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ORIGINAL RESEARCHES

V.A. Alekseeva, A.B. Guryeva

CHARACTERISTICS OF FUNCTIONAL INDICATORS OF YOUNG MEN ENGAGED IN SPORTS, DEPENDING ON THE TYPE OF HEMODYNAMICS

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The aim of the study was to determine the characteristics of the functional indicators of the circulatory system of young men engaged in sports, depending on the type of hemodynamics. The scientific study was conducted on 42 athletes aged 14 to 19 years engaged in boxing and freestyle wrestling. All the examined persons were yakuts by nationality, were born and permanently resided on the territory of the Republic of Sakha (Yakutia). Of these, 22 athletes belonged to the adolescent age (14-16 years), 20-to the youth age (17-21 years). The anthropometric examination included the measurement of the overall dimensions of the body (length and body weight). The surface area of the body was calculated using the Mosteller formula. Changes in the parameters of the circulatory system characterize the functional capabilities of the body and the degree of adaptation to training loads. To assess the functional state of the circulatory system, the cardiac index, minute blood volume, systolic blood volume according to the Starr formula, the index of functional changes, average blood pressure, the coefficient of efficiency of blood circulation, the Allgover index, the double product, the coefficient of endurance according to the A. Kvaas formula and the Kerdo vegetative index were calculated. Statistical processing of the obtained data was carried out using parametric and nonparametric research methods, using the SPSS 17.0 application software package. The assessment of the functional state of the circulatory system was carried out taking into account the type of hemodynamics of the examined persons. The majority of the examined athletes had eukinetic – 42,9% and hyperkinetic - 47,6% types of hemodynamics. The hypokinetic type was determined only in 9,5 % of the examined athletes. Overall indicators of young men, depending on the type of hemodynamics, had no statistically significant differences. According to the Kerdo index, the predominance of the parasympathetic department of the autonomic nervous system was revealed in all the examined young men. Young men with hyperkinetic type of hemodynamics were characterized by high values of pulse pressure, heart rate, double product and coefficient of efficiency of blood circulation. The obtained results indicate the need to take into account the type of hemodynamics in the athlete's training process and the level of physical exertion.

Keywords: athletes, type of hemodynamics, blood pressure, index score.

Introduction. Classes in various sports exert significant loads on all systems of the human body, which leads to the stimulation of adaptive processes [6]. The most reactive is the circulatory system. The change in its parameters characterizes the functional capabilities of the body and the degree of adaptation to training loads [8]. When assessing the functional state of the circulatory system, an index assessment of hemodynamic parameters is widely used. Using the data of integral indicators of blood circulation, it is possible to determine the types of hemodynamics - eukinetic, hypokinetic and hyperkinetic [1]. Knowledge of hemodynamic types opens up prospects for a personalized approach in the training process to achieve higher sports results and reduce the risk of developing pathological processes in the body. The high level of the functional state of the circulatory system of athletes shows the reserve capabilities of the body to adapt to high physical exertion. In this regard, the assessment of the functional state of the blood circulation of athletes and its adaptive reserves is one of the important issues of modern physiology and sports medicine.

Purpose: To characterize the functional parameters of the circulatory system of young men engaged in sports, depending on the type of hemodynamics.

Materials and methods. A morpho-functional examination was conducted on 42 students of the State Educational Institution of the Republic of Sakha (Yakutia) "School of Higher Sports Skills" engaged in boxing and freestyle wrestling. All the surveyed were males aged from 14 to 19 years, by nationality – yakuts permanently residing in the territory of Yakutia. According to the age classification of human ontogenesis, 22 subjects were considered to be adolescents (14-16 years old), and 20 subjects were considered to be adolescents (17-21 years old). The study was conducted after obtaining the voluntary informed consent of the participants. The criteria for exclusion from the scientific study were: refusal of examination, the presence of acute diseases and exacerbation of chronic diseases.

An anthropometric examination was carried out with the measurement of the overall dimensions of the body (length and body weight). The body length is determined by the Martin metal rod anthropometer with an accuracy of 1 mm, the body weight is measured on medical scales with an accuracy of 100 g. All measurements were carried out in the morning, the data obtained were recorded in an individual survey card. According to the results of the anthropometric survey, the body surface area (BSA) was calculated using the Mosteller formula:

$$BSA=\sqrt{(Body\ length \times Body\ weight \div 3600)}$$

To assess the functional state of the circulatory system, CI – cardiac index, MBV – minute blood volume, SBV - systolic blood volume, IFCh – index of functional changes, average blood pressure, CEBC – coefficient of efficiency of blood circulation, IA - Allgover index, DP – double product, EC – coefficient of endurance according to the formula of A. Kvaas, VKI - vegetative Kerdo index [2] were calculated.

Blood pressure was measured by an Omron M2 Basic automatic tonometer with an adapter (HEM-7121-ARU) in mmHg. Heart rate (HR) was calculated on the radial artery for 1 minute. Blood pressure measurement and pulse counting were carried out at rest. Pulse pressure (PP) is determined by the formula PP= SBP-DBP, where SBP is systolic blood pressure, DBP is diastolic blood pressure.

The cardiac index is an indicator of the pumping function of the heart. The calculation of the cardiac index is made

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according to the formula: CI=MBV/BSA. The norm is the CI value in the range from 2,2 to 2,4 l / min/m^2. According to the CI value, the type of hemodynamics was determined in all the examined patients. The hypokinetic type included persons with a CI value of less than 2,7 l/min/m^2, the eukinetic type – with a CI value of 2,7 to 3,5 l/min/m^2, the hyperkinetic type - with a CI of more than 3,5 l/min/m^2.

The SBV is calculated according to the Starr formula: SBV = 90,97 + (0,54 ×PP) – (0,57 ×DBP) – (0,61 × A), where PP is the pulse pressure (mmHg.ct); DBP – diastolic blood pressure (mmHg.st); A – age in years. The MBV was calculated according to the formula: MBV = CS×HR ml / min, where SV is the stroke volume of the heart (ml.); HR is the heart rate per minute (beats/min).

IFCh is calculated by the formula: IFCh = 0,011×HR + 0,014×SBP + 0,008×DBP + 0,014×A + 0,009×BW-0,009×BL – 0,27, where HR is the resting heart rate (bpm), SBP is systolic blood pressure (mmHg), DBP is diastolic blood pressure (mmHg), A is age (years), BW is body weight (kg), BL is body length (cm). The value of IFCh up to 2,6 indicates the normal operation of the circulatory system, IFCh in the range from 2,6 to 3,1 - the stress of the function, IFCh from 3,1 to 3,5 – unsatisfactory function, from 3,5 and higher – the failure of the function of the circulatory system. The CEBC was determined by the formula: CEBC = (SBP-DBP) × HR. CEBC characterizes the energy expenditure of the body to perform the work of the circulatory system.

The double product is calculated by the formula: DP=HR×SBP/100, conv. units, where HR is the heart rate for 1 minute, SBP is the systolic blood pressure. The value of DP equal to 90 and higher was estimated as "below average", from 76 to 89 conv. units – "average", equal to and less than 75 conv. units as "above average". The endurance coefficient was calculated using the formula: EC=HR×10/(SBP-DBP), conv.ed. The norm is the value of EC from 12 to 16 conv. units, the increase in the activity of the CVS (cardiovascular system) - a value less than 12, the reduced load on the cardiovascular system - more than 16 conv. units.

The VKI is defined by the formula: VKI=(1-DBP/HR)* 100, conv. units, the value of the VKI was regarded as "vagotonia" in the case of a negative index value, as "sympathicotonia" with its positive value. An index equal to zero indicated the equivalent activity of the sympathetic and parasympathetic parts of the autonomic nervous system.

Statistical processing was carried out using parametric and nonparametric research methods (SPSS 17,0). The distributions of features and the estimation of the distribution characteristics (mean, standard deviation, minimum, maximum) are calculated. The assessment of intergroup differences was carried out according to the Mann-Whitney U-criterion. To assess the inter-group differences in relative indicators, the Pearson criterion χ^2 was used. The differences were considered significant at p<0,05 [5].

Results and discussion: A total of 42 young men engaged in martial arts were examined. The distribution of young men by type of hemodynamics was as follows: 9,5% belonged to the hypokinetic type, 42,9% - to the eukinetic type and 47,6% - to the hyperkinetic type of hemodynamics (χ^2=9,064; p=0,011). The indicators we obtained are similar to the results of other studies, so, according to N.V. Olyashev and co-authors, the distribution of hemodynamic types among young men of the Arkhangelsk region was as follows: hypokinetic type – 15,4%, eukinetic type – 36,8%, hyperkinetic type – 47,8% [3]. Such a distribution of hemodynamic types among young men in the northern regions of Russia may indicate the intense work of the circulatory system. Mobilization of functional reserves of the cardiovascular system is one of the adaptive processes of the human body. Overall indicators of young men, depending on the type of hemodynamics, had no statistically significant differences. The body length of young hypokinetics was equal to-164,0±4,61 cm, body weight – 56,5±2,88 kg; eukinetics-165,0±8,80 cm, 55,3±8,83 kg; hyperkinetics -163,6±7,71 cm, 53,1±7,17 kg. The average value of the BSA of the surveyed was equal to 1,57±0,14 m^2 (minimum-1,34 m^2, maximum-1,86 m^2).

The blood pressure indicators of young men of the hypokinetic type of hemodynamics were: SBP – 115,0±4,12 mmHg, DBP – 71,0±6,92 mmHg, PP – 44,0±6,93 mmHg. Similar parameters of young men of eukinetics were equal – SBP – 115,11±11,04 mmHg, DBP – 62,56±7,56 mmHg, PP – 52,56±10,90 mmHg. The blood pressure indicators of hyperkinetic boys were equal – SBP – 121,40±6,24 mmHg, DBP – 64,0±8,73 mmHg, PP – 57,40±6,91 mmHg. The heart rate in individuals with the hypokinetic type was 58,0±8,08 beats per 1 min. , with the eukinetic type – 66,22±9,37 beats per 1 min. , with the hyperkinetic type – 87,30±10,29 beats per 1 min. A comparative analysis of the obtained blood pressure parameters revealed significantly high values of pulse pressure in hyperkinetic boys, in contrast to hypokinetic hemodynamic type boys (p=0,002). It was determined that the heart rate of young men in all the examined groups had significant differences (p<0,001). The lowest heart rate value was registered in persons with hypokinetic type, the highest value - in hyperkinetics.

The study of the vegetative index of Kerdo among the students of Yakutia revealed the heterogeneity of the distribution of types of vegetative regulation [4, 7]. In the group we studied, the predominance of the parasympathetic division of the autonomic nervous system was revealed in all the examined young men. Vagotonics are characterized by lower heart rate and SBP values, which indicates a more economical operation of the circulatory system. According to IFCh and EC, all the examined young men have good functional capabilities of the circulatory system (Table). The obtained data indicate stable mechanisms of adaptation of the examined group, as well as successful compensation of unfavorable lifestyle factors by mobilizing internal reserves of the body.

The differences in the indicators of the functional state of the circulatory system depending on the type of hemodynamics were determined. Thus, the assessment of DP showed that in persons with hyperkinetic type, the average value of DP was 105,94±13,51 conv. units. The obtained DP indicators were significantly higher than similar parameters of persons with hypokinetic and eukinetic types, which indicates low aerobic capabilities of young men with hyperkinetic type of hemodynamics. DP characterizes the efficiency of the heart as a whole, the level of tolerance to physical exertion, as well as the adequacy and lability in the work of the CVS.

CEBC characterizes the costs of the body for hemodynamics. The average values of CEBC in young men with eukinetic and hyperkinetic types of hemodynamics were significantly higher than normal, which indicates that the physical exertion presented does not correspond to the functional capabilities of the body of these groups of young men. The value of the MBV in hyperkinetic boys was equal to 6508,54±889,80 ml in 1 min., which is higher than normal indicators.

Conclusions: The conducted study of the functional parameters of the circulatory system of 42 young men engaged in martial arts revealed the heterogeneity of the examined group by types of hemodynamics. The majority of the examined individuals had eukinetic and hyperkinet-

Parameters of the circulatory system of young men. depending on the type of hemodynamics

Parameters	Hypokinetic type (n=4)	Eukinetic type (n=18)	Hyperkinetic type (n=20)	Statistical significance of difference. p*
	1	2	3	
IFCh	1.82±0.15	1.81±0.24	2.12±0.19	p_{1-3}=0.029; p_{2-3}=0.001
EC	13.65±3.98	13.23±4.08	15.50±3.12	p_{2-3}=0.013
DP	66.70±9.26	76.18±12.15	105.94±13.51	p_{1-3}<0.001; p_{2-3}<0.001
CEBC	2510.0±46.18	3437.44±609.32	4988.40±716.58	p_{1-2}=0.002; p_{1-3}<0.001; p_{2-3}<0.001
SBV	51.80±10.88	65.95±13.97	70.03±13.85	p_{1-2}=0.04; p_{1-3}=0.01
MBV	3574.53±7.71	4753.42±446.33	6508.54±889.80	p_{1-2}=0.002; p_{1-3}<0.001; p_{2-3}<0.001

ic types. The length and body weight of young men of different types of hemodynamics did not significantly differ. According to the Kerdo index, the predominance of the parasympathetic department of the autonomic nervous system was revealed in all the examined young men. Significant differences in the functional parameters of the circulatory system depending on the type of hemodynamics were revealed. Young men with hyperkinetic type were characterized by high values of pulse pressure, heart rate, DP and CEBC, which indicates a low level of oxygen supply to the body to adequately meet energy needs during physical exertion, as well as, possibly, a discrepancy between physical exertion and the functional capabilities of the body of this group of young men. Thus, in the training process, it is necessary to take into account the type of hemodynamics of the athlete and the level of physical exertion on the circulatory system.

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INDIVIDUAL PERSONAL CHARACTERISTICS AND RISK FACTORS FOR MALIGNANT NEOPLASMS OF REPRODUCYIVE ORGANS IN FEMALE DOCTORS AND RECEARCHERS WITH HIGH MEDICAL RESPONSIBILITY

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The aim of our work was to study the structure of risk factors for malignant neoplasms of reproductive organs in conjunction with individual personal and emotional characteristics of female doctors and researchers.

Materials and methods. A cross-sectional study, which involved female doctors and researchers who applied for a comprehensive preventive examination.

Results. A significant number of risk factors for the reproductive organs malignant neoplasms development were identified in female doctors and researchers. Female doctors, in comparison with female researchers, are significantly better informed about the structure and significance of risk factors and have more responsibility towards their health. At the same time, in relation to preventive measures and risk factors correction, female researchers are more active than female doctors. Personal profile of the female doctors: sociable, willing to cooperate, average level of intelligence, emotionally sensitive to the external environment, prefer to make decisions in cooperation, focusing on social approval. Personal profile of scientific workers: often closed, focused on personal experience but not on external circumstances, high level of intelligence, independence in judgments, tendency to dominance, they poorly control their emotions and subjected to frustration. All women had low self-esteem, but it was significantly lower among doctors, more than half of women have a feeling of mental exhaustion, as a result of which the effectiveness of professional interaction and the quality of life in general decreases.

Keywords. oncological diseases, risk factors, psychological profile, women, doctors, researchers

Introduction. The increase in the level of oncological morbidity registered worldwide over the past 10 years [6], an increase in the number of tumors of the reproductive organs among women of young reproductive age, insufficient effectiveness of therapy [12,8], low rates of detection of tumors in the early stages cause the search for new ways to solve the problem that can provide timely detection and correction of risk factors (FR) [9], diagnosis of the tumor process at the preinvasive stage and reduction of mortality rates [1].

Nowadays more than 80 types of oncological diseases have been identified, in the structure of which uncorrectable and subject to correction have been identified [5]. Uncorrectable factors include age, gender, race, and burdened genetic inheritance [10]. However, in recent years, it has been noted that correctable factors, the impact on which underlies secondary prevention, are of greater importance in the occurrence and progression of the tumor [2].

The primary source of many health disorders are persistent and deep negative emotions, indicating the lack of a sufficient degree of satisfaction of the basic needs of the individual. The energy intended for the integration of the resource necessary for it in the external environment remains unrealized and must inevitably be compensated in the buffer systems of the body [4,13]. The movement of unrealized energy occurs along the following path: frontal cortex (higher emotions) - temporal lobe (higher vegetative functions and lower emotions) - hypothalamic-pituitary-adrenal complex (neuro-endocrine-immune shunt) - target organs and tissues (executive subsystems and mechanisms) [7,11,14].

With prolonged emotional stress, distress due to hyperproduction of glucocorticoids, damage to the structures of the limbic system occurs, mechanisms for the development of irreversible damage to the central nervous system are triggered, information stresses are transformed into energy, then into metabolic and, finally, into morphological (organic) changes [3.15].

Aim. To study the structure of risk factors for of reproductive organs malignant neoplasms in conjunction with individual-personal and emotional characteristics of female doctors and researchers.

Materials and methods. A cross-sectional study, which included female doctors and researchers who applied for a comprehensive preventive examination at the Belaya Rosa Medical Center in January-March 2021.

All patients underwent: 1) a general clinical survey and anamnesis collection with an assessment of awareness of FR of oncological diseases of the reproductive sphere, an assessment of the presence of the main FR in the patient, an assessment of behavior aimed at correcting existing FR; 2) R. Cattell's multifactorial personality questionnaire, form C for assessing individual personality characteristics; 3) the questionnaire for identifying emotional burnout MBI authored by K. Maslach and S. Jackson; 4) the Lusher test using the Yuryev-Filimonenko ruler; 4) the test Dembo-Rubenstein for self-esteem level analysis; 5) Koch's text and 6) Smishek's test for assessing characterological traits.

All study participants signed a volun-

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tary informed consent. The study was conducted in accordance with the GCP rules.

Statistical analysis was performed using Microsoft Statistica 10.0 software using parametric and nonparametric methods. The values was presented as the mean and standard deviation M±m with normal distribution, or as the median and the 25th and 75th quartiles of Me [25%; 75%] if it is not normal. For pairwise comparisons of indicators in independent samples, Student's t-test or Mann-Whitney test with Bonferroni's correction was used. To compare values in dependent samples, the Wilcoxon test or Student's t-test was used. When testing statistical hypotheses, the critical significance level was taken equal to 0.05.

Results. In the course of the study, R. Cattell's Multifactorial personality Questionnaire, form C, was used and the data were obtained, which are presented in Table 1.

High indicators of factor "A" (from 7 to 7.7) characterize the subjects as naturally manifesting themselves in communication and persons with a good level of intellectual development (factor "B" from 8.4 to 9.7). A high level of severity was inherent in most of the subjects, but female doctors were less emotionally resistant to various life circumstances. Scientists were more domineering in relationships." higher indicators were characteristic of doctors, which indicates their greater emotionality in communication, and scientists are characterized by prudence and restraint.

The analysis of data on factor "E" indicated a high normativity of behavior in all subjects (8,7 - 9,2). According to the "H" factor, researchers were more characterized by social courage, activity and determination, and doctors showed themselves to be less stress-resistant. High scores on factors "I", "L" and "N" in doctors indicate their sensitivity.

The results of the study of factor "M" indicate that both groups are more practical than dreamy. Data on the "calmness – anxiety" scale (factor "O") shows that doctors are more vulnerable and impressionable, and high scores on the "Q1", "Q2" and "Q3" factors characterize a decrease in intellectual interests, analytical thinking, against the background of a preference to make decisions based on social approval. Considering the last factor "Q4", it should be noted that doctors were more prone to frustration.

Thus, the personal profile of female doctors: sociable, cooperative, with an average level of intelligence, emotionally sensitive to the external environment,

Table 1

Comparative indicators of individual and personal characteristics among the subjects

Indicator/factor	Researches (n=116)		Doctors (n=140)	
	%	балл	%	балл
closeness-sociability /A	51.7	7	47.8	7.7
intelligence /B	56.0	9.7	42.8	8.4
emotional stability /C	58.6	6.7	40.7	7.8
subordination-dominance /E	77.5	5.8*	20.7	8.7
expressiveness-restraint/G	31.8	4.8*	67.1	8.2
normativity of behavior / F	55.2	9.2	45.0	8.4
timidity-courage /H	63.8	5.4*	36.0	8.2
rigidity-sensitivity/I	31.1	5.2*	67.8	7.5
credulity-suspicion/L	50.8	6.5	49.2	5.8
practicality-dreaminess /M	42.2	5.1	57.8	6.7
straightforwardness- diplomacy /N	74.1	4.5*	25.7	6.9
calmness-anxiety/O	37.0	5.3	62.8	4.3
conservatism-radicalism /Q1	68.1	5.5*	32.1	8.2
conformism-nonconformism /Q2	72.4	3.7*	27.8	7
self-control /Q3	48.2	8.9*	52.1	6.6
relaxation-tension/Q4	54.3	6.2	62.1	8.4

Note: * - $p < 0.05$

Table 2

Distribution of characterological traits (Shmishek test)

Signs	Researchers (n=116)		Doctors (n=140)	
	%	балл	%	балл
Hyperthymic	-	6.2±0.61*.**	-	17.5±1.61
Stuck	21*	18.3±1.72*.**	-	13.3±1.05
Cyclothymic	-	3.2±0.14*.**	-	7.8±0.59
Emotive	-	7.6±0.62*.**	23*	9.3±0.44
Disturbing	42*	20.6±1.38*.**	38	11.2±1.02
Pedantic	25*	24.1±1.69*.**	29	4.9±0.37
Demonstrative	-	4.4±0.31*.**	6*	18.8±1.71
Excitable Dysthymic	-	6.4±0.47*.**	28*	17.3±1.58
Dysthymic	16	7.9±0.65*.**	17	13.8±1.12
Exalted	-	6.6±0.55*.**	14*	22.8±2.15

Table 3

Awareness of doctors and researchers about the risk factors of oncological diseases of the reproductive sphere (%)

Total	Researches n=116	Doctors n=140	P
They knew about the role of obesity in the development of breast cancer	31.1	53.6	<0.001
They knew about the role of HPV WRC in the genesis of breast cancer	17.2	38.6	<0.001
They knew about the role of smoking in the genesis of breast cancer	13.8	15.0	
They knew about the influence of reproductive history on the risk of cancer	3.4	12.1	<0.01
They knew about the role of heredity in the genesis of breast cancer	57.8	68.9	<0.01

prefer to make decisions together, focusing on social approval.

Personal profile of researchers: they are often closed, more often they focus not on external circumstances, but on personal experience, they have a high level of intelligence, independence in judgments, a tendency to dominance, while poor control of their emotions and behavior, susceptibility to frustration.

Emotional burnout was assessed according "Questionnaire for identifying emotional burnout MBI" by K. Maslach and S. Jackson. Emotional exhaustion was most clearly manifested among doctors (77%), which is expressed in a reduced emotional tone and loss of interest in the environment. Often, doctors demonstrated aggressive types of reactions, a negative attitude to work, perceived as a source of chronic emotional trauma. Also in this group, every second woman registered such a phase of emotional burnout as depersonalization (54%), which was manifested by increased dependence on others, negative attitudes and negative emotions. Among researchers, the development of phases of emotional burnout also occurred in half of the cases and led to depersonalization of relationships with other people. Thus, more than half of the women of both groups subjectively have a feeling of mental exhaustion, which reduces the effectiveness of professional interaction and the quality of life in general.

When analyzing the results of the Dembo-Rubenstein test in both professional groups, features in the field of self-esteem were revealed: in all women, self-esteem was underestimated, but it was significantly lower among female doctors ($p < 0.05$).

In all women, the maximum indicators were recorded on the "character" scale (58.4 ± 3.9 points for scientists and 63.9 ± 6.2 for doctors). For doctors, the lowest results were recorded on the “happiness” scale (33.1 ± 3.6, versus 39.6 ± 5.4 in the group of scientists), and among women researchers, on the “personal life” scale (41.4 ± 4 , 7 versus 31.0 ± 4.2 in the group of doctors). Analyzing the severity of the trait according to the self-assessment scales, we see that the highest indicators are typical for doctors according to the scales "intelligence", "health" and "character", and on the scale "happiness", on the contrary, the lowest.

With a lower reaction to the emotional warmth or coldness of the social environment, research workers were generally more anxious, and due to the difficulties in displaying emotions, the energy potential of unreacted feelings leads to a sustained decrease in mood and passive-defensive position. Doctors, having higher indicators of sensitivity, instability of choice and mood, and more directly and openly responding to stress, transferred anxiety to the level of self-affirmation, offensiveness and aggressiveness of behavior, Table 2.

Among the representatives of both groups, a survey was conducted to assess the awareness of the structure and significance of RFs for the occurrence of malignant neoplasms of the reproductive sphere, the data are presented in Table 3.

In general, we can talk about a significantly better awareness of doctors in comparison with researchers in relation to the structure and significance of RF of malignant neoplasms of the reproductive sphere. For four out of five RFs, doctors showed a significantly better awareness ($p < 0.01$). The most famous in both groups was the RF “heredity” and “obesity”, the lowest awareness in both groups was revealed in relation to the “influence of reproductive history”.

Based on the data of the anamnesis, an assessment of the attitude to one's own health was carried out in both groups, the results are presented in Table 4.

Based on the anamnesis data, we can say that female doctors were more responsible for their health in comparison with female researchers. Doctors reliably more often turned to the gynecologist prophylactically, while the researchers came already with the presence of complaints. A significantly large proportion of doctors underwent examination by a gynecologist during the next year (75.8% versus 25.0%), were regularly examined (96.6% versus 45.4%), performed an analysis for OZ (100% versus 68.8%) and knew her results (59.3% versus 31.8%), regularly underwent MMG (45.4% versus 17.9%), $p < 0.001$. At the same time, in a significantly larger proportion of researchers, the weight corresponded to the normal BMI (75.8% versus 55.7%), there was significantly less eating disorder (31.8% versus 81.4%), sleep disturbances were observed somewhat less frequently (51, 7% versus 66.4%). We may concluded that scientific work is associated with fewer RFs and low medical responsibility, tab. 4.

For the purpose of a detailed study of RF in both groups, based on anamnesis data, an analysis of risk factors associated with the development of malignant diseases of the reproductive organs was carried out. The results are presented in Table 5.

It was revealed that women doctors on average more often have early men-

Table 4

Attitude towards health

Parameters	Researchers, n=116	Doctors, n=140	P
Planned appeal	44.6	78.8	<0.001
Breast symptoms	17.9	10.6	
Pelvic symptoms	37.5	10.6	<0.001
Background.gynecologist's examination 6-12 months ago	25.0	75.8	<0.001
Background.gynecologist's examination 12 months ago	28.6	69.7	<0.001
Background.gynecologist's examination more than 12 months ago	46.4	33.6	0.05
Were examined regularly	45.4	96.6	<0.001
They were examined irregularly	0.04	42.4	<0.001
The OC was handed over within a year before the appeal	68.6	100.0	<0.001
More than 1 year	31.4	-	
I didn 't recognize the results	68.2	31.4	<0.001
I knew	31.8	59.3	<0.001
The norm	25.0	47.2	<0.001
Passed MMG regularly	17.9	45.4	<0.01
Irregular	33.9	27.3	
Replacement of MMG with ultrasound of the mammary glands	48.2	27.3	<0.01
The weight is normal	75.8	55.7	<0.01
Eating disorders (excess calories)	48.2	31.4	<0.01
Eating disorders	31.8	81.4	<0.001
Sleep disturbance	51.7	66.4	0.05

arche and late menopause, sex life was irregular, the vast majority had more than 3 sexual partners and the first birth was older than 30 years. A significantly large proportion of doctors in comparison with researchers were overweight and obese, type 2 diabetes, and GI. Female doctors were significantly more likely to smoke and drink alcohol.

At the same time, menstrual cycle disorders, pelvic inflammatory diseases, endometrial hyperplastic processes, fibroids and endometriosis, cervical erosion and dysplasia, a history of mastitis, abdominal operations, including gynecology, were significantly more common among researchers. Women in this group more often did not use contraception.

We also analyzed the behavior of female doctors and researchers regarding the correction of existing risk factors. The data is presented in table 6.

On average, we can say that with regard to preventive measures in order to correct the existing risk factors for cancer of the reproductive sphere, women scientists were more active than female doctors. They more often used various methods of improvement, followed recommendations for correcting nutrition (at least reducing the total calorie content of food), more often engaged in fitness, observed a sleep schedule, and underwent preventive medical examinations. At the same time, women doctors more often tried to get positive emotions in communication, hobbies and art, they devoted more time to walking and being in the fresh air.

Table 5

The presence of risk factors for cancer of the reproductive sphere in female doctors and researchers

Total	Researchers, n=116	Doctors, n=140	P
Early menarche	3.6	10.6	0.05
Menstrual cycle disorders	26.8	9.1	<0.001
Spontaneous abortion	17.2	1.5	<0.001
The first birth is over 25 years old	34.5	12.1	<0.001
Irregular sex life	13.8	33.6	<0.001
More than 3 p/partners	41.4	84.9	<0.001
Inflammatory chronic diseases	30.4	6.1	<0.001
Hyperplastic processes in the history of fibroids	71.4	1.5	<0.001
Mioma	66.1	16.7	<0.001
Endometriosis	46.4	4.5	<0.001
GPE	21.4	1.5	<0.001
Excess body weight	30.4	57.6	<0.001
Obesity	10.3	27.3	<0.001
Diabetes mellitus	1.8	6.1	<0.001
Diseases of the thyroid gland	21.4	27.3	0.05
Housing and communal services	1.8	15.1	<0.001
Alcohol consumption	1.8	9.1	<0.01
Smoking	6.8	24.3	<0.001
Mastitis	16.1	3.0	<0.001
Contraception no	28.6	3.0	<0.001
Interrupted intercourse contraception	12.5	69.7	<0.001
Cavity operations	25.0	4.6	<0.001
Pathology of w/m-erosion	51.8	3.0	<0.001
Pathology of w/m-dysplasia	8.9	0	<0.001
History of operations	37.5	4.6	<0.001
Oral gynaecology	16.1	6.1	0.05
Operation on the w/m	12.5	27.3	0.05
Prolapse	30.4	18.0	0.05
Recurrent vaginosis, vaginitis	10.7	4.6	
HPV + history	3.6	3.0	

Conclusions. 1) A significant number of risk factors for the malignant neoplasms of the reproductive organs development have been identified in female doctors and researchers; 2) Women doctors, in comparison with women research workers, are significantly better informed about the structure and significance of risk factors and have a more responsible attitude to their health; 3) At the same time, with regard to preventive measures and correction of existing risk factors, women researchers are more active than women doctors; 4) Personal profile of female doctors: sociable, willing to cooperate, with an average level of intelligence, emotionally sensitive to the external environment, prefer to make decisions in cooperation, focusing on social approval; 5) The personal profile of scientific workers: often closed, focused on personal experience but not on external circumstances, high level of intelligence, independence in judgments, tendency to dominance, they poorly control their emotions and subjected to frustration; 5) In all women, self-esteem turned out to be underestimated, but it was significantly lower among doctors, more than half of the women had a feeling of mental exhaustion, as a result of which the effectiveness of professional interaction and the quality of life in general decreased.

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Table 6

Behavior aimed at correcting risk factors for cancer of the reproductive sphere

Total	Researchers, n=116	Doctors, n=140	P
Methods of recovery were used	82.7	47.2	<0.001
Abstaining from alcohol	41.3	27.1	0.05
Smoking cessation	31.8	18.6	0.05
Correction of the diet (restriction of calories)	51.7	27.9	<0.001
Compliance with special principles of nutrition (vegetarianism, raw food)	17.2	11.4	
Restriction of dairy products	13.8	4.3	<0.01
Physical activity (fitness)	72.4	55.0	<0.01
Spiritual development (religion, spiritual practices)	31.0	36.4	
Getting positive emotions (communication, art, hobbies)	58.6	74.3	<0.01
Fasting (for religious beliefs)	-	6.4	
Compliance with the sleep regime	48.2	31.4	<0.01
Walking, staying in the fresh air	65.5	87.9	<0.001
Self-medication	17.2	33.6	<0.001
Preventive medical examinations	51.7	33.6	<0.01
Alternative medicine	-	8.6	

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ASSOCIATION ANALYSIS OF SEROTONIN SYSTEM GENE POLYMORPHISMS (*5-HTT, HTR1B, HTR2A, HTR2C, AND TPH1*) WITH THE RISK OF PARKINSON'S DISEASE IN TATARS

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Disruption of serotonin metabolism may play a role in the pathogenesis of Parkinson's disease (PD). An analysis of the association of polymorphic variants of the genes of the serotonergic system was carried out: *Stin2* and *5-HTTLPR* loci of the *5-HTT* gene (serotonin transporter), *rs6296* of the *HTR1B* gene, *rs6311* of the *HTR2A* gene, *rs6318* of the *HTR2C* gene (serotonin receptors) and *rs1800532 TPH1* gene (tryptophan hydroxylase) with PD and its clinical forms in patients of Tatar ethnicity living in the Republic of Bashkortostan. The study included 257 patients with sporadic PD and 368 healthy individuals. As a result of the study with the development of PD in general and with its akinetic-rigid subtype, associations of the *rs1800532*G* allele and the *rs1800532*G/G* genotype of the *TPH1* gene were established. Associations of the *rs6296*G/C* genotypes of the *HTR1B* gene and *rs6318*C/C* of the *HTR2C* gene were also revealed with the akinetic-rigid subtype of PD. The association of the *STin2*12* allele of the *5-HTT* gene was found with PD and the akinetic-rigid subtype with tremor (mixed subtype). An analysis of the influence of the studied polymorphic variants of genes on the age of PD manifestation revealed an association of the *STin2*12* allele of the *5-HTT* gene with a later age of disease development (after 60 years), and an association of the *rs6318*C* allele of the *HTR2C* gene (in men) and the *rs1800532*G* allele of the TPH1gene with the onset of the disease from 45 to 60 years old.

Keywords: Parkinson's disease, serotonin, polymorphic variants of the gene, tryptophan, serotonin transporter, serotonin receptors.

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Introduction. The interaction of dopamine and serotonin with each other has been studied for many years, but the role of serotonergic transmission in dopaminergic neurons activity modulating has not yet been precisely determined (18). It has been shown that there is a decrease the serotonergic neurons number and Lewy bodies in them in PD patients (19; 12). It is known that the level of serotonin and the expression of the serotonin transporter are reduced in PD (15), but there is an increase in the level of expression of 5-HT2C receptors (7). It was noted that the loss of the transporter does not correlate with the duration of the disease and disability (21). Previously, we presented the results of a large associative study of the influence of the genes of the dopaminergic system on the PD development in ethnic Tatars living in the Republic of Bashkortostan (RB), one of the most numerous ethnic groups of the Republic's population (2).

Purpose: to investigate the effect of six polymorphic variants of genes of the serotonergic system: serotonin transporter (5-HTT), serotonin receptors (HTR1B, HTR2A, and HTR2C) and the enzyme tryptophan hydroxylase (TPH1) on the development of PD and features of the clinical course of the disease; to determine genetic markers of PD risk in Tatars.

Materials and methods. The material for the study was DNA samples from 257 patients with Parkinson's disease and 368 healthy individuals of the control sample, corresponding to the sample of patients by sex and average age. Voluntary informed consent was obtained from patients and controls. This study was approved by the Ethics Committee of the Bashkir State Medical University (Ufa). The persons included in the study live in the territory of the RB and belong to the Tatar ethnic group. The diagnosis of Parkinson's disease was established according to the clinical diagnostic criteria of the UK Parkinson Disease Society Brain Bank Criteria (4). The assessment of the severity of PD was determined using the Hen-Yar scale (11); the clinical form and age of the onset of the disease were also taken into account (these signs remained undefined in some patients, as a result of which a different number of DNA samples were included in the calculations). Genotyping for VNTR loci of the 5-HTT gene was performed by polymerase chain reaction (PCR) for DNA synthesis and subsequent electrophoresis in polyacrylamide gel, at polymorphic loci rs6311 and rs6318 - by the method of restriction fragment length polymorphism (RFLP), by the rs006325 and rs186296 and amplification loci and fluorescence detection using a CFX amplifier (Bio-Rad, USA).The results were statistically processed using a two-sided version of the Fisher test. All statistical tests were performed for a two-tailed level of significance; differences were considered statistically significant at $p < 0.05$.

Results and discussion. The distri-

Table 1

Distribution of allele and genotype frequencies of the studied polymorphic loci of genes of the serotonergic system in PD patients and in the control group

1	2			3					4
5-HTT (STin2)	Allels, n (%)			Genotypes, n (%)					N
Sample	**9*	**10*	**12*	**9/10*	**9/12*	**10/10*	**10/12*	**12/12*	
Controls	21 (3.33)	240 (38.9)	369 (58.57)	11 (3.5)	9 (2.86)	57 (18.1)	116 (36.83)	122 (38.73)	315
PD cases	8 (1.59)	166 (33.07)	328 (65.34)	3 (1.2)	5 (1.99)	33 (13.15)	97 (38.65)	113 (45.02)	251
Tremor-dominant subtype	5 (2.72)	74 (40.22)	105 (57.06)	2 (2.17)	3 (3.26)	18 (19.57)	36 (39.13)	33 (35.87)	92
Akinetic-rigid subtype	0	19 (29.69)	45 (70.31)	0	0	3 (9.38)	13 (40.62)	16 (50.0)	32
Mixed subtype	2 (1.64)	27 (22.13)	93 (76.23)	1 (1.64)	1 (1.64)	5 (8.2)	16 (26.23)	38 (62.3)	61
<45 age at onset	3 (7.5)	15 (37.5)	26 (65.0)	1 (5.0)	2 (10.0)	3 (15.0)	8 (40.0)	8 (40.0)	20
45-60 age at onset	3 (2.06)	47 (32.19)	96 (65.75)	0	3 (4.11)	8 (10.96)	31 (42.47)	31 (42.47)	73
> 60 age at onset	3 (1.36)	66 (30.0)	151 (68.64)	2 (1.82)	1 (0.91)	14 (12.73)	36 (32.73)	57 (51.82)	110
5-HTTLPR	Allels, n (p, %)			Genotypes, n (p, %)					N
Sample	**S*		**L*	**S/S*		**S/L*		**L/L*	
Controls	294 (54.04)		250 (45.96)	76 (27.94)		142 (52.21)		54 (19.85)	272
PD cases	162 (51.27)		154 (48.73)	38 (24.05)		86 (54.43)		34 (21.52)	158
Tremor-dominant subtype	49 (53.26)		43 (46.74)	13 (28.26)		23 (50.0)		10 (21.74)	46
Akinetic-rigid subtype	25 (56.82)		19 (43.18)	9 (40.91)		7 (21.21)		6 (27.27)	22
Mixed subtype	46 (50.00)		46 (50.00)	8 (17.39)		30 (65.22)		8 (17.39)	46
<45 age at onset	10 (41.67)		14 (58.33)	3 (25.00)		4 (33.33)		5 (41.67)	12
45-60 age at onset	31 (51.67)		29 (48.33)	7 (23.33)		17 (56.67)		6 (20.0)	30
> 60 age at onset	53 (55.21)		43 (44.79)	16 (33.33)		21 (43.75)		11 (22.92)	48
HTR1B (rs6296)	**C*		**G*	**C/C*		**G/C*		**G/G*	N
Controls	171 (35.33)		313 (64.67)	32 (13.22)		107 (44.22)		103 (42.56)	242
PD cases	158 (33.62)		312 (66.38)	31 (13.19)		96 (40.85)		108 (45.96)	235
Tremor-dominant subtype	51 (32.28)		107 (67.72)	11 (13.92)		29 (36.71)		39 (49.37)	79
Akinetic-rigid subtype	17 (29.31)		41 (70.69)	5 (17.24)		7 (24.14)		17 (58.62)	29
Mixed subtype	40 (33.33)		80 (66.67)	4 (6.67)		32 (53.33)		24 (40.0)	60
<45 age at onset	6 (21.43)		22 (78.57)	1 (7.14)		4 (28.57)		9 (64.29)	14
45-60 age at onset	25 (27.17)		67 (72.83)	5 (10.84)		15 (32.61)		26 (56.52)	46
> 60 age at onset	51 (38.64)		81 (61.36)	12 (18.18)		27 (40.91)		27 (40.91)	66
HTR2A (rs6311)	**A*		**G*	**A/A*		**A/G*		**G/G*	N
Controls	247 (33.56)		489 (66.44)	49 (13.32)		149 (40.48)		170 (46.2)	368
PD cases	189 (36.77)		325 (63.23)	39 (15.18)		111 (43.19)		107 (41.63)	257
Tremor-dominant subtype	60 (34.48)		114 (65.52)	14 (16.09)		32 (36.78)		41 (47.13)	87
Akinetic-rigid subtype	24 (36.36)		42 (63.64)	7 (21.21)		10 (30.30)		16 (48.49)	33
Mixed subtype	49 (39.52)		75 (60.48)	7 (11.29)		35 (56.45)		20 (32.26)	62
<45 age at onset	10 (31.25)		22 (68.75)	1 (6.25)		8 (50.0)		7 (43.75)	16
45-60 age at onset	35 (35.0)		65 (65.0)	11 (22.0)		13 (26.0)		26 (52.0)	50
> 60 age at onset	65 (40.63)		95 (59.37)	17 (21.25)		31 (38.75)		32 (40.0)	80
HTR2C (rs6318)	**C*		**G*	**C/C*		**G/C*		**G/G*	N
Controls (men)	28 (11.57)		214 (88.43)	14 (11.57)		0		107 (88.43)	121
Controls (women)	60 (13.42)		387 (86.58)	3 (1.43)		27 (12.86)		180 (85.71)	210
PD cases (men)	28 (15.56		152 (84.44)	14 (15.56)		0		76 (84.44)	90
PD cases (women)	18 (8.82)		186 (91.18)	3 (2.94)		12 (11.76)		87 (85.29)	102
Tremor-dominant subtype (men)	12 (16.67)		60 (83.33)	6 (16.67)		0		30 (83.33)	36
Akinetic-rigid subtype (men)	4 (22.22)		14 (77.78)	2 (22.22)		0		7 (77.78)	9
Mixed subtype (men)	4 (11.76)		30 (88.24)	2 (11.76)		0		15 (88. 24)	17
Tremor-dominant subtype (women)	4 (5.00)		76 (95.00)	0		4 (10.0)		36 (90.0)	40
Akinetic-rigid subtype (women)	7 (26.92)		19 (73.08)	1 (7.69)		5 (38.46)*		7 (53.85)	13
Mixed subtype (women)	1 (1.92)		51 (98.08)	0		1 (3.85)		25 (96.15)	26
<45 age at onset (men)	0		12 (100.0)	0		0		6 (100.0)	6
45-60 age at onset (men)	8 (40.0)		12 (60.0)	4 (40.0)		0		6 (60.0)	10
> 60 age at onset (men)	8 (12.12)		58 (87.88)	4 (12.12)		0		29 (87.88)	33
<45 age at onset (women)	0		16 (100.0)	0		0		8 (100.0)	8
45-60 age at onset (women)	8 (9.76)		74 (90.24)	1 (2.44)		6 (14.63)		34 (82.93)	41
> 60 age at onset (women)	5 (6.76)		69 (93.24)	0		5 (13.51)		32 (86.49)	37

The end of the table 1

1	2		3			4
TPH1 (rs1800532)	**G*	**T*	**G/G*	**G/T*	**T/T*	N
Controls	381 (51.77)	355 (48.23)	93 (25.27)	195 (52.99)	80 (21.74)	368
PD cases	288 (59.26)	198 (40.74)	87 (35.8)	114 (46.92)	42 (17.28)	243
Tremor-dominant subtype	108 (60)	72 (40.00)	34 (37.78)	40 (44.44)	16 (17.78)	90
Akinetic-rigid subtype	32 (61.54)	20 (38.46)	14 (45.16)	14 (45.16)	3 (9.68)	31
Mixed subtype	58 (50.88)	56 (49.12)	13 (22.18)	32 (56.14)	12 (21.05)	57
<45 age at onset	16 (50.00)	16 (50.00)	6 (37.50)	4 (25.0)	6 (37.5)	16
45-60 age at onset	90 (62.5)	54 (37.50)	28 (38.89)	34 (47.22)	10 (13.89)	72
> 60 age at onset	124 (56.36)	96 (43.64)	33 (30.00)	58 (52.73)	19 (17.27)	110

n – number of allels/genotypes, N – number of persons.

bution of the frequencies of genotypes and alleles of the studied loci is shown in Table 1, and the comparative analysis according to the obtained data is shown in Table 2. The distribution of genotype frequencies of the studied polymorphic variants corresponds to the Hardy-Weinberg equilibrium in all studied groups (p> 0.05).

The serotonin transporter (5-HTT) carries out serotonergic signaling and regulates the rate of serotonin reuptake in neurons. The serotonin transporter gene (5-HTT or SLC6A4) is located on chromosome 17 (q11.1-q12) and consists of 15 exons. Polymorphic VNTR locus 2 of the intron of the 5-HTT gene (STin2) consists of many repeated copies of the 17 bp element; three alleles are known containing 9 (STin2*9), 10 (STin2*10), and 12 (STin2*12) repeat copies (16). The influence of the locus on the level of gene expression was noted: STin2*9 is associated with an increased level of 5-HTT expression (6). In our study, higher frequencies of the *12 allele were found in patients with PD (p=0.023), especially in patients with a mixed (akinetic-rigid-trembling) form of PD (p=0.0002), and with the onset of the disease after 60 years (p=0.01) in comparison with the control group (Table 2; data on the genotype *9/*9 were omitted in it due to the small size of the group). Analysis of the literature data showed that targeted studies of the role of the Stin2 polymorphic variant of the 5-HTT gene in the development of PD have not previously been carried out.

Allelic variants of another locus of the 5-HTT gene, 5-HTTLPR, contain either 16 repeats (long allele *L) or 14 repeats (short allele *S), with a 43 bp deletion (5). The presence of the long allele *L provides a higher level of gene expression and a greater intensity of serotonin metabolism, compared to the short allele *S (13). Our analysis did not reveal significant associations between allelic variants of this locus and the development of PD.

Table 2

Results of the analysis of associations of the studied polymorphic loci of genes of the serotonergic system with Parkinson's disease

1	2	3	4	5
Allels, genotypes	Study groups	P	OR	95% CI
5-HTT (STin2)				
*9/10	PD cases / Controls	0.104	0.33	0.09-1.2
*9/12		0.594	0.69	0.23-2.09
*10/10		0.132	0.69	0.43-1.1
*10/12		0.663	1.08	0.77-1.52
*12/12		0.145	1.3	0.93-1.82
*9		0.122	0.49	0.21-1.12
*10		0.081	0.8	0.63-1.02
*12		0.023	1.33	1.04-1.7
*10/10	Akinetic-rigid subtype / Controls	0.325	0.47	0.14-1.6
*10/12		0.703	1.17	0.56-2.46
*12/12		0.256	1.58	0.76-3.28
12		0.082	1.68	0.96-2.94
10		0.223	0.69	0.39-1.21
*9/10	Mixed subtype / Controls	0.699	0.46	0.06-3.63
*9/12		1.000	0.57	0.07-4.58
*10/10		0.060	0.4	0.15-1.04
*10/12		0.142	0.61	0.33-1.13
*12/12		0.001	2.61	1.48-4.59
*10		$6x10^{-4}$	0.46	0.29-0.73
*12		$2x10^{-4}$	2.27	1.45-3.55
*9/10	>60 age at onset / Controls	0.529	0.51	0.11-2.34
*9/12		0.465	0.31	0.04-2.48
*10/10		0.235	0.66	0.35-1.24
*10/12		0.489	0.83	0.52-1.31
*12/12		0.019	1.7	1.1-2.63
*10		0.034	0.69	0.5-0.96
*12		0.01	1.55	1.12-2.15
HTR1B (rs6296)				
*G/G	PD cases / Controls	0.462	1.15	0.8-1.65
*G/C		0.461	0.87	0.6-1.25
*C/C		1.000	1	0.59-1.7
G		0.586	1.08	0.83-1.41
*G/G	Akinetic-rigid subtype / Controls	0.115	1.91	0.87-4.17
*G/C		0.046*	0.4	0.16-0.97
*C/C		0.567	1.37	0.49-3.85
*G		0.386	1.32	0.73-2.39

Continuation of the table 2

1	2	3	4	5
*G/G	<45 age at onset / Controls	0.165	2.43	0.79-7.47
*G/C		0.283	0.5	0.15-1.64
*C/C		1.000	0.5	0.06-3.95
*G		0.156	2	0.8-5.03
*G/G	45-60 age at onset / Controls	0.105	1.75	0.93-3.31
*G/C		0.192	0.61	0.31-1.19
*C/C		0.812	0.8	0.29-2.18
*G		0.150	1.46	0.89-2.4
HTR2A (rs6311)				
*A/A	PD cases / Controls	0.559	1.16	0.74-1.83
*A/G		0.510	1.12	0.81-1.55
*G/G		0.288	0.83	0.6 - 1.15
*A *G		0.252	1.15	0.91 - 1.46
*A/A	Akinetic-rigid subtype / Controls	0.198	1.75	0.72 - 4.25
*A/G		0.272	0.64	0.3 - 1.38
*G/G		0.856	1.1	0.54 - 2.24
*A *G		0.684	1.13	0.67 - 1.91
*A/A	Mixed subtype / Controls	0.839	0.81	0.35 - 1.88
*A/G		0.028	1.84	1.07 - 3.15
*G/G		0.074	0.58	0.33 - 1.02
*A		0.220	1.29	0.87 - 1.91
*A/A	45-60 age at onset / Controls	0.129	1.84	0.88 - 3.83
*A/G		0.063	0.52	0.27 - 1.01
*G/G		0.454	1.26	0.7 - 2.28
*A		0.822	1.07	0.69 - 1.66
HTR2C (rs6318)				
*C	PD cases (men) / Controls	0.418	1.41	0.64 - 3.13
*G		0.418	0.71	0.32 - 1.58
*C	Akinetic-rigid subtype (men) / Controls	0.306	2.18	0.41 - 11.55
*G		0.306	0.46	0.09 - 2.44
*C	<45 age at onset (men) / Controls	1	0.57	0.03-10.66
*G		1	1.75	0.09-32.78
*C	45-60 age at onset (men) / Controls	0.031	5.1	1.28 - 20.32
*G		0.031	0.2	0.05 - 0.8
*C/C	PD cases (women) / Controls	0.397	2.09	0.41 - 10.54
*G/C		0.857	0.9	0.44 - 1.86
*G/G		1.000	0.97	0.5 - 1.9
*G		0.354	1.35	0.72 - 2.52
*C/C	Akinetic-rigid subtype (women) / Controls	0.215	5.75	0.56 - 59.5
*G/C		0.025	4.24	1.29 - 13.91
*G/G		0.009	0.19	0.06 - 0.6
*C		0.354	1.35	0.72 - 2.52
*C/C	Mixed subtype (women) / Controls	1	1.12	0.12 - 10.39
*G/C		0.330	0.27	0.04 - 2.07
*G/G		0.216	4.17	0.54 - 31.94
*C		0.038	0.15	0.02 - 1.13
*G		0.038	6.67	0.89 - 50.18
TPH1 (rs1800532)				
*G/G	PD cases / Controls	0.006	1.65	1.16 - 2.35
*G/T		0.160	0.78	0.56 - 1.08
*T/T		0.215	0.75	0.5 - 1.14
*G		0.012	1.36	1.08 - 1.71
*T		0.012	0.74	0.59 - 0.93
*G/G	Tremor-dominant subtype / Controls	0.025	1.8	1.11 - 2.93
*G/T		0.159	0.71	0.45 - 1.13
*T/T		0.471	0.78	0.43 - 1.41
*G		0.055	1.4	1.01 - 1.95
*T		0.055	0.72	0.52 - 1

Nevertheless, according to the literature, the 5-HTTLPR*S/S genotype increases the risk of PD in Italians (26) and in Chinese (22), but not in Norwegians (10). The biallelic meta-analysis performed by Gao L and Gao H. did not reveal the presence of a significant association of the 5-HTTLPR locus with the development of PD (25). Thus, we see contradictory results for the studied polymorphic loci of the serotonin transporter gene 5-HTT, but suggesting that a lower level of expression of this gene may make a certain modifying contribution to the development of PD.

