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ATHEROSCLEROTIC CHANGES IN CEREBRAL VESSELS OF THE ELDERLY AND SENILE PEOPLE: ETHNIC, GENDER AND AGE CHARACTERISTICS

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The study included 522 patients aged 60 to 89 years old, who were divided into three ethnic groups (Evens, Yakuts and Russians) and two age groups (elderly and senile age). Doppler ultrasound examination revealed ethnic features of atherosclerotic changes in cerebral vessels at various stages of chronic cerebral ischemia in elderly and senile patients of the Republic of Sakha (Yakutia). The study revealed that the most pronounced atherosclerotic changes in the extracranial arteries were observed in Russians, then in Yakuts. Evens ranked last in atherosclerotic lesions of the cerebral vascular structure.

Keywords: ethnicity, elderly and senile age, chronic cerebral ischemia, intima-media thickness.

For many years, cerebrovascular pathology remained one of the most pressing problems of medicine, holding one of the first places in the structure of mortality and causes of disability. Ischemic disorders account for about 75% of all cerebrovascular diseases. The observed global aging of the population and the increase in the proportion of elderly and senile people in its structure, associated with an increase in life expectancy, indicates further spread of chronic cerebrovascular insufficiency and a high vulnerability of the brain to ischemia due to involutional development changes. The thickness of the intima-media complex (IMT) in the carotid arteries is one of the independent risk factors for the development of transient ischemic attacks and strokes. The larger it is, the higher the likelihood of developing acute ischemic stroke. Simultaneously, the results of certain studies suggest that the importance of the thickness of this complex as a risk factor for the development of vascular catastrophes requires additional evidence. In this regard, the study of ethnic characteristics of atherosclerotic changes in elderly and senile people is of great importance in planning preventive and therapeutic measures for cerebrovascular diseases.

The aim of the study was to research the ethnic and age-related characteristics of atherosclerotic lesions of the cerebral vessels in elderly and senile patients with chronic cerebral ischemia in the Republic of Sakha (Yakutia).

Materials and methods. The survey was conducted among 522 people aged 60 to 89 years old. All patients were divided into three ethnic groups:

The first group of observations was comprised of 174 patients - representatives of the indigenous small-numbered peoples of the North, living in the Arctic zone. In the subgroup with chronic cerebral ischemia (CCI) I - 87 people, CCI II - 87.

Group II - 177 patients of Yakut nationality (CCI I - 90, CCI II - 87) living in the Vilyuysky district.

Group III - 171 patients of Russian nationality (CCI I - 86, CCI II - 85) living in Yakutsk. These zones differ in their natural and ecological characteristics, and the people who live in them have differences in their lifestyle, food habits, the nature of their main occupations and the level of civilization.

The clinical study included a thorough and in-depth collection of medical history, the study of outpatient records from clinics at the place of residence, archived medical histories, extracts and certificates. During the observation process, all patients were examined by a neurologist, psychiatrist, therapist, and cardiologist.

In order to determine and clarify the stage of chronic cerebral ischemia, the medical histories and complaints of patients were analyzed, and a clinical determination of their neurological status was carried out. To systematize the obtained data on the health status of each patient, a questionnaire was developed.

The diagnosis of chronic cerebral ischemia (CCI) was made in accordance with the classification of vascular brain injuries of the Institute of Neurology of the Russian Academy of Medical Sciences (1985), the diagnosis was made in accordance with ICD-10. The diagnostic criterion was a confirmed lesion of the cerebral vessels with the corresponding clinical picture of the stages of CCI according to the classification of E.V. Schmidt - patients with stage I chronic cerebral ischemia (CCI I) and patients with stage II chronic cerebral ischemia (CCI II). According to the State Statistics Committee of the Republic of Sakha (Yakutia), the average life expectancy for men is 60.6 years, for women - 72.2, the difference is 11.6 years.

The age of the patients ranged from 60 to 89 years (the average age of the examined was 72.7 ± 7.2 years, for men - 72.9 ± 7.2 years, for women - 72.6 ± 7.2 years). As can be seen from Table 2, older people predominate among peers, and in the CCI II subgroup as well; old people are more common among the Yakuts and Russians.

The main method for studying cerebral hemodynamics in this paper was Doppler ultrasound (USG). Doppler study with color scanning and spectral Doppler analysis of the brachiocephalic arteries at the extracranial level was carried out according to the standard technique on ACUSON "Sequoia-512" ultrasound systems using a linear transducer with a frequency of the generated ultrasound signal of 4 and 8 MHz, in continuous wave mode.

To assess the structural and functional state of the arterial blood supply to the brain during duplex scanning, qualitative information on the structural state of the vessels in the form of images of thickening of the intima and the middle membrane complex, atherosclerotic plaques and pathological gyri was collected. IMT was determined at three points of both common carotid arteries in the distal 1.0 cm segment with the calculation of the mean. IMT values of less than 0.9 mm were considered normal.

