Causes of ischemic stroke in patients younger than 45 years: analysis of data from the regional vascular center

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In young patients, the causes of ischemic stroke (IS) are substantially different from those in older patients. Understanding the causes of the disease in patients younger than 45 years is needed to elaborate examination algorithms used in the country's vascular departments.
Objective: *to present the nosological characteristics of IS in patients younger than 45 years according to the hospital register of the regional vascular center.*
Patients and methods. *The data of the hospital register of the neurological unit for patients with acute cerebral circulatory disorders, who were in the Perm Territorial Vascular Center, City Clinical Hospital Four, in 2014 to 2020, were analyzed. The analysis included 126 patients under the age of 45 years with IS verified by magnetic resonance imaging.*
Results and discussion. *The pathogenetic subtypes of IS according to the TOAST criteria were large artery atherosclerosis [n=10 (7.9%)], cardioembolism [n=27 (21.4%)], small vessel disease [n=15 (11.9%)], IS of other determined etiology [n=23 (18.3%)], and IS of undetermined etiology [n=51 (40.5%)]. After excluding incomplete examination cases (n=29), the most common causes of IS were cardiac embolism (patent foramen ovale, atrial septal defect, prosthetic valves, acute infective endocarditis, and chronic cardiac aneurysm) (27.8%), large artery disease (atherosclerosis and unspecified arteriopathy) (21.6%), small artery disease (15.5%), as well as cervical and cerebral artery dissection (10.3%). Cryptogenic stroke was observed in 13% of patients. There was a preponderance of cryptogenic IS in the age subgroup of 21–25 years, cardiac embolism (mainly patent foramen ovale) in the subgroup of 26–35 years; the proportions of cardiac embolism, large and small artery diseases, and dissections were comparable in the subgroup of 36–40 years; large and small artery diseases prevailed in the subgroup of 41–44 years.*
Conclusion. *The most common causes of IS in 18–44-year-old patients are cardiac embolism (mainly through the mechanism of paradoxical embolism) and large artery disease, including dissection. The etiology of IS depended on age: cardiac embolism prevailed in the younger age range, whereas large and small artery diseases were dominant in the older age range.*

Keywords: *stroke; young patients; etiology; patent foramen ovale; dissection.*
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In recent decades, the incidence of ischemic stroke (IS) at a young age has increased by about 40%, which is not least due to the improvement of approaches to diagnosis [1, 2]. The etiological structure of IS in young patients remains controversial due to differences in examination and diagnostic algorithms used in different centers. Unlike stroke in older age groups, many specific, often rare causes and risk factors (RFs) are associated with stroke in young patients, including drug use, pregnancy, dissection of cervical and cerebral arteries, and patent foramen ovale (PFO) [3, 4].

In the domestic literature, there are only few works devoted to the problem of IS at a young age. Among them, the largest and most profound is the research conducted by L.A. Kalashnikova et al. [5], which included more than 600 patients aged 18–45 years. The authors have shown that the most common causes of IS are: dissection of arteries supplying the brain (28%), cardioembolism (12%), antiphospholipid syndrome (11%), coagulopathy of unspecified origin (6%) and isolated cerebral arteritis (5%). Cryptogenic stroke was diagnosed in 25% of patients, and in half of them the clinical manifestations were typical for dissection. It should be noted that the time range for inclusion in the study varied from 1 week to 14 months after a cerebral accident [6]. We have not found any domestic work in which a systematic analysis of the etiology of IS at a young age in patients arriving from the same territory to a regional vascular center or primary stroke department would be carried out. In our opinion, an understanding of the etiological structure of the disease in this category of patients is necessary for the development of diagnostic algorithms that are applicable in the stroke departments of the country.

The aim of the study is to present the nosological characteristics of IS in patients younger than 45 years according to the hospital register of the regional vascular center.