Serotonin receptors are also involved in the serotonergic transmission mechanisms. The rs6296 polymorphic variant of the HTR1B gene is a nucleotide substitution c.861G> C; the rs6296*C allele is associated with a 20% decrease in the average number of serotonin 1B receptors (23). Our analysis did not reveal statistically significant associations with PD in general and with its clinical forms. It was also shown that this polymorphic variant is not associated with the development of PD in two Russian papers earlier (1; 3).

The rs6311 polymorphic variant of the HTR2A gene is a nucleotide substitution --1438G> A in the promoter region of the gene. It is assumed that this variant modulates the promoter activity of 5-HTR2A, which plays a role in neuropsychiatric disorders (24). As a result of our analysis, an association of the rs6311*A/G genotype with a mixed form of PD was revealed (p=0.028). It can also be noted that the frequency of the *A/A genotype and the *A allele is slightly higher in the patient groups compared to the control, but these differences do not reach statistical significance. According to published data, the carriage of the HTR2A*A allele increases the risk of developing PD in Russians (1; 3). There is no association of this locus with the development of PD was found in the samples of Italian patients and patients from the United States (8; 9; 27).

The rs6318 polymorphic variant (nucleotide substitution c.68G> C) of the HTR2C gene located in the Xq24-q28 chromosomal region affects the gene expression: the rs6318*C allele is associated with the formation of a protein with a 2-fold lower affinity for serotonin (14). In our study, women with akinetic-rigid PD were found to have a statistically significant lower frequency of the *G/G genotype (p=0.009) and a higher frequency of the *G/C genotype (p=0.025) compared with the control (Table 2). In men with the onset of the disease from 45 to 60 years, a statistically significant

The end of the table 2

1	2	3	4	5
*G/G	Akinetic-rigid subtype / Controls	0.021	2.44	1.16 - 5.14
*G/T		0.456	0.73	0.35 - 1.52
*T/T		0.164	0.39	0.12 - 1.32
*G		0.197	1.49	0.84 - 2.65
*T		0.197	0.67	0.38 - 1.19
*G/G	<45 age at onset / Controls	0.259	1.77	0.63 - 5
*G/T		0.039	0.3	0.09 - 0.95
*T/T		0.215	2.16	0.76 - 6.12
*T		0.859	1.07	0.53 - 2.17
*G/G	45-60 age at onset / Controls	0.021	1.88	1.11 - 3.19
*G/T		0.439	0.79	0.48 - 1.31
*T/T		0.152	0.58	0.28 - 1.18
*G		0.022	1.55	1.07 - 2.24
*T		0.022	0.64	0.44 - 0.92
*G/G	>60 age at onset / Controls	0.326	1.27	0.79 - 2.03
*G/T		1.000	0.99	0.65 - 1.52
*T/T		0.350	0.75	0.43 - 1.3
*G		0.249	1.2	0.89 - 1.62
5-HTTLPR				
*S/S	PD cases / Controls	0.428	0.82	0.52 - 1.29
*S/L		0.689	1.09	0.74 - 1.62
*L/L		0.711	1.11	0.69 - 1.8
*S		0.437	0.89	0.67 - 1.17
*L		0.437	1.12	0.85 - 1.48
*S/S	Mixed subtype / Controls	1.000	1.02	0.51 - 2.04
*S/L		0.874	0.92	0.49 - 1.72
*L/L		0.842	1.12	0.52 - 2.4
*S		0.910	0.97	0.62 - 1.51
*L		0.910	1.03	0.66 - 1.6
*S/S	Akinetic-rigid subtype / Controls	0.223	1.79	0.73 - 4.36
*S/L		0.078	0.43	0.17 - 1.09
*L/L		0.413	1.51	0.56 - 4.04
*S		0.910	0.97	0.62 - 1.51
*L		0.910	1.03	0.66 - 1.6
*S/S	<45 age at onset / Controls	1.000	0.86	0.23 - 3.26
*S/L		0.245	0.46	0.14 - 1.56
*L/L		0.136	2.88	0.88 - 9.43
*S		0.296	0.61	0.27 - 1.4
*L		0.296	1.65	0.72 - 3.78
*S/S	45-60 age at onset / Controls	0.672	0.78	0.32 - 1.89
*S/L		0.703	1.2	0.56 - 2.57
*L/L		1.000	1.01	0.39 - 2.59
*S		0.785	0.91	0.53 - 1.55
*L		0.785	1.1	0.65 - 1.88
*S/S	>60 age at onset / Controls	0.490	1.29	0.67 - 2.49
*S/L		0.348	0.71	0.38 - 1.32
*L/L		0.697	1.2	0.57 - 2.51
*S		0.912	1.05	0.68 - 1.62
*L		0.912	0.95	0.61 - 1.47

P – p value for two sided fisher exact test; OR - odds ratio, 95%CI - 95% confidence interval; * - p<0,05.

higher frequency of the *C allele (p=0.03) was found in comparison with the control (Table 2). Our data are to a certain extent consistent with the results of a study that showed the presence of a relationship between the HTR2C * C allele and drug-induced parkinsonism in men (20).

Tryptophan hydroxylase (TPH) catalyzes the conversion of tryptophan to 5-hydroxytryptophan (5-HT), being an enzyme that limits the rate of serotonin biosynthesis. The TPH2 gene is located on chromosome 12 (12q21.1); its polymorphic variant rs1800532 is a nucleotide substitution c.218A>C (17). Our analysis revealed in PD patients a statistically significant higher frequency of the *G allele and *G/G genotype: (p=0.012 and p=0.006, respectively), compared with the control (Table 2). Also, in patients with akinetic-rigid form, a statistically significant increase in the frequency of the *G/G genotype (p=0.021) is observed as compared to the control (Table 2). Also, the *G/G genotype and the *G allele are associated with the onset of the disease at the age of 45 to 60 years. Studies devoted to associations of the rs1800532 polymorphic locus of the TPH1 gene with the development of PD have not been found in the literature.

Thus, according to our data, certain polymorphic variants of genes of the serotonergic system contribute to the genetic predisposition to Parkinson's disease and have a modifying effect on the main clinical characteristics (clinical form and age of manifestation). In particular, in the ethnic group of Tatars, an association of the STin2*12 allele of the 5-HTT gene with the development of PD, especially with its mixed form, was found. Also, with the development of PD in general and with its akinetic-rigid form, associations of the rs1800532*G allele and the rs1800532*G/G genotype of the TPH1 gene were established. Associations of certain variants of the HTR1B and HTR2C genes were also revealed with the akinetic-rigid form of PD. As a result of the analysis of the influence of the studied polymorphic variants of genes on the age of PD manifestation, an association of the STin2*12 allele of the 5-HTT gene with a later age of disease development (after 60 years), the rs1800532*G allele of the TPH1 gene, and in men - the rs6318*C allele of the HTR2C gene was found - with the onset of the disease from 45 to 60 years. Analysis of literature data revealed conflicting results of studies of the association of the presented genetic variants with Parkinson's disease in different regions, which may be associated with population differences in the distri-

bution of allele frequencies of the studied genes. Therefore, given the population genetic heterogeneity, it is important to identify polymorphic variants of genes associated with the development of diseases in certain ethnic groups. Such genetic variants can be considered markers of risk or anti-risk of developing multifactorial diseases and used in the examined ethnic groups to diagnose a predisposition to their development.

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VASCULAR DYSFUNCTION FACTORS IN SMOKERS WITH EARLY STAGES OF COPD AND AH

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Relevance. The rapid change in the demographic structure of modern society with a predicted doubling of the proportion of people over 60 years of age in the population by 2050 [14] aims to search for mechanisms that enhance the body's perception of the development of diseases associated with various mechanisms of aging [9]. According to clinical practice data, more than 25% of patients in the older age group have comorbid pathology, a significant contribution to which is made by a combination of cardiovascular diseases and chronic obstructive pulmonary disease (COPD) [3]. One of the hypotheses for the development of the cardiopulmonary continuum associated with aging is the theory of low-grade inflammation with accumulation of circulating pro-inflammatory cytokines, vascular growth factors and vasoconstriction in the blood [4, 5, 12].

Aim of the study. Determine systemic and topical markers of cardiovascular remodeling in individuals with a history of smoking and early stages of arterial hypertension (AH) and COPD by assessing serum levels of growth factors (TGF-β, VEGF, ST-2 protein) and endothelin, as well as duplex scanning of the carotid arteries and strain echocardiography.

Methods. The study included 114 apparently healthy persons 48.8 ± 0.68 years old (men - 55%), 100 of whom are active tobacco smokers with a pack / year index of more than 10 (IHF = 17 ± 2 pack / years). The diagnosis of COPD was established using spirometry before and after the test with bronchodilators. All subjects underwent measurement of blood pressure (BP), duplex scanning of the brachiocephalic arteries (BCA), transthorocal strain echocardiography (strain echocardiography). Laboratory parameters were used to assess the lipid profile (total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL)). The inflammatory potential of blood plasma was investigated by assessing the content of TGFβ-2 ng / ml, VEGF pg / ml, ST2 (1:10 ng / ml, 1:50 ng / ml). To assess the vasoconstrictor potential of blood plasma, the content of endothelin-1 pg / ml (ET-1) was assessed.

Results. COPD was detected in 35% of patients, AH in 45%, 17% of patients with COPD and AH. There was no significant difference in lipid profile indices in the groups. Endothelin-1 values are significantly higher in groups of patients with hypertension, and VEGF in groups with COPD. In BCA in patients with COPD and AH, a significantly greater number of atherosclerotic plaques (ASP) and their total percentage of stenosis were found. Impaired relaxation of the left ventricle was noted in patients with COPD, AH, but more often with a combination of COPD and AH. The mean values of local longitudinal deformity in the basal and medial segments are significantly lower in the group of patients with COPD and AH.

Conclusion. Of the studied systemic markers of cardiovascular remodeling in the early stages of COPD and AH in actively smokers, the most significant determinants are VEGF and ET-1. Despite the absence of differences in the parameters of lipid metabolism between the examined groups, it is in smokers with COPD and AH that more pronounced signs of atherosclerosis in the carotid arteries are present. Also, in the early stages of COPD and AH, violations of local myocardial contractility are observed. Topical changes in vessels of the elastic type and myocardium in smokers with COPD and AH have a relationship in smokers of all groups with ST2 content, in patients with COPD and AH with VEGF levels.

Keywords: smoking, arterial hypertension, chronic obstructive pulmonary disease, endotheliin-1, transforming growth factor TGFβ-2, vasculoendothelial growth factor-VEGF, ST2 protein, cardiovascular remodeling.

The rapid change in the demographic structure of modern society with a predicted doubling of the proportion of people over 60 years of age in the population by 2050 [14] aims to search for mechanisms that enhance the body's perception of the development of diseases associated with various mechanisms of aging [13,9]. According to the data of real clinical practice, more than 25% of patients in the older age group have comorbid pathology, a significant contribution to the presence of which is made by a combination of cardiovascular diseases and COPD [3]. One of the hypotheses for the development of the cardiopulmonary continuum associated with aging is the theory of low-grade inflammation with accumulation of circulating pro-inflammatory cytokines, vascular growth factors, and vasoconstriction in the blood [4,5]. Inflammation of the vascular wall contributes to its remodeling, damage, increased rigidity, and the development of atherosclerosis [1]. According to the dominant concept of preventive medicine, the study of markers of target organ remodeling in persons exposed to risk factors and / or with early stages of chronic non-communicable diseases is of greatest interest.

Materials and methods: The study included 114 conditionally healthy persons 48.8 ± 0.68 years old (55% men) and active tobacco smokers with a pack / year index of more than 10 (IHF = 17 ± 2 pack / years). The control group is conventionally healthy non-smokers (14 people) comparable in age to the main group (48.0 ± 0.66). The study was approved by the independent Interdisciplinary Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education, TSMU, Ministry of Health of Russia. Patients were included in the study after signing an informed consent. The exclusion criteria from the study were any documented chronic non-communicable diseases, obesity. The patients were divided into five groups: group 1 - healthy (control), non-smokers (n = 14), group 2 - conditionally healthy smokers without AH and COPD (n = 37), group 3 - people with AH (n = 28), group 4 - patients with COPD without AH (n = 18), group 5 - patients with a combination of COPD and AH (n = 17). All smokers had a pack / year index over 10 (IRI = 17 ± 2 pack / years). Patients completed questionnaires - mMRC and CAT, data from anamnesis of exacerbations. The diagnosis of COPD was established on the basis of spirometry data performed on a Spirolab III device before and after a test with bronchodilators (FEV1 / FVC <70% and an increase in FEV1 <12% from baseline values). Blood pressure was measured according to GOST 52623.1-2008. To assess the lipid profile, the values of TC,

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Table 1

The content of VEGF, TGF-β2, protein ST2 and ET - 1 in the examined groups

Indicators	Groups				
	1st (n=14)	2st (n=37)	3st (n=28)	4st (n=18)	5st (n=17)
VEGF pg/ml	63.10 (0-111.11)	71.8 (40.01-96.05)	107.27 (75.81-164.47)	150.09 (112.62-198.94)* (p=0.043)	210.31 (121.99-243.77)*' *(p=0.002) '(p=0.001)
Endothelin 1 pg/ml	36.46 (30.31-43.51	49.61 (35.39-67.98)	60.18 (37.37-82.84)* (p=0.044)	59.78 (47.81-84.94)	78.19 (72.16-85.58)* (p=0.02)

*- differences are significant in relation to the group of healthy people (group 1), '- differences are significant in relation to the group of smokers without hypertension (group 2)

TG, HDL and LDL were used. The inflammatory potential of blood plasma was assessed using TGFβ-2 ng / ml, VEGF pg / ml, ST2 (1:10 ng / ml, 1:50 ng / ml). To assess the vasoconstrictor potential of blood plasma, the content of ET-1 pg / m was determined. All patients underwent duplex BCA scanning and transthorocal strain-echocardiography using a Vivid E9 device from GE (USA). The calculation of the degree of stenosis of the carotid arteries was carried out according to the ECST method in terms of diameter. The severity of BCA atherosclerotic lesions was assessed by the number of ASPs and the amount of stenoses as a percentage. Left ventricular diastolic dysfunction (LVDD) was determined by assessing transmitral flow, IVS excursion, left atrial volume, and tricuspid regurgitation. In order to assess the deformation of the left ventricular myocardium, the parameters of the mean values of deformity in the basal (SB), medial (SM) and apical segments (CA) were analyzed. Statistical analysis was performed using Statistica 10.0 software (StatSoft Inc., USA).

Results and discussion. According to spirometry data, 35 (35%) of the examined for the first time were diagnosed with COPD, (FEV1- 86.4 ± 3.3% should) of the 1st degree. According to the questionnaires - mMRC, CAT and the frequency of exacerbations, all patients with COPD were assigned to the group with a low number of symptoms and a low risk of exacerbations (group A). AH was detected in 45 (45%) patients. Systolic blood pressure in hypertension was 145.23 ± 1.1 mm Hg, diastolic blood pressure - 80.88 ± 0.63 mm Hg (p <0.05 in relation to persons without hypertension), i.e. e. AG of 1 degree. In 17 patients with COPD, hypertension was established, that is, half of the patients with COPD had hypertension comorbidity. According to the results of laboratory studies, there are no differences in the content of TGF-β2 and ST2 (1:10 ng / ml, 1:50 and ng / ml) between all 5 groups (p = 0.3). At the same time, the VEGF content was significantly higher in the groups of patients with COPD, regardless of the presence of hypertension in relation to the 1st group (p = 0.043, p = 0.002) and in the 5th group of patients, in relation to the group of smokers. without AH (p = 0.001). The level of ET-1, which is one of the most powerful endogenous vasoconstrictors, was higher in smokers with hypertension and in group 5 relative to group 1 (p = 0.044 and p = 0.02, respectively). In other words, markers of the "aging" cell phenotype - TGF-β2 and ST2 protein associated with the activation of proinflammatory nuclear factor (NF-κB) [10,8] turned out to be insignificant for individuals with early stages of COPD and AH. At the same time, for COPD, the highest value was shown by an increase in the content of VEGF, and for patients with hypertension, ET-1 (Table 1). According to echocardiography, none of the examined patients showed left ventricular (LV) myocardial hypertrophy, dilatation of the heart chambers, and decreased systolic function of the ventricles. Accordingly, the patients with hypertension included in the study had stage I of the disease. LVDV type I was observed in all groups of smokers with different frequency and significantly more often in the 5th group of patients (χ^2 = 11.5; p = 0.009), in the 1st group LV diastolic function was normal. Thus, it can be assumed that in smokers with COPD and AH in the initial stages, there is a violation of the elastic properties of the myocardium. Global longitudinal LV deformity was within the standard values in patients of all groups. The method of strain-echocardiography revealed a decrease in the local longitudinal deformity of the LV in the basal and medial segments, significantly more common in patients with COPD and AH in relation to group 1 (p = 0.017 and p = 0.038), as well as impaired LV relaxation processes in the group of smokers without COPD and AH (p <0.05), which indicates a decrease in the contractile ability of myocardial fibers in smokers with COPD and AH, primarily in the basal and medial segments (Table 2). Perhaps the early signs of myocardial deformation are associated with the activation of the synthesis of ET-1 and VEGF, which are involved in the processes of elastin degradation, changes in the microenvironment of cardiomyocytes with the accumulation of profibrogenic potential, established in our study [10,7]. In the group of patients with COPD and AH, a significant dependence of VEGF parameters with data on mean longitudinal LV deformity in the basal segments and BAP (rxy / ρ = 0.44 and 0.45, respectively) and ET-1 with BAP (rxy / ρ = 0,466). Smoking is one of the significant factors in the development of dyslipidemia and atherosclerosis [1]. In our study, there were no significant differences in lipid metabolism indicators in all groups of the examined. However, ABPs were absent in the 1st group. At the same time, smokers of all groups had ABP and accounted for less than 50% of the vessel lumen overlap. When assessing the

Table 2

Average value of local longitudinal deformity in LV departments

LV myocardial levels	Groups				
	1st (n=14)	2st (n=37)	3st (n=28)	4st (n=18)	5st (n=17)
middle basal strain	-18.83	-17.83	-16.41	-17.83	-15.33 (p=0.017)*
middle medial strain	-22.50	-20.50	-19.66	-19.50	-19.25 (p=0.038)*

Note: * - the differences are statistically significant compared to the 1st group (p <0.05)

total degree of stenosis and the prevalence of atherosclerosis by the number of ASP, the indicators were significantly higher in the 5th group in relation to the group of conventionally healthy smokers (z = 2.51; p = 0.01; z = 2.53; p = 0, 01). Obviously, smoking has an independent proatherogenic effect due to the activation of oxidative stress, a decrease in the activity of the nuclear transcription factor of antioxidants NF-κB, and an increase in the proinflammatory potential of blood plasma [6]. Indeed, according to our data, in all groups of smokers, a significant dependence of the prevalence of atherosclerosis on ST2 indicators was revealed, without significant intergroup differences (rxy / ρ in groups 2-5, respectively: 0.621, 0.492, 0.866, 0.457). The comorbidity of COPD and AH contributes to more pronounced endothelial damage, however, despite similar pathological changes in patients with similar CI, their different severity is noted (the presence of ASB, LVPD, impaired LV relaxation), which is determined by both metabolic cellular dysfunction and genetic factors requiring further study.

Conclusion. Smoking is one of the leading factors in the development of chronic diseases, making the most significant contribution to the morbidity and mortality of the population. COPD and AH, which form pulmonary-cardiac comorbidity in almost 50% of cases, are among the early diseases included in the CNID cohort [12]. Among the early markers of the cardiopulmonary continuum, an increase in the level of VEGF is important for COPD, for hypertension - ET-1 and, accordingly, their combination. In patients with early stages of COPD and AH, there are signs of myocardial damage in the form of a decrease in the mean values of local longitudinal LV strain in the basal and medial segments, which directly depends on the ET-1 content and the VEGF level. Slow inflammation contributes to the development of atherosclerosis during smoking, as evidenced by a direct relationship between its prevalence and the ST2 protein content. Obviously, understanding the signaling and cellular mechanisms of the development of the chain of events at the early stages of the cardiopulmonary continuum will allow us to approach the search for new therapeutic targets for interrupting its progression.

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EFFECT OF HYPOTHERMIA ON THE RAT CEREBRAL MICROVASCULAR REACTIONS UNDER CONDITIONS OF HEMODYNAMIC STABILITY AND BLOOD LOSS

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Accidental hypothermia commonly goes with trauma, which is often accompanied by hemorrhage. The research studies the reaction of microcirculation of the cerebral cortex of rats with hemodynamic stability and the blood loss, with continuous exposure to decreasing body temperature till to the hypothermal arrest of the animal's breathing. Video microscopy of cerebral pial arterioles during the cooling of animals in water with a temperature of 12-130C was carried out on anasthezed rats (uretanum, i/ p, 1000 mg/kg). The results were obtained that in the group of animals without hemorrhage, the cooling led to an initial short-term vasodilation and subsequent vasoconstriction up to 10-20% of the norm. In the group of animals with a pre-caused by hemorrhage, the narrowing of the vessels was 20% at the normothermia and intensified during the animal immersion in water on 35% of the initial state of the vessels.

However, the functional state of the animal during blood loss and the subsequent cooling slightly differed from the normovolemic state of the body under hypothermic influence.

Keywords: hypothermia; blood loss; cerebral microarterioles; video microscopy; rats.

Introduction. Overall study of the mechanisms of hypothermal states is one of the current problems of modern medicine. Benefits and complications after using hypothermia with different kinds of surgical interventions (induced hypothermia) and exposure to low environmental temperature on the body (accidental hypothermia) are discussed. The induced hypothermic effect on the body is actively used in clinical practice during heart operations, for the treatment of patients with hypoxic, ischemic damage after brain strokes, in neonatal encephalopathy and spinal cord injury [7, 12, 14]. The study of the body's reactions to the unintentional cold effect and the methods to escape from this state are relevant not only in the conditions of the Far North and Siberia [3, 5, 17].

Accidental or unintentional hypothermia in a homoeothermic organism is classified into the following degrees: mild (32-35℃), moderate (28-32℃), severe (28-20℃) and deep or profound (<20℃) [1, 5, 12, 17, 19]. The symptoms and clinical manifestations in different degrees of hypothermia are shown in Table 1. Accidental hypothermia together with trauma are often accompanied by hemorrhage. Central hypovolemia leads to hypoperfusion of tissues and hypoxia, including the brain. Acute compensatory mechanisms involved in maintaining perfusion pressure and blood flow to vital organs influence an the increase in heart rate frequency and systemic vasoconstriction [9]. Low environmental temperatures may affect the ability of the body's cardiovascular system to suffiently react to hypovolemia, i.e. tolerance to hemorrhage can be intensified or reduced. In some clinical studies [6, 20], it was revealed that the decrease in body temperature below 35 is a factor predisposing to more severe complications and increased mortality. It is reported [15] that up to 66% of patients entering emergency care for serious injury, suffer from accidental undercooling.

Most clinical studies on hypothermia and circulatory disorders [8, 22] are devoted to the positive use of the temperature lowering of the body or certain organs during surgical interventions, i.e. the use of induced hypothermia and different approaches to the recovery of the body after it. In some experimental models of hemorrhagic shock, moderate hypothermia increases the survival rate of animals [11, 14, 18] by reducing the body's oxygen demand and is considered as a possible therapy for traumatic bleeding. It should be noted that the number of experimental studies on the effect of low temperature on hemodynamics in conditions of hypovolemia is small. For example, it was shown [21] that local hy

Table 1

Symptoms and clinical manifestations at different degrees of hypothermic exposure

Symptoms	Hypothermia		
	Mild	Moderate	Deep
	32-35 °C	28-32 °C	<28 °C
Neuro-muscular	ataxia shivering	stiffness of muscles and joints the disappearance of tremors	muscle contraction loss of reflexes and the ability to voluntary movements
Neurological	confusion apathy	limited consciousness	loss of the corneal reflex coma
Cardiovascular	tachycardia increased cardiac output hypertension peripheral vasoconstriction	bradycardia reduction of cardiac output On the ECG: - widening of QRS complex - inversion of the T-wave - QT segment prolongation - wave J (Osborne) Atrial fibrillation	reducing system pressure progressive bradycardia asystole entricular fibrillation
Respiratory	tachypnae shift of HbO2 curve to the left	bradypnae bronchial constriction	lactic acidosis respiratory arrest

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pothermia does not have a harmful effect on dogs during hemorrhage (20% of the blood volume) and improves the perfusion of the microvessels of the stomach and oral cavity and their oxygenation. Another study revealed [10] microvascular changes in the sublingual region, in the intestinal villi and in the renal cortex in hemorrhagic shock in sheep with 340C hypothermia.

However, the effect of systemic hypothermia in severe hemorrhagic shock on cerebral hemodynamics has not been studied. Since the results of the literature analysis are quite contradictory and there are no data on the effect of hypothermia at different stages of its development during hemorrhagic shock, an experimental work was carried out, the purpose of which was to study the cerebral microvascular circulation of the rats subjected to hemorrhagic shock, with a continuous decrease in body temperature up to hypothermic respiratory arrest of the animal.

Materials and Methods. The experiments were carried out on anesthetized (urethane, i/p, 1000 mg/kg) male Wistar rats weighing 300-320 g. The study was conducted on animals from the biological collection "Collection of laboratory mammals of different taxonomic affiliation" of the I.P.Pavlov Institute of Physiology of the Russian Academy of Sciences in the agreement with the basic norms and rules of biomedical ethics (European Community Council Directives 86/609/EEC).

The animals were subjected to the following surgical procedures: to study the pial microvessels, a 7x5mm trepanation hole was made in the parietal bones, the dura mater was removed. A catheter was inserted into the left femoral artery for direct measurement of blood pressure, and a similar catheter was inserted into the right femoral artery for blood withdrawal. During the operations, the rats maintained a rectal temperature of 37-380C with a heating pad. Then the animals were randomly divided into 2 groups: the first (n=6) – the control group, in which the animals were cooled without blood loss, and the second (n=11) – with a preliminary withdrawal of blood (the features are described below).

Rats of both groups were subjected to gradually developing immersion hypothermia in water with a temperature of 12-130C until hypothermic respiratory arrest. During cooling, the animals were fixed in a special device (dental, ear holders, and soft fixation of the limbs) in a shallow bathtub so that the body was immersed in water, and the head was above water. The arterial blood of animals from the 2nd group, was taken at the rate of 2.1 ml per 100 g of animal weight or 35% of the volume of circulating blood, i.e., from a rat with a weight of 300 g, the total blood intake was 6.3 ml. The blood sampling time was ~20 min, the average withdrawal rate was 0.3 ml/ min., while blood pressure was maintained at the level of 40 mm Hg before cooling.

Visualization and monitoring of the pial microvascular circulation was carried out with the help of microscopy system, which included a LUMAM-1 microscope with a contact dark-field lens and an ACUMEN AiP-B84A color video camera. The resulting image was processed on the computer by the Pinnacle Studio software package. The measurements were calibrated using a standard object-micrometer (the division price is 10 microns).

During the experiment, the reactions of pial arteries with an initial diameter of 10 up to 50 microns to progressively increasing hypothermia were studied. The diameter of the microvessels was measured at 50 different areas of the arteries in the control group and at 100 areas in the 2nd group at twelve stages of the experiment: before the start of exposure, at rectal temperature 36, 35, 32, 30, 28, 26, 24, 22, 20, 18 0C and when the animal stops breathing. The ECG, mean blood pressure and respiratory rate were continuously recorded. With a help of the E-154 ADC (L-Card, Russia) analog signals were digitized and recorded.

The STATISTICA 6.0 software package was used for statistical data processing, the reliability of differences within each group was evaluated using the nonparametric Wilcoxon criterion, the nonparametric Mann-Whitney criterion was used to identify the differences between the groups, the level of reliability of differences was $p<0.05$. All experimental data are presented as the average ± error of the average (M±m).

Results and Discussion. The using of immersion hypothermia in these experiments allowed us to observe changes in the work of the cardiovascular and respiratory systems during cooling of the body in a fairly short time up to hypothermic respiratory arrest.

After surgery, before the start of cooling, the rectal temperature (Tr) in rats of both groups did not differ statistically and was 36.7±0.110C in the control group, 37.14±0.150C in the 2nd group before blood withdrawal, 36.7±0.170C after withdrawal. Thus, the cooling of the animals began with almost the same rectal temperature. Immersion of the animals in water led to a decrease in body temperature and, eventually, to hypothermic respiratory arrest. The temperature threshold for rats breath stop is a stable parameter. Respiratory arrest in rats occurs at Tr in the range of 12-190C [16], and spontaneous restoration of respiration in conditions of deep hypothermia is possible only if the animal is removed from the water and warmed up. The stoppage of respiratory movements in the control group was recorded at Tr 13.1±0.330C, in the 2nd group-at 15.12±0.80C ($p<0.05$). The cooling time in the 1st group was 183±2 min, in the 2nd-160±22 min ($p>0.05$). The average rate of immersion cooling of animals in different groups did not significantly differ: in the control - 0.128±0.010C/min, in the group with preliminary blood withdrawal – 0.158±0.0170C/min.

Table 2 shows the main physiological parameters of animals of both groups before cooling and after hypothermic respiratory arrest. It should be noted that the physiological parameters before cooling of group 2 rats after withdrawal 35% of the circulating blood volume significantly differed from the normal parameters.

The changes in physiological parameters during the cooling of animals show

Table 2

Physiological parameters of rats in different series of the experiment during normothermia and after hypothermic respiratory arrest

Parametres	Before the start of exposure		After blood withdrawal	After breath stop	
	control	2-nd group	2-nd group	control	2-nd group
Rectal themperatire, ^{0}C	36.7±0.11	37.14±0.15	36.7±0.17	13.1±0.33	15.12±0.8*
Mean arterial pressure, Hg mm	99.7±2.49	95.5±5.57	38.7±1.65 †††	28.3±1.8	18.2±1.43***
Heart rate, min^{-1}	432±5.8	442.3±8.99	393.8±9.67 ††	36.7±1.8	36.6±7.56
Breath rate, min^{-1}	104±11.7	104.4±7.99	89.7±6.86 †	0	0

* $p<0.05$, * * * $p<0.001$ between the parameters of the control group and the second group after breath stop. † $p<0.05$; † † $p<0.01$; † † † $p<0.001$ between the parameters of group 2 before exposure and after blood withdrawal.

at Figure 1. The cooling of the animals was accompanied by the development of a response from all organs and systems. At the beginning of hypothermia exposure, a slight increase in mean arterial blood pressure (MAP) was observed in the control group rats with normovolemia, probably [1, 2], due to an increase in the level of metabolism and norepinephrine-mediated peripheral vasoconstriction. In this study, it was shown that with a decrease in Tr below 340C, blood pressure remained quite high (at the normal level) and decreased only after 200C. The breath rate (BR) also increased ($p<0.001$) at the beginning of cooling. This is a typical reaction of the external respiration function, which is characterized by an increase in pulmonary ventilation, frequency and depth of breathing [2]. Then, after reaching the degree of moderate hypothermia, a consistent suppression of the functional state of the body was observed, and BR gradually decreased until respiratory arrest. It was reported [4] that when rats are cooled to a rectal temperature of 310 C, HR decreases slightly, but the results of the standard deviation and the coefficient of variation increase. In our work, a significant decrease in HR was recorded already at a temperature of 320C (by 25%). At temperatures in the range of 32-200C, HR decreased by 3 times, and at the time of respiratory arrest it was 36.7±1.8 beats/min. It is shown [18] that cooling is accompanied by a decrease in the impact volume, along with this, oxygen consumption also decreases.

In the experiment blood loss in rats led to a decrease in blood pressure to the level of 40 mm Hg, which was maintained before the start of immersion. After the start of cooling, MAP increased significantly (up to 55-63 mm Hg) and was on such a plateau, decreasing only in a state of deep hypothermia. In this regard, it is necessary to take into account that with hypothermia, the blood pressure indicator may not correspond to the actual volume of circulating blood and be significantly higher. HR in the 2nd group decreased throughout the entire cooling and did not differ statistically compared to the control group, and BR decreased immediately after the start of cooling, and after reaching Tr 280C, a further decrease in BR was comparable to the indicators in the control. According to [18], hypothermia also suppressed HR and increased MAP in hemorrhagic shock. It is assumed that a lower HR in hypothermia reduces the myocardial oxygen demand, and a higher blood pressure can improve tissue perfusion, which leads to a decrease in metabolic acidosis. The study [13] showed that mild hypothermia (330C) after experimental cardiac arrest improves cerebral microcirculatory and reduces the increased coefficient of oxygen extraction by the brain. Perhaps this provides an additional mechanism for protecting the brain during hypothermia.

Polytrauma is characterized by pathogenesis links called the "triad of death": hypothermia, azidosis and coagulopathy, and is a complex vicious circle that is observed in patients with severe trauma and hemorrhagic shock [6, 18].

The importance of body temperature correction and maintaining normothermy is emphasized in the modern protocol for the treatment of patients with polytrauma. However, most experimental studies [8, 18, 23] have shown the benefit of therapeutic hypothermia in hemorrhagic shock. It is proved that moderate hypothermia at a temperature of 33°C decreases coagulation,

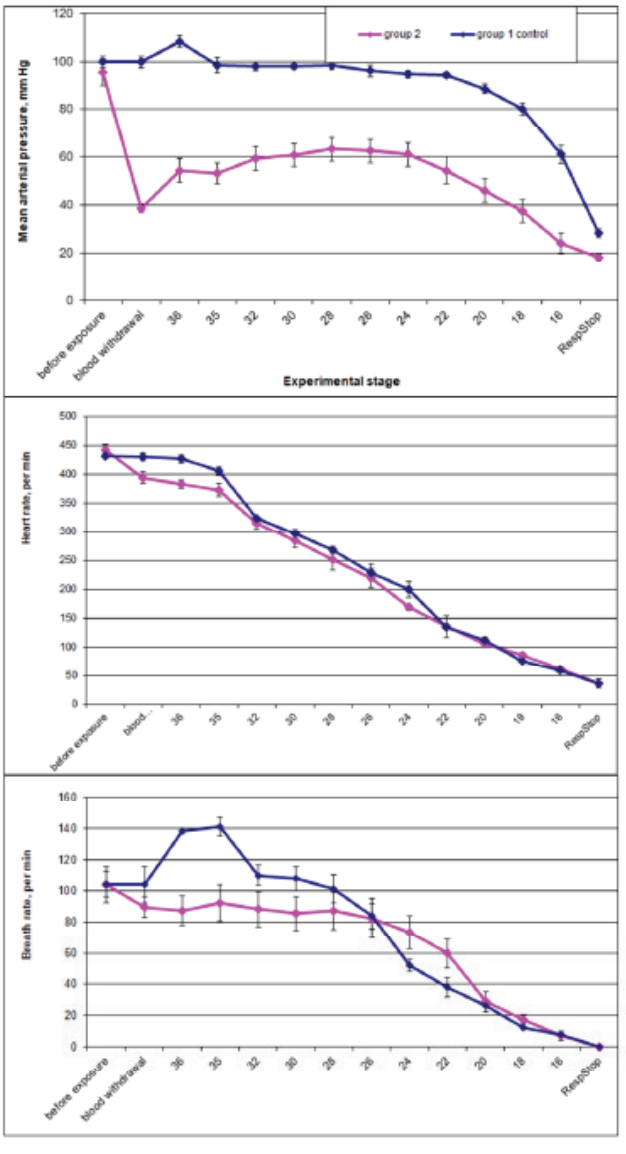

Fig. 1. Blood pressure, heart rate and breath rate in rats during cooling in water 12^{0}C

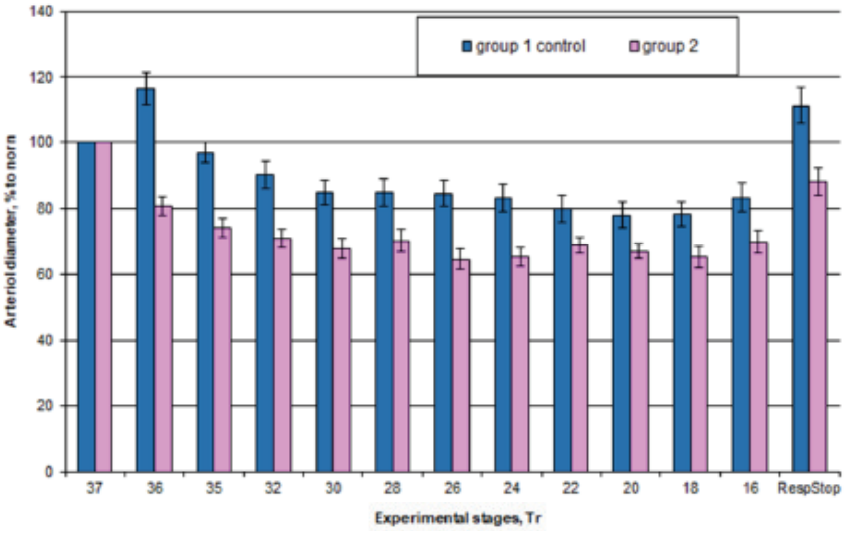

Fig. 2. Changes in the diameter of the pial arteries of rats with developing hypothermia

but, nevertheless, prolongs the survival of rats after hemorrhagic shock and resuscitation. Hypothermia reduces the consequences of secondary brain damage due to several mechanisms, including a decrease in excitotoxicity, oxidative stress, apoptosis, autophagy and inflammation [11, 20]. It was shown [23] that after cooling to Tr 340C for 2 hours after hemorrhagic shock (blood withdrawal of 3 ml/100 g of the animal and subsequent maintenance of blood pressure of 40 mm Hg), the survival of rats improves compared to the same cooling of animals for 12 hours.

Figure 2 shows the change in the diameter of the pial arteries at various stages of the experiment. For 100% (norm) we took the diameter of the cerebral vessels before the start of the effects (in the 1st group-before the immersion cooling, in the 2nd – before blood withdrawal and immersion). In both series of the experiment, about 4-5 minutes passed from the beginning of the animal's immersion in water to reaching the Tr mark of 360C. During this time, the diameter of the vessels in the control significantly increased (by 16.5±4.8%), whereas in the 2nd group, vasoconstriction was observed after blood withdrawal. The diameter of the arteries in group 2 after blood collection was 86.9±3.1% of the norm, and after the start of cooling – 81.0±2.8%. Throughout the experiment, significant statistical differences in the diameter of the arteries in rats between the groups were observed.

It was found that in the control group, after initial vasodilation at a rectal temperature of 360C, subsequent vasoconstriction was observed at a temperature of 350C. At the area of temperature decrease from 30 to 200C, the diameter of the vessels did not significantly change and ranged from 80 to 85% of the norm. In the same temperature range in the group with preliminary blood loss, the diameter of the arterioles ranged from 71 to 65% of the norm. Respiratory arrest is characterized by vasodilation, which is almost comparable to the state of the vessels at the beginning of cooling for both the 1st and 2nd groups.

Conclusion. The study showed changes in vital indicators of the body, such as heart rate, blood pressure and breath rate, during cooling in water 12-130C up to complete hypothermic respiratory arrest. Pre-induced hemorrhage in rats (up to 35% of the circulating blood volume) made worse these physiological parameters to some extent, leading to an increase in the temperature threshold for respiratory arrest. Disorders of cerebral blood flow during hypothermic exposure were assessed by the diameter of the pial vessels change of the rat brain. In hypothermia, after the initial vasodilation by 16%, vasoconstriction by 10-20% followed at the beginning of cooling. When modeling hemorrhagic shock, vasoconstriction during normothermia was 20% and increased during immersion of the animal in water to 35% of the initial state of the vessels. Nevertheless, the functional state of the animal during blood loss and subsequent cooling slightly differed from the normovolemic state of the body under hypothermic exposure.

Thus, the conducted experimental work showed that additional cooling of the body does not make the state of cerebral microcirculation worse in severe blood loss in rats. Hemorrhage with subsequent strong cooling does not lead to significantly greater disorders of cerebral blood flow than in conditions of hypothermia alone. It can be assumed that in extreme conditions, there is no need to focus on warming the body in order to provide emergency care for hemorrhagic shock, since all indicators function at a sufficient level even in conditions of deep hypothermia.

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EVALUATION OF THE MUTAGENIC PROPERTIES OF THE FUROCOUMARIN EXTRACT FROM THE CELL CULTURE OF *CONIUM MACULATUM L.*

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The study presents data on the genotoxicity study of standardized by the amount and ratio of furocoumarins extract from the cell culture of Conium maculatum. The extract containing furocoumarins in the ratio: isopimpinellin - 42.97%, bergapten - 35.18% and xanthotoxin - 15.41%, in experiments demonstrated pronounced antithrombotic, myelo- and hepatoprotective effects under conditions of chemotherapeutic aggression - the introduction of the maximum tolerated dose of cisplatin. The extract is positioned as a promising herbal remedy for the relief of chemotherapeutic complications. The need to assess the genotoxicity of the presented composition and ratio of furocoumarins is primarily determined by ambiguous information on their effect on the genetic apparatus in various test systems. In vivo, the effect of a single and course intragastric administration of a standardized extract of a cell culture of Conium maculatum containing the amount of furocoumarins (isopimpinellin - 42.97%, bergapten - 35.18% and xanthotoxin - 15.41%), at doses of 30 and 150 mg / kg was studied. A cytogenetic analysis of the metaphase plates of the bone marrow of male and female CBA mice was carried out taking into account the number of damaged metaphases, the number of aberrant chromosomes, single fragments of chromosomes and polyploid cells in % per 100 cells. A 1% starch suspension was used as a negative control. Prior to the studies on D. Melanogaster, the dose of the investigated furocoumarin extract was determined by the survival rate of P1 females (wild type), which, at the maximum dose used, should not be less than 50%. The mutagenic activity of the extract was studied by somatic recombination (mosaicism) in D. melanogaster using marker mutations yellow and singed on 1000 females at a dose of 150 mg / kg. Thus, it was determined that the use of a Conium maculatum cell culture extract containing furocoumarins in the ratio: isopimpinellin - 42.97%, bergapten - 35.18%, and xanthotoxin - 15.41%, does not induce genetic damage in CBA mice and D. melanogaster, which is one of the objective criteria for the safety of its use. The results obtained determine the possible prospects for continuing research in terms of developing a new herbal medicinal product.

Keywords: chromosome aberrations, recombination, genotoxicity, furocoumarins.

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A wide range of pharmacological effects of pure furocoumarins and their combinations (antioxidant, anti-inflammatory, antiproliferative, gonadotropic and choleretic effects, the ability to modulate various biochemical pathways, use in dermatology, etc.), draws attention to this group of substances as a potential herbal medicines [7 , 11, 12, 13, 14]. At the same time, their chemical diversity, and more than 50 natural furocoumarins (FC) and a significant number of their combinations are known, when obtained from plant raw materials, complicates the search for the target efficiency of substances [8, 10]. In this regard, it seems promising to obtain furocoumarins standardized in terms of quantity and ratio from cell cultures of *Conium maculatum* (hemlock spotted). It is from the extract from *Conium maculatum* cell cultures containing furocoumarins (isopimpinellin - 42.97%, bergapten - 35.18% and xanthotoxin - 15.41%) that data on pronounced antithrombotic, myelo- and hepatoprotective effects have been obtained, which determines the prospects for its use in conditions of chemotherapeutic aggression [5]. At the same time, it is known that, depending on the chemical structure of the FC molecule, on the number and nature of substituent radicals in the compound, on the arrangement of cyclic systems (angular or linear - the bond of the furan ring with coumarin), as well as on the combinations and concentrations, a number of FCs have genotoxic effects [1, 6, 10, 15]. However, information on genotoxicity is not of a systemic nature, since the results of studies conducted *in vivo* or *in vitro* vary depending on the test systems used, doses and duration of use [7, 15]. The study of the genotoxicity of compounds, including those of plant origin, is the most important preventive measure to identify substances potentially dangerous to humans and their heredity [1].

Based on this, the aim of this work was to study the genotoxicity of the hemlock spotted cell culture extract in vivo in the bone marrow cells of CBA mice and somatic cells of *D. melanogaster*.

Material and methods. The study was carried out on 40 male and female CBA mice weighing 18-25 g. The animals were divided into groups: 1st group - males (n = 5) control for a single injection; Group 2 - males (n = 5), study of the effect of the maximum dose of the FC extract of 150 mg / kg with a single injection; Group 3 - males (n = 5) study of the therapeutic dose of FC 30 mg / kg with a single administration; 4th and 5th groups, males and females (n = 5), who received FC extract 30 mg / kg for 5 days; 6 and 7 groups - males and females (= 5) controls for groups 4 and 5; Group 8 positive control - a single injection of cyclophosphamide (CP) at a dose of 20 mg / kg. CP is a classic mutagen and is used in laboratory studies [3]. The choice of the dose of the extract was determined by the literature data, as well as the results of preliminary studies [5]. Control animals under similar conditions were injected with 1% starch suspension in an equivalent volume. All manipulations with animals were reviewed by the local commission for the care and use of animals for compliance with regulatory acts.

The extract was obtained by the method described in the patent of the Russian Federation No. 2713118 [2]. The qualitative composition of FC was determined using gas chromatography — mass spectrometry (GC-MS) and thin layer chromatography (TLC), quantitative content and purity were determined by high performance liquid chromatography (HPLC). The standard samples of bergapten, xanthotoxin, and isopimpinellin were used (Sigma-Aldrich, USA).

Analysis of chromosomal aberrations in metaphases in vivo takes into account factors such as absorption, distribution, metabolism and excretion, which makes it highly informative and accurate [3]. Bone marrow (BM) chromosome preparations were prepared according to the modified Ford method, stained with azure II-eosin for 40 minutes. Cytogenetic parameters (the number of damaged metaphases, the number of aberrant chromosomes, polyploid cells in% per 100 cells) were assessed 24 hours after the last injection. The analysis included 100 BM metaphase plates from one animal (per group of 500). Statistical analysis was performed using StatPlus Pro [Build 6.7.1.0.]. For each sample, the arithmetic mean (X) and the arithmetic mean error (m) were calculated. The nonparametric Mann-Whitney test was used. The significance level of the criteria was set equal to 1% and 5%.

The classical method of testing for mutagenicity is the method of somatic recombination (mosaicism) in *D. melanogaster* using the *yellow (y)* and *singed (sn)* marker mutations (SMART test) [3]. At the same time, marker recessive mutations of the parents are in a homozygous state, the parents have the corresponding phenotype - yellow females and curly males. When such individuals are crossed in the offspring, the genes pass in the ysn + / y + sn transposition, and due to heterozygosity they do not appear phenotypically, the females in this offspring have a gray body and wings, the body is covered with normal hairs and bristles. When disorders appear in the chromosome, in particular under the influence of various external influences, the genes go into a homozygous state, which leads to a phenotypic change in the shape and color of the bristles. It is believed that the main mechanism for the occurrence of spots is somatic crossing over, the frequency of which can serve as a measure of the effect of mutagens. Depending on the place of chromatid rupture in females, spots of various types appear on the body. The gap between the *sn* gene and the centromere results in the formation of a *yellow-singed* double spot. The gap between the *sn* and *y* genes, as well as double crossing over lead to the appearance of single spots (*y*) and (*sn*), respectively [9].

After 48 hours, the investigated FC extract was added to the nutrient medium, where the eggs were already laid, at a dose of 150 mg / kg. After 9-10 days, the hatched females were examined under a stereoscopic microscope.

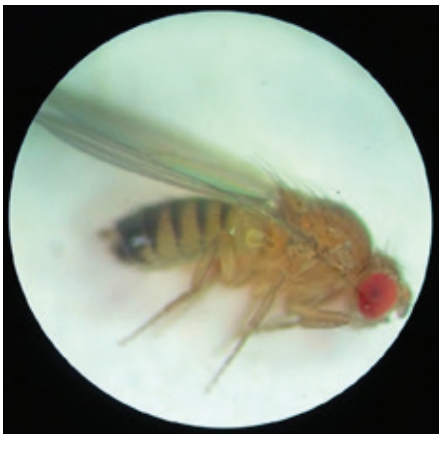
The choice of doses for *D. melanogaster* differs from the choice of doses for mammals. The rationale for the dose used is to conduct a study on the survival of P1 females (wild type), which, at the maximum dose used, should not be less than 50%. [3]. FC doses of 50, 100, and 150 mg / kg were used. In test tubes with a dose of 150 mg / kg, the survival rate of females was more than 50% compared to the control, which indicates the possibility of testing it in this experiment. The significance of differences for the rate of occurrence of females with mutations during statistical processing was assessed using the χ^2 test (chi-square) with Yeits's correction, which is used only for 2 × 2 tables. For a 5% significance level, the critical value of χ^2 is 3.84 [4].

Results and discussion. In animals of the 2nd group, with an exposure of 24 hours, 1.80 ± 0.73% of aberrant metaphases were revealed. All structural changes in chromosomes were single fragments and gaps. The number of aberrations did not change in comparison with the same indicator in the control (group 1). In group 3, 1.00 ± 0.32% of cells with chromosome aberrations were found. Structural disorders are represented by single fragments and gaps, which corresponds to the values of the control. In the 8th group - positive control - the appearance of metaphase plates with aberrant chromosomes is induced in BM, and the proportion of damaged metaphases is 13.4 times higher than that of the 2nd group and 24 times higher than those of the 3rd group. The proportion of damaged metaphases in the 8th group is significantly higher than that of the 1st group. The number of aberrant chromosomes in group 8 reached 45.80 ± 3.76%. Damage was represented by single and paired fragments, exchange violations, gaps, the content of which significantly exceeded those of the 1st, 2nd and 3rd groups.

After the course of administration of FC in the BM of males (4th group) 2.75 ± 0.63% of aberrant metaphases were detected, in females (5th group) the same indicator was 2.20 ± 0.37%. Chromo-

a

b



Phenotypic manifestation of the singed mutation singed bristle - A; D. *melanogaster* wild type, normal bristles - B.

some aberrations were represented by single fragments and gaps, the number of which corresponded to the level of control values.

