant number of cases the course is asymptomatic; there is no unequivocal consensus as to the optimal diagnostic and therapeutic strategies for dissections of various localization and genesis. Dissection of neck arteries leads to rupture of the intima or rupture of the vasa vasorum with bleeding into the media [3], which causes dissection of the vessel wall and yields a false lumen. Hematoma may increase towards adventitia, which translates into subadventitial dissection with pseudoaneurysm of the artery, and if it moves towards intima, the lumen grows narrower [4].

Digital subtraction angiography is the golden standard of diagnostics of craniocervical dissections [5], however, these disorders are mainly looked for with the help of MRI (magnetic resonance imaging) and msCTA (multispiral computed tomography angiography), which are practiced as routine studies [6]. These methods are effective in determining the extent of stenosis and intramural hematoma, and, with sensitivity up to 99%, they allow assessing condition of a vessel over a considerable length, but their ultimate utility is very dependent on the scanning protocols used and equipment enabling the process [7–9].

Ultrasound duplex scanning grows increasingly popular as the method of diagnosing extracranial dissections of brachiocephalic arteries, because resolution of the scanners is improving constantly and they are more and more readily available on the whole [10–12].

This study analyzed a significant array of relatively homogeneous clinical data acquired under similar conditions using various ultrasound diagnostic modes (methods) that complement and/or refine the results obtained, with some of those modes relatively rare.

The purpose of the study was to analyze and compare the results of comprehensive examinations of people who suffered an ischemic stroke with and without brachiocephalic artery dissections.

METHODS

This study includes data on 1451 individuals who had IS not later than 12 months ago. Neuroimaging methods allowed registering or confirming dissections of extracranial BCA (brachiocephalic arteries) in 53 of them (3.65%).

The inclusion criteria were: ischemic stroke verified by CT (computed tomography) or MRI; score 3 or below on the modified Rankin scale.

The exclusion criteria were: contraindications to MRI; history of serious diseases of the central nervous system.

We factored in demographic, anthropometric and anamnestic data: age, gender, height, weight, smoking status, alcohol consumption status, history of hypertension, atrial fibrillation, myocardial infarction, diabetes mellitus, characteristics of the IS (multiplicity, lesion side, basin, pathogenetic variant); body mass index (BMI) was calculated for each patient.

For electrocardiography (ECG), a Neurosoft electrocardiograph with Poly-spectrum software (Neurosoft, Russia) was used. The studies involved registration of the heart rate, direction of the heart's electrical axis, rhythm and conduction disorders, ischemic changes in the ST segment.

A Philips Epiq 7G scanner (Philips; USA) enabled duplex scanning of brachiocephalic arteries (DS BCA) and transcranial duplex scanning (TCDS), as well as duplex scanning of the lower extremity veins. A broadband multifrequency linear sensor operating at 3–12 MHz allowed assessing condition of extracranial stretches of the BCA and lower extremity veins, and another sensor working at 1–5 MHz was used for TCDS and transthoracic echocardiography (TTE).

Examination of extracranial sections of the BCA (B-mode) involved assessment of thickness of the intima-media complex; search for and assessment of severity of formations stenosing the lumens, their localization, degree of stenosis (applying the ECST methodology for the internal carotid artery), diameter of the artery, acoustic structure of the formations, its surface, complications.

Lower extremity veins were examined in a horizontal position. To detect thrombosis or post-thrombotic changes, the veins (all accessible segments of superficial and deep veins of both lower extremities) were subjected to compression tests every 1–2 cm.

Embologicity was established with the help of transcranial Doppler monitoring (TCDM) of blood flow at the base of brain through transtemporal access, in microembolodetection (MED) mode. The minimum duration of an examination was 60 minutes; it was enabled by an Angiodin Universal scanner (JSC NPF BIOS; Russia) operating dual frequency multi-depth sensors. Whenever signs of embolism were detected, its intensity was assessed.

Echocardiography (standard positions) was used to assess size and volume of the chambers of the heart, its contractility, left ventricle systolic and diastolic functions, presence of zones of hypo/akinesis, dyskinesis, pathological formations in the heart's chambers, condition of the valves (valvular stenosis and regurgitation, prosthetic heart valves), presence/absence of signs of blood shunting between the chambers, condition of the ascending aorta and the aortic arch.

