Anamnestic, clinical and laboratory features of the acute period of ischemic stroke in young patients

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Objective: *to study the anamnestic, clinical and laboratory features of the acute period of ischemic stroke (IS) and to determine the risk factors for its development in young patients.*

Patients and methods. *Clinical and statistical processing of data of 256 patients aged 18 to 44 years included, who had IS, confirmed by computed and/or magnetic resonance imaging of the brain in the acute period, was carried out. Furthermore, in 154 patients and in 117 healthy participants, who made up the control group, eight polymorphisms of the thrombophilic spectrum genes were determined – FGB: -455G>A, F2: 20210G>A, F5: 1691G>A, F7: 10976G>A , F13: 103 G>T, ITGA2: 807C>T, ITGB3: 1565 T>C, PAI-1: -675 5G>4G.*

Results and discussion. *154 (60.15%) patients demonstrated good recovery (achievement of a level of ⩽2 points on the Rankin scale by the patient). None of the patients died during their hospitalization. In the evaluated group of patients, we identified allelic variants of the thrombophilic spectrum genes and gene-gene combinations, the carriage of which increased the likelihood of IS development at the young age by 1.74 and 2.19 times, respectively. Taking into consideration additional examination methods, the pathogenetic variant of IS according to the TOAST classification was verified in 226 (88%) patients.*

Conclusion. *In IS at a young age a detailed assessment of risk factors is required, including an analysis of carrier variants and combinations of procoagulant and prothrombotic spectrum gene polymorphisms.*

Keywords: *ischemic stroke; young age; risk factors; thrombophilia; single nucleotide substitutions.*

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Strokes are one of the most significant diseases of civilization that strongly impact people's health and quality of life [1–3]. Moreover, stroke is one of the leading causes of death and disability, demonstrating a one-month mortality rate of 13% to 35% [3–5].

Although the majority of all cases of strokes are diagnosed in elderly patients, a significant number of people (approximately 10–15% of all cases) suffer their first stroke at a young age (the so-called "young" strokes) [6. 7].

The dramatic burden of "young" strokes can be explained, at least in part, by an increase in the number of major vascular risk factors (RFs) in young people [7. 8]. In particular, well-known risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking, alcohol abuse, physical inactivity, coronary heart disease, and obesity are common in young people; some are even becoming more common [7–11].

The significance of the ischemic stroke (IS) problem in young people is primarily determined by a list of causes, identification of which requires additional laboratory and instrumental studies and is often time- and resource-consuming but not always effective [10–14]. In addition, the proportion of various causes of strokes is changing. For example, the frequency of valvular defects as one of the causes of cardioembolic IS is declining, whereas the role of such rare conditions as dissection or antiphospholipid syndrome is growing. Furthermore, socioeconomic factors associated with the young age of patients have also changed [5].

At the same time, the etiology of about 20–30% of stroke cases in young people remains unknown [7. 15]. Therefore, a subgroup of young patients who have had IS should be provided with an extended medical examination, including genotyping methods, which are aimed at developing personalized measures for primary and secondary prevention [7. 16–18].

The purpose of the study was to analyze the anamnestic, clinical, and laboratory features of the course of the acute period of IS and to determine its risk factors in young patients.

Patients and methods. The cohort study included the data of 256 young patients with IS.

The leading *criteria for inclusion* in the study were: age from 18 to 44 years; diagnosis of ischemic stroke confirmed by clinical data and the results of computed tomography of the brain, ("Cerebral infarction," I63.0 – I64.9 according to the International Classification of Diseases of the 10th revision); availability of informed consent of patients or their legal representatives and/or decision of the physicians' council if patients were unable to express their consent. *Exclusion criteria:* patients at the stage of differential diagnosis of acute disorders of cerebral circulation (cerebrovascular accidents – CVA); intracranial hemorrhages of any etiology; onset of a stroke at the age of over 44 years; refusal of patients and/or their representatives to be examined.

A study group was formed from patients admitted on an emergency basis to the primary vascular departments of Ekaterinburg.

Analysis of the history of life and disease, clinical and laboratory characteristics of stroke in the acute period (during hospitalization), and comorbidities was carried out during the evaluation of medical records and personal contact with the patients and their relatives. The assessment of stroke severity, the severity of neurological (focal) symptoms, and the dynamics and degree of self-care of patients of the main group were analyzed using the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS) [19. 20].