Thus, a single and course intragastric administration of an extract of a cell culture of *Conium maculatum* to male and female CBA mice does not change the proportion of damaged BMCs, does not increase the number of aberrant chromosomes and gaps in comparison with the negative control, i.e. does not have a clastogenic effect on chromosomes.

As a part of the study of the mutagenic properties of FC in vivo, the SMART test for *D. melanogaster* was carried out.

Analysis of females that flew out showed that the extract of hemlock did not induce the appearance of mutant spots in them, compared with those in the control. For 1000 examined females, 5 individuals with a singed seta "*sn*" were identified, the χ^2 value was 0.51 (<3.84), which is not a statistically significant change. Females bearing single "*y*" spots and double "*sn*" spots were not identified. Thus, FC at a dose of 150 mg / kg is not genotoxic in this test, does not increase the number of recombination and mutational events in somatic cells of Drosophila larvae after exposure.

In this study was used an extract from a mixture of furocoumarins, most of which is represented by isopimpinellin - 42.97%. The presence of two methoxy groups in the molecule leads to the loss of photosensitizing activity [6]. In the literature, DNA damage by furocoumarins is associated with a photosensitizing effect, because under the influence of light DNA covalent bonds with intermolecular complexes and the spatial structure of nucleic acids changes, and photoinactivation of enzymes occurs due to the oxidation of amino acid residues [6, 16]. The predominance of isopimpinellin, which does not have photosensitizing activity, in the studied extract, and the minimal content of the other two compounds, probably led to the absence of genotoxic action.

The genotoxic properties of plant compounds can undoubtedly depend on the method of obtaining plant substances, the extraction of their components [1]. The investigated extract was obtained according to the original method, its composition is standardized, which can provide the content of the indicated substances in the appropriate amount, and hence the stable effects from its use [2].

Based on the results of the study, it can be concluded that a single intragastric administration of FC at doses of 30 and 150 mg / kg, as well as a course administration of FC to male and female CBA mice for 5 days (30 mg / kg) does not affect the level cytogenetic abnormalities in the BM. In the test system of somatic recombination (mosaicism), when FC was added to the nutrient medium at a dose of 150 mg / kg, no changes in the frequency of appearance of mutant bristles and spots on the body and head were found in *D. melanogaster* when using yellow and singed markers. Consequently, the extract of the *Conium maculatum* cell culture does not cause genetic changes, which is one of the objective criteria for safe use.

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EMOTIONAL DISORDERS OF ELDERLY AND SENILE PEOPLE WITH CHRONIC CEREBRAL ISCHEMIA DEPENDING ON ETHNICITY

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The aim of the study was to study the ethnic and age characteristics of emotional disorders in the elderly and senile people of Yakutia suffering from chronic cerebral ischemia.

The study included 522 patients with chronic cerebral ischemia aged 60 to 89 years, who were divided into three groups by ethnicity (Evens, Yakuts and Russians) and into two age groups (elderly and senile age). Ethnic and age-related features of emotional disorders in persons suffering from chronic cerebral ischemia were revealed, while many patients had a combination of both anxiety and depressive symptoms. With the aggravation of the stage of chronic cerebral ischemia, more pronounced symptoms of anxiety disorders were noted. Emotional disorders prevailed in elderly and senile Russians, less pronounced in elderly Evens. There were no gender differences among them.

Keywords: ethnicity, elderly and senile age, chronic cerebral ischemia, emotional disorders.

Introduction. Currently, depression is one of the most frequently reported mental disorders. The prevalence of depression among the elderly and senile reaches, according to various sources, from 10 to 30%, the frequency of its development is high in comparison with the younger population [7-11]. According to WHO, about 15% of the population over the age of 60 suffer from mental or neurological disorders, while depression occurs in about 7% of the elderly population of the planet [14]. A feature characteristic to depression at a later age, according to some sources, is an increase in the number of atypical presentation of depressive states [2,3]. Anxiety disorders are one of the most common mental disorders; their increase is noted at a later age [6]. This is due to a progressive decrease in the adaptive capabilities of an aging organism when interacting with physical and social factors [3,4]. The study of ethnic characteristics of emotional manifestations at a later age is important in connection with the widespread prevalence of cerebrovascular diseases among them to determine cognitive capabilities.

The aim of the study was to research the ethnic and age characteristics of emotional disorders in the elderly and senile people of Yakutia suffering from chronic cerebral ischemia.

Materials and methods. The study involved 522 patients aged 60 to 89 years who were under inpatient treatment in the neurological department of the Geriatric Center of the Republican Hospital No. 3 with the participation of neurologists and therapists. Patient or guardian consent to the study was obtained according to the protocol of the Ethical Committee of the Yakut Scientific Center for Complex Medical Problems. The average age of patients was 72.7 ± 7.2 years, in men - 72.9 ± 7.2, in women - 72.6 ± 7.2 years. For a more detailed study, all patients were divided into 2 age groups: elderly people aged 60-74 years and senile - ages 75-89.

The diagnosis of chronic cerebral ischemia (CCI) corresponded to the classification of vascular brain lesions of the Institute of Neurology of the Russian Academy of Medical Sciences (1985). The main criteria for diagnosis was an instrumentally confirmed lesion of the cerebral vessels with the corresponding clinical presentation of the stages of CCI according to the classification of E.V. Schmidt - CCI I and CCI II.

The exclusion criteria were the following diseases:

- identified malignant neoplasms or surgeries regarding this pathology in past medical history;
- diseases of the blood system, including anemia;
- angina pectoris of the 4thfunctional class, acute myocardial infarction,presence of congestive heart failure of the III and IV functional classes;
- Alzheimer's disease and vascular dementia;
- stage 3 and more severe chronic renal failure according to M.A. Ratner;
- acute inflammatory pathology of the articular apparatus;
- chronic obstructive diseases of the bronchopulmonary apparatus with respiratory failure (RF) of stages II-III and manifestations of chronic pulmonary heart disease;
- peripheral artery disease of the lower extremities stages III-IV according to Fontaine.

Such strict exclusion criteria are justified by the fact that the manifestations of the above diseases come to the forefront, changing the clinical presentation and the course of chronic cerebral ischemia.

In addition, all patients were divided into three ethnic groups, differing in lifestyle, dietary characteristics, and the nature of their main occupations:

The 1st observation group consisted of 174 patients of Even nationality (representatives of indigenous minorities of the North) living in the Arctic zone. In the subgroup CCI I - 87, CCI II - 87 people.

Group 2 - 177 equally urban and rural Yakut patients (CCI I - 90, CCI II - 87),

Group 3 - 171 patients of Russian nationality, mostly living in an urban environment (CCI I - 86, CCI II - 85).

Gender ratio analysis of the studied persons is presented in Table 1. There is a predominance of female patients in all groups, except for the Yakut group with CCI II, which to some extent can be explained by the longer average life expectancy of women. According to the State

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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 data presented in Table 2 demonstrates that older persons (60-74 years old) of Yakut and Russian nationality were statistically significantly more common in the CCI I subgroup, unlike the Evens, who did not have significant differences in age. CCI II was registered significantly more often among representatives of the Yakut nationality at the age of 60-74 years.

To assess emotional disorders, the Hospital Anxiety and Depression Scale (HADS) was used, which consists of 14 statements and contains 2 subscales: I - assessment of the level of anxiety, II - assessment of the level of depression. When interpreting the data, the total indicator for each scale was taken into account: 0-7 points - the norm; 8-10 points - subclinical anxiety/depression; 11 points and higher - clinical anxiety/depression.

Statistical processing of the results of the study was carried out using the SPSS 22.0 application software package. To describe the quantitative data, the mean value with standard deviation, median and interquartile range were calculated. Qualitative attributes are presented in the form of frequency tables containing absolute values and the relative proportion of the attribute. To study the conjugation of qualitative characteristics, the classical Pearson $\chi 2$ criterion was calculated. To compare the mean values of the studied parameters, the Mann-Whitney paired test was used. In all statistical tests used, the $p < 0.05$ value was taken as the threshold level of significance.

Table 1

Distribution of patients with chronic cerebral ischemia depending on gender and ethnicity

CCI I	Evens		Yakuts		Russians	
	n	%	n	%	n	%
Men	27	31.1	28	31.1	25	29.1
Women	60	68.9	62	68.9	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
	$\chi 2$=3.89; p=0.049		$\chi 2$=1.3; p=0.29		$\chi 2$=35.79; p<0.001	

Table 2

Distribution of patients with chronic cerebral ischemia by age

CCI I	Evens		Yakuts		Russians	
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
	$\chi 2$=0.21; p=0.65		$\chi 2$=22.76; p<0.001		$\chi 2$=11.26; p<0.001	
CCI II						
60-74	46	52.9	58	66.7	40	47.1
75-89	41	47.1	29	33.3	45	52.9
	$\chi 2$=0.58; p=0.45		$\chi 2$=19.33; p<0.001		$\chi 2$=0.59; p=0.44	

Table 3

Emotional disorders in the elderly

Scale	Me (Q_1-Q_3)			
	Evens	Yakuts	Russians	p
	CCI I			
Depression (score)	4.0 (3.0-6.0)	4.0 (2.0-5.0)	5.0 (4.0-7.0)	0.001
Anxiety (score)	4.0 (2.0-6.0)	3.0 (1.0-5.0)	4.0 (2.0-5.0)	0.065
Overall score	8 (8.0-10.0)	7.0 (4.0-9.0)	9.0 (7.75-9.0)	0.009
Scale	CCI II			
Depression (score)	4.0 (3.0-5.0)	4.0 (4.0-5.0)	5.0 (4.-6.0)	0.001
Anxiety (score)	4.0 (3.0-4.0)	4.0 (4.0-4.0)	5.0 (4.0-5.0)	0.028
Overall score	8 (5.0-10.0)	8.0 (7.0-10.0)	10.0 (8.0-10.5)	0.046

Results and discussion. To analyze the severity of emotional disorders, anxiety and depressive manifestations were assessed. A study of the emotional sphere according to the Hospital Anxiety and Depression Scale was conducted separately for the elderly and senile people. The analysis of emotional disorders in the elderly is presented in Table 3. In the subgroup of CCI I, it was shown that in old age the level of anxiety by ethnicity did not differ much, and the level of depression in Russians was statistically significantly higher than in Evens and Yakuts (p=0.001). Emotional distress in the form of anxiety was more common in Even and elderly Russians, but there were no significant differences. The overall score of emotional disorders was significantly higher among Russians compared to other ethnic groups (p=0.009).

Russians also had a statistically significantly higher level of depression in the group of patients with CCI II among people aged 60-74 years than the Evens and Yakuts (p=0.001), and the level of anxiety was higher in Russians (p=0.028). Thus, the overall score of emotional disorders was higher in elderly people of Russian nationality (p=0.046).

Among the elderly (Table 4) Russians and Evens had a higher level of depression in the CCI I subgroup compared to Yakuts, with statistical reliability (p=0.004). The level of anxiety was significantly higher in Russians compared to Evens (p=0.005). The overall score of emotional disorders in this subgroup was higher among Russians compared to other ethnic groups, but there were no significant differences.

Russians also had higher levels of depression and anxiety among senile people in the CCI II subgroup with statistical reliability compared to other ethnic groups (p=0.002 and p=0.004) and, accordingly, the overall score of emotional disorders was significantly higher among representatives of Russian nationality (p=0.007).

Comparing disorders of the emotional sphere depending on gender, we did not receive significant differences between elderly and senile people. Disorders accompanied by anxiety, melancholy, dis-

Table 4

Emotional disorders in senile people

Scale	Me (Q_1-Q_3)			
	Evens	Yakuts	Russians	p
	CCI I			
Depression (score)	5.0 (3.0-7.0)	4.0 (3.0-6.0)	5.0 (4.0-6.0)	0.004
Anxiety (score)	3.0 (1.0-5.50)	4.0 (2.50-4.50)	5.0 (4.0-7.0)	0.005
Overall score	8 (7.0-10.0)	8.0 (7.0-10.0)	10.0 (9.0-10.0)	0.005
Scale	CCI II			
Depression (score)	3.0 (3.0-5.0)	4.0 (4.0-5.0)	5.0 (4.-6.0)	0.002
Anxiety (score)	3.0 (3.0-4.0)	4.0 (4.0-4.0)	5.0 (4.0-5.0)	0.004
Overall score	6 (5.0-10.0)	8.0 (7.0-10.0)	10.0 (8.0-10.5)	0.007

somnia, hypochondriac symptoms with the appearance of anxiety suspiciousness, fixation on exaggerating the degree of deterioration of well-being, do not depend on gender (depression χ^2=8,367, p= 0.869 and anxiety χ^2= 5.43, p=0.942). Although according to other literature sources, anxiety and depression were most common in older women compared to men of the same age [1,12,13].

According to our observations, the prevalence of anxiety-depressive disorders affects the stage of CCI in different ways. Thus, the level of anxiety increases with the stage of CCI (χ^2=21.428, p=0.044), and the frequency of depression is not affected by CCI stage (χ^2=8.019, p=0.888).

Neurological examination in subgroup CCI I revealed common manifestations of clinical disorders: vegetative symptoms, asthenic manifestations in the form of increased fatigue and general weakness, irritability, mood decline, sleep disorders in the form of difficulties falling asleep, multiple awakenings, restless sleep and early morning awakening. In the CCI II subgroup, in contrast to the patients of the CCI I subgroup, more pronounced anxiety disorders were observed in the form of predominantly passive behavior, anxiety suspiciousness and a tendency for anxiety fears, hypochondriac disorders.

In addition, the following subjective neurological symptoms affect the severity of emotional disorders: unsteadiness of gait (χ^2 = 38.624, p = 0.002 in Yakuts; χ^2 = 27.236, p = 0.040 in Russians), speech impairment (χ^2 = 26.816, p = 0.045 in Russians). A more detailed analysis of the scales reveals a link between anxiety and sleep disturbance (χ^2=20.963, p=0.048 in Russians), between depression and instability when walking (χ^2= 24.395, p=0.041 in Yakuts). The development of emotional disorders is influenced by extrapyramidal syndrome (χ^2 = 30.682, p = 0.022 in Russians), an oral automatism reflex (χ^2 = 28.293, p = 0.042 in Russians), sensory disorders (χ^2 = 42.215, p = 0.001 in Yakuts).

It is known from literary sources that emotional disorders, in particular depression and anxiety, significantly reduce "compliance", and have a great influence on the clinical prognosis of many somatic diseases of late age [1,5]. In our study, emotional background disorders are closely related to neurological symptoms and syndromes, the spectrum of this relationship is variable depending on ethnicity.

Conclusion. Thus, ethnic and age-related features of emotional disorders were revealed in people suffering from chronic cerebral ischemia, while many patients had a combination of both anxiety and depressive symptoms. With the aggravation of the stage of chronic cerebral ischemia, more pronounced symptoms of anxiety disorders were noted. Emotional disorders, such as changes in the emotional background, irritability, fatigue, sleep disorders were more often detected in representatives of Russian nationality, both elderly and senile. These emotional symptoms were detected in elderly Evens as well - to a lesser extent, obviously associated with the specific, traditional way of life of rural residents.

Our study confirmed the high prevalence of anxiety-depressive disorders in elderly and senile people suffering from chronic cerebral ischemia. This allows us to conclude that it is necessary to include a scale of emotional disorders in the algorithm of neurological examination, which makes it possible to significantly increase the detection of anxiety-depressive disorders in elderly and senile people with chronic brain ischemia. Since mild forms of mental disorders are often overlooked in primary health care and boarding houses with round-the-clock stay of the elderly.

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DIAGNOSTIC AND TREATMENT METHODS

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TREATMENT OF CHRONIC ARTERIAL HEPARTENSION DURING PREGNANCY: THE INFLUENCE OF THE STATE OF TARGET ORGANS

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The study presents the results of a comparative analysis of the effect of the hypotensive therapy start time on the condition of target organs (left ventricular (LV) myocardium, kidneys) in 134 pregnant women with chronic arterial hypertension (CAH) and 242 with the development of preeclampsia (PE) on its background. Early hypotensive therapy makes it possible to realize a protective effect on the target organs of pregnant women with CAH (adaptive remodeling of the LV myocardium, renal endothelium (MAU) and purine metabolism (synthesis of uric acid).

Delayed hypotensive therapy (after 15-20 weeks of pregnancy) contributes to the dominance of maladaptive mechanisms of regulating the activity of the cardiovascular system.

These pregnant women are distinguished by the progression of morphofunctional changes in the LV myocardium (concentric hypertrophy and diastolic dysfunction), to the greatest extent with the development of PE. The highest frequency of violations in the circadian rhythm of blood pressure ("non-dipper" and "night-picker" types) and metabolic changes (hyperuricemia, MAU) was found in pregnant women with the development of PE.

Keywords: chronic arterial hypertension (CAH), preeclampsia (PE), diastolic dysfunction (DD), left ventricular concentric hypertrophy, microalbuminuria (MAU), hyperuricemia.

Introduction. The management of pregnant women with hypertensive disorders is complicated: the prescription of drugs is often delayed; the low effectiveness of treatment determines the need for their change and selection of a combination [10,19].

The refusal of patients from hypotensive therapy is associated with the fear of side effects and complications, the risk of unwanted effects on the fetus and the newborn due to penetration through the placenta [2,3].

Current recommendations for the treatment of hypertension in pregnant women include preparations of α-adrenergic agonists (methyldopa), calcium channel blockers (nifedipine), β-adrenergic blockers (labetalol) [4,7,10,18].

Difficulty in achieving the recommended target BP values below 160/110 mm Hg is associated with the risk of violations of the uterine-fetal-placental blood flow and fetal growth retardation during aggressive hypotensive therapy [1,4,7,10,18].

The controversial aspects of the problem of hypertensive disorders treatment during pregnancy are the start time of the therapy and monitoring of its effectiveness. Lack of doctors' awareness about the criteria for early diagnosis can lead to late initiation of treatment and inadequate control of the condition [2].

The prognosis of the course of hypertension during pregnancy, the choice of optimal therapeutic and obstetric tactics implies an assessment of both the degree of the disease (moderate and severe) and the condition of the target organs (features of the structure and function of the left ventricular (LV) myocardium and kidneys).

LV myocardial remodeling in pregnant women with CAH is associated with changes in the size and structure of the organ at the molecular-cellular level on the background of increased hemodynamic load [8]. Morphological correlates of LV remodeling in pregnant women with CAH are considered reactive or progressive with the risk of myocardial hypertrophy. There are practically no studies of the variability of LV myocardial phenotypes in pregnant women with CAH, depending on therapy.

Microalbuminuria (MAU) is believed to be a marker of renal endothelial dysfunction and deterioration of renal function in CAH [2,6,22]. The probability of developing PE and pregnancy complications with MAU in women with CAH is believed to be increased, along with reports of high sensitivity and low positive significance in predicting PE (88.9% and 22.2%, respectively) [13].

The role of hyperuricemia as a marker of gestational complications and PE is actively discussed, especially with an increase in uric acid (UA) from the first trimester of pregnancy [17]. The association of an increased UA level with PE is thought to be stronger on the background of gestational hypertension [9].

An increase in uric acid is proposed to be considered as a cofactor of inflammation of the trophoblast and placenta, contributing to fetal growth retardation (FGR) [22] and premature birth in PE [12].

The objective of the study: to assess the effect of hypotensive therapy start time on the condition of target organs (left ventricular (LV) myocardium, kidneys) in pregnant women with chronic arterial hypertension (CAH) and the development of preeclampsia (PE) on its background.

Materials and research methods. The study contingent consisted of 376 pregnant women: 134 with CAH and 242 with the development of PE on its background. Depending on the timing of the prescription/ start of taking antihypertensive drugs, groups with early and delayed therapy (after 15–20 weeks) were identified: with CAH – n = 58 and n = 76, respectively, the development of PE – n = 114 and n = 128, respectively.

Inclusion criteria: single-child progressing pregnancy, the presence of CAH confirmed before pregnancy, the

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woman's informed consent for the use of biological material for scientific purposes.

The diagnosis of CAH was made on the basis of existing national and foreign recommendations with an increase in SBP ≥140 mm Hg and / or DBP ≥90 mm Hg.

Research methods: office BP measurement, 24-hour monitoring (ABPM) with a Shiller device on an outpatient basis at 10-11th, 21-22nd and 32-33rd weeks of pregnancy in a standard mode at intervals of 15 minutes during daytime hours, at night - 30 min. The following blood pressure indicators were taken into account: systolic, diastolic, pulse, mean arterial pressure (MAP).

Based on the degree of a nighttime decrease in blood pressure or the daily index (DI), the type of the daily curve was determined: "dipper" – patients with DI = 10-20%, characterizing a normal decrease in blood pressure at night, "non-dipper" – with insufficient (DI less than 10%) , "over-dipper" – with an excessive drop in pressure at night (DI more than 20%), "night-picker" – with a negative DI value due to the excess of blood pressure at night compared to the daytime.

The uric acid content in the blood serum was assessed at 6-8 and 16-17 weeks of pregnancy (the norm was 120-450 μmol / l), microalbuminuria (MAU) was determined in the general analysis of urine.

Echocardiography (EchoCG) assessed the main parameters of the LV myocardium and the types of its geometry. For grading, the relative thickness of the LV myocardium was calculated using the formula:

RWT = IVST + LVPWT / EDD, where RWT is the relative thickness of the LV walls, IVST is the thickness of the interventricular septum, LVPWT is the thickness of the LV posterior wall, EDD is the end-diastolic dimension. Criteria for determining the type of LV geometry: normal – LV myocardial mass index (LVMMI) within normal limits, RWT <0.45, concentric remodeling – LVMI within normal limits, RWM> 0.45; concentric hypertrophy – more than normal LVMMI, RWT> 0.45, eccentric hypertrophy – more than normal LVMMI, RWT <0.45. Criteria for LV hypertrophy: LVMMI> 110 g / m2.

LV diastolic function (DF) was analyzed by tissue myocardial Doppler imaging (TMDEchoCG).

Statistical processing of the material was carried out using the IBM SPSS Statistics 19 package. The sample was checked for compliance with the normal distribution using the Shapiro-Wilk test. Methods of parametric and nonparametric statistics were used. The analysis of intergroup differences in terms of qualitative characteristics was carried out using the χ2 test, less than five – the exact two-sided Fisher test. The significance level (p) when testing statistical hypotheses was taken to be p≤0.05.

Results and discussion. The study of the results of 24-hour blood pressure monitoring showed the predominance of the "dipper" type in early treatment of hypertensive disorders in pregnant women (rather than in delayed): almost one and a half times more often in CAH, twice – with the development of PE (p=0.00) (Table 1).

"Abnormal" daily blood pressure profile was detected more often in the absence of early therapy for hypertension: in half of pregnant women with CAH and in the majority with the development of PE. The incidence of "non-dippers", "over-dippers", "night-pickers" in early hypotensive therapy and prevention of placental insufficiency (PI) was significantly lower in the group with the development of PE – one and a half times (p=0.00).

In pregnant women with CAH, the early prescription of antihypertensive drugs determined a slightly higher indicator of the "dipper" type of the diurnal curve; however, there were no intergroup differences with delayed therapy.

The effect of delayed hypotensive therapy was realized in violations of blood pressure circadian rhythms (with a predominance of "non-dipper" and "night-peaker" types), determined by high average daytime, nighttime and daily SBP and DBP indicators in pregnant women with PE on the CAH background. The probability of PE with a mean DBP of 75 mm Hg or more and a mean BP of 90 mm Hg or more at 13-20 weeks of pregnancy is confirmed by other researchers [14].

The effectiveness of early hypotensive therapy proves the prevalence of "dipper" types in pregnant women with CAH and the development of PE, indicating a decrease in average daily blood pressure.

Early drug therapy for hypertensive disorders reduced the frequency of impaired LV relaxation function in comparison with the delayed one (20.9% vs 35.6%) (p=0.01) (Figure 2).

Delayed hypotensive therapy influenced the greater frequency of LV DF disorders in pregnant women with the development of PE – one and a half times (p=0.01). The tendency for the predominance of normal relaxation function of the LV occurred in the early treatment of hypertensive disorders in pregnant women (79.1% vs 64.4%).

Early prescription of antihypertensive drugs reduced the violations of LV relaxation in diastole in CAH by half (p=0.004), in the development of PE – by three times (p=0.00) (Figure 3).

Early therapy determined a lower frequency of diastolic dysfunction (DD) in the sample of all pregnant women with hypertensive disorders – 22.6%, three times less often than with the preserved ability of the LV myocardium to relax (78.2%).

The triggering factors for the development of diastolic dysfunction (DD) are considered to be a combination of hormonal, neurohumoral and metabolic processes underlying maladaptive remodeling of the myocardium with subsequent cardiomyocyte hypertrophy [8]. An early intake of antihypertensive drugs

Daily blood pressure profile of pregnant women, depending on the start of hypotensive therapy

Groups			N	2 trimester		3 trimester	
				dipper	other variants	dipper	other variants
Chronic arterial hypertension (CAH)	Early therapy	абс.	58	38	20	36	22
		%		65.5	34.5	62.1	37.9
	Delayed therapy	абс.	76	37	39	41	35
		%		48.7	51.3	53.9	46.1
Preeclampsia on the chronic arterial hypertension (CAH) background	Early therapy	абс.	114	68	46	52	63
		%		59.6	40.4	45.6	55.3
	Delayed therapy	абс.	128	34	94	50	83
				26.6	73.4	39.1	64.8
				p_{2-4}=0.002 p_{3-4}=0.00	p_{2-4}=0.002 p_{3-4}=0.00		p_{2-4}=0.01

improves the conditions for LV relaxation by reducing the processes of hypertrophy and structural disorganization of cardiomyocytes. Delayed prescription of antihypertensive drugs in CAH was accompanied by an increase in LV stiffness and a decrease in its ability to relax. An increase in diastolic stiffness and a change in the trophic skeleton under conditions of metabolic disorders formed the basis of DD in pregnant women with the development of PE with untimely hypotensive therapy.

The results of the analysis of the correlation between the types of LV geometry and MAU in pregnant women with hypertensive disorders at different periods of hypotensive therapy initiation are presented in Figure 4.

The largest number of pregnant women with MAU was determined in the group with delayed hypotensive therapy, with concentric LV hypertrophy – almost five times more often than remodeling (p=0.00). Early hypotensive therapy contributed to the reduction in MAU MAU in pregnant women, more often detected in concentric LV hypertrophy.

The highest frequency of MAU was found in the group of pregnant women with concentric LV hypertrophy – almost three times with delayed hypotensive therapy in comparison with early therapy (p =0.0005) (Figure 5).

Pregnant women with normal LV geometry and concentric remodeling were distinguished by lower MAU frequency during early hypotensive therapy, however, no statistically significant differences were found in comparison with delayed hypotensive therapy.

The effectiveness of early hypotensive therapy was manifested by the predominance of LV remodeling adaptive mechanisms and a low frequency of MAU in pregnant women with CAH. Delayed prescription of antihypertensive drugs led to pronounced structural and functional disorders of target organs – LV concentric hypertrophy and damage to the renal epithelium.

Hyperuricemia (HU) in the sample of pregnant women with hypertensive disorders was noted more often with delayed hypotensive therapy: in the second trimester – in a third of all patients with CAH, one and a half times more often –with the development of PE (p=0.00) (Figure 6).

In the sample with early hypotensive therapy, an increased uric acid (UA) content was determined in a small number of all pregnant women with CAH (6.9% on average), 42.1% of patients with the development of PE in the second trimester,

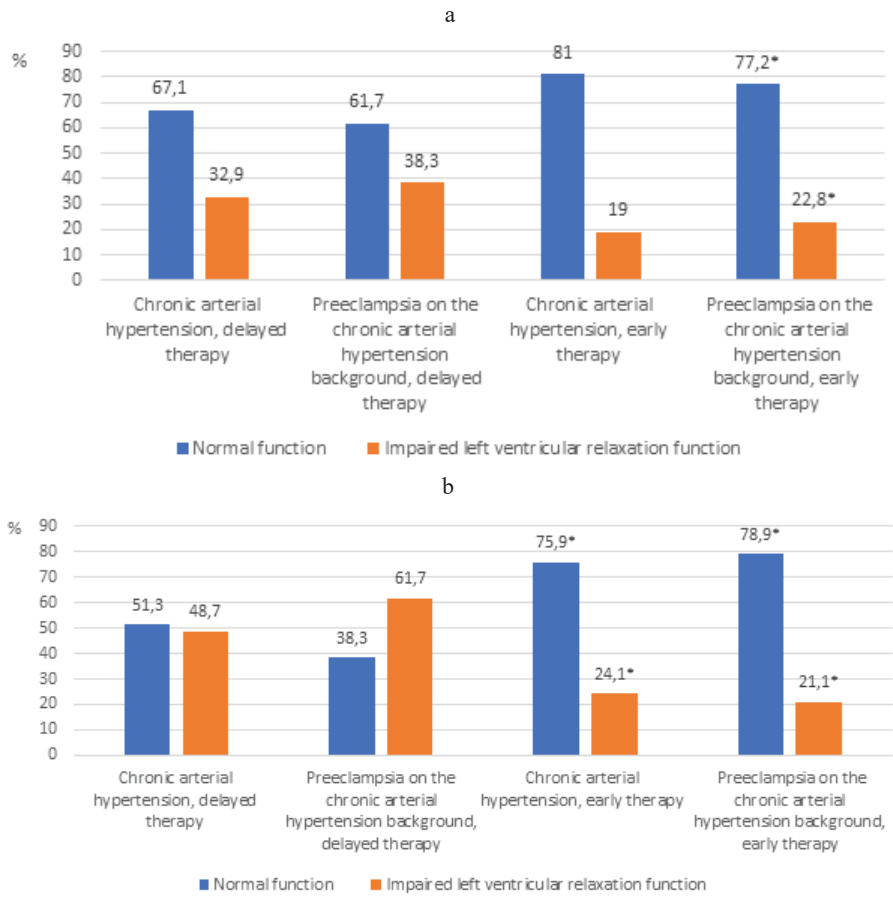

Fig. 1. Features of LV diastolic function (a - in the second, b - in the third trimester) depending on the timing of CAH therapy: (p <0.05) - statistically significant differences from the same groups without treatment in pregnant women * with CAH, ** s PE on the background of CAH

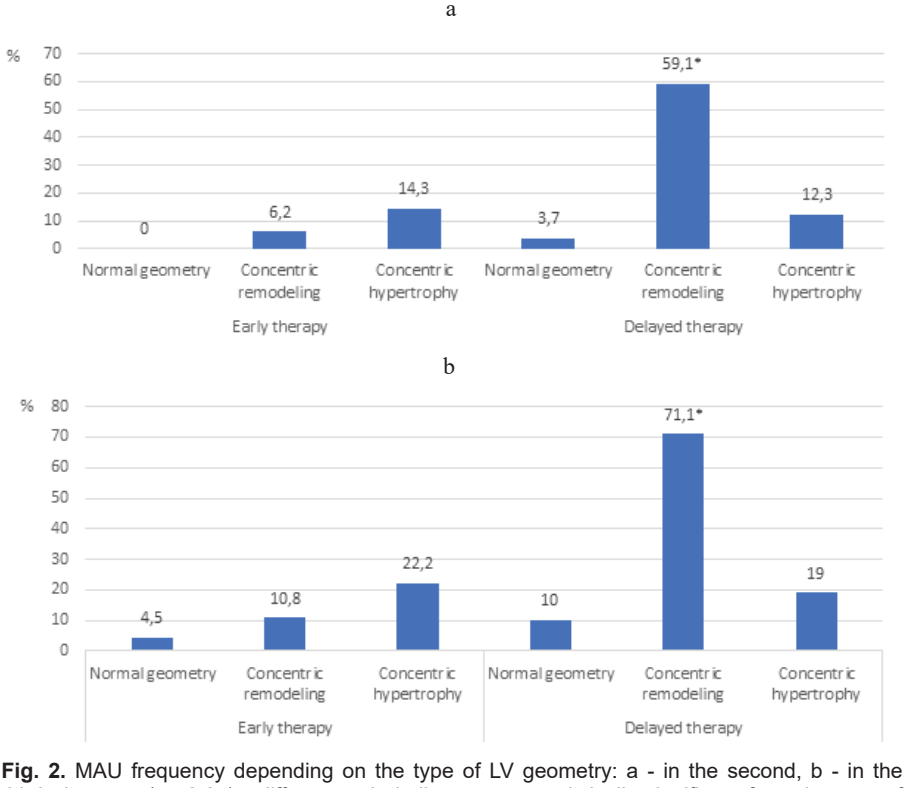

Fig. 2. MAU frequency depending on the type of LV geometry: a - in the second, b - in the third trimester. (p <0.05) - differences in indicators are statistically significant from the type of geometry: * concentric left ventricular hypertrophy in the early therapy group

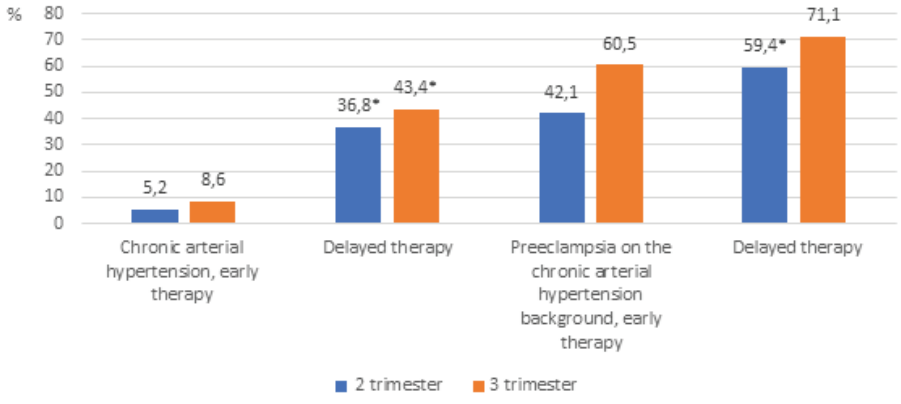

Fig. 3. Frequency of hyperuricemia (HU) depending on the start of hypotensive therapy in the second and third trimesters. (p <0.05) – differences in indicators are statistically significant depending from groups of the same name with early hypotensive therapy in pregnant women with CAH, ** - with PE on the CAH background

60.5% – in the third one. The increased content of MC in pregnant women with the development of PE with delayed therapy was significantly more often detected than with early detection in the second trimester (p=0.009).

The data we have obtained allow us to challenge the opinion about the inexpediency of routine testing for hyperuricemia (HU) [20]. The prognostic significance of increased uric acid (UA) values was established as a predictor of PE, preceding morphofunctional restructuring of the LV myocardium in pregnant women with CAH. Our results do not contradict the data [11] that the level of UA ≥357 μmol/l is associated with proteinuria and increased DBP.

An increase in hyperuricemia in pregnant women with CAH simultaneously with MAU was consistent with the data on a decrease in renal excretion on the background of parenchymal damage [5,21].

The data obtained by us during a comprehensive examination of pregnant women with CAH allow us to note changes in the LV myocardium and impaired diastolic function (DF) as markers of disadaptive cardiac remodeling [15,16], the most significant in the absence of early hypotensive therapy.

Conclusion. Our data confirm the important role of delayed hypotensive therapy in the formation of maladaptive LV remodeling with a predominance of concentric LVH, violations in circadian BP rhythms (prevalence of "non-dippers" and "night pickers") and metabolic disorders (hyperuricemia, MAU). The protective effect of early therapy with antihypertensive drugs in pregnant women with CAH determines the adaptive nature of cardiac remodeling and metabolic changes caused by endothelial renal dysfunction (MAU) and moderate disturbance of purine metabolism (uric acid).

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FEATURES OF THE MANIFESTATION OF THE CHEWING REFLEX IN PATIENTS AFTER DENTAL REHABILIATION WITH DENTURES ON ARTIFICIAL SUPPORTS

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The aim of the presented clinical and pathophysiological study was to study the features of the formation of the chewing reflex in people with missing teeth after dental rehabilitation with orthopedic structures based on dental and / or zygomatic implants. In the course of the study, the indices of the force of compression of the dentition were studied using the method of gnatodynamometry. The indices of resting tone and compression of the masseter muscle were obtained using the method of myotonometry, the effect of occlusion on normal muscle activity was studied using EMG studies. As a result of the work carried out, it was noted that the treatment of complete loss of teeth in one or both jaws with the help of dental and zygomatic implants according to EMG data during the observation period of more than 2 years after the installation of permanent orthopedic structures does not lead to disruption of the neuro-physiological processes of the masticatory-speech apparatus and contributes to the patient's complete adaptation to the restored occlusal relationship, although it is characterized by a slight increase in the resting tone and contraction of the masticatory muscle according to myotonometry data and the force of compression of the dentition according to gnathodynamometry data.

Keywords: osteo-muscular reflex, osteoperception, physiology of the masticatory apparatus, chewing muscles, dental implantation, dental rehabilitation, prosthetics on dental implants.

Introduction. Afferent impulses in the area of the installed (osseointegrated) dental implant comes from the receptors of the jaw bone tissue into which the implant is integrated [4,16]. Taking into consideration the peculiarities and principle of the phenomenon of osseointegration, it can be assumed that the receptor apparatus of the bone tissue on the surface of the implant fully corresponds to the receptor apparatus in the thickness of the jaw bone tissue, due to which the principles of mechanotransduction are realized [1,3,10,18].

In accordance with the theory of chewing links and their functional units, the mechanism of distribution of pressure on the teeth in natural physiological conditions, as well as the generation of the frequency of chewing movements and their amplitude normally depends on the nature of the food taken and other functional indicators (muscle strength, the type of jaw closing, etc.) etc.) [2,5,7,10], and is also regulated by the receptor apparatus of the periodontium [8,14].

Neurophysiological processes in the field of dental and zygomatic implants and orthopedic structures fixed on them have not found wide coverage in modern domestic and foreign literature, although they are characterized by their specificity [2,13,15,17], especially when using full tooth-replacing structures on both jaws [11].

Purpose of the study: to study the features of the formation of the chewing reflex in patients with partial or complete absence of teeth after dental rehabilitation with orthopedic structures on dental and / or zygomatic implants.

Materials and methods: the study of the features of the formation of the chewing reflex after the completion of dental rehabilitation in people with complete absence of teeth on one or both jaws was carried out in the course of a clinical and physiological study, which included several stages. A total of 120 elderly and senile patients were examined, 80 of whom were included in groups 1 and 2 of the study and 40 people in the control group. The distribution of patients into groups is shown in Table 1.

The first part of the study included the study of the features of the functioning of the masticatory link, the supporting part of which on one or both jaws was a dental implant with a fixed orthopedic structure. A comparative analysis of the indices of the compression force of the dentition and the tone of the masticatory muscles was carried out in accordance with the theory of the functional links of the masticatory apparatus of I.S. Rubinov [8].

In the second part of the study, we studied the features of the formation of the chewing reflex after the completion of dental rehabilitation of the complete absence of teeth on one or both jaws with fixed orthopedic structures on dental and / or zygomatic implants. The control group included patients with preserved natural teeth. The first group of the study consisted of patients with included or terminal defects of the dentition, which were replaced by orthopedic structures on artificial supports - dental implants. The period after fixation of the final structure was at least 6 months in order to exclude the adaptation period. The second group of the study included patients with complete absence of teeth on one or both jaws after their replacement with a fixed orthopedic structure supported by dental or zygomatic implants; the period after fixation of the permanent denture structure was at least 2 years. Separately, in this group, clinical cases were identified with complete loss of natural

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teeth in one jaw and their preservation in the other (Table 1), since this could significantly affect the results of the study (preservation of the periodontal-muscular reflex of the teeth of one of the jaws).

In the course of the study, using an electronic gnatodynamometer "Vizir-E1000" (Russia) by the method of gnatodynamometry, the indices of the force of compression of the dentition were studied. The probe of the device was placed between the teeth within the studied chewing unit, and it was suggested to clench the teeth until unpleasant sensations appeared [5, 8]. The values were determined in the area of the anterior group of teeth, premolars and molars.

Indicators of resting tone and compression of the masseter muscle itself were obtained using the myotonometry method using the Myotonometer device (Russia) [2]. All the data obtained were analyzed taking into account the location and nature of the chewing link, namely: "natural tooth - natural tooth", "natural tooth - artificial tooth supported on a dental implant" or "artificial tooth supported on a dental implant - artificial tooth supported on dental implant "(Pic. 1).

In the control group and the second study group, in addition to gnatodynamometry and myotonometry, all patients underwent electroneuromyographic (EMG) examination. Currently, in dentistry, EMG is used to assess muscle tone at rest and during voluntary contraction in order to analyze the dynamics of rehabilitation treatment in cases where it is necessary to assess the general contractile function of the muscle under study, as well as to study the effect of occlusion on normal muscle activity [6,12, 13,14,17].

The examination was carried out on the "Neuro-MEP" apparatus ("Neurosoft", Russia) by the method of surface interference and stimulation EMG. For registration, disposable surface electrodes with an adhesive layer were used. The mean amplitude of the interference EMG at rest and during contraction with mm was analyzed. masseter, temporalis on both sides. In this case, the active skin electrode was located in the projection of the motor zone of the muscle, the reference electrode was located distal, above the muscle tendon [6]. The bioelectrical activity of the masticatory muscles proper and temporal muscles was studied during the period of functional rest of the lower jaw (maximum relaxation of the masticatory muscles, with the appearance of a gap between the dentition, the jaw is held in this position by an anti-gravity reflex) and with maximum compression of the jaws, as well as a turn-amplitude analysis in accordance with domestic and foreign clinical guidelines [6,9,13].

During stimulation EMG, motor responses were obtained with mm. masseter, temporalis on both sides during stimulation of nn.trigeminus (r.mandibularis - nucl.motor.n.trigemini). The obtained values were compared with the norm according to J. Kimura (2001) and the age norm of the comparison group. Beyond stimulation EMG

The significance of differences in the mean values of independent samples was assessed using the parametric Student's test (with a normal distribution law) and the nonparametric Mann-Whitney test (with a difference from the normal distribution). The test for normal distribution was assessed using the Shapiro-Wilks test. For the statistical comparison of the proportions with the assessment of the significance of differences, the Pearson χ2 test was used taking into account the Mantel-Hansel correction for likelihood. In statistical analysis, the achieved level of significance (p) was considered, with a critical significance level of 0.05.

Research results and discussion. The indicators of gnatodynamometry and myotonometry of the masticatory muscles obtained during the examination of the control group were significantly higher in men (Pic. 2) than in women ($p \leq 0.05$), although they corresponded to similar data for older age groups described in the specialized literature [5 ,8,10]. It should also be noted that, regardless of gender, statistically significant differences were not obtained between elderly and old age patients ($p > 0.05$). In this regard, in the course of further research, the average values of the indicators of these two age groups were taken into account together.

The values of gnatodynamometry in

Table 1

Investigation of the features of the manifestation of the chewing reflex in patients with single and total orthopedic constructions on dental implants, pers. (%)

Control group		The first group of the study				Second study group			
Men	Women	Men		Women		Men		Women	
20	20	t/i	i/i	t/i	i/i	ci/r	ci/ci	ci/r	ci/ci
		12	8	10	10	5	12	11	12
20	20	20		20		17		23	
40		40				40			

Note: t – tooth; i – implant; pi – peri-implantitis; ci – complete (total) dental rehabilitation of the jaw on implants; r – jaw with remaining teeth

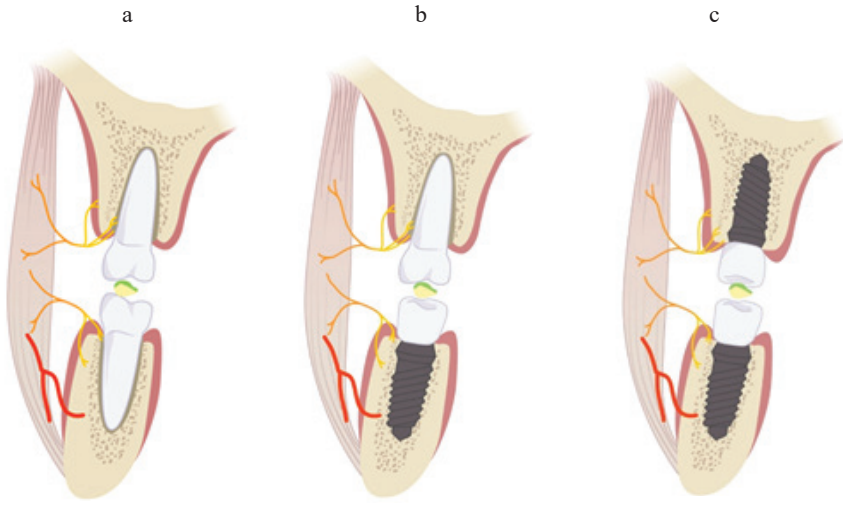

Fig. 1. Schematic representation of the studied chewing links, presented in groups: a) regulation of the function is carried out through periodontal-muscular reflexes from both jaws ("natural tooth - natural tooth"); b) regulation of the function is carried out through the osteo-muscular reflex from the lower jaw ("natural tooth - an artificial tooth supported by a dental implant"); c) regulation of the function is carried out through the osteo-muscular reflex from both jaws ("artificial tooth supported by a dental implant" on both jaws).

the first study group in the area of the frontal group, at the level of the first premolar and the first molar in the presence of masticatory links with natural teeth in these areas of the jaws, corresponded to those in the control group patients (p≥0.05). There were no significant differences in gnathodynamometry indices in patients of both sexes in the control group and the first group of the study when analyzing the masticatory link at the level of the corresponding parts of the jaws, in which a natural tooth was present on one jaw, and on the other there was an orthopedic construction on a dental implant (p≥0, 05), although it should be noted that there is a tendency to higher values in the first group of the study (Pic. 3). Indicators of myotonometry at rest and compression in the first group of the study also did not have statistically significant differences compared with those in the control group (p≥0.05). These facts were most likely associated with the presence of periodontal reflex zones and an afferent signal from them during functional studies in the system "natural tooth - artificial tooth supported on a dental implant" on one of the jaws with the formation of a periodontal-muscular reflex of the masticatory apparatus (according to I S. Rubinov).

The study of masticatory links in patients of the first study group in the presence of single orthopedic constructions on dental intraosseous implants on both jaws, on the contrary, showed that, regardless of gender, the gnatodynamometry indices obtained in all studied areas were significantly higher in relation to the control group (p≤0.05). The indicators of myotonometry, although they had higher values, did not differ statistically in comparison with the control group (p> 0.05).

Thus, according to the nature of the course of neuro-reflex processes in the masticatory link, represented by a dental implant with an artificial crown as its supporting part, as well as bone tissue receptors that perform an afferent and neuro-regulating function - regardless of the location of this masticatory link on the jaw, it is possible talk about the reduced afferentation of sensitive nerve receptors to the force of compression of the masticatory muscles (in this masticatory link) in comparison with the periodontium of natural teeth. By analogy with the terminology of I.S. Rubinov and his teachings on the functional links of the masticatory

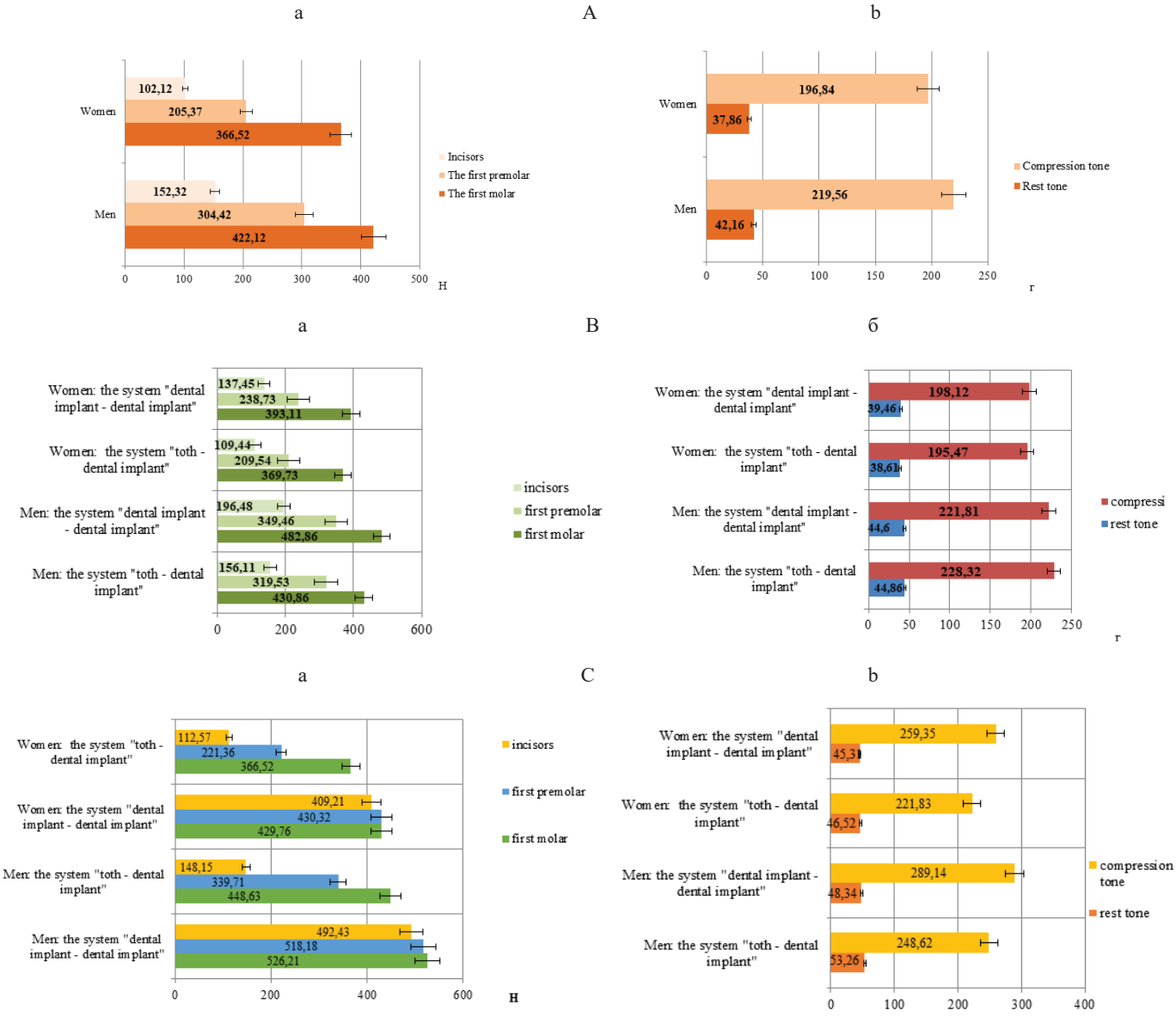

Fig. 2. Values of indicators of gnathodynamometry (a) and myotonometry (b) in patients of the control (A), first (B) and second (C) groups of the study

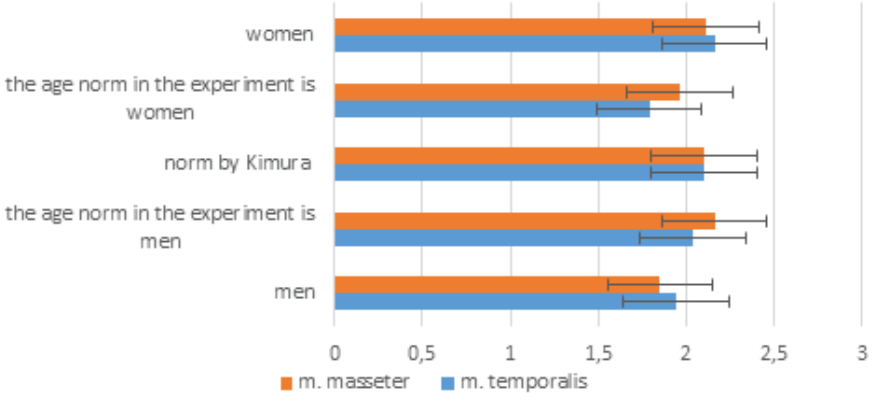

Fig. 3. Indicators of latency of motor responses (diagram men and women)

apparatus, it seems necessary to highlight the features of the manifestation of the masticatory reflex in the case of restoring the continuity of the dentition using dentures on artificial supports (dental implants) as an osteo-muscular physiological reflex. The allocation of this concept is associated with a change in the afferentation of nerve impulses in the presence of an osseointegrated tooth-replacing structure. Good adaptation of patients to different tooth-substituting structures, even after the restructuring of interconnected reflexes with complete prosthetics of both jaws, proves the normal physiological course of nervous processes, despite the increased load during chewing [3,10,11,17]. The process of adaptation of patients after dental rehabilitation to orthopedic structures on artificial supports is carried out with the interaction of a physiological reflex on stretching the masticatory muscles with the paradonto-muscular and osteo-muscular physiological reflexes of the masticatory apparatus.