MR studies of the brain were preformed with a Discovery MR750w system (General Electric, USA), magnetic field induction of 3 T. Results of each MR examination were assessed and described by by three doctors with sufficient experience, randomly selected from six doctors participating in the study.

Regional atrophy of the gray matter was evaluated using the GCA (Global Cortical Atrophy) qualitative scale. Lesions of hyperintensivity (deep and periventricular white matter) were scored on the qualitative Fazekas scale using the T2 weighted images with free fluid signal suppressed. Additionally, the researchers measured width of the third ventricle, looked for obstructive or normotensive hydrocephalus, micro-hemorrhages in the brain substance, hemosiderosis, gliosis/encephalomalacia sites and strategic infarcts (in the thalamus, angular gyrus artery basin, areas of adjacent blood supply in the frontal or parietal lobes, medial part of temporal lobes, in the basins of the anterior cerebral artery bilaterally).

Fifty-three patients from the dissection group and 453 patients from the control group had msCTA done with a 128 slice Optima CT scanner (GE; USA), voltage of 120 kV, current of 350 mAs. In all cases, 60 ml of preheated Ultravist nonionic contrast agent (iodine concentration of 370 mg/ml) were administered at the rate of 5 ml/second, followed by 40 ml of saline, also preheated. Aortic arch and all sections

Table 1. Main characteristics of patients with signs of dissection

Characteristic	Number of patients	Share (%)
Smoking status	20	37.7
Arterial hypertension	38	71.7
History of myocardial infarction	2	3.8
Atrial fibrillation	1	1.9
Diabetes mellitus	4	7.5
Signs of connective tissue insufficiency	3	5.7
History of injuries shortly before development of dissection	4	7.5
ARVI shortly before development of dissection (including Covid-19)	6	11.3
The alleged genesis of dissection: – cryptogenic – traumatic or iatrogenic	49 4	92.5 7.5
Dissection localization – right CCA – left CCA – right ICA – left ICA – right ECA – right VA – left VA – right ICA and right VA – left CCA, ICA and VA	2 4 11 16 1 9 8 1 1	3.8 7.5 20.8 30.2 1.9 17 15.1 1.9 1.9
Ischemic stroke side – right – left – cannot be determined (both sides simultaneously or in the stem structures, medially)	24 23 6	45.3 43.4 11.3
Ischemic stroke basin – vertebro-basilar – carotid	7 46	13.2 86.8
Multiple foci detected by MRI	16	30.2
Initial ischemic stroke	39	73.6
Coincidence of side of dissection and stroke	35	66.0

Note: CCA — common carotid artery; ICA — internal carotid artery; ECA — external carotid artery; VA — vertebral artery.

of the extra- and intracranial arteries were scanned. The images were analyzed using AW server (GE; USA); the process included 3D reconstruction of brachiocephalic arteries, quantitative assessment of arterial stenoses that relied on the NASCET criteria (North American Symptomatic Carotid Endarterectomy Trial) for extracranial artery stretches and WASID criteria (Warfarin-Aspirin Symptomatic Intracranial Disease) for intracranial sections.

Indicators detectable by msCTA, MRI and MRA that ensured admission to the dissections group were demilune symptom, which corresponds to an intramural hematoma [13], eccentric lumen stenosis with increased outer diameter of the artery [14–16], pseudoaneurysm, and "candle flame" symptom [17].

The data obtained were processed (statistical processing) with the help of SPSS Statistics 26.0 (IBM; USA) and R software 4.0.2 (R Core Team; Austria). The null hypothesis was rejected at the level of significance of $p \leq 0.05$. For quantitative variables, we used arithmetic mean and standard deviation or median and quartiles (in case of abnormal distribution), for qualitative variables — frequency and fraction (as a percentage). Normality of distribution of quantitative variables was checked with the help of Kolmogorov–Smirnov test. Pearson's χ^2 test or Fisher's exact test enabled comparison of the frequencies of qualitative dependent variables between categories of independent (grouping) variables. The relationship between quantitative and ordinal variables was assessed with the Pearson correlation. For quantitative dependent variables, the comparison relied on the Mann–Whitney test. Bonferroni correction was used for multiple comparisons.

RESULTS

Twelve (22.6%) of 53 patients with brachiocephalic artery dissections were female, 41 (77.4%) male. The mean age of the patients was 51.9 ± 14.8 (21-83) years. Body mass index in the dissections group was 25.2 ± 3.55 (19.0–33.9 kg/m^2), that is, those with dissections were more likely to have normal body weight (Table 1).