Patients and methods. The data of the hospital register of the neurological department for patients with stroke of the Perm region «City clinical hospital No. 4» for the period from 2014 to 2020 were analyzed. The analysis included patients with verified by magnetic resonance imaging (MRI) IS under the age of 45 years. If there was any doubt about the diagnosis, the patient was not included in the study. To obtain a real clin-

ical and aetiological picture of IS, no other restrictions for inclusion in the study were used. Patients were admitted from the Motovilikhinsky district of the city of Perm with population of 373 627 people.

The analysis included data from 126 patients, of whom there were 79 men (63%) and 47 women (37%). The age of the patients varied from 18 to 44 years and averaged 36.9 ± 5.8 years. The patients were divided into age groups as follows: <20 years old – 1 (1%), 20–25 years old – 5 (4%), 26–30 years old – 13 (10%), 31–35 years old – 26 (21%), 36–40 years old – 42 (33%), 41–44 years old – 39 (31%). As in the general group, among men the most numerous was the subgroup of 36–40 years old, while among women it was 41–44 years old. The general characteristics of the group are presented in table. 1.

Table 1. *General characteristics of patients (n=126)*

Indicator	Number of patients, n (%)
Anamnestic data	
Women / men	47 (37) / 79 (63)
Body mass index > 25 kg / m^2	67 (53)
Smoking	52 (41)
Abuse of alcohol	26 (21)
Drug use	10 (8)
Recent infectious disease	14 (11)
Hormonal contraceptives	6 (5)
Gestation and birth	1 (0.8)
History of stroke	29 (23)
Ischemic heart disease	14 (11)
Hypertension	70 (56)
Diabetes mellitus	9 (0.7)
Prosthetic valves	6 (0.5)
Acute infective endocarditis	4 (0.3)
HIV infection	5 (0.4)
Clinical characteristics of stroke upon admission	
NIHSS upon admission, scores: 0–4 5–14 > 15	 70 (55) 46 (37) 10 (8)
Carotid stroke	84 (67)
Vertebrobasilar stroke	32 (25)
Stroke in both arterial territories	4 (3)
Cerebral venous thrombosis	6 (5)
Functional outcome of the acute period of stroke	
Modified Rankin scale 0–2 points	91 (72)

Table 2. *Causes of IS in patients (n=126)*

Cause	Number of patients, n (%)
Arterial causes	33 (26)
Atherosclerosis: extracranial tandem	10 (8) 6 (5) 4 (3)
Dissection: carotid vertebral cervical cerebral tandem	10 (8) 5 (4) 5 (4) 8 (6) 1 (0.8) 1 (0.8)
Vasculitis (neurosyphilis)	1 (0.8)
Cerebral reversible vasoconstriction syndrome	1 (0.8)
Arteriopathy of unknown origin: extracranial (thrombosis of the internal carotid artery) intracranial tandem	9 (7) 2 (1.6) 4 (3) 3 (2)
Injury of the carotid artery	2 (1.6)
Cardiac causes	27 (21)
Anomalies of interatrial septum: patent foramen ovale patent foramen ovale in combination with an aneurysm of interatrial septum patent foramen ovale in combination with a thrombus in the right ventricle defect of interatrial septum defect of interatrial septum in combination with aneurysm right-left shunt with normal transesophageal echocardiography	16 (13) 9 (7) 1 (0.8) 1 (0.8) 1 (0.8) 1 (0.8) 3 (2)
Prosthetic valves: aortic mitral multiple valves	6 (5) 2 (1.6) 3 (2) 1 (0.8)
Acute infective endocarditis: aortic mitral multiple valves	4 (3) 2 (1.6) 1 (0.8) 1 (0.8)
Chronic heart aneurysm with thrombus	1 (0.8)
Lacunar stroke	15 (12)
Small vessel disease	7 (6)
Unspecified microangiopathy	8 (6)
Venous infarction	6 (5)
Thrombosis of cerebral sinuses	5 (4)
Venous angioma of the pons	1 (0.8)
Other causes	3 (2)
Antiphospholipid syndrome	2 (1.6)
Pulmonary arteriovenous malformations, hereditary hemorrhagic telangiectasia	1 (0.8)
Cryptogenic stroke	13 (10)
Unknown etiology (incomplete examination)	29 (23)

All patients carried out an examination provided according to the local clinical guidelines. The volume of additional examination aimed at identifying the cause of IS varied and depended on individual factors, and also changed in the course of the development of medical care. The range of additional diagnostic methods used included 24-hour Holter monitoring of the electrocardiogram, transcranial dopplerography with bubble test, transesophageal echocardiography (TEE), T1 FS MRI, MR angiography, CT angiography, digital subtractive angiography.