The study of gnathodynamometry indicators in patients of the study group after dental rehabilitation of complete absence of teeth based on dental and zygomatic implants is shown in Picture4.

In all the presented clinical cases of the study groups, the patients showed a balanced EMG activity during compression of the dentition, which was a sign of good adaptation of the neuro-muscular system of the masticatory-speech apparatus to the occlusive state. In 3 (7.5%) patients (1 man and 2 women), there was a decrease in the amplitude of the response with an increase in its latency on one side in relation to the other side. These facts were a sign of a violation of the conductivity for n. trigeminus (m. masseter). For the purpose of an in-depth examination of these patients, needle electromyography was performed, followed by consultation with neurological specialists. In the course of the study, the data obtained from these patients were not taken into account. Further study of the amplitude and latency indices was carried out without taking into account the side of the motor response.

Picture 5 shows the indicators of the amplitude of motor responses and its latency in comparison with the age indicators of the mean values of the control group and the norm described in the literature according to J. Kimura (2001). The latency of the motor response characterizes the travel time of the impulse from the point of stimulation to the appearance of the motor response of the muscle. The average indicators of latency of motor responses in patients in the study groups did not have statistically significant significant differences. (p> 0.05), which is most likely associated with a similar average distance from the point of stimulation to the fibers of the muscle under study.

In the course of the EMG study in elderly and senile patients in the control group and in the second group of the study, a decrease in the amplitude of the motor response was observed in comparison with the normal values according to J. Kimura (2001). Based on the fact that the amplitude of the motor response characterizes the processes of depolarization and repolarization occurring in the muscle fiber, and also indirectly determines the strength of muscle contraction, the lower value of this indicator was most likely associated with older age groups of the examined patients (elderly and senile age) as follows. as the average data described in the literature are presented without taking into account age characteristics. There were no statistically significant differences between the patients of the control group and the study group in the mean values of the amplitude of motor responses (p> 0.05).

At rest, there was a constant weak tonic tension of the proper chewing and temporal muscles, which is characterized on the electromyogram in the form of an interference curve not exceeding 50 μV in amplitude. During the study of the EMG-pattern of rest, spontaneous bursts of biopotentials were not observed. The average value of biopotentials in the phase of bioelectric rest for 20 s and the phase of compression of the right and left masticatory and tem-

Table 2

Electromyographic indices of masticatory muscles at rest * (M+SD). μV

Indicators to be studied	Muscles under study			
	m. masseter (right)	m. masseter (left)	m. temporalis (right)	m. temporalis (left)
Mean value of amplitude at rest (control group) (μV)	41.3±5.7 43.2±6.1	42.8±6.3 39.5±6.5	38.4±4.2 39.2±5.1	38.6±4.6 39.5±6.3
Average value of amplitude at maximum compression (control group) (μV)	532.3±52.1 542.8±64.9	521.1±59.2 534.5±67.3	502.1±56.2 498.5±47.1	498.8±54.7 511.6±65.3
Average value of amplitude at rest (control group) (μV)	41.1±9.3 45.8±7.5	38.8±8.3 44.3±9.5	37.2±7.8 41.1±9.6	36.2±6.3 39.8±7.1
Average value of amplitude at rest (control group) (μV)	542.3±102.4 557.5±94.3	548.1±115.8 549.2±119.7	493.9±89.5 512.3±114.2	512.9±124.5 503.2±102.8

* In the numerator - the value for women. in the denominator - in men.

poral muscles are presented in Table 2.

The data obtained did not have statistically significant gender differences (p> 0.05). In the control group and the second group of the study, where the dental rehabilitation of complete adentia was performed using fixed structures on dental and zygomatic implants in the study of bioelectric activity and the turn-amplitude analysis of the biopotentials of the studied masticatory muscles, the values were comparable, and their statistical processing did not reveal differences between analyzed indicators (p> 0.05). During the interpretation of EMG indicators in the patients of the study group, no pathological spontaneous activity of the masticatory muscles was revealed, which emphasizes the normal course of neuro-muscular processes in the masticatory muscles and conductive nerves.

Conclusion. In the course of the clinical and pathophysiological study, it was noted that the treatment of complete loss of teeth in one or both jaws with the help of dental and zygomatic implants according to EMG data during a follow-up period of more than 2 years after the installation of permanent orthopedic structures does not lead to a violation of the course of neurophysiological processes of the masticatory-speech apparatus and contributes to the patient's complete adaptation to the restored occlusal relationship, although it is characterized by a slight increase in the resting tone and contraction of the masticatory muscle according to myotonometry data and the force of compression of the dentition according to gnathodynamometry data. Thus, a chewing link with a supporting part in the form of a dental intraosseous implant, in comparison with a chewing link with intact natural teeth, is characterized by a normal physiological course of nervous processes with an increased chewing load.

The results obtained in the course of the study explain the increased abrasion of structures that antagonize with dental implants, possible breakdowns of orthopedic structures, which more often occur when prosthetics supported on implants of both jaws, demonstrate the peculiarities of adaptation to fixed orthopedic structures on implants in total restorations associated with changes in afferentation and restructuring. chewing reflex, while not only justifying the feasibility of using night unloading trays, botulinum toxin injections, providing psychotherapeutic support during the adaptation period, the implementation of physiotherapeutic and other methods to prevent abrasion of natural teeth (antagonists) and excessive load of antagonizing orthopedic structures, their chips, fractures and others factors of premature functional and aesthetic unsuitability, but also prove the need already at the planning stage of the choice of modular tooth replacement structures with high by the same indicators of maintainability.

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FEATURES OF THE FORMATION OF THE PORTAL VEIN AND ITS BRANCHES IN THE INDEGENOUS AND NON-INDIGENOUS POPULATION OF THE REPUBLIC SAKHA (YAKUTIA) ACCORDING TO MULTISPIRAL COMPUTED TOMOGRAPHY

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УДК 611.019

We have studied the variant anatomy of portal vein confluence formation and its branching in the cut and non-indigenous population of RS(Y) using vascular reconstruction of multispiral computed tomography data in patients undergoing MSCT with intravenous contrast enhancement without pathology of the hepatobiliary zone. The obtained results of the study indicate the presence of a role for the ethnic component in the formation of confluence and branching (division) of IWs in the studied groups. However, the small sample size of patients on the obtained results of the study should be taken into account.

Keywords: portal vein, portal vein tributaries, variant anatomy, division of the portal vein.

Introduction. It is known that the portal vein (PV) is a large vascular structure that supplies up to 75-80% of blood to the liver. It is formed by the fusion of the splenic, superior and inferior mesenteric veins. The IV pool collects blood from the organs of the gastrointestinal tract (except for the thoracic esophagus and the lower rectum), spleen, pancreas, gallbladder and peritoneum. Its distal part of the IV, flowing into the liver, forms a part of the portal fissure and is divided into lobar branches of the IV [1, 14].

Few early studies confirm possible ethnic differences in the variant anatomy of angioarchitectonics; the works describe the presence of certain types of variant anatomy of blood vessels in various ethnic groups, which are rarely found in the general population [10, 12]. The populations of the regions of Eastern Siberia are distinguished by a special anthropological status, which was formed as a result of a long (over several millennia) settlement in difficult climatic and geographical territories by indigenous peoples [7].

Modern non-invasive diagnostic imaging methods (magnetic resonance imaging — MRI, multispiral computed tomography — MSCT, and ultrasound duplex examination of blood vessels) allow surgeons to plan possible anatomical variants of vessels, including the hepatobiliary zone, at the preoperative stage, which significantly reduces the risk of intraoperative complications [6] Knowledge of the PV variant anatomy in the perioperative period is of crucial importance and allows surgeons and interventional oncologists to plan the course of complex surgical procedures, such as: liver transplantation, liver resection, two-stage liver resection by ALPPS, pancreatic resection, portal vein embolization, formation of transjugular intrahepatic shunts (TIPS), as well as percutaneous liver interventions [9].

Purpose of the Study: analyzing the portal vein in the indigenous and non-indigenous population of the Republic of Sakha (Yakutia), according to multispiral computed tomography.

Materials and Methods. The study included the results of 50 sequential MSCT (multispisral computed tomography) organs of the abdominal cavity and retroperitoneal space with intravenous contrast enhancement according to the standard protocol and with standard packing for the period of 2020 with patients who underwent routine diagnostic examination in the Department of Radiology Diagnostics of the Yakutsk Republican Oncological Dispensary. The main conditions for inclusion were age over 18 years, absence of pathology (portal hypertension, portal vein thrombosis, tumor lesion) in the gastropancreatobiliary zone, absence of surgical intervention (Whipple procedure, splenectomy, extensive operations on the liver and/or colon) or other conditions that would change the blood flow in the PV. Additional condition was high quality MSCT images. The image quality was assessed according to the following parameters: the contrast of the vessel versus tissue contrast, the contrast of the vessel versus the noise level, the presence of motion artifacts, and the presence of metallic artifacts. Failure to comply with this requirement was an exclusionary factor.

All patients included in the study were divided into 2 groups depending on ethnicity living on the territory of the Republic of Sakha (Yakutia): group 1 included patients of indigenous nationality, group 2 — non-indigenous nationality. In group 1, there were 13 (52%) men and 12 (48%) women among 25 patients. The average age of men included in the study was 65±10.9 years, women — 56±15.5 years. Group 2 (25 patients) included 9 (36%) men and 16 (64%) women. The average age of men included in the study was 57±8.1 years, women — 57±10.3 years.

Postprocessing of DICOM (Digital Imaging and Communications in Medicine) files was carried out using the OSiriX software suite; it consisted in performing multiplanar (2D) and 3D reconstructions of MSCT angiograms of the abdominal organs in the venous phase. To study the

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confluence of PVs, we applied the classification of P. Krumm et al. (2011) [13, 17], which identifies 10 types of PV formation and is shown in Figure 1:

Type A — Inferior mesenteric vein (IMV) flows into the splenic vein (SV).

Type B — IMV is located at the corner of the confluence of the superior mesenteric vein (SMV) and SV; this fusion forms the portal vein.

Type C — IMV flows into SMV.

Type D — accessory mesenteric vein enters the confluence angle, as in type B.

Type E — similar to type A with two equal trunks of the IMV and the accessory mesenteric vein, IMV flows into the SV.

Type F — similar to type E, the IMV flows into the accessory mesenteric vein, which, in turn, is equal in diameter to the IMV and flows into the angle of confluence of the IMV and SV.

Type G — similar to type A, but the auxiliary mesenteric vein and IMV flow into the SV at the same point.

Type H — no IMV.

Type I — similar to Type A, IMV flows into the SV, but there is an accessory mesenteric vein between IMV and SMV.

Type J — IMV is equal in diameter to the SMV and flows into the corner of the confluence of the IMV and SV.

To study the division of the portal vein, we used the classification of T. Nakamura et al. (2002) [9], which identifies 5 types of PV division, which is shown in Figure 2:

A — the classic version of PV division into right and left trunks.

B — true trifurcation, without the main trunk of the right PV.

C — extrahepatic discharge of the anterior branch of the right PV.

D — intrahepatic discharge of the anterior branch of the right PV.

E — the absence of an integral branch of the anterior right PV. Departure of individual segmental branches from the PV.

Statistical data processing was performed on a personal computer using Microsoft Excel spreadsheets and the SPSS 20 statistical software package.

Results and Discussion

The portal vein supplies 75-80% of blood to the liver, its main tributaries are the splenic and superior mesenteric veins. In most cases they merge in the posterior surface in the neck of the pancreas, forming a single trunk up to 5-8 centimeters, and then bifurcate at the gate of the liver.

All obtained MSCT images had high image quality, which made it possible to identify 100% of the PV along its entire length.

As we note, the inferior mesenteric vein and accessory mesenteric veins play the main role in the anatomical variation in the formation of PV confluence [5, 13, 15]. The data of PV confluence studies published by a few Russian and foreign authors vary from group to group. We also investigated the confluence of PVs based on the classification of P. Krumm et al. and we have found the following anatomical variations in the formation of the PV: in the indigenous group, Type C was the most frequent at 48% (12 patients) with Type A at 44% (11 patients); Types B & F were less frequent at 4% (1 patient) each. We did not find other variants of confluence formation in this group. When analyzing the patients by gender in the study group, we found that Type A was more common in women — 8 (32%) than in men — 12% (3). At the same time, Type C was more common in men — 9 (36%) than in women — 3 (12%). Types B 3 (12%) and F 1 (4%), which were identified only in the male population of the indigenous population, are much less common. In the group of non-indigenous, studies of the formation of confluence of the PV showed that Type A with 12 patients (48%) and C with 6 patients (24%) were also more common, and Types B (4 patients, 16%) and H (1 patient, 4%) were less common. In addition, one female patient had a case of PV confluence that was not described in our classification, when the main trunk corresponds to Type C, but the inflow of IMV flows into the accessory mesenteric vein. No other options have been identified. When analyzed by gender in the non-indigenous group, Type A was more common in women 7 (28%) than in men 5 (20%), while Type C was more common in women 4 (16%) than in men 3 (12%); Type B was much less common with

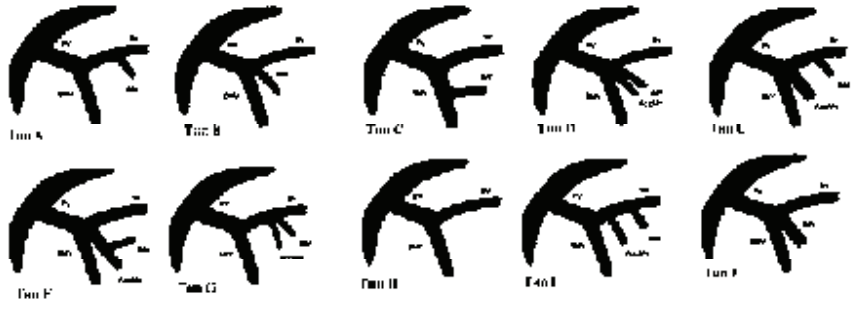

Fig. 1. Classification of types of portal vein confluence formation according to Krumm et al. [13]: Type A – the inferior mesenteric vein (IMV) flows into the splenic vein (SV); type B - IMV is located at the angle of confluence of the superior mesenteric vein (SMV) and the SV, this confluence forms the portal vein; type C - NBV flows into the VBV; type D - the accessory mesenteric vein enters the confluence angle, as in type B; type E - similar to type A with two equal trunks of the IMV and the accessory mesenteric vein, the IMV flows into the NE; type F - similar type E, the IMV flows into the accessory mesenteric vein, which, in turn, is equal in diameter to the SMV and flows into the confluence angle of the SMV and NE; type G - similar to type A, but the accessory mesenteric vein and the IMV flow into the NE at one point; type H - no NBV; type I - similar to type A - the IMV flows into the NE, but there is an accessory mesenteric vein between the IMV and the SMV; type J - NBV is equal in diameter to VBV and flows into the angle of confluence of NBV and SV

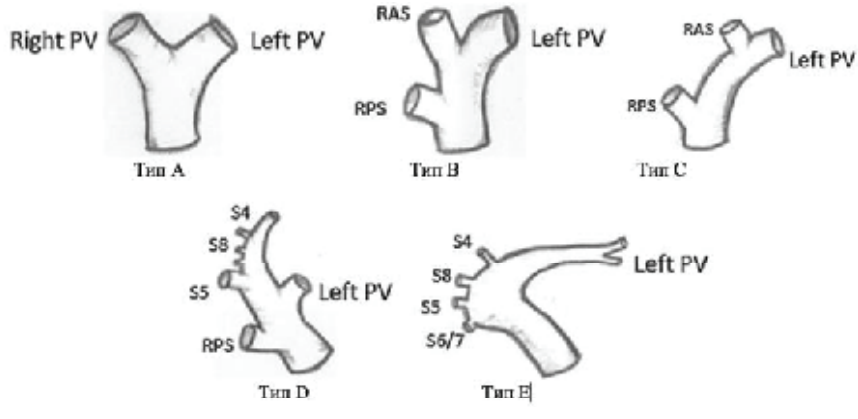

Fig. 2. Classification of division of the portal vein according to T. Nakamura et al. [16]: A - the classic version of the division of explosives into the right and left trunks; B - true trifurcation, without the main trunk of the right explosive; C - extrahepatic origin of the anterior branch of the right BB; D - intrahepatic origin of the anterior branch of the right BB; E - the absence of an integral branch of the anterior right BB. Departure of individual segmental branches from the BB

2 (8%) cases in men and women (1 in each gender), and type H was detected in 1 (4%) woman.

Thus, in our study, we revealed significant differences in the variants of the formation of PV confluence in the studied groups, since Type C prevails (48%) in the first group, while in the second group it is Type A (48%). In the group of the indigenous population, we found 4 variants of the formation of confluence of PV, and in the group of the non-indigenous population we found 6 variants. Also, in the group of the indigenous population the variations were mainly represented by the male sex (72%), while in the group of the non-indigenous population they were evenly distributed. Type A prevailed (32%) in women in the first group, Type C prevailed (36%) in men. In the second group, Type A prevailed in both sexes (52%). The data obtained show that there is a difference in the variants of the formation of the PV confluence, mainly in the inflow of the IMV into the SMV and SV depending on the groups. In the indigenous group, the IMV flows more into the SMV, and in the non-indigenous group, the IMV flows more into the SV, which is reflected in Graph 1. Knowledge of rare variants of PV confluence formation is important for surgeons when planning intervention in the mesenteric root area, as well as during operations on the pancreas or intestines.

Portal vein branching has been studied in more detail than its confluence. Over the past decades, most of the studies have focused on the X-ray testing, but we also see morphological studies. In the Russian Federation, fundamental research on the portal vein variant anatomy can be found in the works of Shapkin V.S., Gaivoronsky I.V., and Kolsanov A.V. [2.6]. The applied value of the PV variant anatomy is extremely important in the surgical disciplines. Special attention should be paid to the distal anatomy of the portal vein in patients undergoing liver resection and transplantation to ensure adequate graft selection and appropriate anastomoses and to avoid unintentional impairment of blood perfusion. Moreover, the morphological deviation of the glisson stem is often associated with variations in the branching of the PV, and their assessment is necessary to reduce the risk of iatrogenic complications. Thus, the preoperative study of PV branching is a guarantee of safety and efficiency in resection and endovascular surgery of the liver [4, 8].

To assess the IV branching in our study, we used the classification of portal vein branching according to T. Nakamura et al. The study revealed: in the indigenous group, Type A was identified as predominant with 20 (80%) cases, Type C with 3 (12%) cases and Type B with 2 (8%) cases. When analyzed by gender, the branching of the portal vein was distributed as follows: Type A — 11 cases in men (42.3%) and 9 cases in women (36%), Type B — 1 case in men and 1 case in women (4%), while Type C was more common in women 2 (8%) than in men 1 (4%). In the non-indigenous group, Type A was found in 24 (96%) cases, Type B in 1 (4%) case, and Type C was not detected at all. When analyzing the patients by gender, we found Type A to be more common in women (64%) than in men 8 (32%), while Type C was found in 1 (4%) case in men of this group. The percentage of standard PV branching, i.e. the branching of the portal vein into two trunks in our study in subgroup analysis was at 80% in the indigenous group, and at 96% in the non-indigenous group, while the deviation from the standard anatomy of the PV branching was 20% and 4%, respectively. The data obtained correspond to the results of large studies of the PV branching [3, 11], which are reflected in Graph 4.

Conclusion. The results of our study indicate the presence of significant differences in the formation and branching of PVs between the studied groups. In the first group of the indigenous population, we found only 4 types of PV confluence formation, with Type C prevailing at 48%. In the second group, we found 6 types of PV confluence formation; in this group Type A prevailed at 48%, and 1 case of confluence formation was not described in the classification of P. Krumm et al. When analyzing the gender characteristics of the indigenous population group, we found gender differences in the formation of PV; for example, Type A prevailed in women, and Type B in men. In the non-indigenous group, Type A prevailed in the non-indigenous group in both sexes. When analysing PV branching variants according to T. Nakamura et al. in both groups, we see Type A prevailing, and the variability of branching types in the indigenous group was 20%; Type C was found in 12% of cases, and Type B was detected in 8% of cases. In the non-indigenous group, Type C was identified in 4% of cases.

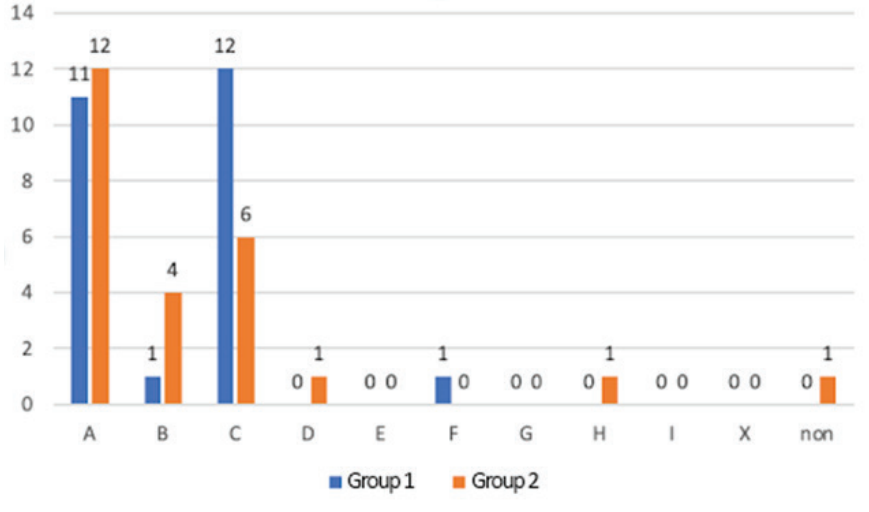

Fig. 3. Variants of PV Confluence According to the Classification by P. Krumm et al. In the Study Groups (non — Missing Applicable Classification)

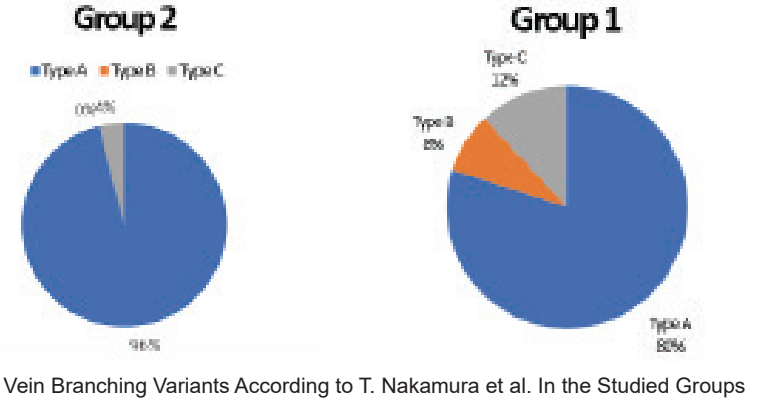

Fig. 4. Portal Vein Branching Variants According to T. Nakamura et al. In the Studied Groups

Thus, a detailed study of the ethnic features of the portal vein variant anatomy is relevant in view of the development of modern surgery in terms of the safety and effectiveness of surgical interventions in the gastropancreatobiliary zone.

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POSSIBILITIES FOR MONITORING THE PHARMACODYNAMICS OF DABITAGRAN ETEXILATE

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The sensitivity and prognostic significance of laboratory tests and methods for assessing pharmacodynamics in relation to the system of regulation of the aggregate state of blood after a single dose of dabigatran etexilate at a dosage of 150 mg were investigated. Determination of the functional state of the hemostatic potential of native blood was carried out using thromboelastography (before and after 2, 4, 12 hours after taking the drug) and low-frequency piezothromboelastography (before taking the drug and after 2, 4, 8, 12 and 24 hours after taking the drug). In parallel with the study of changes in the viscoelastic properties of native blood, the dynamics of the activated partial thromboplastin time was monitored (before taking the drug and 2, 4 and 12 hours after taking the drug).

According to the results of LFPTEG, the maximum severity of the direct pharmacodynamic effect of dabigatran etexilate was recorded 4 hours after taking the drug (which was reflected by a pronounced decrease in the efficiency of the proteolytic stage of fibrinogenesis) with the return of the activity of the proteolytic stage of fibrinogenesis to the initial level at 8 hours with the retention of residual antithrombotic activity up to 12 hours.

The use of thromboelastography was limited to a 4-hour interval, while the APTT test was limited to 2 hours from the moment of taking the drug, after which the level of indicators returned to the initial value.

Keywords: system of regulation of the aggregate state of blood, dabigatran etexilate, hemocoagulation, hemostatic potential, whole blood, global tests, low-frequency piezothromboelastography.

Introduction. To date, anti-thrombotic therapy has a wide range of anticoagulant agents to offer, including a group of direct oral anticoagulants (DOA), associated with new opportunities for pharmacological thrombosis prevention. Distinctive features of this group of drugs are oral administration, targeted action (factor Xa: apixaban and rivaroxaban, factor IIa: dabigatran), and absence of the need for laboratory control of therapy — a feature that most clinicians would appreciate [17]. Dabigatran is the first DOA group drug approved for use in clinical practice. Its efficacy and safety have been confirmed in several studies [15], specifically, RE-MODEL (2007), RE-NOVATE (2007), RELY (2009), RE-COVER (2009), REMEDY (2013), RE-SONATE (2013), RE-ALIGN (2013), RE-DUAL PCI (2017), RESPECT ESUS (2019), RESPECT CVT (2019).

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However, the actual clinical safety and efficacy of the drug observed in the course of routine practice differ from the data obtained in the phase III of clinical trials [2,13], which creates presuppositions for ethical contradictions among practitioners. For instance, the RE-CIRCUIT study (2017) designed to compare the efficacy/safety of dabigatran and warfarin in patients with mechanical heart valves revealed an increased incidence of thromboembolism and hemorrhagic complications in patients receiving dabigatran [8], which was the reason for the early termination of the study. As demonstrated in the work [11], the use of dabigatran, compared to warfarin, is associated with an increased risk of major bleedings, a higher risk of gastrointestinal bleeding, but a lower risk of intracranial hemorrhages. There has also been a number of reports of severe/fatal bleeding in elderly and senile patients [5, 6, 19]. In addition, hypercoagulation that develops after discontinuation of administering dabigatran may also be a significant concern [14]. Thus, lack of laboratory control of dabigatran therapy is quite a significant problem [7].

Currently, dabigatran is recommended as a first-line drug for the treatment of venous thromboembolic complications in patients with non-valvular atrial fibrillation, with advised twice-daily intake of 150 mg [18]. The recommendations for monitoring the efficacy and safety are reduced to the analysis of clinical data (examination findings, medical history) using specialised scales (HAS-BLED, CHA2DS2-VASc, etc.). This approach lacks any objective criteria for the assessment of the functional state of the hemostatic potential – an integrative component of the full-cycle hemocoagulation, which ensures the necessary blood fluidity and restricts extravasation of blood components in cases of disruption of the vascular wall integrity or any damage to it [1,3].

A number of laboratory tests have been proposed to monitor the efficacy/safety of dabigatran, including activated partial thromboplastin time (APTT), ecarin blood clotting time (ECT) and diluted thrombin time (Hemoclot) [4]. All these tests have similar disadvantages: they analyse only a certain "cluster" of hemocoagulation but are not implemented in routine clinical practice (ECT, Hemoclot) and have a low level of standardisation [9, 10, 16].

Dabigatran is known to have an effect not only on free thrombin (and, as a result, on the plasma component of hemostasis), but also on thrombin associated with the formation of fibrin clots, and on the thrombin-induced platelet activation [12], reducing the level of their participation in thrombogenesis. In addition to the weakened functional responses of platelets mediated through PARs receptors, the cellular component is also affected by other components of anti-thrombotic therapy (two- or three-component therapy) prescribed together with dabigatran. This is what identifies the need not only to assess the "peak" effect of dabigatran, determined by integrative hemostasis tests, but also to assess the effect of a combination of anti-thrombotic agents on the hemostatic potential, in general, taking into account

the cellular component of hemostasis.

Thus, the problem discussed above entails the need to develop an algorithm for evaluating the efficacy/safety of dabigatran which would meet the following criteria: (I) it could be performed using native blood; (II) it would provide information on all components of fibrinogenesis (starting from initiation/amplification to the formation of cross-linked fibrin and possible clot lysis), and (iii) it could be carried out in the "Point-of-care testing" mode.

To date, the integral characteristic of the hemostatic potential of native blood can only be obtained using such "global" hemostasis system tests as the rotational (TEG, ROTEM) and vibration (LFPTEG) viscometry. These methods determine changes in the physical state of blood, however they show a fundamental difference when it comes to the comparison of the informative value of the data obtained – the LFPTEG method registers changes in blood viscosity at the initial stages of fibrinogenesis, in the time interval that is identified as the "lag-time" in the TEG [1,3]. This allows us to analyse the intensity of hemocoagulation during the initiation/amplification phases and to determine the activity of the proteolytic stage of fibrinogenesis, whereas the TEG and ROTEM methods provide information only on the post-coagulation phase of fibrinogenesis.

The objective of this study was a comparative assessment of the informative value of global tests of the hemostasis system in relation to the control of the efficacy of dabigatran etexilate.

Table 1

Volunteer selection criteria

Criteria	Approved	Not approved
Male sex	+	–
Age from 18 to 55	+	–
Body mass index: 18.5 – 24.99	+	–
Taking antiplatelet, anticoagulant, fibrinolytic, antihypertensive or other drugs affecting the hemostatic system.	–	+
Suffering from diseases in the acute stage and/or exacerbation of chronic diseases	–	+
Suffering from diseases that affect the hemostatic system	–	+
Thrombotic complications in the medical history	–	+

Materials and methods. The study was conducted at the clinic of the E. D. Goldberg Research Institute of Pharmacology and Regenerative Medicine. Thirty healthy male volunteers participated in the study after signing a voluntary informed consent. The criteria for the volunteer selection for the study is presented in Table 1.

Apart from medical history check (identification of complaints), the screening stage included general and biochemical blood tests. The general blood test was performed on whole stabilized venous blood using an ABX Micros ES 60 analyzer (HORIBA ABX SAS, France). The biochemical blood test was performed on citrate plasma (alkaline phosphatase and total bilirubin were checked on serum) using an automatic biochemical analyzer Erba Mannheim XL 200 (Erba Lachema, Czech Republic). At the end of the screening, provided that the selection criteria were met, the participants' hemostatic potential was monitored over time after a single 150 mg dose of dabigatran etexilate (Pradaxa, Boehringer Ingelheim International GmbH, Germany).

APTT was determined on platelet-poor plasma using a 4-channel semi-automatic coagulometer Amelung KC 4 delta (TRINITY Biotech, Ireland) 2, 4, and 12 hours after the drug intake.

TEG was performed on native venous blood taken without a tourniquet, using a TEG 5000 thromboelastograph (Haemoscope Corporation, USA). The pharmacodynamics of dabigatran were monitored 2 and 12 hours after the drug intake; the following TEG parameters were evaluated:

- R (min) – the time from the start

Table 2

Estimated LFPTEG parameters

Indicator	Meaning
ICC, per units. Intensity of contact coagulation	Displays the aggregation activity of blood corpuscles
ICD, per units. Intensity of coagulation drive	Displays the proteolytic stage and the beginning of the polymerization stage of the third phase of blood clotting
CTA, per units. Constant of thrombin activity	Criterion for assessing the intensity of the proteolytic stage of fibrinogenesis
ICP, per units. Intensity of clot polymerization	Displays the intensity of the polymerization stage
MA, per units. Maximum amplitude of the clot	Characteristics of the maximum density of the clot due to the activity of the blood corpuscles and the qualitative and quantitative characteristics of the cross-linked fibrin after the completion of polymerization and the retraction process
ITC, per units. Intensity of total clotting	General evaluation of the intensity of cross-linked fibrin formation
IRCL, per units. Intensity of the retraction and clot lysis	Evaluation of the lytic activity in the studied blood sample
TAAF, per units. Total anticoagulation activity factor	Displays the total anticoagulation activity in the aliquot
t1, min.	Characterizes the suspension stability of the blood
t3, min.	Blood gelation time
t5, min.	Time to reach the maximum density (retraction) of the clot

of the test to the detection of signs of thrombosis (when the signal reaches an amplitude of 2 mm).

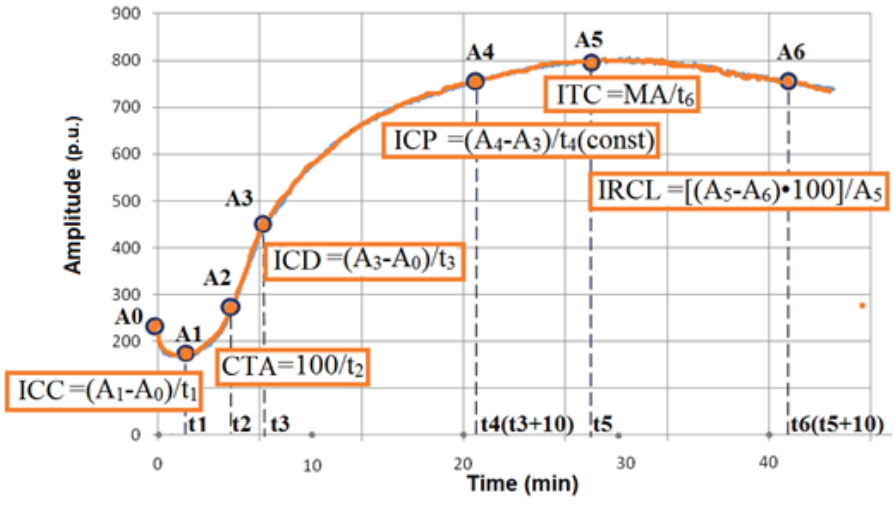
- Angle α (°) – the angle constructed tangentially to the TEG from the point of the beginning of the clot formation, which reflects the rate of growth of the fibrin formation and its structure (increase in the clot strength).
- K (min) – the time of initial thrombosis (reaching the signal amplitude of 20 mm).
- MA, mm – the maximum amplitude of the curve that characterizes the maximum dynamic properties of the connection between fibrin and platelets and shows the content of fibrinogen and the maximum clot strength.

The hemostatic potential was determined using the LFPTEG method on native venous blood collected from the vein in the bend of the elbow joint without a tourniquet, using the ARP-01M Mednord thromboelastograph (Registration certificate of Federal service for surveillance in healthcare № 2010/09767). The estimated parameters of the piezothromboelastogram are given in Table 2; the approximation of the estimated parameters to the piezothromboelastogram curve is shown in Figure 1.

Statistical processing of the obtained data was carried out using the IBM SPSS Statistics 22.0 programme. To check the null hypothesis, the comparison of the independent study groups was conducted using the Mann-Whitney test; the differences were recognized as statistically valid at a significance level of $p < 0.05$. Quantitative indicators are presented as Me [LQ; Uq], where Me is the median, LQ (Q25) is the lower quartile, and UQ (Q75) is the upper quartile.

Results of the research. Dabigatran showed the maximum anticoagulant effect in 2-4 hours after the drug intake (Tables 3-4).

The statistically significant differences in the APTT index compared to the baseline level were recorded only at the start of the second hour after dabigatran intake (an increase of 1.38 times, p = 0.001). TEG demonstrated quite a significant period of time: the second hour showed lengthening of the time of the beginning of clot formation (R increase by 1.11 times, p = 0.009), reduced growth rate of the fibrin formation (alpha angle value decrease by 1.08 times, p = 0.001) and a decrease of the maximum density of the clot (MA decrease by 1.1 times, p=0.001). The changes in level of indicators that are characteristic of structural hypocoagulation persisted for 4 hours: a decrease in the intensity of fibrinogenesis (alpha angle value decrease by 1.05 times, p=0.001) and a decrease in the maximum clot density (MA decrease by 1.09 times, p=0.001) were recorded. In 12 hours after dabigatran intake, no statistically significant differences between the parameters of the thromboelastogram and the initial parameters were registered.



Piezothromboelastogram curve specifying the parameters

LFPTEG was the most informative of all the used methods (Table 4)

According to the results of the LFPTEG, the effect of dabigatran was registered on the 2nd hour after the drug intake, and the maximum effect was reached after 4 hours.

In a two-hour interval after the dabigatran intake, the hemostatic potential was characterized by a decrease in the overall intensity of hemocoagulation (ITC decrease by 1.22 times, p = 0.016). Moderate anticoagulation occurred due to an increase in the suspension stability (t1 increase by 3.07 times, p = 0.001), reduction of the intensity of proteolytic stage of clot formation (CTA and ICD levels decreased by 2.57 times (p = 0.016) and 1.9 times (p = 0.002), respectively), as well as an increase in the time of blood gelation (t3 increase by 3.07 times, p = 0,018). In addition, a decrease in anticoagulant activity against the background of chronometric hypocoagulation was registered (TAAF decrease by 1.82 times, p = 0.002).

The "peak" action of dabigatran is characterised by a general decrease in the intensity of coagulation (ITC decrease by 1.22 times, p = 0.01): increased suspension stability of the blood (t1 increase by 3.15 times, p = 0.001), decreased intensity of proteolytic stage fibrinogenesis (CTA and ICD levels decreased by 3.33 times (p = 0.003) and 2.01 times (p = 0.001) respectively), and an increase in the time of blood gelation (t3 increase by 2.05 times, p = 0.003) compared to the baseline level. Against the background of a general decrease in the intensity of fibrinogenesis, a decrease in the intensity of the anticoagulant potential (TAAF decrease by 1.82 times, p = 0.001) was also registered with regard to the baseline level.

In 8 hours after the drug intake, a number of indicators returned to the initial level (CTA and t3). At the same time, a decrease in the level of the t1 indicator was recorded simultaneously with an increase in the levels of ITC and TAAF indicators, which demonstrated a shift in the hemostatic potential towards normal coagulation, which returned to the previous level of hypocoagulation in 12 hours.

The hypocoagulation state of the hemostatic potential remained for up to 12 hours after the drug intake (ITC decrease by 1.2 times, p = 0.024): suspension stability of the blood remained (t1 increase by 1.66 times, p = 0.015), and the intensity of fibrinogen proteolysis decreased (ICD decrease by 1.48, p = 0.035). At the 24th hour of the study, the HP of the healthy volunteers was characterized by a normal coagulation state comparable to the baseline level. However, at the final point, all volunteers registered an isolated increase in the aggregation activity of the blood corpuscles, which was evidences by an increase in ICC value by 1.71 times (p = 0.029) compared to the initial value. The change of this parameter over time shows an isolated increase in the aggregation activity of the blood corpuscles, observed after the end of the drug effect.

Conclusion. This article presents the results of comparative monitoring of the pharmacodynamics of dabigatran etexilate after a single intake of 150 mg of

the drug by healthy male volunteers with a local APTT hemostasis test, as well as global tests - TEG and LFPTEG.

The APTT test showed informative value only at the "peak" of the dabigatran action (2 hours after the intake), since the blood test sample taken in 4 hours after the intake did not show any statistically significant differences if compared to the baseline level.

The possibility of a longer monitoring of the pharmacodynamics of dabigatran was identified in a study using native blood.

Thromboelastography performed on native blood for the purpose of monitoring the pharmacodynamics of dabigatran proved not to be informative enough – a decrease in the rate of formation (R and α angle indicators), gelation and density of the fibrin-platelet structure (MA indicator) was observed against the background of the maximum effect of dabigatran. However, in 12 hours after dabigatran intake, no statistically significant differences between the parameters of the thromboelastogram and the initial parameters were registered. Thus, the method of thromboelastography was not informative enough to be used for dynamic monitoring of the hemostatic potential, since for the most part it displayed only structural hypocoagulation observed after dabigatran intake and showed practically no chronometric hypocoagulation.

And vice version, the LFPTEG method, which demonstrated the largest time range of the possibility of registering the action of dabigatran, predominantly recorded changes in parameters reflecting the chronometric hypocoagulation of the initial stages, a decrease in the intensity of the proteolytic stage of fibrinogenesis, and an increase in the time of blood gelation. In response to a decrease in the intensity of clot formation, a decrease in the total anticoagulant activity of the blood was recorded. In contrast to the data obtained by the TEG method, according to the results of the LPTEG over 24 hours, there was no decrease in the intensity of fibrin polymerization, the time of formation of cross-linked fibrin and the maximum polymerization stage of fibrinogenesis. Also, the NPTEG method in all study participants at the 24th hour after taking dabigatran showed an isolated increase in the aggregation activity of blood corpuscles. Given the absence of changes in the dynamics of aggregation of blood corpuscles during induced hypocoagulation and its intensification after the end of the action of the anticoagulant, it becomes necessary to conduct further studies with a closer study of platelet aggregation.

Table 3

Dynamic monitoring of activated partial thromboplastin time and thromboelastography in healthy volunteers before and after dabigatran intake

Indicator		Background	In 2 hours	In 4 hours	In 12 hours
APTT		36.0 [35.5; 38.5]	50.0 [47.0; 52.0]*	37.0 [35.0; 42.0]	38.0 [36.5; 42.5]
TEG	R	13.5 [13.0; 15.5]	15.0 [14.5; 16.5]*	13.5 [13.0; 14.5]	13.0 [13.0; 14.5]
	Angle α	49.0 [47.5; 50.0]	45.0 [44.0; 45.0] *	46.5 [45.5; 47.0]*	48.0 [47.0; 49.5]
	K	6.5 [5.0; 7.0]	7.0 [6.5; 7.0]	6.5 [5.5; 6.5]	6.0 [5.0; 6.5]
	MA	51.0 [50.0; 60.0]	46.0 [45.0; 46.5] *	46.5 [45.0; 47.0]*	50.0 [49.0; 56.0]

Notes to Table 3: * - statistically significant differences in comparison with the background level of the indicator, $p \leq 0.05$

Table 4

Dynamic monitoring of low-frequency piezothromboelastography in healthy volunteers before and after dabigatran intake

Indicator	Background	In 2 hours	In 4 hours	In 8 hours	In 12 hours	In 24 hours
T1, min	1.30 [1.15; 1.65]	4.00 [3.90; 4.10]*	4.10 [4.00; 4.20] *	2.20 [2.00; 3.80] *	2.40 [2.20; 2.45]*	1.30 [1.15; 1.35]
ICC, per units.	10.83 [8.00; 15.78]	12.20 [11.90; 12.50]	11.90 [10.47; 12.50]	13.89 [12.11; 18.18]	5.42 [3.71; 15.21]	18.57 [16.98; 24.29]*
CTA, per units.	47.62 [29.76; 69.05]	18.52 [16.39; 19.23] *	14.29 [12.66; 14.93] *	28.57 [24.39; 33.33]	33.33 [33.33; 33.91]	33.33 [32.29; 33.91]
T3, min	7.80 [5.00; 10.40]	12.80 [12.00; 14.10] *	16.00 [15.50; 17.90] *	9.80 [9.20; 12.00]	10.20 [9.10; 12.10]	7.20 [6.60; 7.35]
ICD, per units.	38.63 [27.37; 51.06]	20.31 [20.00; 21.28] *	19.21 [17.14; 19.35] *	25.59 [20.17; 26.12] *	25.98 [25.31; 26.74] *	38.61 [38.31; 41.81]
ICP, per units.	14.60 [12.15; 16.25]	15.00 [13.50; 17.50]	13.00 [12.00; 13.50]	14.00 [12.90; 14.00]	13.80 [11.90; 15.90]	16.30 [15.65; 16.50]
T5, min	37.60 [34.25; 45.90]	46.00 [45.00; 47.00]	45.80 [45.00; 46.00]	44.00 [42.00; 46.00]	45.50 [45.00; 45.75]	37.20 [36.60; 37.85]
MA, per units.	522.0 [493.5; 557.5]	500.0 [480.0; 550.0]	500.0 [490.0; 520.0]	498.0 [490.0; 525.0]	515.0 [501.5; 545.0]	486.0 [483.0; 500.5]
ITC, per units.	13.66 [12.50; 14.85]	11.11 [10.43; 11.70] *	11.36 [10.70; 11.56] *	11.67 [11.62; 11.93] *	11.32 [11.15; 11.91] *	13.33 [12.98; 13.59]
IRCL, %	0.38 [0.32; 0.94]	0.62 [0.46; 1.82]	0.65 [0.50; 1.33]	0.67 [0.31; 0.92]	1.21 [0.85; 1.45]	0.67 [0.34; 1.73]
TAAF, per units.	2.59 [2.21; 3.30]	1.42 [1.16; 1.81] *	1.42 [1.24; 1.51] *	2.11 [1.73; 2.48] *	1.88 [1.71; 2.17] *	2.37 [2.33; 2.69]

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DETERMINATION OF THE PHARMACOKINETIC PARAMETERS OF ISONIAZID USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY IN PATIENTS WITH PULMONARY TUBERCULOSIS

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Tuberculosis is one of the most common diseases worldwide. The pharmacokinetics of isoniazid are unpredictable and vary widely in patients taking standard doses of the drug. In order to find the optimal dose of isoniazid, therapeutic drug monitoring should be carried out, determining the equilibrium concentration of the drug in blood plasma by HPLC.

The aim of this study is to determine the concentration of isoniazid in blood plasma by HPLC and calculate the pharmacokinetic parameters of isoniazid in patients with newly diagnosed pulmonary tuberculosis in the Republic of Sakha (Yakutia).

We determined the equilibrium concentration of isoniazid in blood plasma by high-performance liquid chromatography in 33 patients with pulmonary tuberculosis, using a Milichrome a-02 device manufactured by CI “Econova" LLC (Russia) using a ProntoSIL 120-3-C18 AQ column.

The results obtained confirm the high individual variability of pharmacokinetic parameters: the maximum equilibrium concentration of the drug, the area under the pharmacokinetic curve, the average stationary concentration of the drug, the degree of fluctuation in the concentration of isoniazid in the blood plasma of patients with tuberculosis. Individual differences in the pharmacokinetic parameters of isoniazid indicate the need for therapeutic drug monitoring when prescribing isoniazid.

Keywords: tuberculosis; pharmacokinetics, equilibrium concentration, isoniazid, high-performance liquid chromatography.

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Introduction. Tuberculosis is common in all countries and age groups. According to reports provided by the World Health Organization, 10 million people fell ill with tuberculosis in 2019, 1.4 million people died.

For the treatment of newly detected drug-sensitive tuberculosis, a highly active anti–tuberculosis drug isoniazid is used. Isoniazid disrupts the synthesis of mycolic acids and has a selective bacteriostatic effect on non-dividing and bactericidal effect on Mycobacterium tuberculosis (M. tuberculosis) in the breeding stage.

The pharmacokinetics of isoniazid are unpredictable and vary widely in patients taking standard doses of the drug. Individual differences in the pharmacokinetics of isoniazid depend on many factors: age, gender, body weight, race and ethnicity, the rate of acetylation, the nature and severity of the underlying and/or concomitant diseases, dysfunction of elimination systems, drug interactions, the presence of bad habits, etc. [1,5,12,16].

Isoniazid is a drug with concentration-dependent antimicobacterial action. The level of its concentration in plasma correlates with the speed of tuberculosis recovery, elimination of bacilli, the frequency of adverse drug reactions and drug resistance of M. tuberculosis [7,11,13,14]. In order to determine the optimal dose of isoniazid, it is necessary to know the "dose - concentration of isoniazid or the area under the pharmacokinetic curve" dependance. To do this, therapeutic drug monitoring is carried out with the determination of the equilibrium concentration of the drug in the blood plasma. Carrying out therapeutic drug monitoring of isoniazid will rationalize the treatment of tuberculosis, increase the effectiveness of treatment and minimize the development of undesirable drug reactions.

Currently, the method of high-performance liquid chromatography (HPLC) is widely used in monitoring the concentration of the drug in the blood plasma of patients. The advantage of the HPLC method from the rest is high sensitivity and versatility, the HPLC method simultaneously determines the concentrations of several medicinal substances with sufficient selectivity, accuracy and reproducibility [8]. However, in the Republic of Sakha (Yakutia), the use of the HPLC method for monitoring the concentration of isoniazid to determine the equilibrium concentration of the drug in blood plasma in patients with tuberculosis was not utilized.

In this regard, the purpose of our study was to determine the concentration of isoniazid in blood plasma by HPLC and calculate the pharmacokinetic parameters of isoniazid in patients with newly diagnosed pulmonary tuberculosis in the Republic of Sakha (Yakutia).

Material and methods. The protocol of the study was reviewed and approved by the Ethics Committee at the Scientific and Practical Center "Phthisiology" (Protocol No. 3 of 26.09.2018). The study involved 35 patients with newly diagnosed pulmonary tuberculosis (Table 1). Inclusion criteria: first onset of pulmonary tuberculosis, intensive phase of anti-tuberculosis chemotherapy, age of patients 18-60 years, the presence of signed informed consent. Exclusion criteria: generalized tuberculosis, HIV infection, malignant neoplasms and other concomitant diseases, taking any medication lasting more than a week during the last month, drinking alcoholic beverages, pregnancy.

For three days, isoniazid was injected into the vein 1 time a day at a dose of 10 mg/ kg (no more than 600 mg/day) (Clinical recommendations "Tuberculosis of the respiratory organs in adults" (approved By the Ministry of Health of Russia in 2018). Blood samples were obtained on the 4th day: 15 minutes before the injection of isoniazid, then 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 16 hours, 24 hours after it. Blood was centrifuged at 3000 g for 10 min, plasma was subjected to "shock freezing" with liquid nitrogen.