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The prevalence of atherosclerotic plaques (ASP) in the carotid artery was assessed according to the following principle: grade 0 - no plaque, grade I - one or more plaques with a surface area of less than 10 mm2, grade II - plaques with an area of 10 mm2 or more. Plaque volume was calculated as the difference between vessel and lumen volume.

The statistical processing of the results was carried out using the SPSS 19.0 software package. The mean with standard deviation was calculated to describe the quantitative data. Qualitative characteristics are presented in the form of frequency tables containing absolute values and the relative participation of the characteristic (in percentages). The probability distribution of quantitative characteristics were checked for compliance with the reference distribution using the Kolmogorov-Smirnov test. The test results showed that the distribution of the studied indicators differs significantly from the reference distribution. Based on this, nonparametric tests were used for further statistical analysis. To compare the mean values of the studied indicators, the paired Mann-Whitney test was used. When comparing more than two study groups, the Kruskal-Wallace nonparametric analysis of variance was used. To study the contingency of qualitative characteristics, the classical Pearson chi-square test was calculated, and in cases where the expected frequency in more than 20% of the cells in the contingency tables was less than 5, the Pearson chi-square test was used. Calculated with Yates' correction for continuity. To establish the value of the factor contribution to the overall picture of the contingency tables, we were guided by the value of the normalized remainder in the cells. Provided that the standardized cell remainder was equal to or greater than 2.0, it was concluded that the contribution of this cell was statistically significant with $p < 0.05$. Spearman's rank correlation coefficient was used to assess the relationship between quantitative variables.

Results. It is known that atherosclerosis is a multifocal disease that affects 2-3 vascular basins, and at the same time, the most dangerous location of atherosclerotic plaques is in the vessels of the heart and brain, and especially in the carotid arteries.

Violation of the wall of the main arteries of the head is manifested by thickening of the intima-media, primarily of the carotid arteries, as a result of the progression of atherosclerosis.

In the study of IMT depending on the stage of CCI and ethnicity, we obtained the following results (Table 3). In Evens with CCI stage II, IMT values on the left are significantly higher than in CCI stage I. In Yakuts, statistically significant differences were obtained by comparing the mean values of IMT on the left, which were higher in individuals with stage II CCI. In Russians, we did not obtain significant differences in the main ultrasound characteristics of cerebral vessels between the stages of CCI.

No statistically significant differences were found on the presence of ASP in the cerebral vessels in the three study groups. The characteristics of ASP of the cerebral vessels, depending on the stage of CCI, are shown in Table 4. Both Evens and Russians with stage II CCI were statistically significantly more likely to have hypoheterogeneous than echoheterogeneous ASPs, localized forms were more common and concentric - less common, more often large (> 10 mm) ASPs with a smooth surface were found. In addition, echohomogeneous ASPs were found significantly less frequently among the Evens. In Yakuts with stage II CCI, hypoheterogeneous and, less often, hypoechogeneous ASPs were detected, large (> 10 mm) ASPs were more common.

The study revealed that nationality is one of the factors affecting size ($\chi2 = 18.459$ $p = 0.001$ and $r = 0.181$ $p = 0.042$ for Russians), density ($\chi2 = 30.379$ $p = 0.000$ and $r = -0.144$ $p = 0.043$ for Yakuts), shape ($\chi2 = 27.159$ $p = 0.000$ and $r = 0.195p = 0.042$ for Evens) and surface of the plaques examined ($\chi2 = 23.146$ $p = 0.000$ and $r = 0.192$ $p = 0.042$ for Evens).

There is also a significant association between age and all characteristics of plaques: density ($\chi2 = 38.050$, $p = 0.000$ $r = -0.228$ $p = 0.041$), size ($\chi2 = 38.067$ $p = 0.000$ $r = 0.247p = 0.042$.), shape ($\chi2 = 42.380$ $p = 0.000$, $r = 0.224$, $p = -.042$) and plaque surface ($\chi2 = 29.571$ $p = 0.000$, $r = 0.223p = 0.041$). The results of statistical analysis also revealed the dependence of plaque properties on gender. At the same time, the statistical relationship is stronger between gender and plaque density ($\chi2 = 9.425$ $p = 0.051$ $r = 0.117$, $p = 0.04$ in men), their size ($\chi2 = 7.570$, $p = 0.032$, $r = -0.028$, $p = 0.044$ in men) and shape ($\chi2 = 8.109$, $p = 0.044$, $r = -0.092$, $p = 0.044$ in women).