Most often, cerebral infarction developed in the basin of right (19 patients (35.8%)) and left middle cerebral artery (MCA) (15 patients (28.3%)). There was no relationship between the patient's age and the frequency of coincidence of infarct focus and dissection localizations: among patients below 50 years of age, such were found in 64% of cases. There was no connection between multiplicity of MRI-registered foci and coincidence of localization of the infarct focus and dissection (p = 1.0; Fig. 1). Consequently, the pattern of brain damage with multiple ischemic foci and dissections was as frequent as that without dissections.

There was no association registered between localization of dissection and gender/age. Patients with cryptogenic dissections were somewhat younger than those with traumatic ones (as a trend, p = 0.101).

Microembolic signals, according to TCDM with MED, were registered only in 1 (1.9%) out of 39 (73.5%) tests taken from individuals with dissections.

Patients with brachiocephalic artery dissections did not differ from other participants by gender (p = 0.358), but were significantly younger (age of IS patients without dissections was

Fig. 1. The ratio between coincidence of localization of the infarct focus and dissection, depending on the multiplicity status of the infarction foci

60.73 ± 11.95; $p < 0.0005$; Fig. 2) and had a lower body mass index (in patients without dissections, it was 27.70 ± 4.87; $p < 0.0005$; Fig. 3).

The characteristics of ischemic strokes (pathogenetic variant, side of infarction focus, lesion pool, stroke-affected artery) did not differ between patients with and without dissections. People with dissections were smokers more often (39.2% vs. 21.3%, $p = 0.005$), and less often suffered from atrial fibrillation (1.9% vs. 13.2%, $p = 0.01$), hypertension (71.7% vs. 84.2%, $p = 0.022$), diabetes mellitus (7.5% vs. 21.7%, $p = 0.01$).

As a trend (p = 0.066), there was registered the relationship between dissection and history of thromboextraction. As for the relationship between dissection and history of carotid stenting, the link between them was significant ($p = 0.015$).

ECG revealed no specific features in patients with dissections compared to patients without them ($p > 0.05$).

According to echocadiography, patients with dissections were less likely to have dilation of the left ($p = 0.014$) and right ($p = 0.018$) atria, and atherosclerotic changes in the thoracic aorta (as a trend, $p = 0.073$) (Table 2).

According to echocadiography, patients with dissections were significantly less likely to have signs of aortic stenosis (4.0% vs. 16.7%, $p = 0.017$).

In the dissections group (patients with dissections), according to msCTA, atherosclerotic plaques (ASP) in the CCA were significantly less common (30-40% vs. 60%, depending on the side, $p < 0.002$).

Computed tomography and DS of BCA revealed that brachiocephalic arteries, including ICA, were less frequently deformed in patients with dissections ($p < 0.05$) (Table 3).

According to DS of BCA, patients with dissections were significantly less likely to have intraluminal formations in the right subclavian artery (24.0% vs. 39.3%, $p = 0.037$). No such pattern was revealed for the left subclavian artery, nor for CCA and ICA ($p > 0.05$). The intima-media complex differentiation disruptions in the right and left CCA were significantly less common in dissection cases ($p < 0.0001$).

In the dissection group, signs of thrombosis of right and left ICA were detected with DS of BCA significantly more often (13% vs. 4.6%, $p = 0.021$ and 15.2% vs. 4.2%, $p = 0.004$, respectively) than in the control group. In dissection cases, DS of BCA has also revealed more frequent decrease in the peak systolic blood flow rate in intracranial sections of the right and left ICA ($p = 0.005$ and $p = 0.003$, respectively), signs of anastomosis on the left ($p = 0.058$), and collateralization within the circle of Willis — flow along the anterior ($p = 0.026$) and posterior communicating artery ($p = 0.006$).