All patients in the acute period of the disease underwent neuroimaging on AQUILLION 16 and Somatom Emotion CT scanners, with or without CT angiography, as recommended by the procedures for providing care to patients with strokes (Order of the Ministry of Health of Russia dated November 15. 2012. No. 928n) [21].

Furthermore, all patients during their stay in the hospital underwent ultrasound examinations: extracranial scanning of the brachiocephalic vessels, transcranial doppler ultrasonography, including the use of embryogenic mode with a threshold of 4 Hz, echocardiography.

All patients underwent a routine laboratory examination: complete blood count, biochemical blood tests, including the lipid panel. Interpretation of the findings was carried out in accordance with the local hospital standards.

In this study, several parameters of hemostasis and thromboelastograms were evaluated. It should be noted that, in the entire period of the disease, it was possible to assess the international normalized ratio (prothrombin index), activated partial thromboplastin time, fibrinogen levels, and platelet count.

The study of family characteristics (including hereditary predisposition to hemorrhagic and ischemic events) was carried out according to the questionnaire of the protocol of the All-Russian register "Genetic risk factors for thrombosis in residents living in the Russian Federation, clinical phenotyping and prevention of thromboembolic complications in ontogenesis" [22]. A total of 256 patients and/or their relatives were surveyed.

Verification of several gene polymorphisms was performed: using the molecular genetic method, eight gene polymorphisms associated with the risk of developing thrombophilia were identified in 154 young adults participating in the study. The real-time polymerase chain reaction method was used in DNA preparations obtained from 2 ml of venous blood. The control group consisted of blood samples from 117 healthy individuals of both sexes under the age of 45 recruited on a copy-pair basis, who did not have a history of thrombotic events of any localization, infertility, and reproductive losses. The following single nucleotide substitutions were studied: *FGB:* -455G>A, *F2:* 20210G>A, *F5:* 1691G>A, *F7:* 10976G>A, *F13:* 103 G>T, *ITGA2:* 807C>T, *ITGB3:* 1565 T>C , *PAI-1:* -675 5G>4G (eight points).

The data was analyzed using standard methods of descriptive and analytical statistics. Statistical data processing was carried out using the Statistica 10.0 and SPSS 16 software packages. The non-parametric Mann–Whitney U-test was used to compare groups by qualitative and quantitative characteristics. The χ^2 test was used to compare indicators of qualitative signs (distribution of referral diagnoses, the prevalence of the disease among different ethnic groups). The relationship between two features was analyzed using non-parametric correlation analysis according to the Spearman method. The accepted level of confidence in rejecting the null hypothesis was 95%. Differences were considered statistically significant at $p<0.05$.

Results. The mean age of the patients was 35.87±0.47 years, with a significant predominance of males (n=148 and n=108; 57.81% and 42.19%, respectively; $p<0.05$ for men and women). None of the patients died during hospitalization.

In the vast majority of patients in the main group (95.70%, n=245), neurological symptoms developed against the background of apparent well-being.

One hundred percent of patients (n=256) passed through the intensive care unit (ICU); however, such routing was mainly determined by the procedures for providing care to patients with a stroke (Order of the Ministry of Health of Russia dated November 15. 2012. No. 928n). Only 1.5% of the patients who underwent procedures in the ICU, required mechanical ventilation (n=4).

Assessment of the dynamics of stroke severity and the dynamics of neurological (focal) symptoms severity, along with the degree of self-care of patients in the main group are presented in Tables 1 and 2.

Table 1. *Dynamics of stroke severity at admission and discharge (n=241)*

Number of Patients	NIHSS Score (SD)		
	0–7	8–15	⩾16
On admission, n (%)	152 (59.37)	61 (23.82)	28 (10.93)
On discharge, n (%)	199 (77.73)	32 (12.50)	10 (3.90)

Table 2. *Dynamics of the severity of the condition of patients on admission and discharge (n=248)*

Number of Patients	ISR Score						
	0	1	2	3	4	5	6
On admission, n (%)	3 (1.17)	10 (3.90)	44 (17.18)	96 (37.50)	59 (23.04)	36 (14.06)	0
On discharge, n (%)	10 (3.90)	100 (40.32)	57 (22.26)	50 (19.53)	24 (9.37)	7 (2.73)	0

Table 3. *Indicators of lipid metabolism in patients with IS in the acute period of the disease*

Indicators	TG	CH	HDL	LDL	VLDL	AIP
Average:						
level, mmol/L, M±m	1.86±0.18	4.76±0.17	1.25±0.18	2.94±0.18	0.84±0.18	3.29±0.18
number of patients, n	180	197	185	185	182	184
In patients with dyslipidemia:						
level, mmol/L, M±m	3.46±0.35	6.12±0.33	0.91±0.37	4.35±0.46	1.60±0.36	4.53±0.26
number of patients, n (%)	46 (25.56)	53 (26.90)	40 (21.62)	25 (13.51)	42 (23.08)	84 (45.65)

Note. TG, triglycerides; CH – cholesterol; HDL – high-density lipoproteins; LDL – low-density lipoproteins; VLDL – very-low-density lipoproteins; AIP – atherogenicity index.