Blood plasma in the amount of 200 µl was placed in a 1.5 ml Eppendorf tube, 100 µl of 10% trichloroacetic acid was added, intensively shaken on a vortex for 10 minutes, centrifuged for 5 minutes at 12100 g, 100 µl was taken for analysis. The isoniazid concentration was determined by high-performance liquid chromatography (HPLC) on a Milichrome a-02 device manufactured by CI "Econova" LLC (Russia). Chromatographic examination was carried out on a ProntoSIL 120-3-C18 AQ column. The conditions for determining the level of isoniazid by HPLC were as follows: eluent A – 0,4 % articulant with 0.1 % trifluoroacetic acid, pH 2,2; eluent B: acetonitrile; gradient: regeneration – 700 µl 1% B, 1 tier – 1-60 % B for 2000 µl, 2 step – 100% B 2000-2800 µl; eluent flow rate of 150 µl; wavelength detector – 266 nm; time constant of the detector is 0.18 s; temperature – 40^{0}C; pressure - 2.5-5.5 MPa; sample volume - 20 µl. The chromatogram of the working blood plasma sample of a patient with pulmonary tuberculosis with intravenous administration of isoniazid obtained as a result of HPLC analysis is shown in Figure 1.

Based on the obtained concentrations of isoniazid the following pharmacokinetic parameters were determined: $AUC_{\tau,ss}$ – area under the curve within a dosing interval at steady-state conditions (ss) with repeated administration of the drug; $C_{max,ss}$ – maximum equilibrium concentration of drug in blood plasma; $C_{min,ss}$ – minimum equilibrium concentration of drug in plasma; T_{max} is the maximum measured concentration in blood plasma of the patient C_{av} – average steady-state concentration of drug in blood plasma; DF – degree of fluctuation of drug concentration in plasma; T½ is the half – life of the drug substance; k_{el} – constant of elimination of drug substances; $T_{aboveCav}$ – the period of time during which the concentration of medicinal substance exceeds C_{av} [2; 3].

Statistical processing of research results was carried out using the Microsoft Excel application software package and the IBM SPSS Statistics 24 statistical program. The Kolmogorov-Smirnov criterion was used to check the distribution form. The initial quantitative variables are presented in the form of Me [Q1-Q3] - median and interquartile interval (values of 25 and 75 percentiles). The Mann-Whitney U–test was used to compare two independent samples. When comparing the groups , the differences were considered statistically significant at p<0,05.

Table 1

Demographic and anthropometric indicators of patients included in the study

Parameter		n=35
Age, years (M±SD)		33.00±10.87
Height, cm (M±SD)		164.00± 9.58
Weight, kg (M±SD)		55.00± 8.24
Sex	male, % (person)	22 /35 (62.86)
	female, % (people)	13/35 (37.14)
Nationality	Yakuts, % (people)	31/35 (88.57)
	Russians, % (people)	4/35 (11.43)
Degree of obesity	Deficit, % (people)	5/35 (14.29)
	Norm, % (people)	28/35 (80.0)
	Excess, % (people)	2/35 (5.71)
Diagnosis	Infiltrative tuberculosis, % (people)	16/35 (45.71)
	Focal tuberculosis, % (people)	10/35 (28.57)
	Disseminated tuberculosis, % (people)	9/35 (25.71)

Note: BMI – body mass index; M - average value; SD - standard deviation.

Results and discussion. The patients (35) included in the studies did not have statistically significant demographic and anthropometric differences. On day 4, 2/35 (5.71%) patients developed adverse effects during parenteral administration of isoniazid: 1/14 (7.14%) patient complained of dizziness, 1/14 (7.14%) patient developed nausea, vomiting, drug administration was discontinued, patients were excluded from the analysis. Statistical analysis was performed on the data of 33 patients.

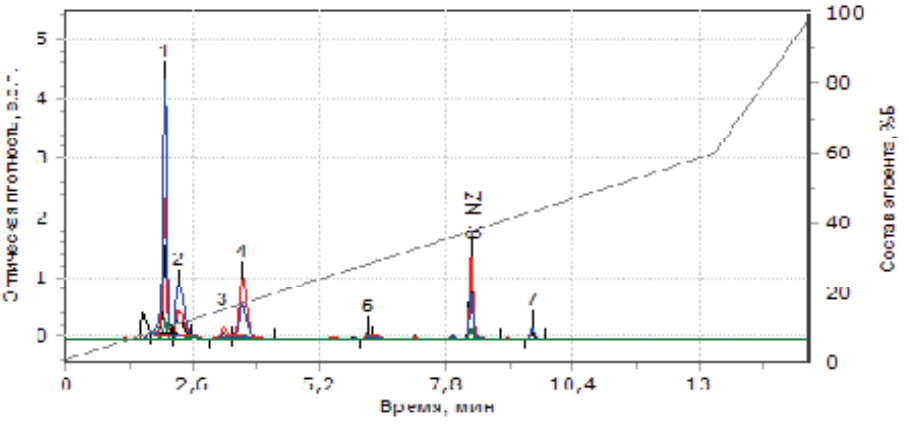

Fig. 1. Blood plasma chromatogram of a patient with pulmonary tuberculosis with intravenous administration of isoniazid (INH)

In accordance with the set goal and objectives, the concentration of isoniazid in blood plasma samples was determined during the study to construct pharmacokinetic curves. The profile "plasma concentration - time" after intravenous administration of isoniazid in the blood plasma of patients included in the study is shown in Figure 2.

Average values of pharmacokinetic parameters of isoniazid in patients included in the study: the area under the curve ($AUC_{t,ss}$) – of 37.69 (22,62-58,76) μg×h/ml; the maximum equilibrium concentration of isoniazid ($C_{max,ss}$) – 12,76 (10,02-16,29) μg/ml; the time to maximum plasma concentration (T_{max}) – 0,50 (0,50-0,50) h; the average steady-state concentration (C_{av}) – 1,57 (0,94-2,44) μg/ml; the degree of fluctuations of drug concentration in blood plasma (DF) – 753,20 (538,90-1149,00) %; the period of preliminarii ($T_{½}$) – 2,23 (1,71 was 3.79) h; the elimination constant (k_{el}) – 0,31 (0,18-0,40) h^{-1}; the time during which the concentration exceeds With$_{av}$ ($T_{aboveCav}$) – 5,50 (4,50-5,50) h

According to the dependence of the concentration of isoniazid on time, pharmacokinetic parameters were calculated, presented in Table 2.

A personalized analysis of the pharmacokinetic parameters of isoniazid showed their significant individual variability (Table 2).

The maximum plasma concentration of isoniazid (C_{max}) and the area under the pharmacokinetic curve ($AUC_{t,ss}$) are the most important pharmacokinetic parameters of isoniazid, determining its effectiveness and tolerability.

The optimal maximum concentration of isoniazid in blood plasma is in the range from 3 to 6 micrograms/ml [6,9] When prescribed 10 mg / kg / day (no more than 600 mg / day) the maximum equilibrium concentration (With $_{max, ss}$) of isoniazid in the blood plasma of all patients was determined above 6 micrograms/ml.

To ensure the necessary therapeutic effect and reduce the risk of adverse drug reactions in the treatment of tuberculosis, the average inpatient concentration (C_{av}) of isoniazid should be within the therapeutic range of 1-2 micrograms/ml [4.10]. The average inpatient concentration (C_{av},) of less than 1 mcg/ml was determined in 9/33 (27.27%) patients, was 0.73±0.17 mcg/ml, more than 2 mcg/ml - 13/33 (39.39%) patients, 4.22±4.45 mcg/ml.

J. Pasipanodya et al. It was established that the values of the area under the pharmacokinetic curve (AUC) of isoniazid ≤ 52 mcg×h/ml are predictors of

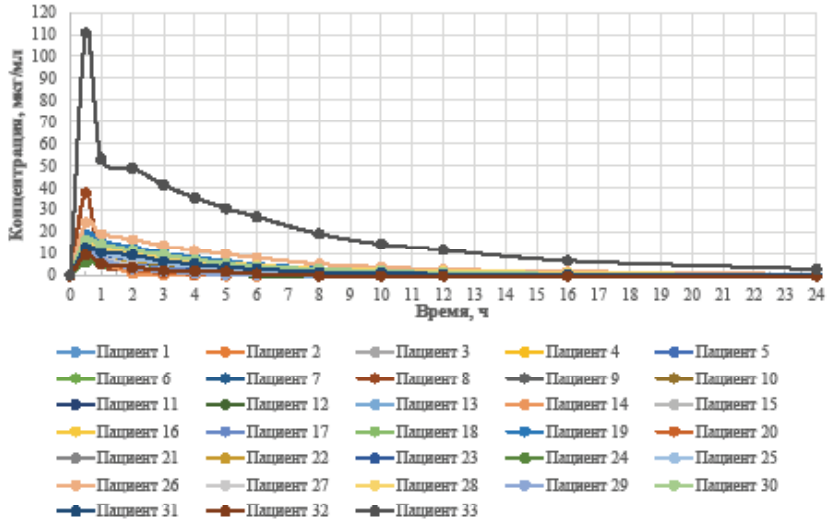

Fig. 2. Pharmacokinetic curves of isoniazid concentration in blood plasma after intravenous administration of the drug to patients included in the study

Table 2

Pharmacokinetic parameters of isoniazid in patients with pulmonary tuberculosis

Patient's No	$C_{max,ss}$, mcg/ml	T_{max}, h	AUC, mcg×h/ml	k_{el}, h^{-1}	$T_{1/2}$, h	C_{av}, mcg/ml	DF, %	$T_{aboveCav}$, h
1	10.72	0.50	29.11	0.40	1.74	1.21	883.91	4.50
2	13.64	0.50	39.17	0.12	6.02	1.63	836.06	4.50
3	18.52	0.50	72.28	0.29	2.44	3.01	614.87	5.50
4	19.22	0.50	54.50	0.37	1.87	2.27	846.50	5.50
5	11.83	0.50	37.69	0.32	2.14	1.57	753.22	5.50
6	6.63	0.50	33.90	0.06	11.33	1.41	469.60	5.50
7	7.85	0.50	24.42	0.42	1.66	1.02	771.31	5.50
8	37.84	0.50	35.12	0.13	5.30	1.46	2586.06	3.50
9	13.98	0.50	74.90	0.18	3.80	3.12	442.69	5.50
10	6.81	0.50	31.17	0.39	1.78	1.30	523.91	7.50
11	10.02	0.50	22.10	0.58	1.20	0.92	1087.82	3.50
12	8.79	0.50	14.30	0.82	0.85	0.60	1475.67	4.50
13	7.65	0.50	15.20	0.76	0.91	0.63	1208.92	4.50
14	8.07	0.50	10.18	0.95	0.73	0.42	1901.66	1.50
15	18.17	0.50	58.76	0.33	2.13	2.45	742.85	5.50
16	16.08	0.50	26.08	0.31	2.24	1.09	1479.47	4.50
17	13.94	0.50	27.29	0.40	1.72	1.14	1225.95	4.50
18	16.29	0.50	78.01	0.19	3.72	3.25	501.23	5.50
19	18.94	0.50	84.35	0.22	3.10	3.52	538.94	5.50
20	10.52	0.50	15.45	0.75	0.92	0.65	1633.89	3.50
21	14.47	0.50	51.64	0.33	2.08	2.15	672.62	4.50
22	10.17	0.50	43.29	0.22	3.21	1.80	563.63	5.50
23	11.17	0.50	49.54	0.19	3.64	2.06	541.29	7.50
24	6.40	0.50	17.88	0.42	1.67	0.75	859.46	4.50
25	13.04	0.50	44.55	0.26	2.64	1.86	702.43	5.50
26	24.48	0.50	131.93	0.14	5.00	5.50	445.30	5.50
27	10.82	0.50	22.62	0.43	1.60	0.94	1147.56	3.50
28	14.67	0.50	75.75	0.09	7.68	3.16	464.88	5.50
29	11.16	0.50	20.12	0.28	2.51	0.84	1331.03	3.50
30	16.46	0.50	79.12	0.17	4.20	3.30	499.12	5.50
31	12.76	0.50	57.24	0.07	9.49	2.39	534.99	5.50
32	9.46	0.50	19.76	0.32	2.14	0.82	1149.03	5.50
33	110.60	0.50	449.44	0.12	5.91	18.73	588.45	7.50

Note: Me [Q1-Q3] is the median and interquartile interval (values of 25 and 75 percentiles).

Table 3

The average values of the main pharmacokinetic parameters of isoniazid for both groups of patients

Parameter	Group 1, n=23	Group 2, n=10	p (Kraskel-Wallis criterion)
$C_{max,ss}$, mcg/ml	12.29 [10.12-16.33]	13.04 [9.46-16.07]	p = 0.98
$T_{max,}$ h	0.50 [0.50-0.50]	0.50 [0.50-0.50]	—
$AUC_{t, ss}$, mcg×h/ml	38.43 [26.57-61.00]	26.08 [19.76-58.76]	p = 0.51
k_{el}, h^{-1}	0.30 [0.17-0.40]	0.31 [0.26-0.32]	p = 0.98
$T_{½}$, h	2.28 [1.70-3.89]	2.23 [2.13-2.64]	p = 0.98
C_{av}, mcg/ml	1.60 [1.10-2.54]	1.08 [0.82-2.44]	p = 0.51
DF, %	712.90 [532.20-1102.80]	859.50 [702.40-331.00]	p = 0.25
$T_{aboveCav,}$ h	5.50 [4.50-5.50]	5.50 [4.50-5.50]	p = 0.65

Note: Me [Q1-Q3] — median and interquartile interval (values of 25 and 75 percentiles); group 1 - patients with body weight < 60 kg, group 2 - patients with body weight > 60 kg; p (Kraskel-Wallis criterion) - statistically significant differences at p.

acquired drug resistance M. tuberculosis [15]. AUC values of $_{T,ss}$ in 22/33 patients (66.67%) were determined below 52 mcg×h/ml for 24 hours, the average $AUC_{t\ ss}$ it was 28.66±11.90 micrograms ×h/ml.

According to the instructions for medical use, the half-elimination period ($T_{½}$) with repeated prescriptions of isoniazid is 2-3 hours. The indicator of the $T_{½}$ varies significantly among patients with fast and slow type of acetylation, is 0.5-1.6 hours and 2-5 hours, respectively (State Register of Medicines: [website]. URL:https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=019337ee-bfad-48fe-b9a7-02c7ac9e-109c&t=).

The half-elimination period ($T_{½}$) of isoniazid in 12/33 patients (36.36%) was less than 2 hours, was 1.39± 0.43 hours. A short period of half-elimination may be due to intensive biotransformation of isoniazid and indicate a rapid type of acetylation of the drug. In 13/33 (39.39%) patients, the half-elimination period was more than 5 h (5.56 ± 2.21 h), a decrease in the rate of acetylation of isoniazid is characteristic of patients with a slow type of acetylation.

When analyzing the pharmacokinetic parameters of isoniazid, a high concentration spread (DF, %) was found in patients, which does not allow maintaining a constant concentration of isoniazid in plasma in these patients.

Sharply distinguished values were found in patient No. 33: $AUC_{t\ ss}$, $C_{max,ss}$, $T_{1/2}$, C_{av} (Table 2). High values of the area under the pharmacokinetic curve ($AUC_{t\ ss}$) and the maximum plasma concentration (With $_{max,\ ss}$) of isoniazid correlate with the development of undesirable side reactions [13].

According to the study design, isoniazid was prescribed to patients at an estimated dose of 10 mg/ kg / day, but not 600 mg per day. We compared pharmacokinetic parameters among two groups of patients: group 1 - patients with body weight < 60 kg; group 2 - patients with body weight > 60 kg. The average values of the main pharmacokinetic parameters of isoniazid for the compared groups of patients are presented in Table 3.

According to the results of the comparison, no differences in pharmacokinetic parameters were found (Table 3).

Conclusions

1. The high specificity, accuracy, sensitivity and speed of the analysis make it possible to use the HPLC method to determine the concentration of isoniazid in blood plasma in order to conduct therapeutic drug monitoring in the treatment of drug-sensitive pulmonary tuberculosis.

2. For the first time, the equilibrium concentration of isoniazid in blood plasma was studied by HPLC in patients with pulmonary tuberculosis living in the Republic of Sakha (Yakutia).

3. High individual variability of pharmacokinetic parameters of isoniazid in the blood plasma of patients was established.

4. Individual differences in the pharmacokinetic parameters of isoniazid indicate the need for therapeutic drug monitoring when prescribing isoniazid.

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HEALTHY LIFESTYLE. PREVENTION

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STUDY OF THE MICRONUTRIENT COMPOSITION OF ACTUAL DIETS IN THE ELDERLY POPULATION OF YAKUTSK

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The data obtained allowed us to conclude that the elderly population had a deficit of vitamins, microelements in the diet of the actual consumption, especially there was a decrease with age. Gender differences in the content of some vitamins and minerals in the diet were revealed.

Keywords: nutrition, micronutrients, vitamins, minerals, old age, epidemiology.

Relevance. The most important of the national project "Demography" in the Russian Federation is to increase the healthy life expectancy of the population. There is no doubt that this task is inseparable, connected with the state of health of the elderly and senile aged population and becomes an important factor for achieving an increase in life expectancy. One of the important factors influencing both the state of health and well-being of the mentioned category of population is a balanced nutrition. It is known that a balanced diet is necessary for the physiological needs of the body in nutrients (macro- and micronutrients) and energy. Rational and balanced nutrition contributes to the body's resistance to the negative effects of environmental influences, reducing the risk of alimentary-dependent diseases and increasing life expectancy [4, 8, 12]. The elderly population is often considered to be at higher risk for a number of reasons, one of which is a decrease in food intake that can lead to the development of malnutrition (malnutritional deficiency) syndrome. Current nutritional problems in the elderly population are one of the important reasons for the formation of numerous geriatric syndromes (sarcopenia, senile asthenia, falls, bedsores, depression, cognitive decline, etc.), which worsen not only the quality of life, the functional status of the elderly person, but also worsen the forecast of morbidity and mortality indicators [5, 11, 12]. In this connection, it becomes relevant to study the actual nutritional status of this age group for the prevention and possible correction of geriatric syndromes in the elderly population living of the Republic of Sakha (Yakutia).

Aim: of this study was to study the micronutrient (vitamins and minerals) composition of the actual dietary intake in the elderly population of Yakutsk.

Materials and methods of research. This paper uses the materials of an epidemiological study conducted as part of the research work «Epidemiology of some chronic non-infectious diseases and risk-factors in the elderly population (including long-livers) of Yakutsk» by the Yakut Scientific Center of complex medical problems. The study design corresponds to a one-stage cross-sectional population study described in a previously published paper by the authors [1].

The population of the city of Yakutsk aged 60 and older was chosen for the study. The selected representative sample of the population aged 60 years and older was 5.3% of the total number of residents of the city. Data from 775 people were collected for the survey. The mean age of those surveyed was 75.7 years with a standard deviation of 9.4 years, and the response was 79.9%. Data from 244 men and 331 women were used to analyze micronutrients (vitamins and microelements) in the diet.

Validated questionnaires and questionnaires that included sociodemographic characteristics and data on actual nutrition were used for the study [1].

The method of analyzing the frequency of food consumption was used to assess actual nutrition. The database "Tables of the chemical composition of dishes and culinary products", taking into account losses during heat treatment, was used to determine the micronutrient composition of diets. Daily food rations were analyzed based on an assessment of both the quantitative content and the ratio of micronutrients. To analyze the data obtained, the norms of physiological need for nutrients and energy for different population groups were used [6].

Statistical processing and data analysis were performed using the SPSS software package (11.5 version). Values p <0,05 were considered authentic.

Results and discussion. The analyzed data assessing the average daily content of micronutrients (vitamins A, B1 and B2, β-carotene, PP, C and minerals - sodium, potassium, calcium, magnesium, phosphorus and iron) in the diet of the actual diet showed insufficient consumption at the level of the recommended physiological norms for men and women aged 65 and older.

Average levels of vitamin intake are shown in table 1. Deficiencies in dietary vitamin intake relative to recommended levels were noted in both groups. However, the average daily intake of vitamins was statistically significantly higher in the male population compared with the same

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indicators in women, except for vitamin C and β-carotene (Table 1).

As follows from the data in table 2, sodium intake in diets in the general elderly population exceeds the recommended values. The reasons for this excess may be the increased use of salt in the diet ("I always add salt" in cooking indicated by 83.3% of the respondents and "I add salt to cooked food" indicated by 25.6%). The recommended values for persons aged 60 years and older did not exceed potassium intake levels (2207.92±42.41 mg/day) in the daily diet of the actual diet.

According to the results presented, all the examined had a pronounced deficit in the intake of potassium (2207.92±42.41 mg/d), calcium (515.89±11.50 mg/d) and magnesium (255.70±3.90 mg/d) in the diet of the actual diet (Table 2). At the same time, elevated levels of phosphorus (941.80±14.73 mg/d) and iron (17.44±0.21 mg/d) were detected in the examinees, which is associated with increased consumption of meat, fish products in the daily diet (38,4%). It should be noted that the male population had significantly higher intake of sodium, magnesium, phosphorus and iron than the female population. There were no significant gender differences in potassium and calcium intake (Table 2).

Analyzing the level of average daily intake depending on age, both vitamins and minerals, it was found that in the

Table 1

The average content of vitamins (mg/day) in the diets of men and women aged 60 years and older in Yakutsk. M±m

Vitamins	Total number of respondents (n=575)	Men (n=244)	Women (n=331)	P_{m-w}	Recommended values. mg
Vitamin A. RE[Δ]	0.49±0.02	0.53±0.04	0.45±0.02	0.045	0.9
β-carotene	3.09±1.07	2.86±1.27	3.24±1.6	0.075	5.0
Vitamin B_1	0.91±0.01	0.99±0.02	0.86±0.02	0.000	1.5
Vitamin B_2	1.18±0.02	1.25±0.03	1.12±0.03	0.001	1.8
Vitamin PP	11.66±0.18	12.72±0.27	10.89±0.23	0.000	20
Vitamin C	86.13±2.42	82.49±3.36	88.81±3.41	0.198	100

Note: [Δ] vitamin A in retinol equivalent (RE)

Table 2

Average daily minerals content (mg/day) in the diets of men and women in Yakutsk aged 60 years and older, M±m

Minerals	Total number of respondents (n=575)	Men (n=244)	Women (n=331)	P_{m-w}	Recommen-ded values, mg
Na	1457.34±22.85	1632.31±38.01	1328.36±25.97	0.000	1300
K	2207.92±42.41	2251.42±59.96	2175.84±58.95	0.379	3500
Ca	515.89±11.50	530.43±19.50	505.17±13.86	0.278	1200
Mg	255.70±3.90	265.95±5.78	248.15±5.24	0.024	420
P	941.80±14.73	1015.35±24.58	887.59±17.52	0.000	700
Fe	17.44±0.21	18.33±0.32	16.78±0.28	0.000	men – 10, women – 18

Table 3

Average daily vitamins and minerals (mg/day) in the diets of men and women as a function of age in Yakutsk 60 years and older, M±m

Age groups / indicators	60-69 years (I group) (n=179)	70-79 years (II group) (n=192)	80-89 years (III group) (n=132)	90 years and older	p*
Vitamin A, RE	p*	0.46±0.03	0.52±0.06	0.52±0.06	I- III***, II-III**
β-carotene	3.88±2.47	3.19±1.62	2.49±1.76	2.15±1.67	I- III***, I-IV***, II-III***, II-IV***
Vitamin B_1	1.03±0.02	0.96±0.02	0.80±0.03	0.72±0.04	I- II*, I- III***, I-IV***, II-III***, II-IV***
Vitamin B_2	1.32±0.04	1.21±0.03	1.05±0.04	0.96±0.05	I- II*, I- III***, I-IV***, II-III***, III-IV***
Vitamin PP	13.05±0.34	11.64±0.28	10.41±0.33	10.58±0.54	I- II**, I- III***, II-III***, II-IV**
Vitamin C	102.70±4.47	92.54±4.45	68.56±4.29	60.04±4.65	I- II*, I- III***, I-IV***, II-III***, II-IV***
Sodium	1632.95±44.39	1541.80±35.90	1266.52±36.92	1145.39±62.55	I- III***, I-IV***, II-III***, II-IV**, III-IV***
Potassium	2528.16±93.10	2286.47±63.0	1934.86±71.75	1702.87±82.85	I- II*, I- III***, I-IV***, II-III***, II-IV***, III-IV*
Calcium	577.81±20.26	540.17±19.44	463.78±23.17	392.75±31.76	I- III**, I-IV***, II-III***, II-IV***, III-IV***
Magnesium	291.64±7.59	266.78±5.66	225.61±7.25	191.96±9.22	I- II*, I- III***, I-IV***, II-III***, II-IV**, III-IV***
Phosphorus	1055.04±26.67	971.33±23.22	837.66±28.44	772.49±42.55	I- II*, I- III***, I-IV***, II-III***, II-IV***
Iron	19.13±0.41	18.09±0.32	16.07±0.41	14.02±0.52	I- III***, I-IV***, II-III***, II-IV***, III-IV***

Note: *p- reliability of differences between age groups, *p<0.05; **p<0.01; ***p<0.001.

age group 60-69 years old consumption is higher, while in the diet a tendency to lower vitamins and minerals was revealed, reaching a minimum in long-livers (90 years and over).

In our study, the average micronutrient status scores based on actual dietary intake in the elderly were comparable to those of other studies [2, 3, 7, 9, 10, 13]. It should be noted that micronutrient deficiencies in the daily diet contribute to changes in the chemical composition and energy value of the diet. Such changes lead to an imbalanced diet and indicate a high risk of developing malnutrition syndrome (malnutrition) in the elderly. The main reasons are both physiological features and a decrease in the amount of food intake, restriction of food intake, decreased physical activity and the presence of chronic diseases with age.

This indicates the need for timely and regular nutritional assessment in the elderly, identification of causes, correction and treatment of identified disorders [5].

Conclusion. Analysis of the results of our study showed that in all respondents the profile of micronutrient composition of the studied vitamins and microelements in the daily diet of the actual diet was assessed as deficient. The average daily intake of vitamins in the male population was significantly higher compared to that in women, with the exception of the intake of vitamin C and β-carotene, where no significant differences were found.

The daily diets of the general elderly population revealed an increased intake of sodium, phosphorus, and iron and a deficit in calcium and magnesium intake. Men were found to have significantly higher intake of sodium, magnesium, phosphorus, and iron than the female population. No significant gender differences were found in potassium and calcium intake. It should be noted that with age there is a tendency to decrease the level of consumption of micronutrients in the diet. Such changes are associated with the physiological characteristics of the elderly, changes in eating behavior (reduction of food intake, limitation of food intake), decreased physical activity and the presence of chronic diseases with age.

Thus, the identified disorders of nutritional status in older age groups suggest the presence of manifestations of malnutrition syndrome, which worsens the health prognosis of the elderly and senile population.

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TESTOSTERONE LEVEL AND BODY MASS INDEX IN YOUNG PEOPLE IN YAKUTIA

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The aim of this study was to assess the levels of testosterone in serum as a function of body mass index (BMI, 15-30 kg/m2) in young men in Yakutia, aged 18 to 28. The total sample (n=87) was subdivided into three BMI groups: underweight (n=11), normal weight (n=64), and overweight (n=12). It was found that underweight in young men does not affect the level of testosterone in the blood. Thus, no significant differences in testosterone levels were found between the groups of men with underweight (23.06±5.66 nmol/L) and those with normal weight (22.9±8.24 nmol/L; p=0.703). In contrast, being overweight and obese led to lower testosterone levels. Thus, in overweight individuals, testosterone levels were significantly lower (18.54±5.73 nmol/L), compared with those who had an underweight (23.06±5.66 nmol/L; p=0.04) or the weight was normal (22.9±8.24 nmol/L; p=0.03). A comparative analysis of testosterone levels based on global data was conducted, including 1866 men. The age of the participants ranged from 18 to 30 years old. The control group comprised 528 men with normal body weight (18.5-24.99 kg/m2), and a group with an excess of overweight and obese (25-35 kg/m2) 1338 men were included. The results of testosterone level according to global data confirmed the inverse correlation of a decrease in testosterone levels with an increase in BMI (p<0.01). The assessment of heterogeneity of studies in the "Overweight/obese" subgroup was I2=46% (average heterogeneity), and in the "Normal weight" subgroup heterogeneity was I2=3% (unimportant heterogeneity), such insignificant heterogeneity in both subgroups may indicate a negative correlation of testosterone levels with BMI, regardless of race and ethnicity.

Keywords: testosterone, men, underweight, overweight, obesity.

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Introduction. According to the World Health Organization (WHO), many countries with low and middle income per capita face simultaneously several forms of malnutrition: undernutrition and overnutrition [9]. Undernutrition leads to wasting, stunting, and underweight, and overnutrition to energy imbalances and obesity develops because of this imbalance [9]. It is considered that being underweight can lead to osteoporosis [31], lowering of immune systems, muscle weakness, damage to the cardiovascular and nervous systems [10, 14]. Critical underweight can be fatal because of extreme wasting [15]. In turn, obesity is associated with an increased risk of cerebral ischemia of the heart, type 2 diabetes, and reproductive disorders [11, 12].

In recent years, obesity rates in men have increased, which can lead to long-term consequences for several homeostatic processes, including reproductive function [25]. In men, obesity negatively affects testosterone levels [23], sperm quantity, and quality [24], and is considered the most common cause of male hypogonadism [19]. In overweight the degree in men, the total testosterone decreases because of insulin resistance, which leads to a decrease in sex hormone-binding globulin [34]. More severe obesity is additionally associated with a decrease in the level of free testosterone because of the suppression of the steroid hormone-interrelated system: the hypothalamic-pituitary-testicular axis [34]. A decrease in testosterone in the blood itself leads to an increase in obesity, creating a self-reproducing cycle of metabolic complications [16].

There is currently very little research on the problems of undernutrition and underweight in men. Basically, such studies concern infants, children (under 5 years old), and women of reproductive age. Being underweight is not only related with several diseases [14, 25, 31] but is also a predictor of chronic energy deficit, which negatively affects people's ability to work [33]. There is also little research on the effect of being underweight on reproductive hormones in men, including testosterone. Basically, such studies on the effect of underweight on testosterone levels in the blood were conducted on samples of elderly men, as part of the therapy of age-related androgen deficiency [20, 21, 26].

The aim of this study is to assess the dependence of serum testosterone levels on body mass index (underweight, normal weight, overweight) in healthy young men in Yakutia, aged 18 to 28, in comparison with global data.

Materials and research methods. Sample. The present study included 87 men, whose average age was 20.15±2.15 years. All participants are Yakuts who were healthy during the study and were questioned about gender, nationality, and age. The participants in the study did not complain about their health condition and were not registered with the dispensary for chronic diseases. All subjects gave written informed consent to participate in the study and to process personal data. This work was approved by the local eth-

ical Committee on biomedical ethics at the YSC CMP (Yakutsk, Protocol № 16 of December 13, 2014).

Anthropometric measurements. Anthropometric indicators (body weight in kilograms, height in centimeters) were determined for all participants using standardized methods. BMI was calculated by dividing weight (kg) by height (cm) squared. According to the WHO classification [37], the sample was divided into 3 groups according to BMI: underweight (≤18.49 kg/m2), normal weight (18.5-24.99 kg/m2), overweight (≥25 kg/m2), and obesity (≥30 kg/m2).

Testosterone levels test. Venous blood for the study was taken in the morning after a 12-hour fast from all participants. To determine the level of testosterone circulating in the blood, an enzyme immunoassay kit "SteroidIFA-testosteron" (Company Alkor Bio, Russian Federation) was used. The testosterone concentration in the samples was measured at a wavelength of 450 nm in a VICTORX5 Multimode Plate Reader (Perkin Elmer Inc., USA).

Search criteria for publications for comparative analysis. For this analysis, they carried the main search for suitable studies out in the electronic databases PubMed-Medline and eLibrary.Ru. The following search strings were used: "testosterone AND men OR young men AND body mass index OR BMI". The last search was carried out on 10/04/2021. Details of each study included were collected in a pre-designed form. Thus, data were collected: first author, publication date, study location, sample size, age of participants, BMI (mean average), serum testosterone levels (mean average), methods for measuring testosterone levels (electrochemiluminescence immunoassay - ECLIA, enzyme immunoassay - ELISA, radioimmunoassay - RIA). The methodological quality of the included studies was assessed using the Newcastle-Ottawa scale. In total, 9 points were involved in this form. The final scores of the articles in this analysis ranged from 6 to 9 points. Comparative analysis was performed using The RevMan 5.3 software (The Cochrane Collaboration, UK). The difference in blood testosterone levels between obese and normal weight subjects was assessed using the total inverse variance. Heterogeneity was assessed using the Q-test based on the χ-square analysis and the I2 test (p<0.10 denoted significance). The inclusion criteria for studies in this analysis: studies were to be controlled, crossover, prospective, or clinical, studies were to investigate serum testosterone levels in men aged 18 to 30 with normal weight (<24.9 kg/m2) and/or overweight and obese (≥25 kg/m2). The exclusion criteria: uncontrolled studies, lack of sufficient information on testosterone concentrations, no data on BMI, duplicate study.

Literature search and relevant research. A literature search in electronic databases revealed 110118 publications (PubMed-Medline - 106644 and eLibrary.Ru - 3474). After applying different filters (sample age, gender, and unit of measurement of testosterone in the blood) 109882 articles were excluded. The full texts of 198 articles were reviewed, and this resulted in the exclusion of 186 articles. As a result, 12 publications [2, 3, 5-7, 13, 17, 18, 29, 30, 32, 35] met the inclusion criteria and were included in the final analysis (Figure 1).

Statistical analysis. The results were analyzed using a computer program for statistical data processing Statistica 13.5 (TIBCO Software Inc., USA). All results are expressed as mean (±)standard deviation, and p<0.05 were considered statistically significant. Comparative analysis between the three BMI groups was performed using the Mann-Whitney U-test.

Results and discussion. In the present study, the mean serum testosterone level in young men (18-28 years old) was 22.47±7.75 nmol/L. Earlier, serum testosterone levels were determined in Yakuts (18-25 years old), which varied from 12 to 30 nmol/L [1, 2, 4]. In general, the results of this study are consistent with earlier studies in which testosterone levels were studied in comparison with some parameters of male fertility (spermogram) [1], with the psycho-emotional state of athletes during breaks, during the competitive period [4] and depending on metabolic parameters [2].

Table 1 presents anthropometric characteristics and serum testosterone levels for the entire sample (n=87). Evaluation of the effect of BMI on testosterone levels showed that in the group of overweight men, the average testosterone level was statistically significantly lower – 18.54±5.73 nmol/L, than in the group

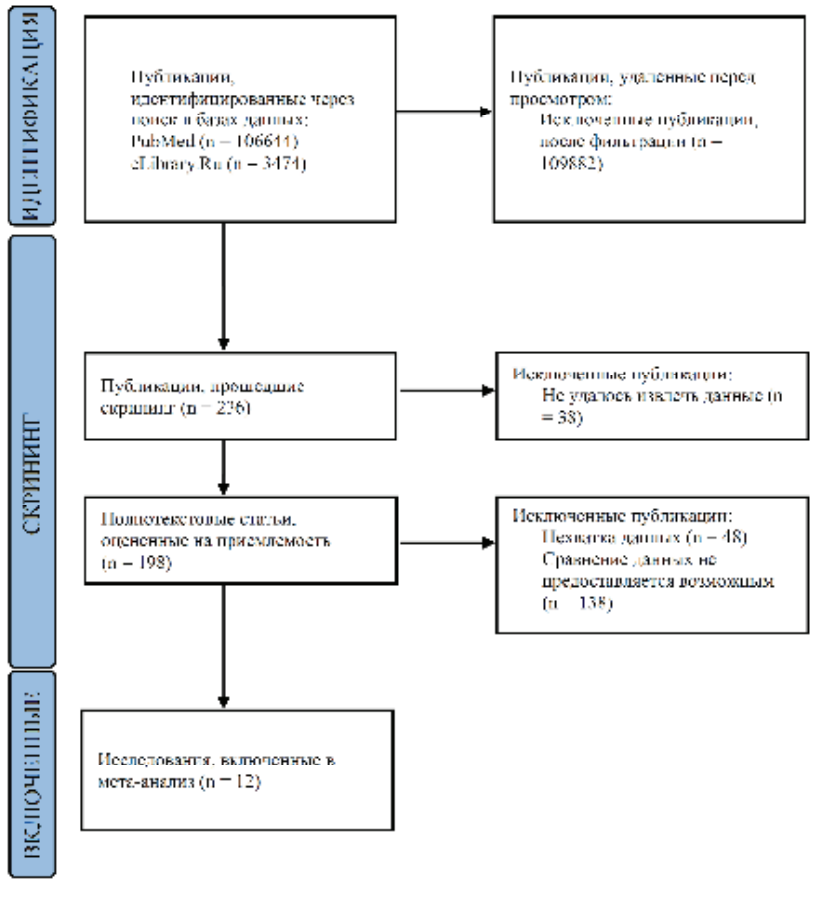

Fig 1. Block diagram of the selection of publications for comparative analysis.
Note: A representation of the process by which relevant studies were extracted from databases, selected or excluded. Preferable moments for presenting the results of systematic reviews and meta-analyses (PRISMA). From: Page M.J., McKenzie J.E., Bossuyt P.M., Boutron I., Hoffmann T.C., Mulrow C.D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.**n71**

Table 1

BMI and testosterone levels in young men (n=87)

Parameters	Underweight (n=11)	Normal weight (n=64)	Overweight (n=12)	Overweight and Underweight	Overweight and Normal weight	Normal weight and Underweight
Age (years)	18.91±0.83	20.25±2.26	20.75±2.05	p=0.01	p=0.231	p=0.09
Height (cm)	170.36±5.87	173.81±5.33	175.75±7.63	p=0.157	p=0.648	p=0.144
Weight (kg)	50.45±3.42	67.25±7.51	83.25±10.13	p<0.01	p<0.01	p<0.01
BMI (kg/m^2)	17.39±0.91	22.22±1.85	26.87±1.68	p<0.01	p<0.01	p<0.01
Testosterone (nmol/L)	23.06±5.66	22.9±8.24	18.54±5.73	**p=0.04**	**p=0.03**	p=0.703

Note: statistically significant differences are in bold.

of men with a underweight – 23.06±5.66 nmol/L (p=0.04) and with normal weight - 22.9±8.24 nmol/L (p=0.03) (Table 1). The results of the present study are consistent with those of Osadchuk et al., [2] where decreased testosterone levels were also found in overweight and obese men.

The average testosterone levels in the groups of men with normal weight and weight deficiency did not significantly differ from each other (p=0.703) (Table 1). In studies conducted in the United States and Germany, testosterone levels were lower in men with anorexia nervosa than in men of normal weight [8, 28, 36]. However, in anorexia nervosa, weight loss can be caused by excessive physical and mental stress, which leads to a violation of some reproductive and endocrine parameters [22]. It is possible that low testosterone levels may be associated with these disorders. In the present study, young men were relatively healthy, and it is possible that underweight in men, without increased physical activity, does not significantly affect testosterone levels in the blood.

Although the difference in serum testosterone levels in young men reached statistically significant differences (p<0.05), because of the small sample size, these differences were still on the level of error. To extrapolate this state-

Table 2

Publications included in the comparative analysis

Authors of the article and year of publication	Age	Methods for determining testosterone levels	Research location	n	BMI, kg/m^2	Testosterone, nmol/L
Subgroup 1. Overweight or obesity						
Abolovich et al., 1999	22-30	RIA	Argentina (Buenos Aires)	10	25.8	18.74±5.55
Kehinde et al., 2004	20-29	RIA	Kuwait (Kuwait City)	59	25	15.73±8.76
Gapstar et al., 2002	24-34	RIA	USA (Birmingham, Chicago, Minneapolis, Auckland)	482	25.8±4.7	22.55±6.94
Gapstar et al., 2002	24-34	RIA	USA (Birmingham, Chicago, Minneapolis, Auckland)	692	25±3.7	22.21±6.94
Velasco-Orjuela et al., 2018	21-28	ECLIA	Colombia (Bogota)	14	28.75±2.01	14.92±5.93
Roberts et al., 2013	20-23	ECLIA	USA (Los Angeles)	36	33.6 (31.2-34.7)	14.23±0.52
Popova et al., 2012	23-29	ELISA	Russia (Novosibirsk)	28	27.3±0.2	15.71±1.01
Popova et al., 2012	24-29	ELISA	Russia (Novosibirsk)	5	35.0±2	11.88±0.78
This work	18-30	ELISA	Russia (Yakutsk)	12	26.87±1.68	19.28±5.9
Total				**1338**		
Subgroup 2. Normal weight						
Sarita Sanke et al., 2016	19-30	ELISA	India (New Delhi)	32	21.1±2.4	20.57±4.93
Wright et al., 1995	25-29	RIA	USA (Raleigh)	16	24±1	23±2
Wright et al., 1995	26-28	RIA	USA (Raleigh)	17	24±1	22±1
Osadchuk et al., 2013	25-28	RIA	Russia (Syktyvkar)	39	22.8±0.2	25.85±1.21
Popova et al., 2012	23-24	ELISA	Russia (Novosibirsk)	50	22.1±0.2	23.35±1.04
Osadchuk et al., 2016	21-22	ELISA	Russia (Kemerovo)	54	23.04±0.4	22.59±0.93
Luisetto et al., 1995	19-31	RIA	Italy (Padua)	24	23±2.3	30.4±9.1
Pospísilová et al., 2012	23-34	RIA	Czech Republic (Prague)	232	22.5±2.79	18.5±6.05
This work	18-30	ELISA	Russia (Yakutsk)	64	22.22±1.85	22.9±8.24
Total				**528**		

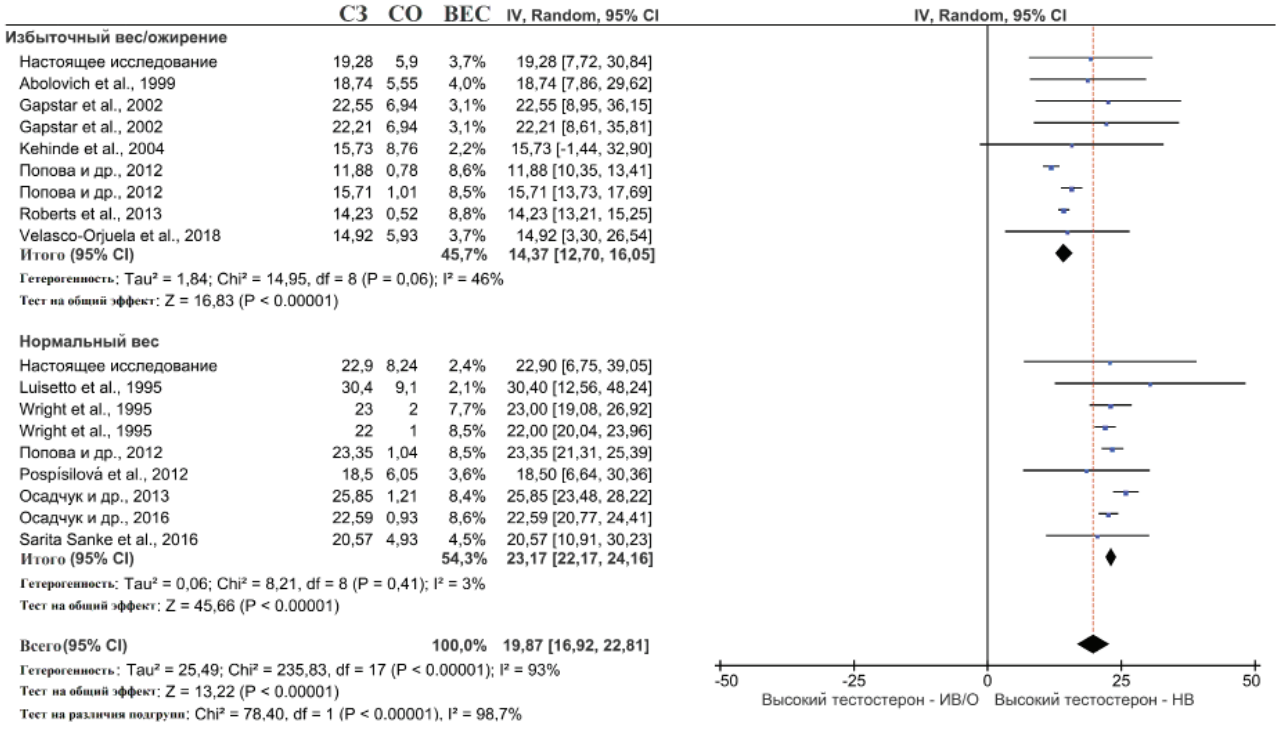

Fig 2. Comparative analysis of average serum testosterone levels in overweight/obese and normal-weight men (n=1866 men, 18-30 years old)

ment, we conducted additional research on the literature data on the effect of BMI on testosterone levels in men. A total of 1866 individuals were included in the comparative analysis, sample sizes varied from 5 to 692 in individual studies. All studies were published between 1995 and 2018. The age of the participants ranged from 18 to 30 years old. Detailed characteristics of these studies are shown in Table 2. The control group comprised 528 men with normal body weight (18.5-24.99 kg/m2), and a group with an excess of overweight and obese (25-35 kg/m2) 1338 men were included (total analysis 1866 people were included).

Comparative analysis of testosterone levels in men depending on BMI revealed statistically significant differences: in the "Overweight/obesity" subgroup, the average testosterone level (14.37; CI: 12.7-16.05 nmol/L) was significantly lower compared with subgroup "Normal weight" (23.17; CI: 22.17-24.16 nmol/L) (p<0.01) (Figure 2). This analysis showed that testosterone levels can depend on BMI: the higher the testosterone level, the lower the BMI. Assessment of heterogeneity of studies in the subgroup "Overweight/obesity" was I2=46% (average heterogeneity), and in the subgroup "Normal weight", heterogeneity was I2=3% (unimportant heterogeneity). The results got are consistent with previous studies [12, 23]. In an earlier meta-analysis [27] on the effect of racial differences on the concentration of sex steroid hormones found statistically significant differences between black and white men for free testosterone. Thus, in black men, the average levels of free testosterone were 2.5-4.9% higher than in white men. The authors believe that differences in lifestyle and anthropometry can explain these slight differences [27]. In the present study, no differences in average testosterone levels in men with normal weight from different populations of the world (21-24 kg/m2) were found (I2=3%, unimportant heterogeneity), which may indicate that there are no differences in testosterone levels depending on the racial and ethnic affiliation of the subjects. The average heterogeneity in overweight and obese men may be associated with a high variation in average BMI values (from 25 to 33 kg/m2), which shows a strong negative correlation of testosterone levels in the blood depending on BMI.

Conclusions

1. It was found that in young men (18-28 years old), underweight does not affect the level of testosterone in the blood, and the level of testosterone is more affected by overweight and obesity. So, we found that in a subgroup of overweight men, the average serum testosterone level was significantly lower compared to the subgroups of men with normal weight and weight deficiency, and in a subgroup of men with weight deficiency; the average testosterone level did not significantly differ from the subgroup of men with normal weight.

2. The results of a comparative analysis of average testosterone levels in 1866 men (18-30 years old) from different regions of the world indicate a negative correlation of testosterone levels with BMI, regardless of race and ethnicity.

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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COMPARATIVE ANALYSIS OF THE INDICATORS OF MILITARY POPULATION HEALTH IN CONTRAST CLIMATIC AND GEOGRAPHIC CONDITIONS

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Determination of certain diseases spread patterns in military population depending on geographical latitude, climate and heliocosmic factors is an urgent area of research. The aim of the study is to determine significant differences and establish patterns in the course of military population's health status comparative analysis in the Black Sea and Arctic regions. Materials and methods: Using statistical reports on form 3/med. for the period from 2013 to 2019, relative medical and statistical indicators characterizing of military personnel health state in the northern and southern latitudes were calculated. For comparative analysis, Student's t-test or Mann-Whitney test was used. Arithmetic averages with 95% confidence intervals (95% CI) were calculated to represent quantitative data. Dynamics analysis was carried out by calculation of growth indicators and polynomial trend of 2 degree with determination coefficient. Microsoft Excel 2016 and the IBM SPSS Statistics ver.28 were used for data processing. Results: Statistically significantly higher rates of primary incidence (p=0.001) and incidence with hospitalization (p=0.045) at high latitudes region were established. In the Northern Fleet, the share of respiratory diseases was 50.53%. Statistically significantly higher levels of mental disorders were established in the south (p=0.016), in high latitudes region - higher levels of VI (p=0.001), VIII (p=0.027), IX (p<0,0001), X (p=0.026), XI (p<0,0001), XIII (p=0.001) disease classes. Significant positive trends were noted for the military personnel incidence in the north with II (R^2=0.7494), X (R^2=0.9192), XIII (R^2= 0.9353), XIV (R^2=0.722) classes of disease. In the south, negative trends in the primary incidence of I (R^2=0.8469), IV (R^2=0.838) and VII (R^2=0.724) classes of disease were stable. Conclusions: The results of the study make it possible to conclude that there are significant differences in the health status of military populations in the Arctic and Black Sea regions due to a different combination of climatogeographic, heliocosmic and latitudinal factors. The Arctic region is characterized by both higher rates of primary morbidity in general and higher rates of X, XIII, XI, IX, VI and VII classes of diseases incident with a proportion in the overall primary morbidity structure of more than 50% by respiratory diseases.

Keywords: Far North; the military population state of health; the incidence of military personnel; Arctic region; Black Sea region.

Introduction. Depending on the geographical latitude, the angle of the sun's rays incidence determines the light, electromagnetic and temperature modes, which in turn form other environmental factors, such as atmospheric pressure, wind, the temperature of reservoirs and the earth's surface, humidity and other [4], which have a direct impact on the population health [5] and constitute the concept of "latitude factor" [2]. The angle of the sun, translated into Greek sounding as κλίματος [9], that is the base of the term "climate". Latitude and climate are inseparable concepts, but climate is a perennial combination of weather conditions in a particular area [9] and depends largely on the geographical characteristics of the area, while latitude is a concept of planetary scale, depending on the planet axis of rotation position in relation to the Sun. In the works of Yu.G. Solonin, it was proved that in similar climatogeographic conditions, differing only a few degrees of geographical latitude, there are significant differences in the level of population physical health [15].

A number of researchers published data confirming the presence of an association between latitude factor and sleep duration [17], prevalence of various diseases such as depression [21], multiple sclerosis [20], breast cancer [22], dementia [18], acute respiratory viral infections, including COVID-19 [19, 24], cardiovascular diseases [10]. As probable reasons, excess or lack of solar radiation is given, which itself has a damaging effect [22] and indirectly causes decreasing vitamin D content with its deficiency [18 – 21, 24] or vitamin B12 - with excess [23], as well as fluctuation of the Earth's electromagnetic field [10]. Thus, the latitude factor is significant for human health and should be taken into account on an equal basis with climatogeographic conditions [14].