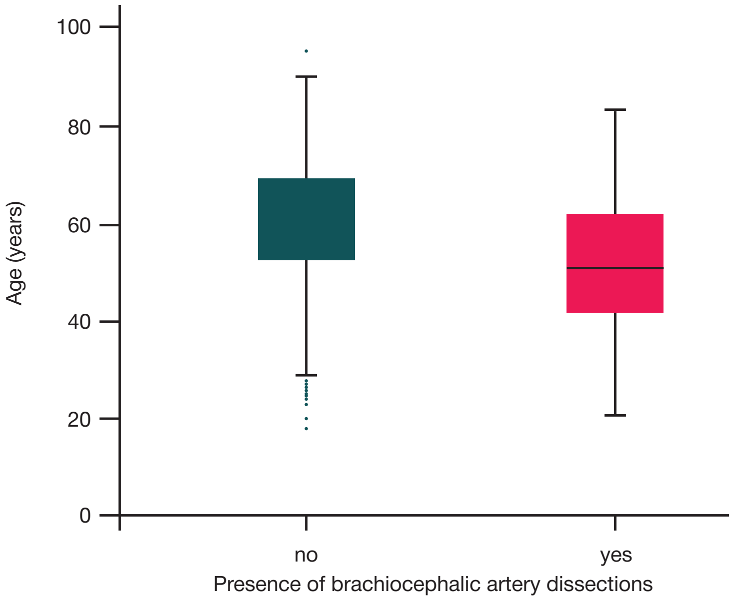

Fig. 2. Stroke patients with and without dissections: comparison of age

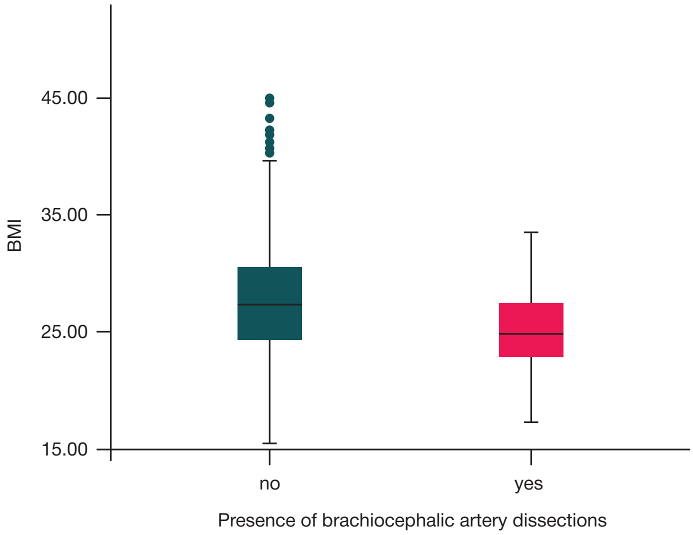

Fig. 3. Stroke patients with and without dissections: comparison of BMI

Lower extremities DS has shown that patients with dissections had signs of superficial vein thrombosis significantly more often ($p = 0.037$).

According to the msCTA, there was no relationship between dissections and structure of ASP (calcified, soft, mixed), as well as signs of their ulceration and localization features relative to the walls of the arteries ($p > 0.05$).

In the dissection group, according to MRI, changes in the periventricular and deep white matter of the brain were less pronounced ($p < 0.0005$ and $p = 0.001$). A noteworthy fact revealed by this examination is lack of strategic infarcts affecting the thalamus area in dissection cases (0% vs. 40.2%; $p < 0.0005$).

DISCUSSION

Considering that the sample analyzed in our study consists of IS patients, the data demonstrate lack of serious differences in the characteristics of strokes in cases with and without dissections. It is possible that, regardless of the intravascular thrombosis triggering factor (ASP or dissection), further events (arterio-arterial embolism) develop stereotypically. This opinion is the prevailing one in the published papers [18].

Patients with dissections tend to be younger than IS patients without dissections, which is a fact deserving attention. That noted, the mean age of participants of our study was similar to that reported by other authors [19–25]. It is possible that the pattern reflects the role of hereditary background predisposing to the development of BCA dissections.

The relationship between presence of dissections and thromboextraction in the acute IS period, as well as carotid artery stenting, may show the significance of the role of some interventions in certain cases with BCA dissections.

Various diagnostic methods revealed differences that depend on the dissections status, i.e., presence or lack thereof. In particular, patients with dissections were less likely to have intraluminal formations in individual arteries, and disrupted differentiation of the intima-media complex into layers signaling of the atherosclerotic process. At the same time, these patients exhibited signs of ICA thrombosis significantly more often. It cannot be excluded that the reason behind this is adhesion of platelets in the area of damage (or secondary involvement) of intima against the background of dissection of artery walls.