A level of ⩽2 points on mRS was considered a good recovery (n=154; 60.15%), 2 points on the mRS was considered a very good recovery (n=147; 57.42%).

An assessment of hereditary predisposition to hemorrhagic and ischemic events, carried out according to the questionnaire [22] in 256 patients, did not reveal any significant predisposition to thrombotic events in the anamnesis of young patients.

During the first days of hospital stay, the clinical picture of the disease included both cerebral and focal symptoms. Meningeal symptoms were not recorded in any of the patients.

In the structure of focal symptoms, the primary symptoms were paresis and palsies of the extremities of a central nature, speech disorders (n=199; 77.73%), vestibulocerebellar and cerebral symptoms (n=110; 42.96%), as well as pain syndrome (n=100. 39.06%).

Upon admission, imaging investigations were performed in 100% of patients, while the focus of infarction was found in 73 out of 256 examined patients (28.51%). Clinical and neuroimaging data of the patients of the main group allowed to verify the area of the ischemic infarcts: the internal carotid artery – 55.08% (n=141), the vertebrobasilar area – 26.17% (n=67); a combined lesion of the involved areas was revealed in 18.25% of patients (n=48).

In 95 cases, brachiocephalic artery stenosis of varying severity was detected: 59 (23.04%) patients had less than 50% stenosis; 17 (6.64%) – 50–70% stenosis, and 19 (7.42%) – more than 70%.

Embologenic syndrome during transcranial doppler ultrasonography in the acute period was registered in 27.70% (n=41) of patients in the main group, while in three cases, it was the presence of a significantly pronounced embologenicity of atherosclerotic plaque that made it possible to clarify the atherothrombotic pathogenetic variant of IS.

Changes in the blood count in the acute period of IS were characterized primarily by an inflammatory reaction: one third of patients had an increase in ESR. The presence of signs of hyperlipidemia and dyslipoproteinemia in a significant number of young patients may indicate that lipid metabolism disorders are one of the significant risk factors for IS development at this age (Table 3).

Table 4. *Calculation of the probability of IS development in young patients depending on the carriage of thrombophilic spectrum gene polymorphisms*

Gene	The state of the gene	Control (n=117)	Adults with IS (n=154) abs.	OR	95% CI	LDA
FGB: -455	GG	84	83	0.46	0.27–0.77	0.999
	GA	**29**	**61**	**1.99**	**1.16–3.42**	**0.007**
	AA	4	10	1.96	0.59–6.58	0.198
	GA+AA	**33**	**71**	**2.18**	**1.29–3.67**	**0.002**
F2: 20210	GG	114	144	0.38	0.10–1.45	0.967
	GA	3	10	2.64	0.69–10.08	0.111
	AA	0	0	–	–	–
	GA+AA	3	10	2.64	0.69–10.08	0.111
F5: 1691	GG	115	143	0.23	0.05–1.07	0.994
	GA	**2**	**11**	**4.42**	**0.93–21.00**	**0.033**
	AA	0	0	–	–	–
	GA+AA	**2**	**11**	**4.42**	**0.93–21.00**	**0.033**
F7: 10976	GG	108	65	0.06	0.03–0.13	1.000
	GA	8	19	1.92	0.79–4.63	0.097
	AA	**1**	**70**	**96.67**	**12.6–739.36**	**0.000**
	GA+AA	**9**	**89**	**16.43**	**7.63–35.37**	**0.000**
F13: 103	GG	76	81	0.60	0.36–0.99	0.985
	GT	39	64	1.42	0.85–2.37	0.105
	TT	2	9	3.57	0.73–17.38	0.078
	GT+TT	**41**	**73**	**1.67**	**1.01–2.77**	**0.027**
ITGA2: 807	CC	52	45	0.52	0.31–0.86	0.997
	CT	**50**	**87**	**1.74**	**1.06–2.86**	**0.017**
	TT	15	22	1.13	0.55–2.33	0.435
	CT+TT	**65**	**109**	**1.94**	**1.16–3.24**	**0.007**
ITGB3: 1565	TT	85	110	0.94	0.54–1.63	0.639
	TC	30	43	1.12	0.64–1.96	0.391
	CC	2	1	0.38	0.03–4.41	0.921
	TC+CC	32	44	1.06	0.61–1.84	0.467
PAI-1: -675	5G5G	24	34	1.10	0.60–2.00	0.437
	5G4G	59	65	0.72	0.44–1.18	0.929
	4G4G	34	55	1.36	0.80–2.30	0.153
	5G4G+4G4G	93	120	0.91	0.50–1.66	0.676