Contracted military personnel are a specific population with a special epidemic processes and structure of diseases, which makes it impossible to interpolate the results of studies involving the civilian population into this category.

The aim of the study is to determine significant differences and establish patterns of the military population health status in the Arctic and Black Sea regions by the course of a comparative analysis

Methodology and materials. The headquarters of the Russian Federation Navy fleets were analyzed with obtained from open sources the deployment areas geographical components for determining comparison sample sets. The most optimal for comparison were the military populations of the Northern and Black Sea fleets, located at the same longitude and significantly remote in latitude.

Statistical reports containing information about compared military populations state of health in form 3/med for the period from 2013 to 2019 were processed for the study. Medical and statistical indicators of incidence (primary morbidity, general morbidity, hospitalization rate, incidence with temporary disability (ITD) per 1000 people for each year studied and on average [3] was calculated. The nosological pattern of morbidity was assessed in accordance with the international classification of diseases (ICD) of the 10th revision [8], dental morbidity and XV-XVIII classes of diseases were not taken into account (Table 1).

To determine the dynamics of incidence indicators, the average absolute increase (AAI) and the growth rate for the period (GR) were calculated, graphs were plotted with subsequent data equalization by calculating the polynomial

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Table 1

Classes of ICD-10 diseases used in comparative analysis of military populations health

Class	Title
I	Certain infectious and parasitic diseases
II	Neoplasms
III	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
IV	Endocrine, nutritional and metabolic diseases
V	Mental and behavioural disorders
VI	Diseases of the nervous system
VII	Diseases of the eye and adnexa
VIII	Diseases of the ear and mastoid process
IX	Diseases of the circulatory system
X	Diseases of the respiratory system
XI	Diseases of the digestive system
XII	Diseases of the skin and subcutaneous tissue
XIII	Diseases of the musculoskeletal system and connective tissue
XIV	Diseases of the genitourinary system
XIX	Injury, poisoning and certain other consequences of external causes

trend of the 2nd degree and the determination coefficient (R^2) to estimate the trend severity.

For the comparison of the total health status, the health coefficient (CH) [16] was calculated using the formula CH = (I*100)/(I+2*II+3*III), where I is the proportion of people with health group I (healthy people) in %, II is the proportion of people with health group II (relatively healthy people) in %, III is the proportion of people with health group III (with chronic diseases) in %, 2 and 3 are the "severity" ratios.

After checking the normality of the data distribution, parametric (Student's t-test) or non-parametric (Mann-Whitney U-test) methods of statistics were used. Compared parameters having statistically significant differences in tables are highlighted by *.

Extensive values were mapped using an arithmetic mean with a 95% confidence interval (95% CI) or a percentage in the structure.

Microsoft Excel 2016 and IBM SPSS Statistics ver.28 software capabilities were used for statistical data operations.

Results and discussion. The cities with Main Offices of the compared military units has greatest climatic characteristics differences in the average annual temperature, atmospheric pressure and in the amount of sunshine (Table 2). The location of the responsibility zone of the Northern Fleet on the territory of the Arctic zone of the Russian Federation is an important factor, which determines the impact of adverse climatogeographic and heliocosmic factors of the region in complex to the military population.

The incidence rate with hospitalization is not an environmentally friendly indicator, therefore, the differences identified are primarily due to the organizational aspects of medical care and may not be taken into account in the analysis of the environmental factors impact to the military personnel health.

The primary morbidity rate is an indicator of the population physical health level. In the study of VYu Semenov, higher levels of primary morbidity were established in high latitudes in almost all classes of diseases, with the exception of the circulatory system and cerebrovascular diseases pathology [11]. Significantly higher level of primary incidence among the military personnel in the Arctic region (AR) in comparison with Black Sea (ChR) found in this research and confirms results of other researchers about existence of correlation between the geographic latitude and physical human health [10, 13, 14] that allows to draw a conclusion about

Table 2

The Main Offices of the compared military units basing areas climatic parameters on average per year, abs.

Criteria	Severomorsk	Sevastopol
Temperature	- 0,2° C	+12,2° C
Atmospheric pressure	753 mm Hg.	662 mm Hg.
Amount of precipitation	475 mm.	393 mm.
Humidity	78%	72-74%
Wind speed	4,2 m/s	4,3 m/s
Sun radiance	<1700 hours (2,9 kWh/sq.m)	2342 hours (4,14 kWh/sq.m)

Table 3

The medical and statistical indicators of military populations health status in comparison for the period from 2013 to 2019, ‰ (95% CI)

Relative indicators	Arctic region	Black Sea region	Results, importance, abs.
Primary incidence *	474.73 (422.65-526.80)	199.09 (118.73-279.46)	U=0.000; p=0.001
General incidence	971.95 (935.11-1008.79)	1009.45 (583.90-1435.01)	t=-0.215; p=0.837
ITD	3729.83 (3508.47-3951.19)	4262.82 (3000.98-5524.67)	t=-1.018; p=0.346
Incidence with hospitalization *	159.07 (133.56-184.58)	220.19 (158.59-281.78)	t=-2.243; p=0.045
Mortality per 100 thousand people.	107.71 (90.81-124.61)	89.29 (48.06-130.52)	t=1.012; p=0.332
Health dismissal rate	9.15 (7.37-10.93)	7.62 (5.15-10.08)	U=22.00; p=0.805
Health coefficient	41.66 (38.06-45.26)	42.06 (29.11-55.01)	U=13.00; p=0.165

Table 4

Incidence of different classes pathology in compared military populations for 2013-2019, ‰ (95% CI)

Relative indicators	Arctic region	Black Sea region	Results, importance, abs.
Class I	6.46 (5.17-7.76)	6.07 (1.71-10.43)	t=0.212; p=0.836
Class II	4.23 (3.49-4.96)	4.84 (3.71-5.99)	t=-1.125; p=0.286
Class III	0.49 (0.28-0.71)	0.64 (-0.13-1.4)	U=19.00; p=0.535
Class IV	5.22 (4.34-6.11)	6.19 (0.95-11.44)	t=-0.447; p=0.670
Class V*	1.74 (1.32-2.17)	3.24 (2-4.49)	t=-2.787; p=0.016
Class VI*	15.81 (13.39-18.23)	8.6 (6.73-10.47)	U=0.00; p=0.001
Class VII	12.07 (10.78-13.37)	12.61 (1.61-23.61)	U=14.00; p=0.209
Class VIII*	10.55 (10.01-11.1)	7.59 (5.08-10.1)	t=2.824; p=0.027
Class IX*	27.38 (25.15-29.61)	10.7 (7.41-13.98)	t=10.282; p<0.0001
Class X*	235.89 (205.75-266.03)	86.77 (-7.94-181.47)	U=7.00; p=0.026
Class XI*	28.14 (24.28-32.0)	14.21 (8.4-20.01)	t=4.892; p<0.0001
Class XII	30.58 (27.54-33.63)	28.77 (15.67-41.87)	U=13.00; p=0.165
Class XIII*	63.39 (49.09-77.7)	29.43 (17.89-40.96)	t=4.522; p=0.001
Class XIV	13.2 (11.43-14.97)	13.26 (9.46-17.07)	t=-0.037; p=0.971
Class XIX	11.68 (11.33-12.03)	11.32 (9.23-13.42)	U=19.00; p=0.535

the importance of a latitude factor for this military population health indicator.

In the average over the study period structure of the military population primary incidence in the northern latitudes, more than 5% were diseases of X (50.53%), XIII (13.58%), XII (6.56%), XI (6.02%) and IX (5.87%) classes, other types of pathology had a smaller contribution. In the Black Sea region, X (35.53%), XIII (12.05%), XII (11.78%), XI (5.82%), XIV (5.43%) and VII (5.16%) disease classes became the most significant from the same position.

Statistically significantly higher levels of mental disorders in the south, while statistically significantly higher levels of VI, VIII, IX, X, XI and XIII diseases classes at high latitudes were established in comparison of mean primary incidence rates over the analyzed period (Table 4).

When estimating the dynamics of primary incidence rates over the study period (Table 5), statistically significant positive trends were noted for incidence among military personnel in Arctic region conditions for II, X, XIII and XIV disease classes.

In the military population of the Black Sea region (BSR), negative trends in primary incidence for I, IV and VII classes of diseases were stable.

The absence of primary incidence rates long-term dynamics in V, VIII and IX diseases classes, as well as the presence of a statistically significant difference between them in the compared populations, allow us to conclude that the differences can only be due to the influence of environmental factors.

Table 5

Indicators of primary incidence dynamics by ICD-10 classes in the compared military populations for the period 2013-2019

Classes		AAI, ‰	GR, %	Polynominal trend equation, R^2
I	AR	0.26	31.77	$y= -0.1958x^2 + 1.9727x + 2.49$, $R^2=0.6696$
	BSR	-1.94	-77.67	$y= 0.5059x^2 - 5.8553x + 19.373$, $R^2=0.8469$*
II	AR	0.18	30.3	$y= -0.0087x^2 + 0.3863x + 2.8543$, $R^2=0.7494$*
	BSR	-0.06	-5.89	$y= 0.2031x^2 - 1.6645x + 7.445$, $R^2=0.3854$
III	AR	0.05	75.0	$y= 0.0152x^2 - 0.0398x + 0.3471$, $R^2=0.6498$
	BSR	-0.08	-60.37	$y = -0.0431x^2 + 0.2186x + 0.6253$, $R^2=0.1459$
IV	AR	0.39	61.44	$y= -0.0212x^2 + 0.4924x + 3.6771$, $R^2=0.5403$
	BSR	-1.32	-45.96	$y= 1.2348x^2 - 10.973x + 25.391$, $R^2=0.838$*
V	AR	-0.07	-19.47	$y= 0.0407x^2 - 0.3414x + 2.2957$, $R^2=0.1162$
	BSR	0.18	38.35	$y= 0.1269x^2 - 1.1422x + 5.275$, $R^2=0.1656$
VI	AR	0.21	10.02	$y= -0.494x^2 + 4.1324x + 9.16$, $R^2=0.5204$
	BSR	-0.12	-7.35	$y= 0.2862x^2 - 2.6434x + 13.449$, $R^2=0.4216$
VII	AR	0.13	6.89	$y= -0.1785x^2 + 1.3315x + 10.317$, $R^2=0.2496$
	BSR	-5.14	-82.71	$y= 1.3428x^2 - 14.809x + 44.995$, $R^2=0.724$*
VIII	AR	-0.05	-2.74	$y= 0.0602x^2 - 0.4333x + 11.083$, $R^2=0.1755$
	BSR	0.3	31.62	$y= -0.3475x^2 + 2.7099x + 3.6986$, $R^2=0.2325$
IX	AR	0.72	16.53	$y= 0.1943x^2 - 0.7843x + 26.629$, $R^2=0.5663$
	BSR	0.83	54.91	$y= 0.1202x^2 - 0.4711x + 10.179$, $R^2=0.1051$
X	AR	11.75	38.22	$y= -4.039x^2 + 44.97x + 136.79$, $R^2=0.9192$*
	BSR	-44.79	-90.21	$y= 10.521x^2 - 117.71x + 347.19$, $R^2=0.6485$
XI	AR	0.92	22.47	$y= -0.3612x^2 + 4.326x + 18.061$, $R^2=0.658$
	BSR	2.04	110.38	$y= 0.424x^2 - 1.9365x + 13.476$, $R^2=0.3151$
XII	AR	-0.2	-4.39	$y= -0.5277x^2 + 3.5887x + 26.784$, $R^2=0.5335$
	BSR	-0.56	-13.64	$y= -1.4496x^2 + 10.867x + 14.294$, $R^2=0.1591$
XIII	AR	5.81	81.48	$y= -0.6602x^2 + 12.112x + 28.149$, $R^2=0.9353$*
	BSR	-1.97	-25.06	$y= 1.4358x^2 - 13.803x + 55.921$, $R^2=0.3463$
XIV	AR	0.61	37.23	$y= -0.249x^2 + 2.6095x + 7.7443$, $R^2=0.722$*
	BSR	-0.09	-3.66	$y= 0.1919x^2 - 2.2115x + 18.272$, $R^2=0.1567$
XIX	AR	0.04	1.8	$y= 0.016x^2 - 0.0262x + 11.463$, $R^2=0.3598$
	BSR	0.62	43.4	$y= -0.296x^2 + 3.0496x + 5.0466$, $R^2=0.6585$

The low amount of Sun energy reaching the surface of the planet in the Far North regions, covered with ice and snow, causes low ambient temperatures, which in turn are the reason for the low absolute humidity of the atmosphere. Inhalation of dry cold air causes a cascade of reactions in the lungs of human similar to transpiration and complicated by sorption hysteresis, leading to pulmonary edema, impaired oxygen transport through the surface of the alveoli, the development of fibrous changes, and drying of the upper respiratory tract mucous membrane makes it vulnerable to the penetration of pathogens of various infectious diseases [13]. This explains the fact that respiratory diseases in military personnel in Arctic conditions accounted for more than half of the total structure of primary morbidity and were almost three times higher than among military personnel in the Black Sea region.

Another important consequence of the low angle of sunlight at high latitudes is the deficiency of ultraviolet light, which causes a lack of vitamin D in the human body, which can cause the known list of pathology [7]. Significantly low levels of this vitamin in the Far North were established at military personnel in earlier studies by other authors [1].

A complex of factors that increase morbidity in the VI, VIII, IX, XI, XIII classes of diseases, which in this study showed significantly higher levels of primary morbidity in military personnel in the Arctic Region compared to the Black Sea region, are: the special nature of the Earth's geomagnetic field at high latitudes, affecting the electrical function of endotheliocytes, heart, tissue respiration function, conductance of nerve pulses; low ambient temperatures, causing hyperstimulation of the catecholamine system and spasm of vessels on the periphery, desynchronization of thyroid and pancreatic hormone production; desynchronoses caused by impaired melatonin production as a result of specific photoperiodism [6]; sharp differences in atmospheric pressure, accompanied by fluctuations in the partial pressure of oxygen in the air and capable of leading to hypoxic hypoxia [12]. Therefore, it allow us to conclude that the influence of environmental conditions Far North region on both the civilian population [11 – 14] and military personnel is similar.

Conclusions. The results of the study make it possible to conclude that there are significant differences in the health status of military populations in the Arctic and Black Sea regions due to a different combination of climatogeographic, heliocosmic and latitudinal factors.

The Arctic region is characterized by a higher rate of primary morbidity in both the general and X, XIII, XI, IX, VI and VIII classes of diseases with a proportion of respiratory diseases in the common primary morbidity structure of more than 50%.

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ASSESSMENT OF THE IMPACT OF INVASIVE INTERVENTIONS ON THE RISK OF URINARY TRACT INFECTIONS ASSOCIATED WITH THE PROVISION OF MEDICAL CARE IN PATIENTS OF OLDER AGE GROUPS ON THE EXAMPLE OF THE LARGE MULTIDICSIPLINARY HOSPITAL IN ALTAI KRAI

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In order to assess the impact of invasive interventions on the prognosis of urinary tract infections (UTIs) associated with the provision of medical care among patients of older age groups 700 case histories of patients over 65 years of age were selected. Using the method of discriminant analysis the indicators of invasive interventions, surgical intervention were analyzed as well as the combination of these indicators with the most common somatic diseases that were identified among patients at risk of developing UTIs associated with medical care.

Keywords: urinary tract infections, infections associated with medical care, invasive interventions, epidemiology, morbidity, risk factors.

Introduction. Urinary tract infections occupy the second place among infectious diseases in the structure of infections associated with the provision of medical care (ISMP) of patients after respiratory tract diseases [1, 2]. Most hospital UTIs in patients of older age groups are complicated because they occur in patients with various somatic diseases (diabetes mellitus, immunodeficiency conditions), as well as in connection with the use of invasive methods of examination and treatment [3, 4, 5].

Endogenous infection of the urinary tract is associated with natural contamination of the external urethra and with various diagnostic transurethral manipulations, the introduction of microorganisms into the bladder is possible [6, 7]. Exogenous nosocomial infection occurs from patients with acute and chronic UTIs and from the hospital environment. The main places of infection with UTIs associated with the provision of medical care are dressing and cystoscopic rooms, wards (in the case of dressing patients in them and using open drainage systems) [8, 9, 10].

The aim of the study was to evaluate the impact of invasive interventions on the prognosis of UTI related to medical care among patients of older age groups.

Materials and methods

In the period from 2007-2019, 700 case histories of patients over 65 years of age were selected. In order to evaluate invasive interventions for the prognosis of the development of UTIS associated with the provision of medical care using the method of discriminant analysis (the IBM SPSS 23 statistical computer package was used), a prognostic function was built for patients of older age groups, in the calculation of which only the indica-

tors of surgical intervention in the kidney and bladder and catheterization of the bladder were analyzed. To assess the combination of indicators of invasive interventions with the most common somatic diseases that were identified during the study of patients' medical histories, an analysis by the method of variance analysis (ANOVA/ MANOVA) was carried out.

Results. In order to evaluate invasive interventions for the prognosis of UTI development related to medical care, a predictive function was constructed using the discriminant analysis method (the IBM SPSS 23 statistical computer package was used) (Table 1), when calculating which only the oper (kidney and bladder surgery) and catet (bladder catheterization) indicators were analyzed, the remaining indicators were excluded from the non-normalized prognostic function.

Thus, when assessing the impact of invasive factors (oper (kidney and bladder surgery) and catet (bladder catheterization) on the risk of developing UTIs associated with medical care in patients over 65 years of age, oper (kidney and bladder surgery) has a greater impact on the development of UTIs associated with medical care by 20.9% than catet (bladder catheterization).

Further, the most promising combinations of descriptors (signs) (chronic diseases + invasive interventions) were selected by the method of expert evaluation:

1. x1 sign: chronic pyelonephritis + surgical intervention, pieloneph * oper;
2. x2 sign: chronic pyelonephritis + catheterization of the bladder, pieloneph*catet;
3. x3 sign: chronic cystitis+ surgical intervention, chrcis*oper;
4. x4 sign: chronic cystitis + catheterization of the bladder, chrcis*catet;
5. x5 symptom: chronic pyelonephritis + surgery + hypertensive disease with predominant heart disease (congestive) heart failure, chrcis*oper**hypetho;
6. x6 sign: chronic pyelonephritis + catheterization of the bladder + hypertensive disease with predominant heart disease (congestive) heart failure, pieloneph*catet*hypetho;
7. x7 sign: chronic pyelonephritis + surgery + insulin-dependent diabetes mellitus with neurological complications, pieloneph*oper*insnerv;
8. x8 sign: chronic pyelonephritis + catheterization of the bladder + insulin-dependent diabetes mellitus with neurological complications, pieloneph*-catet*insnerv;
9. x9 sign: chronic cystitis + surgical intervention+ Insulin-dependent diabetes mellitus with neurological complications, chrcis*oper*insnerv;
10. x10 sign: chronic cystitis + catheterization of the bladder + insulin-dependent diabetes mellitus with neurological complications chrcis*catet*insnerv.

Table 1

Coefficients of the canonical discriminant function of the influence of invasive factors (oper (surgical intervention in the kidney and bladder)) and catet (catheterization of the bladder)) risk of developing UTI, as ISMP, for patients over 65 years of age

Signs	function 1	module	%
oper	1.953	1.953	60.484
catet	-1.276	1.276	39.516
(Constant)	-0.029		
Non-standardized coefficients	3.230		

Note. In Tables 1-2, UTIs are urinary tract infections, HAIs are health care-associated infections.

Table 2

Prognosis of the development of UTI, as ISMP with a combination of risk factors in patients over 65 years of age

Combination of features	Function 1	module	%
x2	-2.134	2.134	19.871
x3	-2.134	2.134	19.871
x4	6.343	6.343	59.055
(Constant)	10.741		

For patients, the influence of a combination of signs (chronic diseases + invasive interventions) on the prognosis of UTIS associated with the provision of medical care was assessed by the method of variance analysis (ANOVA / MANOVA). Most of these combinations did not show statistically significant predictive power. Combinations of features that turned out to be statistically significant are collected below in Table 2. Their predictive power was evaluated in the same way as it was done earlier for individual indicators (the method of variance analysis (ANOVA/ MANOVA, the IBM SPSS 23 package was used).

The greatest impact on the risk of developing UTIS associated with the provision of medical care with a combination of risk factors in patients older than 65 years has the following combination of signs:

- x2 sign: chronic pyelonephritis + catheterization of the bladder, pieloneph*catet (19.8%);
- x3 sign: chronic cystitis + surgical intervention, chrcis*oper (19.8%);
- x4 sign: chronic cystitis + catheterization of the bladder, chrcis*catet (59.05%);

Discussion. According to the literature, most urological pathologies are accompanied by a violation of the normal outflow of urine, which is a predisposing factor of infection of the urinary tract; the main contingent of patients are elderly people with reduced immunological reactivity, the use of various endoscopic equipment and instruments, the cleaning and sterilization of which is difficult, the use of transurethral manipulations and drainage systems, increasing the likelihood of penetration of microorganisms into the urinary tract [3, 4]. The activity of modern medical organizations is unthinkable without ensuring the quality of medical care and the safety of medical activities. The greatest potential for improving the quality of medical care is provided by quality management systems (QMS). SOPy is the basis of the QMS. In this regard, their implementation in medical organizations is a feasible and strategically correct solution.

Conclusions. The results of this study showed that when assessing the impact of invasive factors (oper (surgery in the kidney and bladder) and catet (catheterization of the bladder) on the risk of developing UTIs associated with medical care in patients over 65 years of age, oper (surgery in the kidney and bladder) has a greater impact on the development of UTI as an ISMP by 20.9% than catet (catheterization of the bladder).

In patients of older age groups, the

following combination of signs have the greatest impact on the risk of developing UTIs associated with medical care: chronic pyelonephritis + catheterization of the bladder (19.8%), chronic cystitis + surgery (19.8%), chronic cystitis + catheterization of the bladder (59.05%). Based on the results obtained, using the method of discriminant analysis, we can predict the development of UTIs associated with the provision of medical care in patients of older age groups when planning invasive interventions and to create computer programs and databases for urologists, epidemiologists and specialists of other related specialties.

In order to improve the information subsystem of epidemiological surveillance of UTIs related to the provision of medical care, it is necessary to use SOPs. Their implementation in medical organizations can be used to conduct an internal quality audit in order to identify critical points when performing various medical procedures and checking violations of the sanitary and anti-epidemic regime in medical organizations, as well as simplifies the commissioning of new employees.

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ANALYSIS OF THE EPIDEMIOLOGICAL SITUATION ON COVID-19: THIRD AND FOURTH WAVES

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The dynamic analysis of prevalence, morbidity, mortality rate and case fatality rate from COVID-19 for the period from April 1, 2021 to September 30, 2021 was carried out. The highest prevalence of COVID-19 is registered in the USA, the UK, France. China has consistently low levels of prevalence and morbidity of new coronavirus infection. Increase in the proportion of fully vaccinated persons reduces morbidity of COVID-19.

Keywords: new coronavirus infection, COVID-19, epidemiology, prevalence, morbidity, mortality rate, case fatality rate.

Introduction. 1.5 years have passed since the announcement of the novel coronavirus infection (COVID-19) pandemic (March 11, 2020) [4]. As of September 30, 2021, 234 385 740 people fell ill with COVID-19 in the world, 4 792 794 (2.04%) died, 18 403 816 (7.9%) people are sick on this date [13]. It has been found that SARS-CoV-2 is prone to genetic evolution, adapting to its new human hosts with the development of mutations over time, resulting in a variety of variants. Periodic genomic sequencing of viral samples helps detect any new genetic variants of SARS-CoV-2 circulating in communities, especially in the face of a global pandemic. Based on the latest WHO epidemiological data as of June 22, 2021, four variants (strains) of SARS-CoV-2 have been identified since the beginning of the pandemic [5]:

• Alpha (B.1.1.7): first variant of SARS-CoV-2 described in the United Kingdom (UK) at the end of December 2020.

• Beta (B.1.351): first reported in South Africa in December 2020.

• Gamma (P.1): first recorded in Brazil early January 2021.

• Delta (B.1.617.2): first recorded in India in December 2020.

The identified new genetic mutations in SARS-CoV-2 also lead to new phenotypic manifestations of the disease. During the pandemic, "Temporary guidelines for the prevention, diagnosis and treatment of a new coronavirus infection" have been developed, which are regularly updated in Russia. Nowadays the 13.1th version of 17.11.2021 is in force [3]. The introduction of border restrictions, social distancing and infection control has reduced the pandemic in some settings, but such measures do not provide a real long-term solution given that SARS CoV-2 has become endemic [8]. Vaccination can significantly reduce the incidence of serious illness, morbidity and mortality, provided that "herd immunity" is achieved. By January 2021, more than 10 vaccines were in production using a range of established and emerging vaccine technologies, including new approaches to mRNA [9]. Mass vaccination against COVID-19 in the world began in November 2020 [7]. In the Russian Federation, mass vaccination against COVID-19 started in December 2020, at that time the United States was the world leader in the number of people who received the first dose of the vaccine. As of September 14, 2021, 42.4% of the world's population received at least one dose of COVID-19 vaccine. Globally, 5.79 billion doses have been administered and 31.56 million are currently being administered every day. Only 1.9% of people in low-income countries received at least one dose [6].

In the previous two articles, we analyzed the dynamics of the spread of COVID-19 in the Republic of Sakha (Yakutia) in comparison with other regions of the Russian Federation and a number of foreign countries from the beginning of the pandemic to January 4, 2021. As the pandemic continues, we decided to continue the analysis of the epidemiological situation in terms of COVID -19 in the same countries that were included in the previous study, and to assess the impact of vaccination on the spread of the new coronavirus infection.

Purpose of the work: to analyze of the dynamics analysis of the epidemiological situation of COVID-19 for the period from April to September 2021 in the Russian Federation, the Republic of Sakha (Yakutia) and a number of foreign countries.

Tasks:

1. Calculate the growth rate of the spread of COVID-19 in different regions for the period from April to September 2021 (26 weeks of observation)

2. Conduct a comparative analysis of the spread of COVID-19 for three analyzed periods (I period: from January 1 to July 31, 2020 (29 weeks of observation); II period: from September 1, 2020 to January 4, 2021 December (18 weeks), III period: from April 1 to September 30, 2021 (26 weeks)).

3. Compare the mortality and case fatality rates from a new coronavirus infection for the three analyzed periods.

4. To study the impact of vaccination on the prevalence of COVID-19.

Materials and methods. Epidemiological data for SARS-CoV-2 was obtained using an online platform collecting data from government agencies from April 1 to September 30, 2021, reaching 26 weeks [10-18]. The study included the same countries that were analyzed in the previous two articles: China, the USA, Spain, Italy, France, Germany, the UK, Russia, Brazil, Norway, Finland, Thailand [1-2]. For the Russian Federation, a comparison was made of data in Moscow, St. Petersburg and the Republic of Sakha (Yakutia). We analyzed the

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following indicators: prevalence, morbidity of COVID-19 for 26 weeks, mortality per 100 thousand of the population, case fatality rate in % during the observation period as of September 30, 2021.

Research results. Analysis of the total number of patients in the compared countries in dynamics in terms of 100 thousand of the population (prevalence) for 26 weeks of follow-up (end date 09/30/2021) showed that the highest prevalence of new coronavirus infection was registered in the USA - 13310.4, then in the UK - 11345, in France - 10699, in fourth place is Spain - 10631.2, in fifth place is Brazil - 9820.4 cases per 100 thousand of the population (Figure 1). The lowest prevalence of COVID-19 remains in China, amounting to 6.9 cases per 100 thousand of the population (this figure remains the same). Compared to the previous observation period (September 2020 - December 2021), there is a widespread high level of the number of patients with COVID-19, in the United States there has been an increase in the number of patients by 2 times, in the UK - by 2.8 times, in France - 2.6 times, in Spain - 2.5 times, in Brazil - 2.8 times.

We also calculated new cases of coronavirus infection per 100 thousand of the population weekly (Figure 2). According to the analysis results, the “red” zone included (more than 100 cases per 100 thousand of the population per week): the USA, the UK, Norway, Thailand, Brazil, where there is a steady increase in the number of cases and the highest prevalence rates, there is no trend towards a decrease in the morbidity noted. In the "yellow" zone (the weekly morbidity rates range from 40 to 90 cases per 100 thousand of the population) are Italy, France, Finland, Russia. In the "green" zone - China, Spain, Germany, where the weekly morbidity is below 40 per 100 thousand of the population. So, in the United States, in the first week of observation, the morbidity of COVID-19 was at the level of 118.2, and at 26 weeks it increased to 515.2 per 100 thousand of the population. In the UK, the morbidity increased from 38 to 344.6 per 100 thousand of the population in 26 weeks of observation, in Norway - from 150.3 to 212.1 per 100 thousand of the population. A significant increase in the morbidity is noted in Thailand: from 0.9 to 127.9 per 100 thousand of the population for the entire analytical period, from the “green” zone, Thailand moved to the “ red" zone. Italy, France, Russia have moved from the "red" to the "yellow" zone in terms of the weekly number of new cases of COVID-19, that is, in these countries, the weekly increase

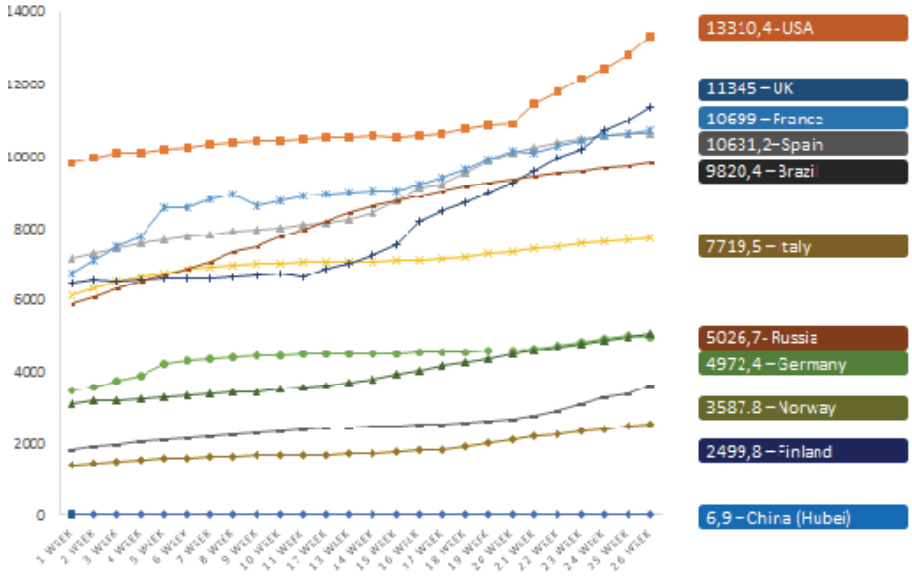

Fig. 1. The number of confirmed cases of COVID-19 (per 100 thousand of the population) in the compared countries

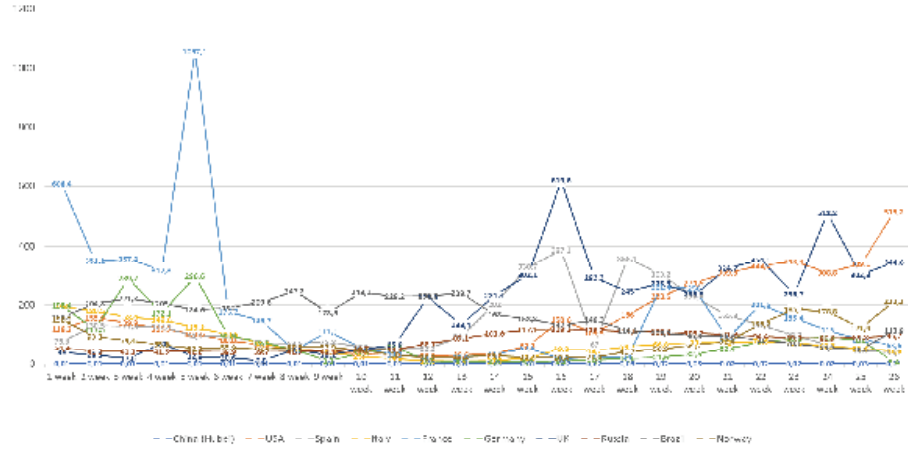

Fig. 2. New cases of COVID-19 (per 100 thousand of the population) over 26 weeks (04/01/2021 to 09/30/2021) in the compared countries

in patients has significantly decreased. Spain and Germany moved from the “yellow” and the “red” zones to the “green” zone, respectively.

Given these changes in the morbidity rates in the analyzed countries, we decided to assess the impact of vaccination on the number of new cases of COVID-19. Vaccinations in most of the countries included in our study began in December 2020. So, in the UK, the start date of vaccination falls on December 13, in China, Russia - December 15, USA - December 20, Germany, Italy, Norway, France - December 27, Finland - December 31, Brazil - January 17, 2021, Thailand - March 1, 2021.

Figure 3 shows the relationship between the proportion of fully vaccinated persons and the morbidity at 1 and 26 weeks of our analytical period. As can be seen from Figure 3, in Spain, Italy, France, Germany, Finland, there is a decrease in the morbidity against the background of an increase in the proportion of fully vaccinated residents. For example, in France, the morbidity decreased from 608.4 to 63.6 per 100 thousand of the population when the proportion of fully vaccinated people reached the level of 67.9%. In Germany, a decrease in the morbidity rate for 26 weeks was recorded from 198.4 to 5.4 per 100 thousand of the population, while the proportion of fully vaccinated persons increased from 5.1% to 63.8%. At the same time, in countries such as the USA, Thailand, Great Britain, Norway, an increase in the morbidity of COVID-19 is noted, despite the vaccination being carried out. So, in the United States, the morbidity increased over 26 weeks of observation from 118.2 to 515.2

per 100 thousand of the population, and the proportion of fully vaccinated people reached 55.3%. In the UK, an increase in the morbidity is planned from 38 to 344.6 per 100 thousand of the population, the proportion of fully vaccinated by the 26th week of observation is 65.7%. In Norway, the morbidity increased from 150.3 to 212.1 per 100 thousand of the population against the background of reaching the proportion of fully vaccinated to the level of 66.8%. In Thailand, against the background of the late start of vaccination, the proportion of fully vaccinated persons reached 22.7% and a significant increase in the morbidity rate from 0.9 to 127.9 per 100 thousand of the population was noted. 28.9% of the population, the increase in the morbidity for 26 weeks amounted to 54.3 to 96.7 per 100 thousand of the population. In China, the morbidity for all three observation periods did not change, remaining extremely low, while fully vaccinated as of 09/30/2021 72.8% of the population

We calculated the mortality and case fatality rates in the compared regions, taking into account the total number of deaths over 26 weeks of observation as of 09/30/2021 (Figure 4). The highest mortality rate is in Brazil - 104.7, followed by Russia - 62.7, then France - 40.8 per 100 thousand of the population. The lowest mortality rate was found in China, amounting to 0.003 per 100 thousand of the population. It should be noted that in comparison with the mortality rates of the first and second waves, there is an increase in mortality in Brazil and Russia. Case fatality rate in the countries included in the study ranged from 0.09 to 1.2%, that is, we note a decrease in this indicator compared to the previous two observation periods. The lowest case fatality rate in Finland is 0.09%. In first place in case fatality rate is Russia (1.2%), in second - Brazil (1.1%), in third - Thailand (0.8%).

The mortality rate in St. Petersburg was 152.6 in Moscow - 83.5, in the Republic of Sakha (Yakutia) - 105.7 per 100 000. Mortality in St. Petersburg was 1.3% in Moscow – 0.7%, in the Republic Sakha (Yakutia) – 1.9%. Mortality rates in Russia, such large cities as St. Petersburg and Moscow, as well as in the Republic of Sakha (Yakutia) have grown significantly in comparison with the previous analytical periods.

During the analyzed period in the Republic of Sakha (Yakutia), the prevalence of COVID-19 by week 26 reached 5444.8, and the morbidity - 128.2 per 100 thousand of the population. The epidemiological situation in Russia, the rates of

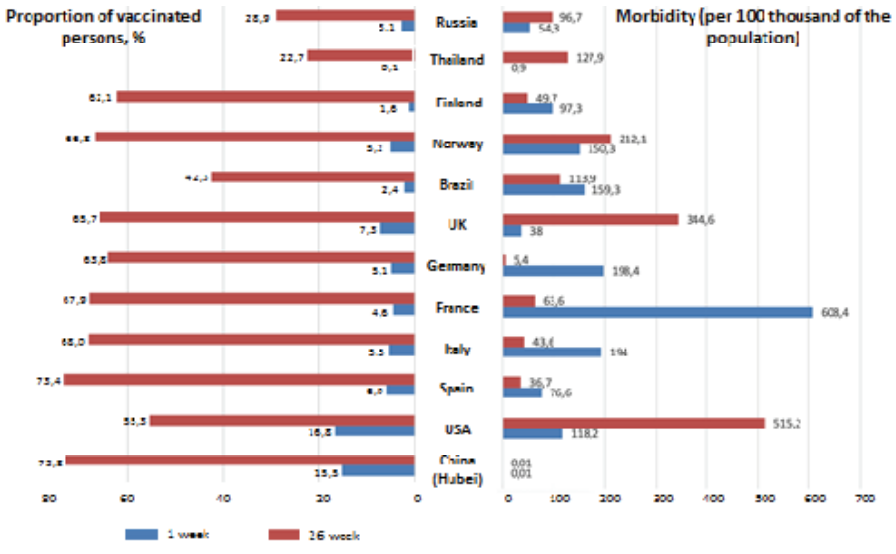

Fig.3. Vaccination and morbidity (per 100 thousand of the population) in the compared countries at the 1st and 26th weeks of observation

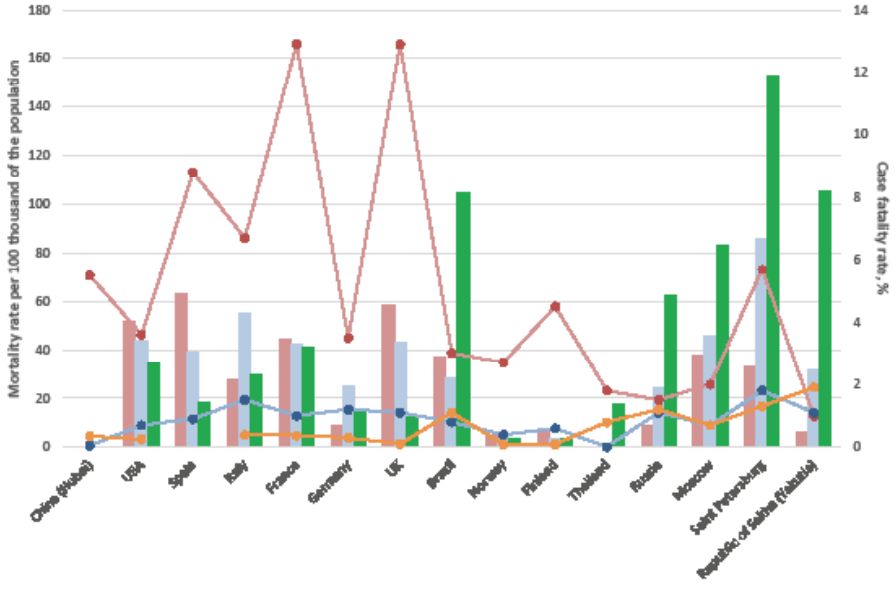

Fig.4. Mortality and case fatality rates from COVID-19 for all three observation periods: lines - case fatality rate in %, columns - mortality rate per 100 thousand of the population

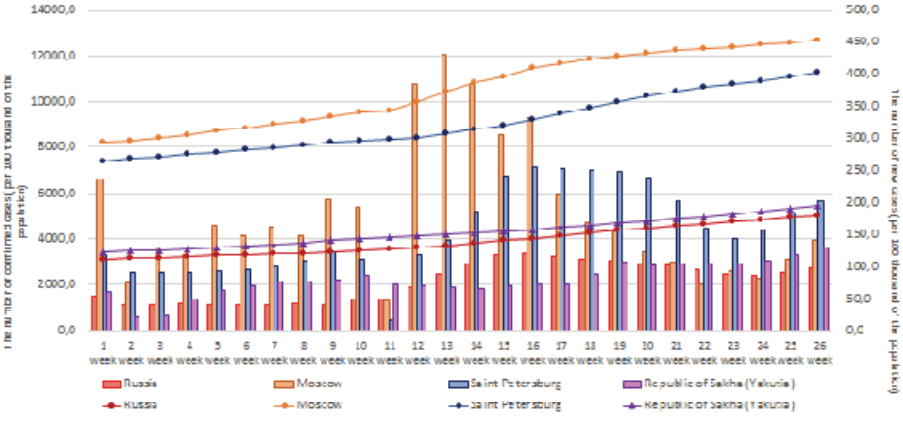

Fig.5. The number of confirmed and new cases of COVID-19 in the Republic of Sakha (Yakutia) and Russia (per 100 thousand of the population), as of 09/30/2021

both prevalence and morbidity in the Republic of Sakha (Yakutia) are comparable (Figure 5).

Conclusion. Over the almost two-year period of the COVID-19 pandemic, we have noted a continuing increase in the number of cases, the prevalence of the new coronavirus infection remains consistently high. According to our analysis, the USA, the UK, and France are leading in terms of prevalence. In China, over all three observation periods, the prevalence of COVID-19 remains at a low level, amounting to 6.9 per 100 thousand population.

In countries such as Russia, Italy, Spain, Germany, France, there is a significant decrease in the morbidity over 26 weeks of observation. In Thailand, Norway, Brazil, the USA, the UK, a steady increase in the incidence is recorded. The third and fourth waves of a new coronavirus infection in the world are caused by the spread of the SARS-CoV2 delta strain [12]. When analyzing the rate of vaccination and its effect on morbidity in the compared countries, it can be concluded that in those countries where there is a decrease in new cases of COVID-19, herd immunity has formed. In the USA, Norway, the UK, despite the sufficient coverage of the population with vaccinations, the detected increase in the incidence can be explained by the removal of restrictive measures. Also, certain questions may arise in terms of whether all vaccines used in Europe are equally effective. In Brazil, the increase in the number of cases and case fatality rate is associated with the lack of restrictive measures in the country. China has shown a strong example of the effectiveness of strict restrictive measures and a culture of ethics that have been a key success factor in the fight against COVID - 19. In addition, as of 9/30/2021, China ranks first among the countries compared in terms of vaccination coverage. Thus, only full vaccination coverage of the population and compliance with restrictive measures in the aggregate can make a positive contribution to reducing the number of COVID-19 cases and an early victory over the pandemic.

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TOPICAL ISSUE

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SURGICAL TREATMENT OF CHILDREN WITH LIVER TUMORS: COMPARISON OF THE RESULTS OF OPEN AND LAPAROSCOPIC OPERATIONS

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УДК 616-006.04

One of the main methods of treating patients with liver neoplasms is surgical. Today in medicine there is an important tendency to reduce trauma. The aim of the study was to select the optimal tactics for the surgical treatment of children with liver tumors. The analysis included the results of treatment of patients with hepatoblastomas who underwent laparoscopic liver resections. The use of laparoscopic technologies made it possible to reduce the operation time, reduce the amount of blood loss and prevent the development of complications both intraoperatively and in the postoperative period, shorten the duration of inpatient treatment, start early patient mobilization, enteral load, chemotherapy, reduce the drug load, and carry out radical surgery.

Keywords: pediatric oncology, surgery, laparoscopy, surgical oncology, hepatoblastoma, case report, liver, laparotomy

Background. Recently, thanks to the development of imaging methods and the improvement of the standards of dispensary observation, the number of patients with neoplasms of various localization and etiology has begun to increase. Liver lesions in the structure of this nosological group occupies one of the leading places, both due to the primary localization of the focus in the organ parenchyma, and due to metastatic lesions. The most optimal treatment for patients with liver tumors is their surgical removal [1].

Today in medicine there is an important tendency to reduce trauma in the treatment of many diseases, and one of the options for solving this issue is the development and implementation of minimally invasive surgical techniques that facilitate the course of the postoperative period and rehabilitation, which is not unimportant in pediatric practice. However, unfortunately, there is no reliable data on the use of laparoscopic technologies in pediatric practice in patients with tumor lesions. This article provides data on the surgical treatment of children with various oncological diseases of the liver.

Based on new data on the structure of the liver, new methods of liver resection have been developed using the principles of preliminary ligation of vascular-isolated elements of certain zones of the liver (lobe, segment), or access to them through low-vascular zones with ligation at the gate or in the planes of division of the liver tissue (fissural method), which made it possible to perform more radical operations on the liver [2, 3].

An important point in resection is the method of tissue dissection in order to isolate tubular structures before the moment of intersection, followed by precision clipping or ligation. In the last decade, ultrasonic and water-jet dissectors-aspirators have been widely used in specialized foreign and domestic clinics. The advantages of using these technologies are a decrease in the time of surgery, a decrease in intraoperative blood loss and a reduction in the time to achieve final hemo- and cholestasis in the remaining liver parenchyma [4, 5, 6]. However, to date, there is no evidence of the superiority of this or that technical means over the method of crushing the parenchyma with a clamp (clamp crushing) [7].

The first report of laparoscopic atypical liver resection for solid lesions appeared in 1991 from Reich et al. [4].

5 years later, in 1996, S. Azagara et al. published a report on the first anatomical liver resection in the volume of left-sided lateral segmentectomy for liver adenoma [5].

Laparoscopic technologies have been actively introduced into practice since the mid-90s of the last century and have not spared hepatobiliary surgery. This was primarily due to the development of efficient high-energy platforms for liver parenchyma dissection (waterjet and ultrasonic dissectors, Liga Sure, Tissue Link, etc.), which in the laparoscopic version allowed performing liver resections relatively safely [7, 8].

The lack of a large number of observations in the pediatric group of patients determines the urgency of this problem.

The authors do not aim to compare the results of open and laparoscopic operations in this article, since the group of patients is not comparable in size, which makes the use of statistical methods incorrect. The article describes the first experience of performing laparoscopic resections in patients with liver tumors. Comparison with the group of patients who underwent surgery using laparotomy is given for clarity.

Aim. Describe the first experience of performing laparoscopic resections in patients with liver tumors

Materials and methods. In the period from 2014 to 2020. 25 liver resections were performed at the Morozov Children's City Clinical Hospital, of which 5 (20%) patients underwent a laparoscopic technique (Table 1). Most (16 people) were boys. The age of the patients ranged from 1 to 17 years. The group of children operated on using the laparoscopic technique is represented by a smaller age group (from 3 to 9 years old).

In most cases (68%) we observed patients with hepatoblastoma. Hepatocellular carcinoma (HCC), embryonic sarcoma of the liver and focal nodular hyperplasia (FNH) were encountered equally (8% each), adenoma and hamartoma were less common (4% each) (Table 2).

The preoperative examination in patients included the following:

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• determination of the level of tumor markers (fcmaf-alpha-fetoprotein, human chorionic gonadotropin);
• ultrasound examination with preliminary assessment of tumor topography and angioarchitectonics;
• computed tomography with intravenous contrast enhancement;
• magnetic resonance imaging with intravenous contrast enhancement.

Results. In 16 (64%) patients, hepatoplastoma was diagnosed, and half of them are in the PRETEXT III stage. Surgical treatment of these patients was performed using a laparotomic approach. Laparoscopic operations were performed in patients with liver adenoma (1) and hamartoma (1). Patients with HCC (2), liver sarcoma (2), FNG (2) underwent open approaches.

When performing laparoscopic surgical interventions, bisegmentectomy was performed in two cases, and segmentectomy in three cases. In the case where laparotomic approach was preferred, hemihepatectomy or extended hemihepatectomy were the options of choice.

During the surgical intervention, preference was given to the use of various modern methods of achieving hemostasis - monopolar coagulation, bipolar coagulation (including measurement of tissue impedance). At the stages of accumulation of experience in this area, water-jet dissection has been repeatedly used, however, today the preference is given to ultrasound dissection.

Evaluating the results of surgical treatment of the liver (Table 3), it is worth noting that the duration of the operation in the group of patients operated on by the laparoscopic approach (30-60 minutes) is significantly shorter than in the laparotomic approach (180-270 minutes).

The volume of intraoperative blood loss in laparotomy was 50 - 70 ml / kg, which is more than 5 times higher than in laparoscopy. During open operations, intraoperative blood transfusion was required in 28% of cases, which was not required for laparoscopic resections. And only in the group of patients operated on using open access, intraoperative complications were noted in 2 (8%) cases: lethal outcome (4%) and damage to the extrahepatic biliary tract (4%).

The course of the postoperative period also differs in children operated openly and laparoscopically (Table 4)

Discussion. Performing CT and MRI allows the most accurate assessment of the boundaries of tumor invasion. These studies complement each other and, if possible, should be performed on each patient. In addition, they can be used to perform non-invasive volumetric measurements in patients with advanced neoplastic process (PRETEXT III) and to predict possible postoperative complications.

Today, the diagnosis can be made without morphological verification based on the level of tumor markers. In two patients, the diagnosis was verified by the clinical picture. In 4 cases, morphological verification of the diagnosis was required (Table 2). For this purpose, two children underwent a tru-cut percutaneous biopsy under ultrasound navigation, and two patients underwent laparoscopic biopsy.

An important advantage of the laparoscopic approach is the reduction in the trauma of the operation and the reduction of the rehabilitation period for patients, the availability and use of special equipment in order to prevent massive intraoperative bleeding, which undoubtedly meets all the requirements of modern surgery.

To date, the place and principles of laparoscopic interventions in the surgery of focal liver lesions are clearly defined:

1.To perform laparoscopic liver resections, specialized equipment is required, including one of the dissector options, as well as a device for final hemostasis;

2. The optimal volume for such oper-

Table 1

General characteristics of patients

Indicators	Total	Types of access	
		Open	Laparoscopic
Number of patients	25 (100%)	20 (80%)	5 (20%)
Female	9 (36%)	7 (28%)	2 (8%)
Male	16 (64%)	13 (52%)	3 (12%)
Age, years	1 – 17	1 – 17	3 – 9

Table 2

Morphology of tumors

Indicators	Total (%)	Types of access	
		Open (%)	Laparoscopic (%)
Total	25 (100)	20 (80)	5 (20)
Hepatoblastoma:	17 (68)	14 (56)	3 (12)
PRETEXT I	4 (16)	2 (8)	2 (8)
PRETEXT II	5 (20)	4 (16)	1 (4)
PRETEXT III	8 (32)	8 (32)	0 (0)
Adenoma	1 (4)	0 (0)	1 (4)
Hamartoma	1 (4)	0 (0)	1 (4)
Hepatocellular carcinoma	2 (8)	2 (8)	0 (0)
Liver sarcoma	2 (8)	2 (8)	0 (0)
Focal nodular hyperplasia	2 (8)	2 (8)	0 (0)

Table 3

Results of surgical treatment

Criterion	Total	Types of access	
		Open	Laparoscopic
Total	25 (100)	20 (80)	5 (20)
Duration of surgery, min		180 – 270	30 – 90
Blood loss, ml / kg		50 – 70	не более 10
Intraoperative blood transfusion	7 (28)	7 (28)	0 (0)
Intraoperative complications	2 (8)	2 (8)	0 (0)
Mortality	1 (4)	1 (4)	0 (0)
Damage to the extrahepatic biliary tract	1 (4)	1 (4)	0 (0)

ations is atypical resections of the "anterior" or "laparoscopic" liver segments (III-VI segments), as well as bisegmentectomy for relatively small focal liver lesions;

3. resection of "complex" segments (VII-VIII) is possible, however, this requires special equipment that can change the angle of bending of the working area of the instrument; here, there is also the use of "hybrid" resections.