Echocadiography demonstrated that patients with dissections are less likely to have left and right atrial dilation, as well as atherosclerotic changes in the thoracic aorta and aortic stenosis. Previously published papers contain no such findings. In addition, msCTA revealed ASP in CCA less frequently in such cases. There was also no relationship between the presence of dissection and structure and localization of ASP. Obviously, the prevalence of these phenomena increases with age, so it is quite natural that in younger patients with dissections, atherosclerotic lesions of the aorta and main arteries, as well as manifestations of cardiac pathology, were less common. In addition, a DNA analysis seeking to determine polymorphism of apolipoprotein E has shown that the epsilon4 allele appears to be involved in the development of premature atherosclerosis of carotid arteries, and, at the same time, can protect against dissections [26]. Therefore, it cannot be completely excluded that hereditary characteristics could have played a part in our study in addition to the age-related intergroup differences.

The fact that dissection cases more frequently present decreased linear blood flow rates in the intracranial ICA, functioning of the ocular anastomosis on the dissection side, collateralization towards the affected artery basin along the anterior and posterior communicating arteries, may indicate the

Table 2. Echocadiography data, patients with and without dissections

Indicator	No dissection detected	Dissections
Left atrium dilation, persons (share, %) – yes – no	716 (54.2%) 606 (45.8%)	18 (36%) 32 (64%)
Right atrium dilation, persons (share, %) – yes – no	537 (40.8%) 778 (59.2%)	12 (24%) 38 (76%)
Thoracic aortic lesion, persons (share, %) – yes – no	272 (20.7%) 1045 (79.3%)	5 (10%) 45 (90%)

Table 3. Deformations of ICA as registered with DS of BCA, depending on dissections status

Characteristic	No dissections	Dissections
Deformation of right ICA – yes – no	91 (7.0%) 1211 (93%)	1 (2.1%) 46 (97.9%)
Deformation of left ICA – yes – no	96 (7.5%) 1185 (92.5%)	1 (2.1%) 46 (97.9%)

hemodynamic significance of a number of identified dissections, but it is still difficult to make conclusions about their role in the genesis of cerebral stroke if localization of the infarct focus and the dissection coincide. The frequency and nature of stroke do not depend on the degree of stenosis associated with artery dissection, however, in cases with occlusive dissections, infarctions turned out more extensive in comparison to non-occlusive cases [27].

On the context of this study, msCTA returned various BCA deformations in dissection cases less often, which may have links to the younger age or be a manifestation of greater stiffness of the vessel walls (perhaps, this is one of the important factors predisposing to dissections). There are opposite conclusions in the earlier studies, which state association of connective tissue weakness, tortuosity of the carotid arteries and their dissections against the background of fibromuscular dysplasia [28], which, apparently, should be attributed to the excessive "softness" (insufficient stiffness) of artery walls in cases of connective tissue insufficiency. There were few such cases in our sample, which is also confirmed by lack of association between dissections and signs of lower limb varicose veins. Nevertheless, in individuals with dissections, signs of superficial vein thrombosis were detected significantly more often, which, in addition to the state of the hemostasis system, may be a consequence of the structural features of vessel walls.

In dissection cases, MRI-detected manifestations of microangiopathy, i.e., changes in the periventricular and deep white matter of the brain, were less pronounced, which, apparently, was also associated with a younger age. At that, there were no significant differences in the severity of local atrophy of the cerebral cortex.

It is difficult to explain the lack of lesions in the thalamus zone in IS cases with dissections. This fact needs to be verified on more numerous samples.

It is known that, according to MRI data, the nature of infarction in carotid artery dissection is predominantly cortical (80%), subcortical (60%), in the MCA basin (99%), in the areas of adjacent blood supply (5%), anterior (4%) and posterior cerebral artery (3%) [29, 30]. According to the results of our study, 94% of patients with carotid artery dissections had infarction in the MCA basin, which is consistent with these data.

CONCLUSIONS

According to the results of this study, IS patients with BCA dissections were younger than those without dissections, they were less likely to have dilated left and right atria, signs of atherosclerotic changes in the thoracic aorta and common carotid arteries, and deformities of various BCA. In this dissection group, changes in the periventricular and deep white matter of the brain were also less pronounced (MRI-registered manifestations of microangiopathy or small vessel disease).

Comparison of the results of comprehensive examinations of IS patients with and without extracranial BCA dissections revealed that the differences identified are most likely related to age (younger age of patients with dissections), as well as other factors, including hereditary characteristics.

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