Note. 95% CI – 95% confidence interval; LDA – Fisher's criterion. Significant values are highlighted in bold.

Evaluation of the parameters of hemostasiograms and thromboelastograms in the acute period of the disease did not reveal significant deviations.

We analyzed the variants of carriage and combinations of procoagulant and prothrombotic spectrum gene polymorphisms in young patients with IS. It is possible to evaluate the influence of carriage of individual single nucleotide substitutions in each gene on the probability of IS onset by calculating the odds ratio (OR); this data is presented in Table 4.

It should be noted that the most well-studied thrombophilic candidate genes -*F2:* 20210 and *F5:* 1691, the level of which among patients in some regions of Europe reaches 20%, and whose role in the genesis of cerebral thrombosis at a young age has been proven [23], in our patients were registered rarely, and their occurrence was comparable with the control group. When evaluating the contribution of the carriage of specific gene polymorphisms as a risk factor for the debut of IS at a young age, it was noted that the appearance in the genotype of even a heterozygous allelic variant of the gene increases the chance by 1.74 times or more – this trend was noted for five of the eight assessed genes. At the same time, an increase in the risk of IS with the carriage of polymorphisms of genes of coagulation factors V and VII seems doubtful due to the lack of available data (despite the demonstrated reliability). The association of these polymorphisms with the development of IS at a young age should be established on larger samples.

Assessment of the frequency of occurrence of gene-gene combinations and their role as risk factors for stroke began with the evaluation of combinations that included mutations of *F2:* 20210G>A and *F5:* 1691G>A, the role of which as a risk factor for thrombosis of any localization at a young age is not disputed. Five such combinations were recorded in five cases. None of the combinations found in the patient population were repeated in the control group, and the calculation of the OR did not make sense (due to the impossibility of dividing by zero). Apparently, each case of the disease, each case of asymptomatic carriage, and each combination involving *F2:* 20210G>A and *F5:* 1691G>A is unique, and only the combination with other modifying risk factors leads to clinical manifestation in the form of thrombosis (in our case, IS).). It is possible that the participants of the control group, who did not develop thrombosis in childhood or young adulthood are carriers of a set of "protective" factors.

At the next stage, we searched for gene-gene combinations (without the participation of *F2:* 20210G>A and *F5:* 1691G>A), analyzed all occurring combinations of polymorphisms, and obtained five combinations that significantly increase the risk of IS in comparison with the control sample; the results are presented in Table 5.

Assessment of the state of the cardiovascular system was carried out on all patients. Changes in the work of the heart according to the results of electrocardiography and/or Holter monitoring were detected in a large number of cases – 81 (31.64%). Rhythm disturbances (bradycardia or tachyarrhythmia) were often present in 15 (5.85%) examined patients, atrial fibrillation – also in 15 (5.85%) patients.

According to the ultrasound examination of the heart in young adult patients, signs of organic (including acquired) diffuse changes were registered, in particular, signs of heart failure with a decrease in ejection fraction (n=23; 8.98%), signs of left ventricular hypertrophy (n=40; 15.62%), mitral valve prolapse (n=34; 13.28%).

Undoubtedly, rhythm disturbances and structural changes in the heart become a factor that can serve as a potential mechanism of development of a cardioembolic or hemodynamic variant of IS. Therefore, it is believed that these defects, as sources of latent embolism, should be sought and excluded in the case of IS of unclear etiology. At the same time, the presence of cardiac sources of moderate embolism risk (in the absence of other apparent causes of IS) was interpreted as criteria for a cardioembolic stroke.

As a result of the analysis of the history and clinical picture, as well as the patients' examination data, we were able to determine the pathogenetic variants of IS according to the TOAST criteria (Trial of Org 10172 in Acute Stroke Treatment; Table 6).