Statistical analysis was carried out using the Statistica 10.0 software package (StatSoft Inc., USA). Comparative analysis of two independent groups in terms of quantitative characteristics was performed using the Mann–Whitney test, for a qualitative characteristic – using the χ^2-test. In the tables, the data are presented as a median [25th; 75th percentile].

Results. The patients were characterized by both traditional cardiovascular RFs for stroke (overweight, smoking, hypertension), and specific RFs (alcohol abuse, drug use, recent infectious disease, hormonal contraceptives). One patient developed a stroke in the early postpartum period, five patients suffered from HIV infection. The majority of patients on admission to the hospital had a slight neurological deficit, severe stroke occurred in 8% of the examined. In most cases, carotid IS was diagnosed; in every fourth patient, the lesion was located in the vertebrobasilar system. Cerebral sinus thrombosis was verified in six patients. Most of the patients had a good functional outcome of stroke after 1 month.

Pathogenetic subtypes of IS according to TOAST criteria: atherosclerosis of large arteries – in 10 (7.9%) patients, cardioembolism (including sources of medium risk) – in 27 (21.4%), occlusion of small vessels – in 15 (11.9%), other established etiology – in 23 (18.3%), unknown etiology – 51 (40.5%). Detailed nosological structure of SI is presented in table. 2.

In almost a quarter of patients in the main group, the cause of IS remained unknown due to incomplete examination. These patients were excluded from further analysis; thus, the final cohort size was 97 patients. In the final sample, the three most common causes of IS were: anomalies of the interatrial septum (16.5%), occlusion of small arteries (15.5%), and unspecified arteriopathy (11.3%). Atherothrombosis and dissection occupied 10.3% in the structure of IS causes (Fig. 1).

For the convenience of further analysis, all causes of IS were combined into 7 subgroups: pathology of large arteries (atherosclerosis and unspecified arteriopathy) – 21.6%, cardiac embolism (PFO, interatrial septum defect, prosthetic valves, acute infective endocarditis and chronic heart aneurysm) – 27, 8%, cervical and cerebral dissection – 10.3%, lacunar IS – 15.5%, venous IS – 6.2%, other specified IS – 5.2%, and cryptogenic IS – 13.4%.

When analyzing the causes of IS, depending on age, it was revealed that cryptogenic IS prevails in the age subgroup of 21–25 years (60%); 26–30 years old – cardiombolism (40%; equally against the background of anomalies of the interatrial septum and valve pathology); 31–35 years – cardiombolism (41%; almost equally against the background of anomalies of the interatrial septum and pathology of the valves); 36–40 years – cardioembolism is equally dominant (anomaly of the interatrial septum prevails) and IS associated with the pathology of large arteries (24% each), a large proportion of dissection (18%) and occlusion of small arteries (21%); 41–44 years old – pathology of large arteries (31%) and occlusion of small arteries (26%) predominate. At the same time, patients under the age of 30 did not have dissection, and in patients under 25, there was no venous stroke and occlusion of small arteries (Fig. 2). There were no statistically significant differences in the proportion of the presented causes of IS in these age subgroups.

Analysis of data from 75 patients with four main pathogenetic subtypes of IS (pathology of large arteries, including dissection; cardioembolism; occlusion of small arteries and cryptogenic IS) over 30 years (three age subgroups) showed that the proportion of arterial and cryptogenic IS is stable (approximately 40 and 10 % respectively), the proportion of patients with cardiac embolism decreases with age from 45 to 22%, while the percentage of patients with lesions of small arteries increases from 5 to 26%.