Many authors recommend performing laparoscopic atypical resections for neoplasms less than 5 cm in diameter, hoping that operations for large tumors can be accompanied by significant technical difficulties and the risk of trauma to large vessels increases. However, at present, with the accumulation of experience in such interventions, many surgeons successfully perform anatomical resections with the removal of a significant part of the liver [9, 10].

Today, there are several ways to classify this type of surgery depending on the resection method, volume, access and degree.

Analysis of the available literature shows that wedge-shaped (segmentectomy) (45%) laparoscopic liver resection is performed more often than others. Next in frequency are followed by anatomical left lateral section (20%), right-sided hemihepatectomy (9%), left-sided hemihepatectomy (7%), 19 extended right-sided hemihepatectomies (0.7%), 3 extended left-sided hemihepatectomies (0.1%), 18 caudate lobectomies (0.6%), 8 central resections (0.3%). This statistics has been accumulated by foreign colleagues involved in the treatment of the adult population [11, 12, 13].

Contraindications to the use of the laparoscopic method are:

• heart defects associated with the risk of decompensation during surgical treatment under conditions of pneumoperitoneum;

• the presence of coagulopathies complicated by thrombosis of the visceral vessels of the abdominal organs;

• the presence of subcompensated respiratory failure;

• overweight;

• widespread adhesions in the abdominal cavity.

According to the literature, as a result of the performed liver resection by the laparoscopic method, the incidence of complications varied from 0% to 50%. Of 2804 patients, 295 (10.5%) complications were registered [14].

Of the complications presented, bile leakage, the possibility of massive intraoperative bleeding, and the risk of gas embolism are more common. In addition, it is worth noting the technical difficulty of performing various surgical maneuvers laparoscopically. Let's dwell on some of the complications in more detail.

Surgical blood loss, complications in the postoperative period, and length of hospital stay were significantly less in the laparoscopic group, even if the patients were comparable in the degree of resection and the presence of malignant neoplasms.

After open surgery, postoperative complications were observed in 17 (51.5%) cases and acquired more severe forms that required longer treatment, while after using the laparoscopic approach, a complicated course was observed in 13 (35.1%) patients [15].

The length of stay in the ICU is reduced from 3 - 5 days with open to 1 - 3 days with laparoscopic operations. Enteral loading, verticalization of the patient during laparoscopic operations are possible in the early stages (from 1 p / o day). In the postoperative period, chemotherapy was started at 8 p / o days for minimally invasive operations and at 12 for laparotomic approaches, which reduces the number of bed days before chemotherapy starts after surgery.

The treatment of children in the postoperative period was carried out using combined anesthesia in combination with prolonged epidural anesthesia. With laparoscopic liver resection, the duration of analgesia (1 - 3 days) and antibiotic therapy (7 - 10 days), which is almost half as long as with laparotomy (3 - 5 and 12 - 14 days, respectively). Drainage of the abdominal cavity and fermentemia continued for a maximum of 4 postoperative days. In the p / o period, complications occurred in 16% of cases: 3 (12%) patients with biloma and 1 (4%) with bleeding. In the group of patients operated on by the laparoscopic approach, radical surgical treatment (R0) was performed in 5 (20%) cases; in 1 (4%) child, the resection volume was R1. In children who underwent open liver resection, radical surgical treatment was performed in 9 cases (36%), and the R1 volume was

Table 4

The course of the postoperative period

Criterion	Total	Types of access	
		Open	Laparoscopic
Length of stay in the intensive care unit, days	1 – 3	3 – 5	1 – 3
Timing of patient activation (beginning of enteral load, verticalization)		с 3 п/о сут	с 1 п/о сут
Length of hospital stay, days	5 – 14	12 – 14	5 – 8
Number of bed-days before starting chemotherapy after surgery, days	8 – 12	12	8
Duration of drainage of the abdominal cavity, days	до 3 – 4	до 3 – 4	до 3 – 4
Duration of antibiotic therapy, days	7 – 14	12 – 14	7 – 10
Duration of analgesia, days	1 – 5	3 – 5	1 – 3
Duration of fermentemia, days	до 4	до 4	до 4
Complications in the postoperative period:	4 (16)	4 (16)	0 (0)
bile leak	3 (12)	3 (12)	0 (0)
bleeding	1 (4)	1 (4)	0 (0)
Radicality:	–	–	–
-R0	14 (56)	9 (36)	5 (20)
-R1	12 (48)	11 (44)	1 (4)
Total	25 (100)	20 (80)	5 (20)

performed in 11 patients (44%). Patients were discharged from the hospital twice as fast with endoscopic liver resections (5-8 days).

Potential disadvantages and limitations in the use of endoscopic technologies for liver resection are significant laboriousness and labor input, high cost of education and training of a specialist, difficulty in controlling bleeding in comparison with open surgery, and an increased risk of gas embolism. Large tumor volumes and tumors with extensive vascular invasion can also impede laparoscopic access [16].

No deaths were observed in any of the clinical cases after laparoscopic surgery, no repeated surgery or blood transfusions were required. In the structure of postoperative complications, the main share was made up of fluid accumulations in the area of surgical intervention, which developed in 8 (47.1%) patients. Five patients were cured using conservative therapy, three received aspiration treatment. In 6 (35.3%) patients, hydrothorax developed in the postoperative period. This complication was arrested by a single pleural puncture. Lower lobe pneumonia on the side of the intervention developed in 1 (5.9%) patient, suppuration of postoperative wounds in 1 (5.9%) [17].

The main part of the complications after using the laparotomic approach during surgical interventions - in 13 (31.7%) patients, also consisted of fluid accumulations in the area of surgical intervention. In this case, seven patients required 3-4 punctures. Hydrothorax was detected in 12 (29.3%) cases, of which pleural puncture was performed in 4 cases. Seven (17.1%) patients had local complications in the form of seroma and suppuration of postoperative wounds. In 2 (4.9%) patients, pneumonia developed in the postoperative period, which resolved after prolonged conservative therapy. Intra-abdominal bleeding was noted among severe complications in 3 (7.3%) people in the early postoperative period [18].

Bile leakage in the postoperative period occurred in 1.5% of the total number of cases. This group of patients was usually treated conservatively with percutaneous drains and / or endobiliary stents. The incidence of this complication in laparoscopic cases does not differ from most open series of liver resections [18].

The duration of inpatient treatment ranged from 1.2 to 15.3 days and varied both from access (by the laparotomic method for about 5 days, laparoscopic - about a day in the p / o period) and from the patient's place of residence (in the USA (1.9– 2.9 days), in Europe (3.5–8.3 days), in Asia (4.0–14.9 days)). The average hospitalization time was 4 days, which is on average 2 days less than in the case of open surgery. It should be noted that there is no data on the relationship between the volume of resection and the duration of hospitalization in the world literature [17, 18].

According to the literature we analyzed, the average time of surgery was 360 minutes. In the postoperative period, observation in the intensive care unit was required in 12% of cases, and one patient died from concomitant pathology. The initiation of oral analgesic therapy and physical activity is earlier when using a minimally invasive technique [17, 18].

In the pediatric group of patients, indications for liver resection are the presence of liver neoplasms, metastatic lesions, liver trauma, cystic lesions.

Among the children's contingent, the following cases of complications are described: seroma formation (2.8%), hypertrophic scar formation (2.8%). Infectious complications occurred in 5.6% [17, 18].

The development of technologies and the improvement of techniques have made it possible to apply robotic-assisted technologies in pediatric surgery. According to Reich H., blood loss, complications and mortality in the postoperative period after the operation using robotic-assisted technologies do not differ from the laparoscopic method. The disadvantages of using robotic-assisted technologies are the long duration of the operation and the high cost of equipment [15].

Conclusion. Preference for liver resection in patients with benign formations and hepatoblastoma PRETEXT I-II should be given to the laparoscopic method. When performing liver resection with this method, special attention should be paid to the following aspects:

• use of 10 mm optics for adequate visualization;

• preliminary volumetric marking of the resection boundaries;

• predominant use of monopolar dissection in coagulation mode for parenchymal dissection;

• safe ligation of vascular structures using impedance methods of bipolar coagulation;

• constant smoke evacuation with an aspirator or through a slightly opened trocar valve;

• the use of various methods of intraoperative hemostasis, taking into account the nature and intensity of bleeding;

• extraction of the resectate in the endomesch without fragmentation through the minilaparotomic approach.

Children with hepatoblastoma PRETEXT III can potentially be operated on using minimally invasive technologies, however, further accumulation of experience in this area and a comparative analysis of treatment results are needed.

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COMPARATIVE ANALYSIS OF THE DURATION OF SPORADIC FORMS OF MOTOR NEURON DISEASE IN THE REPUBLIC OF SAKHA (YAKUTIA)

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The article describes a study of the duration of the disease in patients with different forms of motor neuron disease (MND) in the Republic of Sakha (Yakutia). Motor neuron disease is a group of neurodegenerative diseases of unknown etiology and pathogenesis, accompanied by the death of central and / or peripheral motor neurons, steady progression and inevitable death. The results obtained correlate with the data of researchers in the world and depend on the combined or isolated damage to the motor neuron (p = 0.00001).

Aim: to study the duration of the cases of illness in different forms of motor neuron disease in the RS (Y), depending on ethnicity, age and gender.

Keywords: motor neuron diseases, amyotrophic lateral sclerosis, progressive muscle atrophy, primary lateral sclerosis.

Introduction. Motor neuron disease (MND) is a group of neurodegenerative diseases of unclear etiology, characterized by selective damage to central and / or peripheral motor neurons with an invariable lethal outcome.

MND classification

Currently, there is no uniform accepted international classification of MND

In the most common North American [16] and British [27] classifications of MND, in addition to the division into sporadic and familial forms of MND, its varieties are indicated, depending on the isolated peripheral lesion (progressive bulbar palsy, progressive muscle atrophy) of the central (primary lateral sclerosis) or mixed motor neuron lesion (amyotrophic lateral sclerosis). In the Russian modified classification of ALS (MND) by G. Levitsky and V. Skvortsova (2006), progressive bulbar palsy, progressive muscle atrophy, primary lateral sclerosis are also separated from ALS, in which there is a combined lesion of the motor neuron [2]. In the classification of O.A. Hondkarian ALS is not differentiated from the degree of motor neuron involvement, but its forms have been described, depending on the onset of the disease [4]. Many researchers adhere to the principle of separation in which MND is divided into a disease with a "pure" lesion of the lower motor neuron - progressive muscle atrophy (PMA), with a "pure" lesion of the upper motor neuron - primary lateral sclerosis (PLS) and a combined lesion of the lower and upper motor neurons, amyotrophic lateral sclerosis (ALS) [6, 7, 19, 20, 21, 24, 25]. Some authors consider PMA and PLS to be atypical forms of ALS or its variants of the course, believing that a single molecular mechanism may be compatible with clinical heterogeneity. [6, 10, 24].

Epidemiology of ALS.

Since ALS is the most common motor neuron disease in comparison with PMA and PLS, we present data on its prevalence. PMA and PLS are rare forms of MND and we have not found data on their prevalence in the available literature. According to researchers and co-authors from the Institute of Neuroepidemiology and Tropical Neurology (France), who published in 2017 a comparative meta-analysis on the prevalence of MND in the world, the total cumulative incidence of ALS in the world was 1.68 (1.50-1.85) per 100,000 population after standardization. Heterogeneity was found in the standardized incidence of ALS between Northern Europe 1.89 (1.46–2.32) per 100,000 population and East Asia (China, Japan) 0.83 (0.42–1.24) per 100,000 population (p = 0.00) and South Asia (Iran) 0.73 (0.58-0.89) / 100,000 population (p = 0.02). In contrast, homogeneous rates were reported in populations from Europe, North America and New Zealand: pooled standardized ALS incidence 1.81 (1.66–1.97) / 100,000 population for these regions [18]. In Yakutia, the incidence as of 2018. was 0.5 cases per 100,000 population. Taking into account the severity of the patient's condition and the absence of biomarkers for early detection of MND, specific treatment, a group of these diseases is a medical and social problem for public health authorities and social protection of the population and requires the organization of a multidisciplinary approach in the management of such patients.

Materials and methods. Materials: We retrospectively analyzed the hospital register of patients with MND, as well

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as their medical records for the period from 2006 to 2019, who received medical care at the neurological department of the republican hospital № 2 and the neurological department of the Clinic of the Yakutsk Scientific Center for Complex Medical Problems. All patients were diagnosed with MND after excluding other diseases that might have a similar clinical picture.

MND inclusion criteria:

1. Patients with "significant ALS" were included according to the revised El Escorial criteria [12].

2. The presence of clinical signs of an isolated lesion of the lower motor neuron, confirmed by the electromyography (ENMG) method, without signs of damage to the upper motor neuron within 4 years after the onset of the first symptoms;

3. The presence of clinical signs of an isolated lesion of the upper motor neuron without signs of damage to the lower motor neuron;

MND exclusion criteria:

1. A family history of Kennedy disease, spinal muscular atrophy, and hereditary spastic paraplegia;

Research methods. When making a diagnosis, the clinical picture of the disease took into account the combination of signs of damage to the lower and central motor neurons or its absence, the rate of development of the disease. In this case, the defeat of the lower motor neuron, if possible, was confirmed by the electrophysiological method. The diagnosis was made only after excluding other diseases that mimic the MND clinic. The clinical method included the study of the demographic data of the patients, the age of onset, the duration of the disease and its clinical manifestations; neuroimaging techniques included magnetic resonance imaging of the brain and spinal cord; electroneuromyography was performed to confirm damage to the lower motor neuron;

Statistical analysis was carried out using the STATISTICA 13.3 software (developed by StatSoft.Inc). Quantitative indicators were assessed for compliance with the normal distribution, for this, the Kolmogorov-Smirnov test was used. In the case of describing quantitative indicators with a normal distribution, the obtained data were combined into variational series in which the arithmetic mean values (M) and standard deviations (SD) were calculated. Aggregates of quantitative indicators, the distribution of which differed from normal, were described using the values of the median (Me) and the lower and upper quartiles (Q1-Q3). The

Frequency of MND by gender

Gender	Form DMN PLS	Form DMN ALS	Form DMN PMA
Female (n=41)	7	30	4
	17.07%	73.17%	9.76%
Male (n=57)	1	50	6
	1.75%	87.72%	10.53%
All Grps	8	80	10
	χ^2 =7.46; p=0.006	χ^2 =3.37; p=0.067	χ^2 =0.02; p=0.9

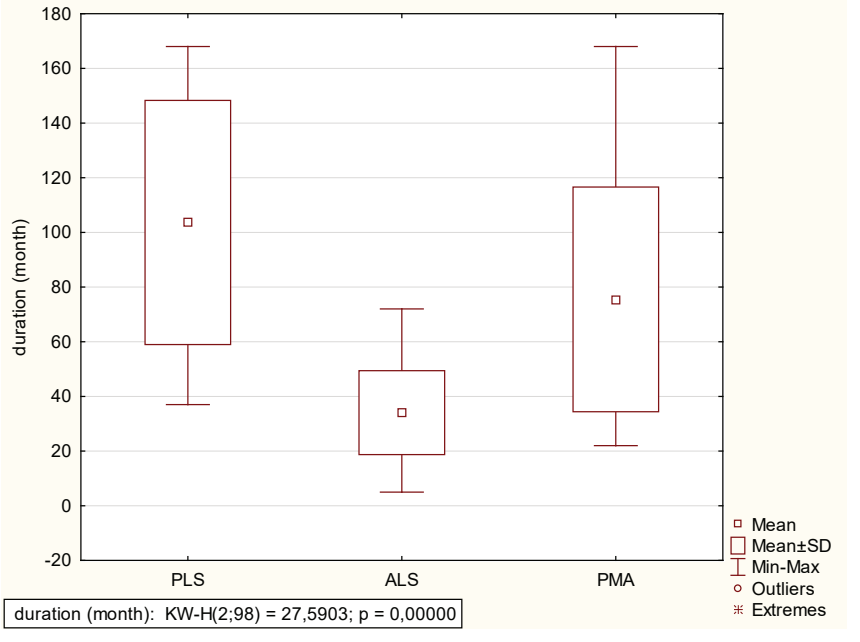

Fig. 1. Duration of the disease with different forms of MND (months)

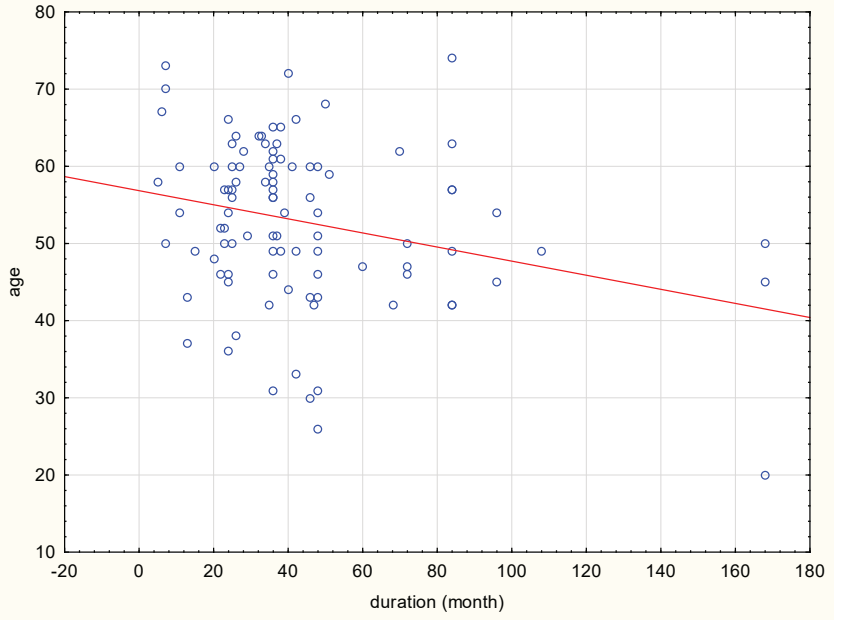

Fig. 2. Relationship between age and duration of disease in MND (n = 98)

nominal data were described with the indication of absolute values and percentages. When comparing the means in normally distributed populations of quantitative data, Student's t-test and Fisher's F test were calculated. The Mann-Whitney U-test and the Kruskal-Wallis test were used to compare independent populations in cases where there were no signs of normal distribution of the data, while the comparison of nominal data was carried out using the Pearson χ2 test. In the case of the analysis of four-field tables with the expected phenomenon in at least one cell less than 10, we calculated the χ2 criterion with the Yates correction. In cases where the number of expected observations in any of the cells of the four-field table was less than 5, Fisher's exact test was used to assess the level of significance of the differences. Differences in indicators were considered statistically significant at a significance level of p <0.05.

Informed consent was obtained from all patients before the study.

Results and discussion. Results: The observation period for the patients averaged 48 months. The male to female ratio was 1: 1.4. Patients with ALS accounted for 81.6% (n = 80), with PLS 8.6% (n = 8), with PMA 10.2% (n = 10). At the same time, no significant differences in age depending on gender were found (p> 0.05).

But when analyzing by forms, it turned out that PBS is much more common in women than in men - 17.07% versus 1.75% (p = 0.006). There were no gender differences in the frequency of ALS and PMA (p> 0.05) - Table.

The mean age of onset was 52.8 ± 10.42 years, with the oldest patient being 74 years old at the time of symptom onset.

The median duration of MND in the entire group (n = 98) was 36 months, while the minimum duration was 5 months, and the maximum duration was 168 months. In PBS (n = 8), the median duration was 90 months, while the minimum duration was 37 months, the maximum duration was 168 months. With PMA (n = 10), the median duration was 84 months, while the minimum duration was 22 months, the maximum duration was 168 months. From fig. 1 shows that the duration of the disease in ALS is statistically highly significantly less than in other forms: the median duration is 36 months in ALS versus 90 months in PLS and 84 months in PMA (p <0.00001). In ALS, death occurred on average after 36 months from respiratory failure.

In PLS, spastic tetraparesis with symptoms of pseudobulbar paralysis, leading to real estate and complete dependence on others, was observed in 3 female patients and 1 male patient. In the remaining 4 cases, spastic lower paraparesis and tendon insufficiency in the upper extremities were observed with a moderate revival of oral automatism symptoms. At the same time, none of the patients had bedsores. In 2 cases, the death occurred as a result of acute cerebrovascular accident, in 1 case from pulmonary tuberculosis and in 1 case from complications of hypostatic pneumonia

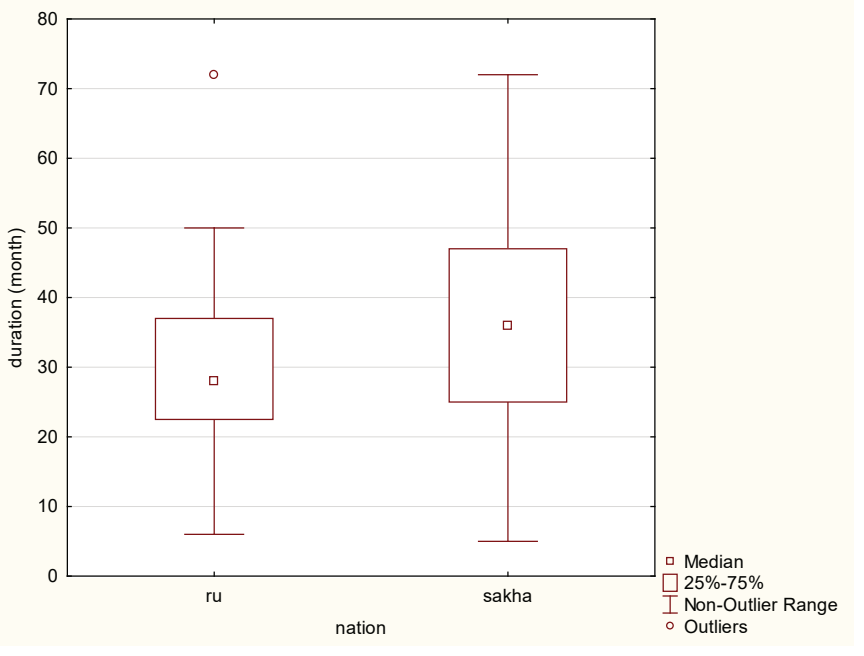

Fig. 3. Duration of MND (months) in ethnic groups

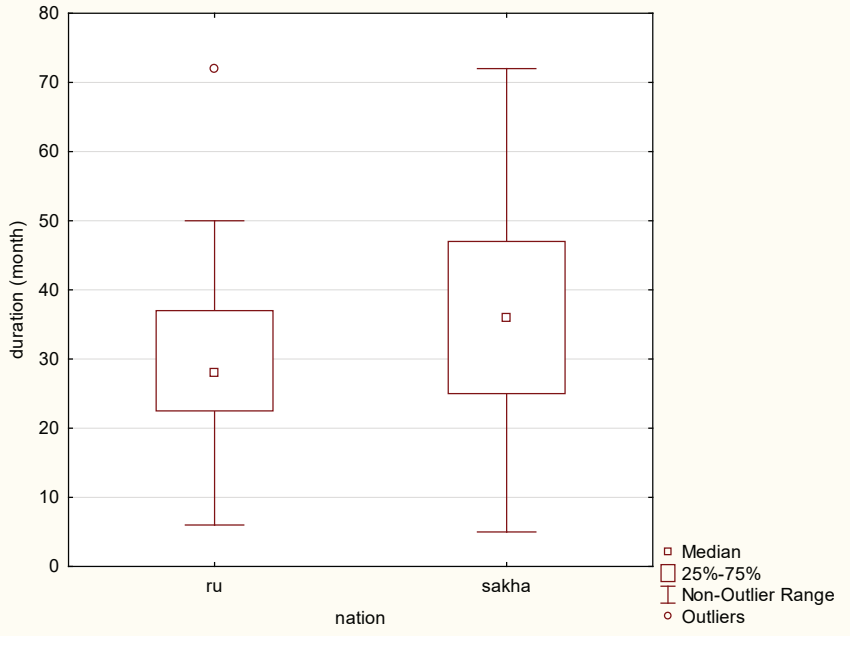

Fig. 4. Duration of ALS (months) in ethnic groups

With PMA (n = 10), in 1 case the disease had a rapidly progressive course and was 38 months. At the first visit of the patient, a clinically isolated lesion of the lower motor neuron at all levels of the spinal cord attracted attention. Flaccid tetraparesis with low reflexes was noted; the patient turned when the disease became generalized. Symptoms of bulbar palsy and a symptom of damage to the upper motor neuron were absent. The neuronal lesion was confirmed by needle electromyography. 6 months after the first visit, the patient was re-hospitalized due to

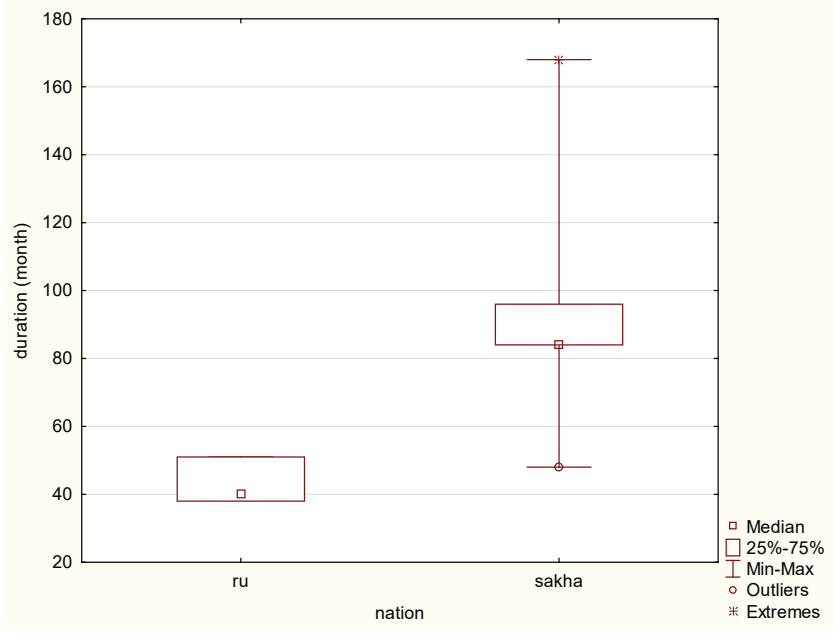

Fig. 5. Duration of PMA (months) in ethnic groups

worsening of his condition. Examination revealed bulbar disorders in the form of choking and swallowing disorders, flaccid deep tetraparesis, pronounced manifestations of respiratory failure. The patient was bedridden, completely dependent on others. No symptoms of central motor neuron involvement were found. Due to the development of restrictive respiratory failure, the patient was transferred to a ventilator, which he continued after being discharged from the neurological hospital at home. Death occurred 18 months after the 1st treatment [1]. In this case, despite the fact that the duration of the disease was slightly more than 3 years, given the clinical picture with "pure" damage to the lower motor neuron and the rapid development rate of neurodegeneration of motor neurons, this patient was included in the PMA group. The postmortem examination was not carried out due to the refusal of relatives from this study. All patients with PMA also had no pelvic abnormalities or pressure ulcers.

Figure 2 shows that with increasing age, the duration of the disease in MND decreased statistically significantly, i.e. negative correlation of duration with age was obtained (rsp = -0.22; p = 0.03).

When studying the incidence of diseases in ethnic groups Sakha (n = 58) and Russians (n = 40) with ALS, PMA and PLS, despite the predominance of the Yakut ethnic group (Sakha), no differences were found depending on belonging to a particular ethnic group (p> 0.05).

Figure 3 shows that the duration of MND in the Sakha group is significantly higher than in the group of patients belonging to the Russian ethnic group and is 38.5 months versus 33.5 months, respectively (p = 0.03).

When studying the duration of PLS, ethnic differences were not revealed (p> 0.05)

The duration of ALS was significantly higher in Yakuts than in Russians: the median duration was 36.0 (25.0-47.0) months and 28.0 (22.5-37.0) months, respectively (p = 0.03).

In fig. 4 it can be seen that when studying the duration of PMA, it turned out that the median of PMA duration was more than 2 times higher in Sakha than in Russians: 84.0 (84.0-96.0) months versus 40.0 (38, 0-51.0) months, respectively (p = 0.03).

Thus, the study revealed a feature in the duration of the disease in MND: the duration in ALS and PMA was significantly higher in representatives of the Yakut nationality than in Russians.

Conclusion. Despite the probable unity of the pathogenesis of diseases of the MND group, there is still a need for the clinical separation of diseases of this group, both for solving bioethical problems when presenting a diagnosis to a patient, and for organizing multicenter scientific studies in PBS and PMA to determine the causes affecting the duration of the disease.

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POST-COVID 19 SYNDROME OF CHRONIC FATIGUE AND EMOTIONAL DISORDERS IN RESIDENTS OF YAKUTSK

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The analysis of chronic fatigue syndrome and the level of anxiety and depression in 161 patients aged 20 to 72 years was conducted who had an acute infection with COVID-19 from 3 to 12 months ago. Young and middle-aged women are more susceptible to COVID-19 viral pneumonia in a severe and critically severe form. Men are more severely affected by COVID-19 compared to women aged 32-51 and 61-70. Anxiety-depressive disorders and chronic fatigue syndrome can develop at any time in the post-ovarian period, from 3 months to 12 months.

Keywords: COVID-19, post-COVID 19 syndrome, anxiety-depressive syndrome, chronic fatigue syndrome, HADS scale.

Relevance: In March 2020, the World Health Organization (WHO) announced the global COVID-19 pandemic. Like any major epidemic outbreak, it has caused negative consequences for individuals and society as a whole, covering almost all aspects of life. Neurological disorders caused by human coronaviruses, including SARS-CoV-2, are attracting the attention of researchers.

Thus, chronic angioencephalopathy, structural epilepsy, parkinsonism, leukoencephalopathy, and other progressive forms of neurodegenerative and autoimmune pathology are long-term complications from the central and peripheral nervous system in persons who have undergone COVID-19 [2]. Neurological syndromes that develop during the acute period are also described. diseases and after, which last more than 12 weeks - long-COVID hypostolic syndrome (PCS). PMS is included in the new edition of the International Classification of Diseases, revision 10, where it is designated as "post-COVID-19 condition" under the code U09.9 [1, 9].

E.M. Amenta et al. [12], classifying the manifestations of COVID-19, identified residual symptoms that persist after recovery from an acute infection, organ dysfunction that persists after initial recovery, and new symptoms or syndromes that develop after an initial asymptomatic or mild infection. The incidence of postcoid syndrome as a whole is 10–35%, while for hospitalized patients it can reach 85% [10]. The possibility of developing postcoid syndrome in patients with a mild form of the disease or asymptomatic course is very important, which must be taken into account when managing these patients [11]. The clinical picture of postcoid syndrome is very diverse. Fatigue is the most common symptom after COVID-19, with an incidence of 17.5% to 72% among hospitalized patients, and duration in some cases exceeding 7 months. after the onset of the disease [13]. Up to 40% of patients hospitalized with COVID-19 within 2-4 months. after discharge, a decrease in exercise tolerance is noted [5]. These symptoms, as well as pain in joints and muscles for no apparent reason, headaches, decreased memory and concentration, insomnia, lack of feeling of rest after a full night's sleep, dizziness, can be attributed to chronic fatigue syndrome (CFS), which can develop after suffering viral infection [4]. Also, patients with postcoid syndrome may experience emotional disturbances such as anxiety and depression, which are detected in 40% of patients even after 6 months. after COVID-19 [1]. According to foreign and domestic studies, during the first wave of COVID-19, clinically completed anxiety and depressive disorders (TDR) were diagnosed in 20-40% of the population, in 20-35%

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of cases, clinically significant symptoms of post-traumatic stress disorder and an acute reaction to stress, disorders sleep patterns were found in almost 50% of the population [3].

There are a large number of theories explaining the pathogenesis of the development of postcoid disorders. Undoubtedly, one of the leading roles is played by respiratory failure with the development of hypoxia. Endothelial damage caused by either viral invasion or inflammation, increased blood clotting, a tendency to coagulopathy and thromboembolic complications, damage to the microvasculature are also associated with the development of postcoid disorders [8]. The virus can directly infect peripheral neurons or olfactory sensory neurons and thus use axonal transport to gain access to the central nervous system (CNS). The molecular mechanism underlying the cellular invasion of SARS-CoV-2 is related to its ability to selectively bind to receptors for angiotensin-converting enzyme 2. These receptors are highly expressed in both glial cells and neurons, making the CNS a potential target for SARS-CoV- 2 [7]. At the same time, experimental studies have shown a special vulnerability of the hippocampus with a large loss of neurons in the CA1 and CA3 regions, which may be directly related to cognitive impairment (CI) [15]. SARS-CoV-2 induces a significant immune response up to the development of cytokine storms, which have both acute and delayed effects on the central nervous system. Neuroinflammatory processes can cause changes in the metabolism of neurotransmitters, dysregulation of the hypothalamus-pituitary-adrenal axis, activating microglia, affecting neuroplasticity and causing structural and functional changes in the brain. It was suggested that proinflammatory cytokines are the basis for the disruption of all these systems, becoming the pathogenetic basis for the development of CI and affective disorders (AR) [14].

Persistent or re-emerging symptoms, functional disorders associated with COVID-19, in> 50% of cases, according to questionnaires and analysis of disease outcomes in hospitals and clinics, negatively affect the quality of life, mobility and independence of patients seeking medical care [2] ... The quality of life of patients who have undergone COVID-19 suffers primarily from chronic fatigue syndrome and disorders of the psycho-emotional sphere, and knowledge of not only the delayed long-term consequences of coronavirus infection is necessary to develop therapeutic strategies and prevent these complications.

The aim of the study is to study chronic fatigue syndrome and anxiety-depressive disorders in patients after suffering COVID-19 3-12 months after the disease and to identify their relationship with the degree of lung damage.

Materials and methods. The study was approved by the local committee on biomedical ethics at the Federal State Budgetary Scientific Institution YSC CMP N52 dated March 24, 2021 and was conducted subject to the voluntary informed consent of the participants.

Object of study. The study involved 161 people aged 20 to 72 years who had had COVID-19 from 3 to 12 months. ago, which were divided into 4 age groups: young age from 18-44 years old, average age from 45-59 years old, elderly from 60-74 years old, senile from 75-89 years old.

The materials of the study were medical records of patients with CT protocols of the lungs, questionnaires that included complaints of patients in the postcoid period and data of neurological status.

Inclusion criteria:

1. Patients who have undergone COVID-19, confirmed by medical records;

2. Patients in the postcoid period from 3 to 12 months or more;

3. The age of the patients is from 18 to 72 years;

4. Patients who voluntarily agreed to participate in this study.

Exclusion criteria:

1. Patients in the early skovidny period up to 3 months;

2. The age of the patients is less than 18 years;

3. Patients who refused to participate in this study.

Research methods.

1. The clinical method included the study of the demographic data of patients, age, duration of the disease and its clinical manifestations from the nervous system;

2. Method of questioning. The questionnaire included questions about fatigue during the day, disturbances in the rhythm of sleep, muscle pain, headache, chills, visual impairment, impaired sensitivity, impaired smell and taste, unsteadiness of gait, dizziness, memory impairment, blood pressure drops, gastrointestinal upset;

3. Research on hospital scale of anxiety and depression Hospital Anxiety and Depressoin Scale (HADS) on a point system (0-21 points). Patients with anxiety and depression were divided into 2 groups, respectively: subclinical severe anxiety / depression syndrome (from 8-10 points) and severe anxiety / depression syndrome (11 points or more) on the HADS scale.

4. Method of neuroimaging - computed tomography of the chest organs (CT); According to the CT lung protocols, the patients were divided according to the degree of lung involvement into V groups: Group I “CT-0” (zero) - no signs of viral pneumonia; II group "KT-1" (light) - the presence of a zone of compaction of the type of "frosted glass", the involvement of less than 25% of the lung volume; III group "KT-2" (moderate) - the presence of a zone of compaction of the type of "frosted glass", the involvement of 25 to 50% of the lung volume; IV "KT-3" (heavy) - zones of compaction of the "frosted glass" type, involving from 50 to 75% of the lung volume; V "CT-4" (critical) - diffuse compaction of the lung tissue like "ground glass" and consolidation in combination with reticular changes. Involvement of more than 75% of the lung volume.

5. Statistical research method: The accumulation, correction, systematization of the initial information and visualization of the results were carried out in Microsoft Office Excel 2016 spreadsheets. Statistical analysis was carried out using the STATISTICA 13.3 program (developed by StatSoft.Inc). Quantitative indicators were assessed for compliance with the normal distribution, for this, the Shapiro-Wilk test was used (with the number of subjects being less than 50) or the Kolmogorov-Smirnov test (with the number of subjects being more than 50). Aggregates of quantitative indicators, the distribution of which differed from normal, were described using the values of the median (Me) and the lower and upper quartiles (Q1-Q3). Ratings were described with absolute values and percentages. The Mann-Whitney U test was used to compare independent populations in cases where there were no signs of normal data distribution. When comparing several samples of quantitative data with a distribution other than normal, the Kruskal-Wallis test was used, which is a nonparametric alternative to one-way ANOVA. The comparison of nominal data was carried out using the Pearson $\chi 2$ test, which allows us to assess the significance of differences between the actual number of outcomes or qualitative characteristics of the sample falling into each category and the theoretical number that can be expected in the studied groups if the null hypothesis is valid. The critical value of the significance level was taken equal to 0,05.

Results and discussion. All patients (n = 161) were divided into 4 groups according to the terms of the post-covid syndrome:

from 3 to 6 months; from 6 to 9 months; from 9-12 months; more than 12 months. 159 patients (98.7%) belonged to the Yakut ethnic group, 2 patients were Russians (1.3%). Of these women - 93 (57.5%), men - 68 (42.5%). Of these, 125 are employed (77.6%).

In this study, no statistically significant differences in gender were found among the examined patients. The median (Me) age in the general group of the surveyed was 53 years (42.0-61.0), while in men Me of age was 51 years (40.0-60.5), in women Me of age was 54 years (42 , 0-62.0). Thus, men and women were comparable in age, which made it possible to carry out a comparative analysis of CT data by age in the general group (Table 1).

It follows from Table 1 that the mild form of COVID-19 (CT-1) was experienced by patients at a young and middle age by 42.86% (n = 48), respectively, in both groups compared with elderly patients, whose share was 25%. (n = 12). In old age, CT-1 was not registered. The largest proportion of patients with moderate viral pneumonia (CT-2) was in elderly patients, which amounted to 43.75% (n = 21) compared with other age groups. At the same time, severe COVID-19 pneumonia (CT-5) was experienced by young and middle-aged patients compared to elderly patients (p =, 026077).

We also conducted a separate study depending on the gender of the surveyed. In men, the highest median age was revealed at CT-4 and amounted to 67.0 (61.0; 70.0) years. At the same time, 50% of men in the CT scan group - 5 were under the age of 39.5 (32.0; 51.0). Thus, men aged 32 to 51 years and from 61 to 70 years in our study were most susceptible to the development of severe viral pneumonia (H = 14.65; p = 0.006).

When examining the relationship between lung lesions and age by CT scan groups among women, it was found that the highest median age was found at CT-3 and amounted to 61.5 (57.0; 70.0) years. The lowest median age was found at CT-4: 50% of women were younger than 43.5 (24.0; 63.0) years. At the same time, in the groups with CT-1 and CT-2, there were isolated cases of the disease over the age of 70 years. Half of the cases with CT-5 were women younger than 50 years. Thus, younger women were more likely to be affected by severe and critically severe COVID-19 viral pneumonia. And for an older age, mild and moderately severe forms of pneumonia are characteristic (H = 13.21; p = 0.01).

Table 1

Distribution by age group and CT scan group

age group	CT Group					Total:
	1	2	3	4	5	
18-44	24 42.86	9 16.07	9 16.07	1 1.79	13 23.21	56
45-59	24 42.86	11 19.64	9 16.07	1 1.79	11 19.64	56
60-74	12 25.00	21 43.75	8 16.67	4 8.33	3 6.25	48
75-89	0 0.00	1 100.00	0 0.00	0 0.00	0 0.00	1
Total:	60	42	26	6	27	161

Pearson Chi-square: 23,1998, df=12, *p=,026077.*

Table 2

CT scan groups in men and women

floor	CT Group					Total:
	1	2	3	4	5	
Men	19 27.94	15 22.06	20 29.41	4 5.88	10 14.71	68
Women	41 44.09	27 29.03	6 6.45	2 2.15	17 18.28	93
Total:	60	42	26	6	27	161

Pearson Chi-square: 18,0689, df=4, *p=,001196.*

Table 2 shows that when comparing the CT groups, CT-1 is much more common in women: in 44.09% of cases, no signs of viral pneumonia were found. While in men the proportion of CT-1 was only 27.94%; CT - 3 was more common in men: 29.41% versus 6.49% in women. Thus, men were statistically significantly more severely affected by COVID-19 than women. The results obtained correlate with the data of other researchers [5].

The timing of the development of symptoms of CFS and TDR in the postcoid period. We investigated the following symptoms of CFS: fatigue, not dependent on physical activity, decreased performance, memory impairment, dizziness, pain in muscles and joints, unsteady gait, headache, sleep disturbance, swollen lymph nodes. When establishing the diagnosis of chronic fatigue syndrome, the time period for the onset of symptoms of 3 months or more was taken into account, as well as the presence of at least four of the symptoms listed above, although some authors recommend using the main 3 criteria and an additional 1 criterion for CFS with a time period of 6 or more months when making a diagnosis. contract. [4]. TDD was determined using the HADS scale. Emotional disorders of 161 patients with postcoid syndrome had 46 (27.9%) people, including 12 men (26.1%) and 34 women (73.9%). Depressive disorders were observed in 40 (24.8%) patients. At the same time, in 30 (18.6%) patients, subclinical severe depression was noted, in 10 (6.2%) patients - clinically significant. Anxiety disorders were detected in 39 (24.2%) patients. At the same time, 25 (15.5%) of the examined had subclinically expressed anxiety, and 14 (8.7%) had clinically significant anxiety. At the same time, the degree of depression and anxiety did not depend on the degree of lung damage (p = 0.6).

CFS was detected in 40 (24.8%) patients, including 18 (45%) men and 22 women (55%). As a result of the study, in the general group (n-161), in 46.5% (n = 75) of cases, the patients were not diagnosed with CFS and TDR in the postcoid period. Of these, 38 were women and 37 were men. In addition, this group included patients who noted feelings of anxiety and fear that appeared before the illness and were associated with the fear of COVID-19 disease by the patient and his close environment, as well as other reasons, although these patients have clinically significant anxiety and depression on a background of low mood dominated after suffering COVID-19. This group also included patients who were bothered by

complaints of headaches, fatigue, memory loss, sleep disturbance before the development of COVID-19, which were associated with various neurological manifestations of other diseases (hypertension, diabetes mellitus, brain trauma, cervical osteochondrosis) ... We carried out a separate study of the development of CFS and TDR, depending on the timing of the postform period.

When studying the timing of the development of symptoms of CFS and TDS in the postcoid period, no statistically significant results were obtained in terms of gender. In the rest of the subjects (n = 86), the symptoms of CFS and TDS were manifested at all periods of the postcoid period, while none of its periods prevailed over the others. We also studied the dependence of the symptoms of CFS and TDR on the degree of lung damage. At the same time, not a single symptom in CFS and TDR depended on CT data, except for a shaky gait. 92 patients complained of unsteadiness of gait. Stiffness in the postcoid period was more common in middle-aged women than in young and old age. It can be assumed that the wobbly gait in middle-aged women is associated with autonomic dysfunction of the nervous system caused by the transferred COVID-19, while in old age this symptom can be explained by concomitant vascular diseases, and at a young age by the absence of concomitant vascular diseases. Pearson Chi-square: 10.1883, df = 3, p =, 017032.

Conclusions:

1. Men aged 32 to 51 years and from 61 to 70 years in our study were most susceptible to the development of severe viral pneumonia.

2. In women with previous viral pneumonia of moderate severity, it was found in elderly patients compared with other age groups. At the same time, young and middle-aged patients suffered from COVID-19 viral pneumonia in a severe and critically severe form.

3. Men were statistically significantly more severely affected by COVID-19 than women;

4. Anxiety-depressive disorders and chronic fatigue syndrome can develop at any time in the post-covid period from 3 months to 12 months.

5. Stiffness in the postcoid period was more common in middle-aged women than in young and old age.

This study was carried out as part of the initiative project of the Yakutsk Scientific Center for Complex Medical Problems "Comprehensive assessment of the health of patients who have undergone a new coronavirus infection (COVID-19)."

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INDICATORS OF ANTIBODIES IgM AND IgG TO SARS-COV-2 IN RESIDENTS OF YAKUTSK AFTER RECOVERY FROM COVID-19

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A study of IgM and IgG antibodies to SARS-COV-2 was carried out in 161 residents of Yakutsk at the age from 20 to 72 years old who had a new coronavirus infection COVID-19 from 3, 6, 9 and 12 months ago. The aim of the work was to assess the content of serum immunoglobulins IgM and IgG to SARS-COV-2 in persons who have had COVID-19, depending on the duration and severity of the disease. The intensity of the immune response was assessed using the coefficient of positivity (CP) as the ratio of the optical density of the sample to the critical value of the optical density. According to the results of the study, the seroprevalence in all 4 groups of patients with Covid-19 was 100%. Antibodies IgG and IgM to SARS-CoV-2 in those who had been ill with COVID-19 persisted up to 12 months and depended on the postcovid period, age and severity of lung lesions on CT.

Keywords: IgG, IgM, SARS-CoV-2, antibodies, COVID-19.

Introduction. Since December 19, 2019, after the first outbreak of a new coronavirus infection in Wuhan (China), the disease has spread rapidly and within a few months has spread to the whole world. In April 2020, the first cases of the disease were diagnosed in Russia, and in March - in the Republic of Sakha Yakutia.

Currently, to diagnose COVID-19 infection, a laboratory RT-PCR (PCR) test is performed to detect SARS-CoV-2 RNA in samples taken from the nose and throat, but the PCR method does not always determine the presence of infection, since there is a possibility of obtaining false negative results [10.7]. One of the additional methods of timely diagnosis at an early stage of the disease of a new coronavirus infection is the enzyme-linked immunosorbent assay (ELISA) for antibodies (AT) to SARS-CoV-2 (1,5). Joint testing for the detection of class M and G antibodies is of great importance for the epidemiological prognosis and understanding of the treatment of SARS-CoV-2 infection [13].

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The mechanisms of the development of the body's immune response to the SARS-CoV-2 coronavirus are being studied. Experts are interested in the question of how long antibodies can persist in the body in persons who have had COVID-19. Some studies provide data on the presence of (AT) M and G not only in persons with a positive, but also a negative PCR result after 1-3 weeks from the moment of infection with the virus, as well as pregnant mothers and newborns, seriously ill, and deceased patients [1,6,12,14]. From the moment the coronavirus enters the body, immunoglobulins G (IgG) are synthesized last 5-6 weeks about the coronavirus, i.e. are the archive of the memory of the transferred infections, in most cases for life, or for several years. It remains unclear whether persistent immunity is being formed, which requires in-depth study. But in any case, the detection of IgG indicates the fact that the coronavirus has entered the body and the body's immune response. Currently, various sources provide data on the presence of AT in patients with COVID-19 from 3 months to a year ago [7,8]. Of great interest is the timing of maintaining a high level of antibodies after suffering COVID-19, which requires further study of the resistance, weakening and duration of protection of antibodies to SARS-CoV-2.

The aim of the study was to assess the content of serum immunoglobulins IgM and IgG to SARS-COV-2 in people who had been ill with COVID-19, residents of Yakutsk, depending on the duration and severity of the disease.

Materials and methods: On the basis of the Yakutsk Scientific Center for Complex Medical Problems clinic, 161 people who had undergone COVID-19 with laboratory-confirmed 2019-n CoV infection by PCR were examined, with varying degrees of lung damage. Age ranged from 20 to 72 years, of which 56 (34.8%) young people (20-44 years old), 53 (32.9%) middle-aged (45-59 years old); (60-74 years old) elderly - 51 (31.7%) and (75-90 years) old age - 1 (0.6%) age, respectively (Table 2). Women accounted for 101 (62.7%) and men - 60 (37.1%). The criterion for exclusion from the group was persons with signs of ARVI and active infection with COVID-19 at the time of the study. Data on the degree of lung lesions by the type of "ground glass" were assessed according to the results of computed tomography (CT), taken from the discharge epicrisis: CT0 (zero) - no manifestations; CT1 (lung) - the prevalence of the lesion is less than 25% of the lung volume; CT2 (moderate) –25-50%; CT3 (heavy) 50 -75%; CT4 (critical) - more than 75%. All subjects were divided into 4 groups, depending on the duration of recovery from the moment of the illness: up to 3, 6, 9 to 12 months ago. The study was approved by the decision of the Local Ethics Committee at the Federal State Budgetary Scientific Institution "YSC CMP" no 52 dated March 24, 2021 and was carried out with the informed consent of the subjects in accordance with the ethical standards of the Declaration of Helsinki (2000).

The study material was venous blood serum. Blood sampling was performed from the cubital vein in the morning hours from 8-10 hours on an empty stomach. A qualitative determination of antibodies (AT) M and G against SARS-CoV-2 was carried out by the enzyme immunoassay using the test systems of the "Vec-

tor-Best" company (Novosibirsk), on the "Uniplan" photometer (the "Picon" company, RF), according to the instructions manufacturer's firm. The intensity of the immune response was assessed using the coefficient of positivity (CP) as the ratio of the optical density of the sample to the critical value of the optical density, which reflects the relative amount of the corresponding antibodies in the sample. This indicator allows you to track the dynamics of the level of antibodies in human blood by examining samples taken at different times, and thus to clarify the patient's immune status. According to the value of the coefficient of the qualitative test, the sample was considered negative or borderline (CP less than 1.1), positive (CP from 1.2 and higher) result. Seroprevalence (presence of AT G) and the presence of serological markers of acute infection (IgM) were assessed. The level of rheumatoid factor (RF) and C-reactive protein (CRP) was also determined on a biochemical analyzer "Sapphire" (Japan).