The main causes of IS in pathogenetic variant IV were the presence of congenital thrombophilia (n=85; 65.38%), migraine (n=12; 9.23%), malformations of the cerebral vessels (n=9; 6.92%), and various types of vasculitis (n=11; 8.46%).

Discussion. Population characteristics were obtained from a relatively large group of patients with the onset of IS under the age of 45 years. The main features of this group were: a significant predominance of male patients, a typical clinical presentation in the acute period of the disease, a relatively mild course of the disease, and a good forecast for recovery with a low mortality rate. Thus, the course of strokes in this age group can be considered favorable.

On admission to the hospital, more than half of the patients had an NIHSS score of <7; focal neurological symptoms dominated the clinical picture. A decrease in the level of consciousness and a convulsive syndrome occurred in few patients; technologies

Table 5. *Calculation of the probability of IS development in young adult patients depending on the carriage of gene combinations*

Gene-gene combination	Control (n=117)	Young adult patients (n=154)			
	abs.	abs.	OR	CI	LDA
FGB: -455G>A + *F13:* 103G>T + *PAI-1:* -675 5G>4G*	9	30	2.90	1.30–6.49	0.008
FGB: -455G>A + *ITGB3:* 1565T>C + *PAI-1:* -675 5G>4G*	5	19	3.15	1.12–8.89	0.029
FGB: -455G>A + *ITGA2:* 807C>T + *PAI-1:* -675 5G>4G*	11	45	3.98	1.93–8.22	0.000
FGB: -455G>A + *ITGA2:* 807C>T + *ITGB3:* 1565T>C + *PAI-1:* -675 5G>4G*	3	12	3.21	0.86–11.96	0.052
FGB: -455G>A + *F13:* 103G>T + *F7:* -10976G>A + *ITGA2:* 807C>T*	4	15	3.05	0.96–9.66	0.035

Note. For clarity, only reliable values are given. * – both hetero- and homozygous variants of all genes indicated in the combination were taken into account.

Table 6. *Pathogenetic variants of stroke according to the TOAST criteria in the main group (n=256)*

Pathogenetic variant	Number of patients aged 18–44 years old	
	abs.	%
I – atherothrombotic	39	15.23
II – cardioembolic	56	21.88
III – lacunar	1	0.39
IV – other established etiology	130	50.78
V – unknown etiology	30	11.72

for prosthetics of vital functions were required exceptionally rarely. Every fifth patient (n=57; 22.98%) had a low score on the mRS on admission.

Carriage of thrombophilic gene polymorphisms (65.38%), heart disease (31.64%), and dyslipidemia (45%) are high-risk factors for ischemic strokes and determine the pathogenetic variant of the disease at a young age.

The data of medical histories, complete blood count and coagulogram, did not show any significant signs of thrombophilic predisposition in this group. At the same time, when genotyping the patients, we were able to identify such allelic variants of thrombophilic spectrum genes and such gene-gene combinations, the carriage of which increased the likelihood of IS at a young age by 1.74 and 2.19 times, respectively. "Fatal" allelic variants of the *F2:* 20210G>A and *F5:* 1691G>A genes did not demonstrate their exclusive role in the studied patient population, neither in the case of isolated carriage, nor in combinations; they had no significant effect on the risk of IS morbidity. Evidently, their clinical effect in the form of cerebral infarction can be realized only in combination with other modifying RFs.

For the first time, we have identified gene-gene combinations that increase the risk of IS onset (*FGB:* -455G>A+*ITGA2:* 807C>T+*ITGB3:* 1565T>C+*PAI-1:*-675 5G>4G and *NOS3:*786 T>C+ *NOS3:*894 G>T), as well as such combinations of gene polymorphisms that had a predictive value in relation to the onset of IS only at a young age (five combinations, OR 2.9–3.98).

At the same time, a detailed assessment of risk factors made it possible to clarify the pathogenetic variant of strokes in this age group. There was a high prevalence of dyslipidemia, which, of course, can be regarded as a separate and potentially progressive risk factor for IS in young patients already at the initial stages of brachiocephalic vessel stenosis. Based on the results of the study, new information was obtained regarding the identification of pathogenetic variants of IS according to TOAST in young patients (dominant – type IV, mainly against the background of genetically determined thrombophilia, previous migraine, and vasculitis of various etiologies), which in the future can serve as the basis for a personalized approach in the development of tactics for secondary prevention of IS in such patients.

Conclusion. The study results indicate the need for a detailed assessment of RF, including the analysis of variants of carriage and combinations of procoagulant and prothrombotic gene polymorphisms in patients with IS onset at a young age.

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