The analysis of the variability of the causes of IS depending on gender showed that among women, cardioembolism predominates, while in men – disease of large arteries (excluding dissection; 27%) and cardioembolism (25%). The proportion of small artery occlusion was also noticeably higher in men (19% vs 9%), although the differences did not reach the level of statistical significance (Fig. 3).

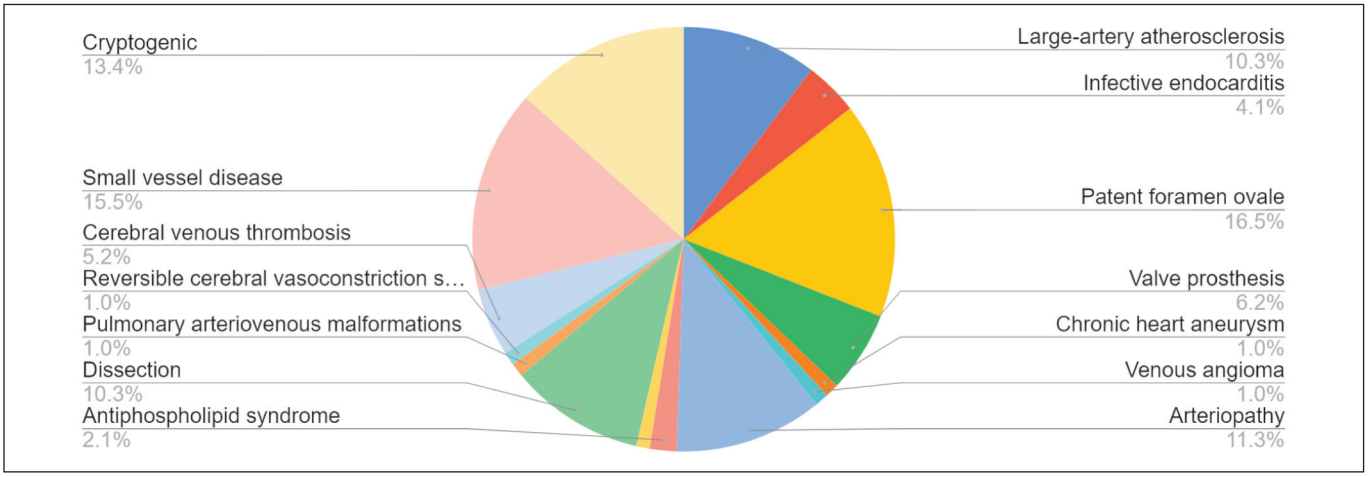

Fig. 1. *Nosological pattern of IS after exclusion of incompletely examined patients (n=97)*