Table 1

Distribution of patients with chronic cerebral ischemia by gender and ethnicity

CCI I	Groups					
	I		II		III	
	n	%	n	%	n	%
Men	27	31.1	28	31.1	25	29.1
Women	60	68.9	62	69.9	61	70.9
	χ^2=25.04; p<0.001		χ^2=25.69; p<0.001		χ^2=30.14; p<0.001	
CCI II						
Men	37	42.5	47	54.1	23	27.1
Women	50	57.5	40	45.9	62	72.9
	χ2=3.89; p=0.049		χ2=1.3; p=0.29		χ2=35.79; p<0.001	

Table 2

Distribution of patients with chronic cerebral ischemia by age

	Groups					
	I		II		III	
CCI I						
Age	n	%	n	%	n	%
60-74	42	48.3	61	67.8	54	62.8
75-89	45	51.7	29	32.2	32	37.2
	χ2=0.21; p=0.65		χ2=22.76; p<0.001		χ2=11.26; p<0.001	
CCI II						
Age	n	%	n	%	n	%
60-74	46	52.9	58	66.7	40	47.1
75-89	41	47.1	29	33.3	45	52.9
	χ2=0.58; p=0.45		χ2=19.33; p<0.001		χ2=0.59; p=0.44	

Table 3

The thickness of the intima-media complex depending on the stage of CCI

Indicator	Group I (n=174)			Group II (n=177)			Group III (n=171)		
	Stage of CCI		p	Stage of CCI		p	Stage of CCI		p
	I (n=87)	II (n=87)		I (n=90)	II (n=87)		I (n=86)	II (n=85)	
IMT on the right, mm (M ± SD)	1.12±0.15	1.07±0.23	0.240	1.19±0.18	1.16±0.18	0.292	1.24±0.19	1.25±0.24	0.492
IMT on the right >0.9 mm, n (%)	79 (90.8%)	66 (75.9%)	**0.008**	84 (93.3%)	80 (92%)	0.725	82 (95.3%)	81 (95.3%)	1.0
IMT on the left, mm (M ± SD)	1.10±0.20	1.15±0.19	0.086	1.13±0.21	1.21±0.22	**0.035**	1.21±0.23	1.27±0.23	0.122
IMT on the left >0.9 mm, n (%)	68 (78.2%)	80 (92%)	**0.011**	80 (88.9%)	80 (92%)	0.489	78 (90.7%)	82 (96.5%)	0.124
IMT >0.9 mm с обеих сторон, n (%)	66 (75.9%)	63 (72.4%)	0.603	80 (88.9%)	77 (88.5%)	0.936	77 (89.5%)	79 (92.9%)	0.431
Presence of ASP, n (%)	33 (37.9%)	37 (42.5%)	0.536	50 (55.6%)	46 (52.9%)	0.720	47 (54.7%)	45 (52.9%)	0.823

Table 4

Characteristics of a sterosclerotic plaque of cerebral vessels with CCI depending on the stage

Indicator, n (%)	Groupe I (n=70)			Groupe II (n=96)			Groupe III (n=92)		
	Stage of CCI		p	Stage of CCI		p	Stage of CCI		p
	I (n=33)	II (n=37)		I (n=50)	II (n=46)		I (n=47)	II (n=45)	
Density of ASP: Hypoechoic Hypogeterogeneous Echoheterogeneous Echohomogeneous	 3 (9.1) 7 (21.2) 16 (48.5) 7 (21.2)	 6 (16.2) 24 (64.9) 7 (18.9) 0	 *0.485* ***<0.001*** ***0.009*** ***0.004***	 18 (36) 10 (20) 11 (22) 11 (22)	 4 (8.7) 22 (47.8) 14 (30.4) 6 (13)	 ***0.001*** ***0.004*** *0.347* *0.251*	 5 (10.6) 10 (21.3) 19 (40.4) 13 (27.7)	 6 (13.3) 23 (51.1) 9 (20) 7 (15.6)	 *0.690* ***0.003*** ***0.033*** *0.159*
The size of ASP: ≤10 мм >10 мм	 25 (75.8) 8 (24.2)	 19 (51.4) 18 (48.6)	 ***0.035***	 46 (92) 4 (8)	 12 (26.1) 34 (73.9)	 ***<0.001***	 37 (78.7) 10 (21.3)	 14 (31.1) 31 (68.9)	 ***<0.001***
The form of ASP: Localized Semi-concentric Concentric	 8 (24.2) 1 (3) 24 (72.7)	 26 (70.3) 5 (13.5) 6 (16.2)	 ***<0.001*** *0.203* ***<0.001***	 22 (44) 9 (18) 19 (38)	 21 (45.7) 9 (19.6) 16 (34.8)	 *0.871* *0.844* *0.744*	 9 (19.1) 6 (12.8) 32 (68.1)	 23 (51.1) 6 (13.3) 16 (35.6)	 ***0.001*** *0.936* ***0.002***
Surface of ASP: Smooth Uneven	 4 (12.1) 29 (87.9)	 26 (70.3) 11 (29.7)	 ***<0.001***	 25 (50) 25 (50)	 22 (47.8) 24 (52.2)	 *0.831*	 12 (25.5) 35 (74.5)	 24 (53.3) 21 (46.7)	 ***0.006***

Violation of the wall of the main arteries of the head is manifested by thickening of the intima-media, primarily of the carotid arteries, as a result of the progression of atherosclerosis.