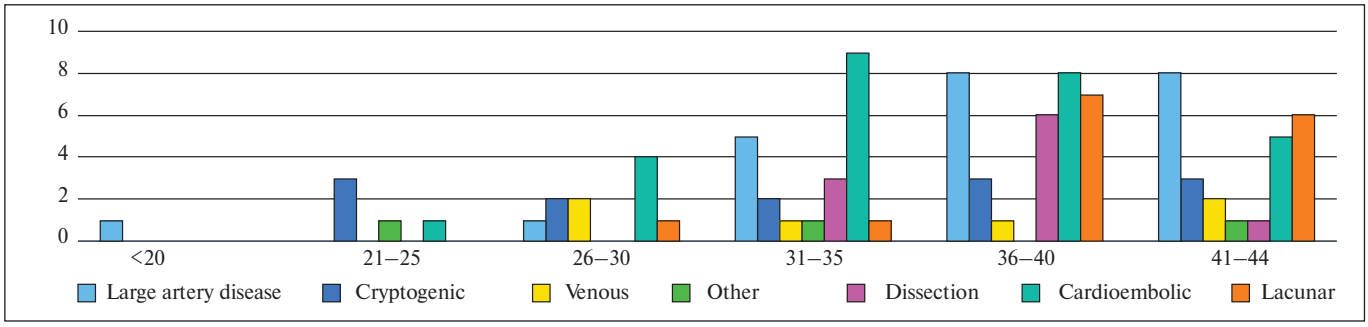

Fig. 2. *Age-dependent nosological pattern of IS (n=97)*

Discussion. The study analyzed the causes of IS in patients aged 18–44 years living in a large urban area directly attached to the regional stroke center. When using the TOAST classification, the etiology of IS remained unknown in 40.5% of patients, which is consistent with the data of E. G?kcal et al. [7]. After excluding cases with incomplete examination, the most common causes of IS were: cardioembolism (PFO, AS defect, prosthetic valves, acute infective endocarditis and chronic heart aneurysm) – 27.8%, pathology of large arteries (atherosclerosis and unspecified arteriopathy) – 21.6 %, pathology of small arteries – 15.5%, as well as cervical and cerebral dissection – 10.3%. When arteriopathies and dissection are summed up, the proportion of arterial causes reaches 31.9%. Cryptogenic stroke was observed in 13% of patients.

In general, the results of the study are consistent with the data of R. Renna et al. [8] (Rome, stroke department, patients under 50 years old, n=150) according to which the etiological structure of IS according to TOAST was represented by cardioembolism (36%, mainly against the background of PFO); atherosclerosis of large arteries (11.3%); occlusion of small arteries (8%); other specified etiology (27.3%), including most often – dissection (n=21), vasculitis (n=6) and antiphospholipid syndrome (n=4), and unknown etiology (29.3%). It is noteworthy that not a single patient had prosthetic heart valves or acute infective endocarditis.

In comparison with the research results of L.A. Kalashnikova and L.A. Dobrynina [5, 6], the lower frequency of dissection is noteworthy (10.3% vs 28%). It is believed that cervical dissection is the cause of every fifth stroke in young patients [9, 10] and is the main cause of IS at a young age [11, 12]. According to the analysis of hospital registries in Zurich and Bern, cervical dissection causes 24% of IS in patients aged

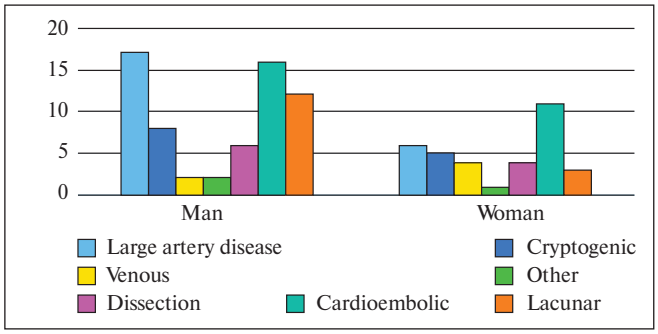

Fig. 3. *Gender-dependent pathogenetic subtypes of IS (n=97)*

18–44 years [13]. The lower dissection frequency in the present study may be related both to the specificity of the population (less selection of the sample due to the direct admission of patients from the attached territory, high prevalence of cardiovascular RFs), and to the fact that not all patients underwent MRI with T1 / T2 FS. If we assume that 11.3% of patients could have an undiagnosed dissection, then the total contribution of this cause reaches 21.6%, which is more consistent with the works discussed.

In the study, a higher, in comparison with the data of L.A. Kalashnikova and L.A. Dobrynina, the incidence of cardiogenic embolism (27.8% vs 12%), which were predominantly (16.5%) associated with interatrial septum abnormalities. According to J.L. Saver et al. [14], approximately half of young and middle-aged patients with cryptogenic IS have PFO, and in 2/3 of them the anomaly is the cause of stroke. PFO was detected in 1/3 of patients in the population of stroke department in the study of R. Renna et al. [8]. The pathogenetic role of PFO increases when it is combined with congenital and acquired thrombophilia, including the Leiden factor mutation and the prothrombin G20210A gene mutation, the occurrence of which in the European population, however, does not exceed 6% [11]. Other causes of cardioembolism, identified by us in 9 patients, were represented by prosthetic valves (6.2%), infective endocarditis (4.1%) and a thrombus in the heart (1%). For comparison, when analyzing the data of 741 patients with IS at the age of 18–54 years in Estonia, the share of acute infective endocarditis was 1%, and prosthetic valves were present in only 0.5% of patients [15].

Traditional causes of stroke were encountered in the surveyed sample much less frequently than in the general population [16]. Atherothrombotic stroke was diagnosed in 10.3% of patients, and lacunar stroke against the background of small vessel disease – in 15.5% of patients. Thus, in a quarter of the examined patients, acquired angiopathy (atherosclerotic, hypertensive) was the basis for the development stroke. This is consistent with data, according to which the burden of traditional cardiovascular RFs has increased among young patients in recent decades: physical inactivity, smoking, alcoholic excesses, arterial hypertension, hypercholesterolemia, diabetes mellitus and obesity, the first four of which account for about 80% of the population attributable risk of developing IS [17, 18]. In the population of two large European vascular centers (Lisbon, n=156, and Innsbruck, n=110; 18–55 years old), pathology of large arteries was observed in 12.3 and 13.6%, respectively, and small vessel disease – in 11 and 5, 5% of patients [6].

Antiphospholipid syndrome caused stroke in only 2% of patients, which is significantly less than in the works of other authors [19, 20]. N.A. Maaijwee et al. [20] showed that 10–20% of patients with IS under 50 years of age suffer from antiphospholipid syndrome. antiphospholipid syndrome occurs in women 5 times more often than in men, and, as a rule, is diagnosed at the age of 30–40 years [11]. The low incidence of antiphospholipid syndrome in this study is probably due to screening for thrombophilia was not included in the examination protocol. The feasibility of this screening is ambiguous: in the work of S.S. Omran et al. [21] (USA, n=196) showed that in two out of five patients with IS at the age of 18–65 years, screening for thrombophilia showed at least one positive test, but only in every twelfth patient this leads to a change in treatment, which is not in favor of routine screening in all young patients with IS. In addition, a study by B. Crespo Pimentel et al. [19] intensive laboratory screening (search for thrombophilia and autoimmune diseases) did not have a significant effect on determining the cause of IS, which confirms the correctness of a clinically oriented approach.

This study shows the following features of the causes of IS, depending on the age of patients: in the youngest subgroup (21–25 years old) cryptogenic IS dominates, in the subgroup of 26–35 years – cardioembolic stroke (mainly associated with PFO), in the subgroup of 36–40 years the proportions of cardioembolic stroke, pathology of large arteries, pathology of small arteries and dissection are approximately equal; in the 41–44-year-old subgroup, pathology of large arteries and lacunar stroke prevail. Thus, paradoxical embolism and valves pathology play a more significant role in younger patients, whereas the disease of large and small arteries is actual in older patients. The results are consistent with the review by M.S. Ekker et al. [4] and a number of other authors [9, 22–24]: atherosclerotic angiopathy usually develops at 40–49 years old, small vessel disease acquires clinical significance in patients over 35 years old, while the significance of PFO in the etiology of IS decreases with age, being the greatest in patients 18–29 years old, and cryptogenic IS occurs more often in patients younger than 35 years old.

The analysis of sex differences in the causes of IS showed that men have a higher proportion of large and small artery disease, which indirectly indicates a higher prevalence of vascular RFs.

Conclusion. Thus, the study showed that the most common causes of IS in patients aged 18–44 years are cardioembolism (mainly by the mechanism of paradoxical embolism) and pathology of large arteries, including dissection. The difficulty in verifying dissection lies in the need for widespread implementation of the neuroimaging protocol, including MRI with T1 / T2 FS sequences. The role of thrombophilia in the development of IS in young patients may also be underestimated due to routine diagnostic process in the stroke departments does not imply appropriate screening. The cause of IS in the examined patients depended on age: in the younger age range, cardiac embolism prevailed, while in the older age, pathology of large and small arteries prevailed. The revealed features substantiate various directions of secondary prevention – endovascular closure of PFO and correction of vascular RFs, respectively.

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