In the study of hypertrophy and initial atherosclerotic transformation of elastic vessels (Table 5), the mean IMT in group I had a statistically significant difference and was 1.0 ± 0.34 mm in patients with CCI I, CCI II - 1.1 ± 0.28, which was significantly lower than that of other groups. The maximum mean IMT value was found in patients of group III, in whom several main arteries of the head were affected: (in the CCI I subgroup - 1.15 ± 0.33 and in the CCI II subgroup - 1.18 ± 0.34). Group II patients occupy an intermediate place in this indicator (1.13 ± 0.24 and 1.15 ± 0.27, respectively). The study revealed the influence of ethnicity on IMT

Table 5

The thickness of the intima-media complex in patients with chronic cerebral ischemia depending on age and ethnicity (mm)

Category	CCI I			CCI II		
	IMT	χ^2	p	IMT	χ^2	p
Ethnos						
Groupe I	1.0±0.34	228.21	0.001	1.1±0.28	246.29	0.001
Groupe II	1.13±0.24	274.82	0.001	1.15±0.27	262.63	0.001
Groupe III	1.15±0.33	281.58	0.001	1.18±0.34	274.29	0.001
Gender						
Women	1.08±0.31	13.079	0.001	1.14±0.30	13.054	0.001
Men	1.11±0.30	68.949	0.001	1.16±0.31	89.332	0.001
Age						
60-74	0.99±0.30	293.61	0.001	1.00±0.29	298.85	0.001
75->	1.21±0.28	317.93	0.001	1.28±0.30	322.4	0.001

with an average correlation strength ($\chi 2 = 11.374$, $r = 0.118$, $p = 0.044$).

Elderly patients more often have an intima-media thickness of 0.9 cm, and senile patients - more than 0.9 cm thickness. The age distribution showed that the older the subjects are, the higher the thickness of their intima-media is.

Thus, the age factor enhances the degree of remodeling of the vascular wall of the carotid arteries, which is consistent with the works of other authors [3,4].

Comparative analysis of IMT as a function of gender shows that IMT in men is, on average, statistically significantly higher than in women. (1.11 ± 0.31; 1.18 ± 0.31 versus 1.08 ± 0.31 and 1.14 ± 0.30, $p = 0.04$).

Conclusion. Ethnicity-dependent variability of intima-media thickness of the common carotid artery was revealed in elderly and senile residents of the Republic of Sakha (Yakutia). Indirect changes in cerebral blood flow, which influenced the formation and development of cerebrovascular disorders, are due to ethnic, age and gender characteristics.

An analysis of intima-media thickness demonstrated that the Yakuts and Russians have significantly greater IMT than the Evens. In all groups with the second stage of chronic cerebral ischemia, hypoheterogeneous and large atherosclerotic plaques were the most common. When compared by gender, it is significantly higher in men. With age, a remodeling and thickening of this indicator in the form of an increase and hardening of plaques was observed.

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CREATION OF A MODEL OF OVARIAN CANCER IN IMMUNODEFFICIENT MICE OF THE BALB / C NUDE LINE

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The purpose of this study was to create an in vivo model of ovarian cancer allowing control of the dynamics of tumor growth and adequate data on its size. As a model Balb/c Nude mouse lines were used. Removal of the mouse ovary with an implanted tumor fragment under the skin made it easier to visualize and to control the dynamics of xenograft growth.

Keywords: ovarian cancer, PDX model, patient-derived xenograft, Balb/c Nude, xenograft, in vivo models.

Ovarian cancer (OC) is the fifth most common malignant tumor in females aged 55 to 69 years, and the fourth most common cancer in females aged 40-54 years. According to the data on the world morbidity, OC is diagnosed in 9.1 cases per 100 000 female population. According to the Rosstat statistics, 17.8 cases on average were registered per 100 thousand female population in 2016. OC causes more deaths than any other cancer of the female reproductive system in Russia: 7 616 women died from OC in 2018 [6].

OC has several histological and molecular subtypes. Serous carcinomas are the main group of malignant epithelial tumors of the ovaries. Low-grade serous carcinoma consists of cystic, papillary and solid components [11,13]. Early diagnosis of OC is complicated, and its therapy effect is poor, so it is important to study the nature of this disease and develop methods for its treatment using various biological models [7,8].

Today, one of the tasks of researchers creating various animal tumor models is to reproduce the complexity of the tumor