The results were processed using the SPSS Statistics 26 statistical software package. The descriptive analysis data are presented in the tables as Me (median), Q1 and Q3 (quartiles 25% and 75%). The significance of differences was assessed using Student's t-test and ANOVA for independent samples with normal distribution and Mann-Whitney test for abnormal distribution. The critical value of the level of statistical significance of differences (p) was taken equal to 5%. Correlation analysis of the data was performed using the Pearson method.

Results and discussion. A positive test for immunoglobulins suggests that the person has potentially been exposed to SARS-CoV-2. According to the results of the study, seroprevalence in all 4 groups of patients with Covid-19 was 100%, had no gender differences, which is consistent with literature data [9]. However, IgG antibodies were not at a high level in all and differed significantly.

According to the value of KP IgG, all the patients were divided into three subgroups. Low CP from 1 to 3,49 was detected in 8,7%, the average level of antibodies from 3,5 to 9,99 was recorded in 19,3%, high - from 10 or more was found in 72,0% of patients (Table 1) There was a direct correlation relationship (r = 0,309; p<0,000), (r = 0,312; p<0,000), respectively, between the level of CP IgG and the groups who underwent Covid-19 with varying degrees of severity (CT) and age groups. The mean CP IgG value increased depending on the degree of lung damage and was statistically significant between the groups CT0 with CT2, 3, CT4 (p = 0,005; p = 0,001; p = 0,007) and CT1 with CT2, CT3 (p =0,038p = 0,0210) (Table 1). According to our data, the frequency of occurrence of a high IgG content increases from CT1 to CT4; in those examined with CT3 and CT4, individuals with a low IgG content were not detected (Table 1). In age groups, statistically significant differences in IgG CP were found between young and middle-aged people with the elderly (p =0,001 and p =0,017) (Table 2). In the elderly group, the most significant incidence of IgG with a high KP value is noted, which is possibly associated with the high severity of the disease in this age group. According to the literature, the severity of the course of COVID-19, according to the CT protocol, had a direct relationship with age; in young age groups, a mild form of lung lesion with CT1 was more common, in middle-aged and elderly groups with lung damage with CT2 and CT3 [4].

Depending on the duration of the Covid-19 disease, an inverse correlation was obtained (r = -0,238; p<0,002). The frequency of occurrence of persons with a high content of CP IgG remained the highest in 3 groups in those who had recovered from 3 months ago in 12 (80%), from 6 in 58 (77,3%) to 9 months in 36 (75 In those who had been ill up to a year ago, the frequency of AT decreases by 10 (43,5%), which does not contradict the literature data, antibodies can persist for up to 1 year (11). postform period (Table 3). IgG, as a rule, are the main factor of the humoral link of the immune defense, which counteracts the development of the infectious process in the body. The presence of specific immunoglobulins of class G, which appeared in a person as a result of a previous illness or vaccination, in most cases indicates the formation of sterile immunity to the corresponding bacterial or viral infection [5].

When the infectious disease passes without complications, the anti-IgM antibodies that appear from the first week of acute infection should gradually de-

Table 1

Indicators of IgG seropositivity depending on CT

Level CT	CP Me (Q1 – Q3)	Level CP IgGn/%			Total «+» Absolute number/%
		low	medium	high	
CT(0)	10.30 (4.04;11.53)	5/18.5	8/29.6	14/51.9	27/16.8
CT(1)	11.44 (6.00;11.60)	6/10.0	16/26.7	38/63.3	60/37.3
CT(2)	11.52 (11.13;11.69) [1]p=0.005; [2]p=0.038;	3/7.1	4/9.5	35/83.3	42/26.1
CT(3)	11.59 (11.38;11.77) [1]p=0.001; [2]p=0.007	-	3/11.5	23/88.5	26/16.1
CT(4)	11.59 (11.42;11.59) [1]p=0.021	-	-	6/100	6/3.7
Total		14/87	31/19	116/72	161/100

Note: n - is the number of patients who have been ill; "+" - the number of persons with the presence (AT); 1-statistically significant differences from CT0; 2-significance of differences from CT1.

Table 2

Indicators of IgG seropositivity in different age groups

Age group	CP Me (Q1 – Q3)	Level CT IgGn/%			Total «+» Absolute number/%
		low	medium	high	
Young	11.42 (4.90-11.60)	9/16.1	14/25.0	33/58	56/34.8
Middle aged	11.42 (7.84;11.56)	5/9.4	11/20.8	37/69.8	53/32.9
Old-aged	11.59 (11.47;11.72) [1]p=0.000; [2]p=0.017;	-	6/11.8	45/88.2	51/31.7

Note: n - is the number of patients who have been ill; "+" - the number of persons with the presence (AT); 1-statistically significant differences from CT0; 2-significance of differences from CT1.

Table 3

Indicators of IgG seropositivity depending on the postcovid period

Postcovid period, month	CP Me (Q1 – Q3)	Level CT IgGn/%			Total «+» Absolute number/%
		low	medium	high	
up to 3	11.28(11.52;11.62) [1]p=0.005	1/6.7	2/13.3	12/80.0	15/9.3
up to 6	10.88 (11.50;11.66) [1]p=0.001	4/5.3	13/17.3	58/77.3	75/46.6
up to 9	10.20 (11.47;11.59)[1]p=0.004;	5/10.4	7/14.6	36/75.0	48/29.8
up to 12	4.34 (9.4;11.60)	4/17.4	9/39.1	10/43.5	23/14.3

Note: "+" - the number of persons with the presence (AT); 1-statistically significant differences with a postcovid period of up to 12 months.

crease and disappear after a month. The specific gravity of the serological marker of acute IgM infection in patients with Covid-19 was 62,1%, a negative IgM result was detected in 61 (37,9%) people, a low CP from 1,2 to 2 in 41 (25,5%), the average CP was 2,1 to 4,9 in 36 (22,4%) and a high level of CP was higher than 5 in 23 (14,3%) examined (Pic.1). It is possible that these results may be associated with a weakened immune response or a strong attack by the SARS-CoV-2 virus in critically ill patients and with a nonspecific M antibody response, leading to a false positive result. Processes associated with inflammation in the body can lead to a nonspecific reaction with the test system: acute and chronic inflammatory processes, autoimmune diseases, problems with the thyroid gland, pregnancy, and so on. Our data are consistent with the literature data that with coronavirus IgM can persist for a long time (up to 1,5-3 months from the onset of symptoms, when the virus is gone) [8]. Also, the IgM level had a direct correlation with the severity of the disease (CT) (r = 0,192; p<0,014), rheumatoid factor (RF) (r = 0,191; p<0,016) and an inverse relationship with the duration of the disease (r = -0,240; p <0,002), possibly due to the defeat of Covid-19 joints. There were no differences in the CRP content in the groups. A negative result of CP IgM was more often observed in the group of patients with CT0 (48,1%) and CT1 (40,0%), CT2 (35,7%), CT3 (30,8) CT4 (16,7) gradually decreased (Pic. With an increase in the postcovid period, the frequency of occurrence of persons with a negative IgM result increase, and with an average and high level of IgM CP, it decreases.

The highest frequency of occurrence of a high level of IgM is observed in those who have been ill up to 3 months (33,3%), then a decrease is observed from the duration of the recovery period (Pic.3).

Conclusions:

1. A high level of seroprevalence per-

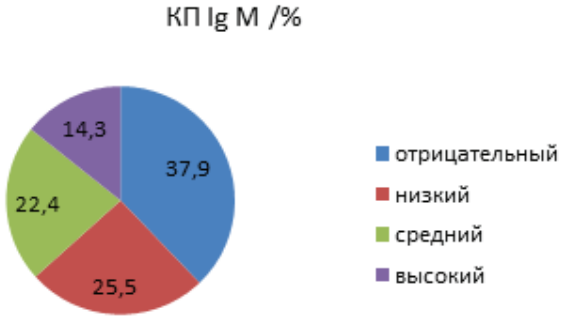

Fig. 1. CP level Ig M in patients with COVID-19, %

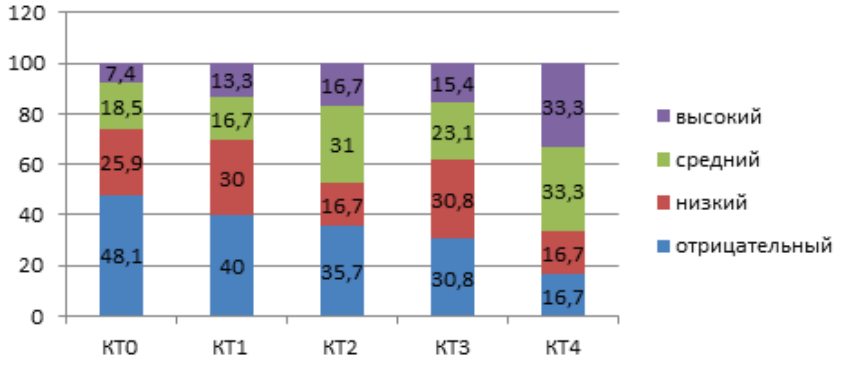

Fig. 2. Frequency of occurrence of persons with different levels of CP IgM depending on the severity of the disease according to CT, %

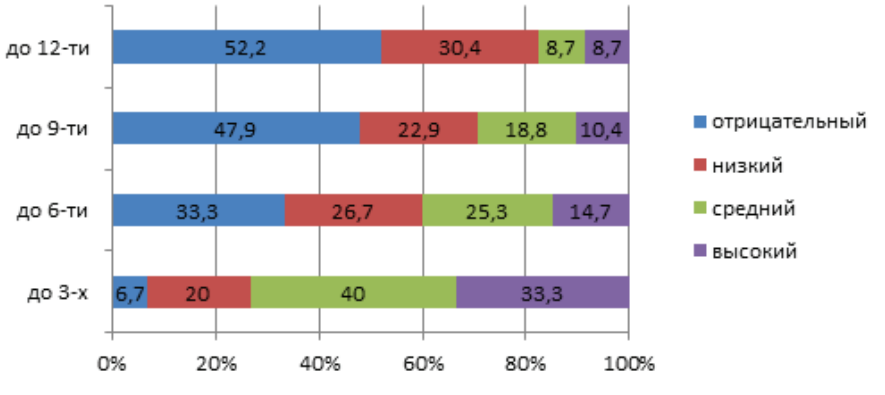

Fig. 3. Frequency of occurrence of persons with different levels of CP Igg depending on the waxy period, %

sists in persons who have undergone COVID-19 with a more severe form of lung damage, since the maximum seropositivity was observed in 100% of patients with CT4, 88,5% with CT3, and 83,3% with CT2.

2. The content of antibodies of immunoglobulin G to SARS-CoV-2 in patients with COVID-19 depends on age: a high level of seroprevalence was found in the group of elderly people (60-74 years) in 88,2% and average (45-59 years) in 69,8 %.

3. IgG antibodies to SARS-CoV-2 in those who have had COVID-19 persist for up to 12 months, and the frequency of high levels of antibodies decreases over time: The maximum level of serovalence in those who had recovered up to 3 months ago was detected in 80%, up to 6 months - in 77,3%, up to 9 - in 75,0%, up to 12 - in 43,3%.

4. The presence of IgM antibodies to SARS-CoV-2 in patients with COVID-19 depends on the postcovid period, the severity of lung damage on CT, and the possibility of obtaining false positive results associated with an increase in rheumatoid factor.

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TRYPTOPHAN METABOLITES IN SERUM AND FECES OF PATIENTS WITH NON-SMALL CELL LUNG CANCER

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The kynurenine pathway of tryptophan metabolism (IDO1 / TDO2-KYN-AhR) plays an important role in carcinogenesis, tumor growth, the formation of the immunological microenvironment of tumors, and may be a potential target for the treatment of oncological diseases. Our objective was to study the content of tryptophan metabolites in blood serum and feces in patients with NSCLC for further estimation of possible correction of microbiomes` functional state and its role in the providence of the efficiency of treatment. The levels of tryptophan metabolites in blood serum and feces of 100 patients with NSCLC in comparison with 100 healthy donors were studied by HPLC-MS / MS. A number of differences were obtained: in the serum of patients, a statistically significant decrease in the levels of tryptophan, its` dominant metabolites of microbiotic origin - tryptamine, serotonin, downtrend for xanthurenic acid along with an increase of the levels of quinolinic acid (in tendency). In feces, the levels of indole in patients were higher than in healthy individuals, this may indicate the activation of the indole pathway of tryptophan metabolism in them or reflect a decrease in the absorption of these metabolites in the intestine. We consider that the decrease of tryptophan and its` dominant metabolites in the serum of patients with NSCLC, apparently, is not associated with an enhanced microbiotic synthesis in the intestine or the consumption of this amino acid with food, but may rather be due to the utilization of tryptophan by tumor cells, since its content in the feces of patients corresponds to that in healthy donors.

Keywords: non-small cell lung cancer, healthy donors, tryptophan metabolites, blood serum, feces.

Introduction. Recently the role of the regulatory system of cellular differentiation, carcinogenesis, tumor growth with enzymes of kynurenic pathway of tryptophan catabolism like IDO1, TDO2, KYN, its` metabolites and its` ligand AhR as key components was described. This system also plays an important role in immune regulation (activation of T regs, suppression of T-effectors and dendritic cells, participation in mucosal immunity) [8, 14]. At the same time, AhR activates PD1 expression in CD8+Tlymphocytes. Since application of immune checkpoint inhibitors (ICI), namely of PD-1/PDL-1 system, is known to be one of the most modern and promising approaches in immunotherapy of cancer, its` effect largely depends upon the patients` immune status. The source of AhR ligands are not only endogenous tryptophan metabolites but also metabolites of gut microflora, in particular, kynurenines of microbial origin [7] with their production depending upon phase metabolic state of bacteria [5, 6]. It was demonstrated that some kinds of malignant tumors (prostatic and breast cancer, glioma, lymphoma etc) produce a great amount of kynurenine and its` level correlates with unfavorable prognosis [12], because IDO1/TDO2KYN-AhR participates in immunosuppressive microenvironment formation which results in immune evasion. In gut IDO1/TDO2KYNAhR system seems to be one of the central regulators of microbiota/mucosal barrier interaction as well as a possible target for treatment of the diseases with its` impairment. Thus, through the IDO1/TDO2KYNAhR mechanism the double-component model macroorganism-microbiota is formed, which is able to transform in tumor-bearing organism to triple-component one: macroorganism-tumor-microbiota. The investigation of the system is likely to enable us to approach the solution of such problems as resistance to immune evasion of tumors and to the development of metabolic complications in tumor patients. Taking into account high incidence, severe course, insufficient effect of treatment and poor prognosis of non-small cellular lung cancer (NSCLC), active research is carried out all over the world to develop new methods of its` treatment based on biologic characteristics of the tumor, among which tryptophan metabolism plays an important role [1, 4, 11].

Our objective was to study the content of tryptophan metabolites in blood serum and feces in patients with NSCLC for further estimation of possible correction of microbiomes` functional state and its role in the providence of the efficiency of treatment.

Material and methods. Two groups were included in the research: group 1 was represented by 100 healthy donors (21 men and 79 women aged 23-70 years, Me 33,82) without any malignant or other chronic diseases; group 2 consisted of 100 patients (76 men and 24 women aged 36-81 year, Me 61,2) with verified NSCLC of various morphology and TNM stage. The I stage was diagnosed in 6%, II - in 22%, III - in 32%, IV - in 10% of the patients. Criteria of inclusion were the absence of application of antibiotics, pre- or probiotics during 3 months before the investigation and signed informed consent to participate in it. Criteria of exclusion for donors were age <18 years, for patients – tumors except NSCLC, severe comorbid disease, any gastrointestinal pathology, respiratory infections, psychosis, alcoholism, drug addiction, pregnancy, lactation. In all the persons included in the research samples of blood and feces were taken. Samples of serum prepared from blood and feces taken in tubes with ethanol were stored up to testing in Biobank at -20oC и -80oC respectively.

The quantitative analysis of Trp metabolites in blood serum and feces was carried out by high performance liquid chromatography with mass spectrometric detection (HPLC-MS/MS) using an Agilent 1200 liquid chromatograph (Agilent inc., USA) [2]. Chromatographic separation was performed using a Discovery PFP HS F5 analytical column (2.1*150 mm; 3 μm). The composition of the mobile phase: phase A - 0.1% solution of formic acid in dionized water; phase B - 100% acetonitrile for chromatography. The gradient of the mobile phase is from 1% B to 10% within 4 minutes, then up to 90% B by the 9th minute of the analysis. The flow rate of the mobile phase is 0.40 ml / min. For detection, a mass spectrometric detector based on an Agilent 6460 triple quadrupole (Agilent inc., USA) MRM and electrospray ionization was used. The resulting signal was processed using the Masshunter software (Agilent inc., USA). The concentration of metabolites was calculated by the internal standard method (2-hydroxynicotinic acid). Analytical standards were prepared using an artificial matrix containing bovine serum albumin and sodium chloride. The studied metabolites were added to the matrix and prepared according to the analysis method. For blood serum sample preparation, an internal standard (2-hydroxynicotinic acid) was added to 100 μL of serum, proteins were precipitated with acetonitrile, the supernatant was evaporated and re-

The content of tryptophan and its metabolites in serum and feces of healthy donors and patients with NSCLC (nmol/L)

Sample	The investigated metabolite	Number of patients with NSCLC	Number of patients in the control group	NSCLC patients Me [HQ …LQ]	Control group Me [HQ …LQ]	p-value	Corrected p-value
Serum	5-hydroxyindole acetate	97	95	63.8 [88.9 ... 39.1]	54.3 [67.2 ... 41.4]	0.035	0.322
	Anthranilic acid	97	95	13 [22.6 ... 10.6]	15.7 [20.9 ... 12.4]	0.075	0.644
	Indole-3-acrylate	98	96	7.4 [14.4 ... 4.2]*	14.5 [23.9 ... 8.3]	Менее 0.001	Менее 0.001
	Indole-3-acetate	99	96	1532 [2143 ... 984]	1793 [2249 ... 1353]	0.006	0.075
	Indole-3-butyrate	99	96	11 [15 ... 6.4]	10.4 [14.9 ... 7.8]	0.622	1.000
	Indole-3-carboxaldehyde	99	96	37.3 [53.7 ... 30.3]*	56.3 [79 ... 43.8]	Менее 0.001	Менее 0.001
	Indole-3-lactate	99	96	564 [713 ... 436]	662 [890 ... 518]	0.007	0.075
	Indole-3-propionate	99	96	405 [849 ... 230]*	870 [1363 ... 481]	Менее 0.001	Менее 0.001
	Kynurenine	99	96	2483 [3033 ... 2075]	2541 [2988 ... 2131]	0.950	1.000
	Kynurenic acid	98	96	14.1 [20.3 ... 10.8]	15.5 [19.2 ... 10.4]	0.960	1.000
	Xanthurenic acid	99	96	1.6 [2.7 ... 0.915]	2.7 [4.1 ... 1.3]	0.004	0.064
	Serotonin	99	96	414 [661 ... 264]*	648 [898 ... 500]	Менее 0.001	Менее 0.001
	Tryptamine	99	96	0.107 [0.163 ... 0.071]*	0.221 [0.337 ... 0.125]	Менее 0.001	Менее 0.001
	Tryptophan	99	96	18705 [22675 ... 15332]*	24062 [27806 ... 19792]	Менее 0.001	Менее 0.001
	Quinolinic acid	99	96	118 [179 ... 78.1]	93.7 [126 ... 69.4]	0.004	0.064
Feces	5-hydroxyindole acetate	97	95	0.109 [0.511 ... 0.043]	0.207 [0.529 ... 0.06]	0.191	1.000
	Anthranilic acid	99	96	0.106 [0.169 ... 0.078]	0.106 [0.149 ... 0.08]	0.816	1.000
	Indole	99	96	327 [595 ... 186]	243 [368 ... 157]	0.007	0.075
	Indole-3-acrylate	98	96	1.2 [2.3 ... 0.677]	1.6 [2.6 ... 0.815]	0.115	0.875
	Indole-3-acetate	99	96	6.1 [14.4 ... 2.8]	4.2 [9.1 ... 2.1]	0.018	0.180
	Indole-3-butyrate	99	96	0.447 [0.721 ... 0.284]	0.384 [0.677 ... 0.228]	0.153	1.000
	Indole-3-carboxaldehyde	99	96	1.7 [3.5 ... 1.1]	1.8 [3.3 ... 0.861]	0.596	1.000
	Indole-3-lactate	97	96	0.178 [0.361 ... 0.118]	0.196 [0.436 ... 0.128]	0.691	1.000
	Indole-3-propionate	99	96	3.6 [6.3 ... 1.5]	2.9 [7.1 ... 1.4]	0.836	1.000
	Kynurenine	99	96	0.184 [0.478 ... 0.106]	0.206 [0.379 ... 0.109]	0.938	1.000
	Kynurenic acid	99	96	3.3 [8.3 ... 1.2]	2.9 [7 ... 1.2]	0.439	1.000
	Xanthurenic acid	99	94	1.7 [4 ... 0.255]	1.1 [2.5 ... 0.256]	0.210	1.000
	Tryptamine	99	96	0.18 [0.924 ... 0.062]	0.117 [0.569 ... 0.055]	0.117	0.875
	Tryptophan	97	95	39.1 [81.3 ... 18]	38.5 [84.7 ... 20.1]	0.899	1.000
	Quinolinic acid	99	96	2.3 [4.6 ... 1.1]	2.6 [5.4 ... 1.4]	0.219	1.000

Note: * - statistically significant differences at $p \leq 0.05$ in comparison with the group of healthy donors.

dissolved in 10% methanol in water with the addition of ascorbic acid to prevent oxidation of analytes. Feces samples were lyophilized to a dry residue, then a sample of about 5 mg was extracted with 50% methanol in water with the addition of an internal standard and ascorbic acid. After centrifugation, the sample was analyzed by HPLC-MS / MS.

Statistical processing of the data was carried out by the methods of nonparametric statistics with the use of R programming language, version 4.1.0 and Rstudio softwear package, version 1.4.1717. The statistical significance of the differences of the mean values were represented by median (Me), higher (HQ) and lower quartile (LQ). Before intergroup comparison we performed the purification of the data from outliers which were accounted as doubtful. For calculation of statistically significant differences between values of the 2 groups Mann-Whitney criterion was used. For exclusion of the re-prediction errors the obtained p-values were corrected according to the Benjamini-Yekutieli method. Intergroup comparison was recognized as statistically significant when adjusted p was < 0.05 and the tendency - when adjusted p was from 0.05 to 0.1 (upward and downward trends).

Results and discussion. According to the obtained results in both groups the main – dominant - products of tryptophan metabolism, which present in serum and feces at the highest levels, were kynurenine, indole-3-acetate, indole-3-propionate, indole-3-lactate and serotonin (table).

In serum of patients with NSCLC the statistically significant decrease of tryptophan level in comparison with donors was found. Besides the lung cancer patients had statistically lower levels of tryptamine, serotonin, indole-3-propionate, indole-3-acrylate and indole-3-carboxaldehyde and tendency to decreased amounts of indole-3-acetate and indole-3-lactate; the majority of these metabolites are of microbial origin. Amongst the metabolites of kynurenine pathway upward trend of quinolinic acid level and downward – of xanthurenic acid level in serum were noted.

Assessment of tryptophan metabolites in feces of healthy donors and in NSCLC patients showed that uptrend of indole levels in the last group, but no statistically significant differences was found (table).

It is worth noting that indole is the dominant tryptophan metabolite in gut both in donors and in NSCLC patients. Unlike serum (in which the downtrend of the level of indole-3-acetate was registered), in feces it had no difference from the donors` values. Indole-3-acetate is able to be metabolized to quinolinic acid via anthranilic acid in enterocytes and immune cells of the gut, as the uptrend of quinolinic acid in patients` serum indicates.

Thus, in serum of NSCLC patients compared to the donor group the concentrations of almost all the tryptophan metabolites are decreased while the levels of NAD+ precursor quinolinic acid demonstrates an uptrend. Quinolinic acid is accounted to be toxic [3], it is known as an important regulator of proinflammatory cytokines` synthesis and is produced by macrophages in high amounts [10], evidently contributing to inflammatory microenvironment of the tumor.

The published data concerning the tryptophan metabolites in cancer patients are rather contradictory. Some authors describe statistically significant increase of both tryptophan and kynurenine levels [13], the other ones demonstrate the increase of kynurenine and decrease of tryptophan in cancer patients` serum [9]. It could be explained by different types of studied tumors as well as by their heterogeneity in cellular composition and metabolic peculiarities. Obviously the activity of microbiota may contribute in these differences, however it is not yet studied.

Conclusion. The decrease of tryptophan and its` dominant metabolites in serum of NSCLC patients is apparently related neither to impairment of their microbial synthesis in large intestine nor to lack of food consumption of the amino acid, but is due to utilization of tryptophan by tumor cells because its` content in feces of patients and donors is similar. Probably this indicates the activation of indole pathway of tryptophan metabolism or reflects the inhibition of their intestinal absorption in patients. Our data demonstrate that not only colorectal cancer but also tumors of anatomically distant organs, namely, lung cancer, may play a role of a tryptophan trap. High level of quinolinic acid may characterize the imbalance of tryptophan metabolism with the result of toxic metabolites` production in our cohort of patients.

The authors declare no conflict of interest.

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BROWNING MARKERS IN ADULT INDIGENOUS RESIDENTS OF YAKUTIA IN CONDITIONS OF NATURAL COLD

In this work, the expression profile of markers of brown adipose tissue activity (CIDEA, PRDM 16), markers of browning of white adipocytes (HOXC9, Slc27A1) and marker of β-oxidation of fatty acids (Cpt1a) in 150 indigenous residents of Yakutia, miners of a diamond mining company, who were exposed to natural cold for 3 months, was analyzed in peripheral blood mononuclear cells. To determine the metabolic status, anthropometric data, glucose level and blood lipid profile of the subjects were evaluated.

Keywords: brown adipose tissue, cold, thermogenesis, browning, Yakutia, obesity.

Introduction. Obesity is characterized by an aberrantly increased amount of white adipose tissue resulting from dysfunctional regulation of the energy balance [13]. The modulation of energy consumption and expenditure is extremely complex and is the result of the integration of numerous neuroendocrine and environmental signals. Exposure in the cold is one of the main available stimulants that contribute to energy consumption by activating thermogenic pathways and thus ensuring survival in adverse temperature conditions [8, 12]. It is known that cold promotes beta-adrenergic stimulation through the sympathetic nervous system, which, in turn, induces thermogenesis, while activating brown adipose tissue (BAT) [7, 8, 12]. The activation of BAT promotes the oxidation of fats to produce heat, while an increased expression of the UCP1 protein is produced [8]. It is known that when stimulated by cold, white adipocytes can transdifferentiate into beige and brown-like adipocytes (a phenotype with increased expression of UCP1) in a process known as browning, leading to heat production [3]. It is important to note that during the browning process, the proliferation and differentiation of precursors of brown adipocytes also occurs, contributing to the growth of the population of heat-producing cells [14, 32]. A number of studies have shown that the activation of BAT in mouse models is able to prevent diseases such as obesity, type 2 diabetes and atherosclerosis [2, 6]. Thus, the study of the regulation of BAT was particularly important as a potential target for the treatment of obesity [14, 17]. It is known that adults have a different volume and amount of BWT, which decreases depending on age and BMI [11,33]. Studying the activation and browning of BZHT in humans is not easy due to several limitations. The most commonly used method available for this purpose is the study of the absorption of (18)F-FDG (2-deoxy-2-[18F]fluoro-d-glucose) by positron emission tomography-computed tomography (PET-CT), which, in addition to various technical limitations, is expensive and complex. In the search for alternative methods for assessing the activation of BAT in humans, we found the study of Palou and his colleagues, which was conducted on female rats, interesting. The results of this work showed that the expression of the regulators of the activity of BAT (CIDEA, Prdm16), browning of white adipose tissue (Hoxc9 and Slc27a1) and β-oxidation of fatty acids (Cpt1a) in both tissues correlates with the expression of the same markers in peripheral blood mononuclear cells (PBMC) when stimulated by cold [23]. The authors concluded that these genes can be considered suitable markers for assessing the activity of BAT in peripheral blood mononuclear cells (PBMC), avoiding the use of invasive procedures [23]. However, it was not clear whether the expression of these markers in the human PBMC is possible and whether it changes depending on exposure to cold. An earlier study conducted by us showed that adult indigenous residents of Yakutia exposed to cold showed greater beta-adrenergic activation and darkening of visceral fat depots compared to the comparison group living in thermoneutral conditions [12]. The aim of our study was to evaluate the expression of browning marker genes in the PBMC in cold-exposed adult indigenous residents of Yakutia compared with the control group, as well as to assess differences in metabolic status between the study groups.

Material and methods. The study was conducted in 2015 in the Verkhoyansk and Anabar districts of Yakutia in accordance with the guidelines of the Helsinki Declaration on the Ethical Treatment of People. The Protocol was approved by the Supervisory Board of the Ethics Committee of the YANC KMP (Protocol No. 46 of May 7, 2015).

Study participants. This study included 150 healthy male tunnellers of indigenous nationality engaged in open-pit diamond mining in the Anabar region of Yakutia (Polar zone, cold exposure group), and 29 healthy control subjects living in the city of Yakutsk (urban zone) in thermoneutral conditions. The subjects included in the cold exposure group spent an average of 8 hours a day working in the mine for 3 months (from

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December to February) at an average temperature of -45/-52 °C. A questionnaire interview was conducted to assess the amount of time spent in cold conditions, based on professional responsibilities. Twenty-nine healthy men were included in the control group in the summer (August), when the average air temperature ranged from +16 °C to +18 °C. Similarly, during blood sampling, the study coordinator conducted a questionnaire to make sure that none of the individuals belonging to the control group had been exposed to cold during the last three months before the study. A special questionnaire prepared by the research group was used for this purpose. Healthy control subjects were recruited through the clinic of the Yakut Scientific Center for Complex Medical Problems. Individuals with a documented diagnosis of a metabolic disease such as metabolic syndrome, type 2 diabetes, dyslipidemia or any other chronic disease, as well as those taking any medications that may affect glucose or lipid metabolism, were excluded from this study.Before registering for the study, all participants signed a written consent form.

Assessment of anthropometric parameters. The weight and height of the subjects were measured using standard weights and a stadiometer, respectively. BMI (kg/m2) was calculated by dividing weight (in kilograms) by height (in meters) squared. Waist circumference (cm) was measured in a standing position at the midpoint of the distance from the lower edge of the costal arch to the iliac crest of the iliac bone. Hip circumference (cm) was measured in a standing position at the level of the large femoral spits.

Blood sampling and biochemical studies. Blood samples were taken in the morning between 8:00 and 11:00 am from the subjects on an empty stomach. Sampling was carried out in February for the cold exposure group and in August for the control group, after 3 months of exposure to cold and thermoneutral conditions, respectively. After collection, the samples were immediately frozen at a temperature of -60 °C and delivered to the laboratory of the Yakut Scientific Center for Complex Medical Problems.

Glucose, triglycerides, total cholesterol and high-density lipoprotein (HDL) cholesterol were determined using an automated biochemical analyzer Labio 200 (Mindray Medical International Limited, Nanshan, Shenzhen 518057, (China)) using Biocon kits (Biocon, Electronic City, 560100 Bangalore (India)). The cholesterol levels of low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) were evaluated using the following formulas:

LDL = total cholesterol-VLDL-HDL;

VLDL = (tg)/2.2.

The atherogenicity coefficient (Ca) was calculated by the formula:

Ka = (total cholesterol-HDL)/HDL [16];

Collection of PBMC and quantitative PCR analysis. Whole blood samples were collected in vacutainers with EDTA. PBMC was isolated by gradient separation using the OptiPrepTM kit (D1556, Sigma-Aldrich, St. Louis, MO, (USA)) in accordance with the manufacturer's instructions and modifications previously described in the Palou study [19]. The quality of the obtained RNA samples was evaluated on the IMPLEN P-300 nanophotometer (Germany). After determining the quality, the RNA samples were stored at a temperature of -80 0C.

Gene expression in PBMC was determined by RT-PCR SFX96 (Germany). Reverse transcription was performed on a thermal cycler T-100 Thermal Cycler (Bio-Rad). The reaction conditions were as follows: 5 minutes at 25 °C, 30 minutes at 42°C, and 5 minutes at 85 °C. Each PCR sample consisted of a diluted cDNA sample (1:5), a direct and reverse primer (1 μm), a solution of SYBR Green PCR Master Mix (Bio-Rad) and DEPC water, the total volume was 20 μl.

PCR reaction conditions: 15 minutes at 95 °C, 1 minute at 60°C and 15 seconds at 95 °C. The primers used in this work are presented in Table 1.

Statistical analysis. The normality of the variables was assessed using the Kolmogorov-Smirnov criterion. Due to the small sample size, a nonparametric method was used. Median and interquartile ranges (IQR) were used to sum the variables. The Wilcoxon rank sum criterion between the two groups was used to assess the differences. To study the differences between the groups, a nonparametric ANCOVA with smoothed regression and the Young and Bowman test was used. Markers and biochemical variables were dependent variables, and age and BMI were covariates. One model was performed for each dependent variable. Nonparametric ANCOVA was also applied to evaluate the effect of the number of hours of cold exposure on the distribution of each marker and biochemical variables in subjects exposed to cold exposure, using BMI as a covariate. Based on the distribution of cold exposure time, four classes were considered: 1 or 2 hours, 4 or 4.5 hours, 8 or 10, 11 hours. To test the hypotheses, the Benjamin–Hochberg P-value correction method was used. For biochemical variables, the interaction between the classes of cold exposure and BMI was also considered. The significance level (p) when testing statistical hypotheses was taken to be $p<0.05$.

Results. A total of 179 people participated in this study: 29 of them belonged to the control group, and 150 subjects were in the group with cold exposure. The distribution of each variable was asymmetric, so a nonparametric statistical approach was chosen. The average age of the subjects was 32 years (IQR: 28; 38). Among those who were exposed to cold, 35% were exposed to cold for less than 5 hours, while 21% of the subjects were exposed to cold for less than 2 hours; 65% were exposed to cold for more than 5 hours and 55% were exposed to cold for 11 hours. There were no significant differences in age, waist circumference (FROM) and waist-to-hip circumference ratio (FROM/ABOUT) between the two groups. The parameters of weight, height, BMI and hip circumference were significantly lower in the cold exposure group compared to the control group (Table 2).

The study of gene expression in the PBMC revealed significantly lower levels of CIDEA expression and higher levels of HOXC9 expression in the cold exposure group compared to the control group, while no significant differences in the expression of other markers were found (Table 3). After age adjustment (as well as adjusted for BMI and without it), circulating total cholesterol, LDL, HDL, VLDL and triglycerides, as well as the atherogenicity coefficient were comparable between the two groups in analyses. However, in the group with cold exposure, the level of circulating glucose was significantly higher than in the control group (Table 3).

Table 4 shows the results of the analysis conducted in the cold exposure group, and due to the number of missed marker values, we compared subjects exposed to cold for less than 11 hours and subjects exposed to cold for 11 hours. There was no clear trend in the adjusted medians and statistically significant differences in the distribution of markers. This can be explained by the high variability of the distribution of markers in each study group. A statistically significant difference between the study groups was observed for such indicators as BMI, total cholesterol and atheroge-

nicity coefficient, for which the adjusted medians decreased with an increase in the number of hours spent in the cold.

This is the first study devoted to the study of gene expression of regulators of activation of brown, beige adipocytes and fatty acid oxidation in PBMC in people who have been chronically exposed to extremely low temperatures. Our data showed that the cold-exposed subjects expressed lower levels of the brown adipocyte marker CIDEA and higher levels of the beige adipocyte marker HOXC9 compared to the control, while the expression of other genes studied by us did not significantly differ between the groups. Interestingly, the people exposed to cold in this study had higher blood glucose levels, but lower body weight, BMI, and hip circumference compared to controls, which may have reflected a healthier metabolic status. The data obtained by us proved that certain markers of brown and beige adipocytes can be detected in the human PBMC and change depending on exposure to cold, potentially reflecting changes in the activation of BAT, browning process in white adipose tissue and the associated metabolic status of the subjects.

The increased energy costs associated with cold-induced activation of BAT and browning have attracted huge interest in its potential in the treatment of obesity and metabolic diseases [9, 11,14, 19,

Table 1

Sequence of nucleotides of primers used for real-time PCR

Gene	Forward Primer (5'-3')	Reverse Primer (5'-3')
Cidea	ATCGGCTCCTTAACGTGAA	AACCGCAGCAGACTCCTCA
Cpt1a	TCCACGATTCCACTCTGCTC	CAGCAACCCCGTGGCC
Hoxc9	CAGCAACCCCGTGGCC	CCGAGGTCCCTGGTTAAA
Prdm16	CCCAACAAGTACAGCCTGGA	GCGGATGAGGTTGGACTTCC
Slc27a1	GCGATATACCAGGAGCTGCA	TCTTGAAGGTGCCTGTGGTG
GAPDH (reference gene)	GTCGGAGTCAACGGATTTGGT	AGTGATGGCATGGACTGTGG

Note: Cidea, cell death-inducing DNA fragmentation factor-α-like effector A; Cpt1a, carnitine palmitoyl transferase 1a; Hoxc9, homeo box C9; Prdm16, PR domain containing protein-16; Slc27a1, solute carrier family 27.

Table 2

Anthropometric characteristics of the studied groups

	control group n=29	Cold exposure groupn=150	p
Age [years, median (IQR)]	34 (29;38)	32 (28;38.5)	0.522
Height [см, median (IQR)]	174 (171;176)	172 (168;176)	0.011
Weight [кg, median (IQR)]	75 (73;81)	70 (64;78)	<0.001
BMI [кg/м2, median (IQR)]	25.61 (23.84; 27.04)	24.06 (22.15; 26.51)	0.023
WC[см, median (IQR)]	92 (84;96)	85 (78;95)	0.082
HC[см, median (IQR]	100 (99; 102)	95 (92; 101)	0.001
WC/HC[median (IQR]	0.91 (0.85; 0.93)	0.89 (0.85; 0.95)	0.872

Table 3

Expression of browning and fatty acid utilization marker genes in PBMC and biochemical parameters when exposed to cold

	Control group n=29	Exposure in cold n=150			
Markers PBMC	Adj.Median (CI 95%)	Adj.Median (CI 95%)	RSE	Coefficient	p*
CIDEA	0.49 (0.43;0.58)	0.30 (0.22; 0.43)	0.467	0.019	0.042
PRDM16	2.97 (1.99;3.64)	1.74 (0.66; 3.42)	3.727	0.362	0.622
SLC27A1	1.30 (0.92; 1.88)	1.12 (0.73; 1.78)	3.772	0.125	0.761
HOXC9	0.96 (0.61;1.18)	1.75 (0.90; 2.42)	2.891	0.271	0.038
CPT1A4	2.40 (1.73; 2.83)	2.30 (0.55; 2.99)	4.167	0.155	0.931
	Biochemical parameters				
Glucose (mmol/l)	4.42 (4.35; 4.69)	5.29 (5.22; 5.36)	0.851	0.121	0.025
Triglycerides (mmol/l)	1.27 (1.00; 1.61)	1.22 (1.08; 1.47)	0.563	0.016	0.763
Total cholesterol (mmol/l)	5.12 (4.71; 5.54)	4.99 (4.81; 5.17)	0.728	0.019	0.888
LDL (mmol/l)	3.30 (2.95;3.63)	3.08 (2.79;3.20)	0.842	0.191	0.856
HDL (mmol/l)	1.21 (1.02; 1.41)	1.59 (1.13; 1.99)	0.534	0.011	0.557
VLDL (mmol/l)	0.71 (0.58; 0.84)	0.55 (0.49; 0.62)	0.474	0.021	0.899
Ka	3.42 (2.56; 4.51)	3.33 (2.61; 4.07)	0.062	0.062	0.878

Note: RSE - residual standard error; Adj. Mediana - adjusted median with smoothed regression; CI 95% - 95% confidence interval.
* nonparametric ANCOVA test using smoothing regression with correction of the p-value of the Benjamini-Hochberg; each model was adjusted for age and BMI. Ka is the coefficient of atherogenicity.

Table 4

MPCP markers and biochemical parameters in comparison groups depending on exposure time

Duration exposure in the cold									
	1-2 ч		4-4,5 ч		8-10 ч		11 ч		p
[Median (CI 95%)]	n=31 31	26.26 (23.51;28.54)	n=21 21	25.51 (24.57;26.39)	n=14 14	24.33 (23.70; 25.39)	n=82 82	23.12 (21.73; 24.49)	<0.05
Markers PBMC									
CIDEA [Adj. median (CI 95%)]	1	-	8	0.36 (0.11;0.82)	7	0.33 (0.01; 0.848)	22	0.30 (0.02; 0.58)	0.974+
PRDM16[Adj. median (CI 95%)]	15	0.64(0.12; 2.55)	16	2.57 (0.74; 4.39)	8	0.85 (0.15; 3.46)	43	1.77 (0.68; 2.89)	0.684+
SLC27A1[Adj. median (CI 95%)]	6	0.18 (0.01; 2.74)	7	1.68 (0.05; 4.14)	8	3.05 (0.78; 5.26)	20	1.20 (0.03; 2.59)	0.799+
HOXC9 [Adj. median (CI 95%)]	24	2.02 (0.61; 3.42)	14	1.78 (0.11; 3.50)	11	3.33 (1.24; 5.41)	52	1.68 (0.72; 2.64)	0.524+
CPT1A4 [Adj. median (CI 95%)]	9	0.27 (0.08; 3.44)	9	2.58 (0.15; 5.80)	8	4.25 (0.86; 7.64)	22	2.29 (0.26; 4.32)	0.668+
Biochemical parameters									
Glucose (mmol/l) [Adj. median (CI 95%)]	31	5.10 (4.74; 5.47)	20	5.28 (4.86; 5.70)	14	5.46 (4.91; 6.02)	82	5.20 (4.98; 5.42)	0.831
triglycerides (mmol/l) [Adj. median (CI 95%)]	31	0.96 (0.75; 1.18)	20	0.98 (0.74; 1.23)	14	1.29 (0.96; 1.61)	82	1.22 (1.09; 1.35)	0.217
Total cholesterol (mmol/l) [Adj. median (CI 95%)]	31	4.99 (4.71; 5.27)	20	4.63 (4.31; 4.96)	14	4.39 (3.96; 4.72)	82	4.43 (4.16; 4.68)	<0.05
LDL (mmol/l) [Adj. median (CI 95%)]	31	2.93 (2.58; 3.27)	20	3.22 (2.83; 3.62)	14	2.87 (2.36; 3.89)	82	3.10 (2.90; 3.31)	0.881
HDL (mmol/l) [Adj. median (CI 95%)]	31	1.78 (1.35; 2.16)	20	1.19 (0.95; 1.49)	14	1.26 (0.93; 1.68)	82	1.38 (1.25; 1.51)	0.679
VLDL (mmol/l) [Adj. median (CI 95%)]	31	0.45 (0.35; 0.55)	20	0.48 (0.36; 0.59)	14	0.56 (0.41; 0.72)	82	0.56 (0.50; 0.62)	0.558
[Adj. median (CI 95%)]	31	3.34 (2.97; 3.72)	21	3.04 (2.46; 3.46)	14	2.61 (2.04; 3.18)	82	2.64 (2.41; 2.86)	<0.05

32]. In fact, in recent decades, numerous studies have been undertaken to identify browning regulators and alternative markers responsible for the activation of BAT [11, 14, 15, 17, 20, 28, 32]. However, since only invasive methods are available to evaluate browning [18], the study of these processes in the human body has limitations. Therefore, the determination of browning markers or browning-associated metabolic changes is of scientific value. In the work of Villarroya and co-authors, circulating "batokines" were found [30], although none of them was recognized as a valid marker of the activation of BAT. Interestingly, the Palou data showed that cold-induced changes in the expression of several genes regulating browning and oxidation of fatty acids of BAT and white adipose tissue in rats are reflected by changes in the expression of the same markers in the PBMC, indicating attention to new potential analytical markers in the PBMC [23]. However, this discovery has never been investigated and confirmed in humans.

Our recent study showed that adult residents of Yakutia exposed to cold have a more intense darkening of visceral fat depots compared to people living in thermoneutral conditions [12].One of the objectives of the study was to find an answer to the question of whether residents of Yakutia belonging to the same population also show differential expression of PBMC markers identified by Palou and his colleagues. The cold-exposed subjects included in our study expressed higher levels of the beige adipocyte marker HOXC9 and lower amounts of the brown adipocyte marker CIDEA compared to the control. This conclusion is somewhat consistent with the conclusions of Palou and his colleagues, whose studies were conducted on female rats of different ages (1, 2, 4 and 6 months) exposed to cold for one week [23]. According to our results, in fact, cold exposure leads to a significant increase in the expression of HOXC9 in adult rats (4 and 6 months) [23]. It is believed that this marker is specific for beige fat depots, and it is known that its expression increases with browning stimulation (with the introduction of rosiglitazone) [31].

Thus, an increase in HOXC9 in the PBMC of people exposed to cold exposure may reflect changes in expression in their fat depots, which makes it a potential candidate for use as a browning marker. Our data are consistent with the results of RNA sequencing studies showing that human BAT has a gene expression signature resembling that of beige adipocytes [25]. On the other hand, Palou and his colleagues did not find significant changes in the expression of CIDEA in the PBMC in adult rats exposed to cold, but they revealed only a clear decrease

in the mRNA level of this marker in the BAT [23]. CIDEA is widely expressed on the surface of lipid droplets of brown adipocytes and is responsible for the formation of large lipid droplets through the stimulation of lipid metabolism between them [4]. The expression of adipocyte CIDEA increases under conditions conducive to triglyceride deposition [22], which is the opposite phenomenon compared to what happens when BAT is activated. According to some studies, it actually antagonizes UCP1 expression [26].

The lower expression of CIDEA in the PBMC in the studied group exposed to cold compared with the control may reflect similar differences in the expression of this marker of BWT, whose levels decreased after exposure to low temperatures in animal models [23]. Evaluation of CIDEA expression in the PBMC has the potential of great clinical significance in the study of human BAT activation and requires further study. In our study, we were unable to detect differences in the expression of Cpt1a4, Scl27a and PRDM16 in individuals exposed to cold when compared with the control group. This finding contrasts with the study of Palou and his colleagues, who observed increased expression of Cpt1a4 and Scl27 in female adult rats when exposed to cold [23]. The differences in our findings and Palou's findings can be explained by several factors, for example, different experimental models, gender, age, the conditions studied and the variability of these markers in the study groups. The group exposed to cold in the present study also had a lower body weight, BMI, and hip circumference, which may have reflected a healthier metabolic status [1]. Although we found no significant differences in cholesterol levels between our two groups, our data showed lower levels of BMI, total cholesterol, and atherogenicity coefficient with increasing daily exposure time to cold. This finding is consistent with data indicating an increase in lipid utilization and an improvement in the lipid profile induced by the activation of BAT caused by cold stimulation [5,6,10]. On the other hand, other reports have revealed a U-shaped relationship between ambient temperature and cardiovascular risk, with the latter increasing at temperatures below -1 °C and above 20 °C [21]. However, most of these studies analyzed temperatures ranging from ~-15 to -30°C, different from our study in which people exposed to cold were exposed to temperatures below -30°C. In addition, the experimental group exposed to cold had a higher fasting glucose level compared to the control group. Although this finding may seem counterintuitive, given that acute activation of BAT increases glucose uptake, plasma glucose levels do not change with acute exposure to cold in humans. Thus, it is possible that in individuals with normal glycemia, chronic stimulation of BAT requires higher basal glucose levels for its use, without leading to metabolic disorders (impaired fasting glucose or insulin resistance). It should be noted that the fasting glucose level in both our groups was within the normal range.

The group exposed to cold in the present study also had a lower body weight, BMI, and hip circumference, which may have reflected a healthier metabolic status [1]. Although we found no significant differences in cholesterol levels between our two groups, our data showed lower levels of BMI, total cholesterol, and atherogenicity coefficient with increasing daily exposure time to cold. This finding is consistent with data indicating an increase in lipid utilization and an improvement in the lipid profile induced by the activation of BAT caused by cold stimulation [5, 6].

Conclusion. In conclusion, it should be noted that this is the first study demonstrating that human peripheral blood mononuclear cells express markers of brown adipocytes and browning, CIDEA and HOXC9 mRNA levels vary depending on exposure to cold. Based on our results, we believe that the expression of CIDEA in human PBMC may reflect its expression in BAT in a state of chronic activation, while the expression of HOXC9 may reflect the expression of white adipocytes undergoing transdifferentiation from white to brown adipocytogenesis, which makes both markers potentially useful markers of BAT activation and browning process worthy of further study and validation.

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ANALYSIS OF THE CERVICAL CANCER INCIDENCE IN THE ARCTIC ZONE OF THE RUSSIAN FEDERATION TO IDENTIFY REGIONS IN FIRST NEED OF ITS PREVENTION

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To identify the territories of the Arctic in which urgent measures are needed for the cervical cancer prevention, including vaccination, a comparative analysis of cervical cancer incidence (CCI) was carried out among Arkhangelskaya and Murmanskaya Oblasts, republics Karelia, Komi, Sakha (Yakutia), Krasnoyarski Krai, Chukotski , Yamalo-Nenetski and Nenetski Autonomous Okrugs and Russia as a whole. The annual rates of CCI per 100 thousand populations, standardized by age, were analyzed. Multiple and paired rank analyzes, as well as the calculation of annual changes from baseline in CCI, showed that cervical cancer prevention is an important task in these state entities, and the population of the Nenetski Autonomous Okrug, which is characterized by a significant proportion of indigenous people and ethnic minorities, needs it most urgently.

Keywords. HPV, vaccination, immunization, ethnic groups, indigenous population, North.

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Introduction. Development and availability of a vaccine against human papillomavirus (HPV) has provided an exceptional opportunity for the prevention of HPV-associated cancers, such as cervical cancer, oropharyngeal, anal, vaginal, vulvar and penile cancer [1].

28 countries in the WHO European Region have added HPV vaccination to their routine immunization schedules [2], as the United States and Canada have [1,3].

In its global strategy for the period 2020-2030 the WHO recognized it is extremely important to include immunization against HPV in the National Health Programs of all countries of the world to accelerate the cervical cancer elimination. To eliminate cervical cancer the WHO emphasizes that all countries must achieve and maintain cervical cancer incidence at a rate of less than 4 cases per 100,000 women per year. Among the measures to eliminate cervical cancer the WHO notes the roadmap of complete vaccination of 90% of girls by the age of 15 years in all countries by 2030 [4].

In the Russian National Immunization Schedule named "Russian national preventive vaccinations and the vaccinations by epidemic indicators calendar" immunization against HPV has not yet been included. The Ministry of Health of the Russian Federation approved Order

No. 125n of March 21, 2014 [5]. At the same time, in the Russian Federation (RF), in the structure of cancer incidence and mortality, cervical cancer has a significant proportion. For example, in 2020 in the RF cervical cancer incidence and mortality took the 4th place in the structure of all cancer sites in women, and cervical cancer incidence had the rate 14.1 cases per 100 thousand populations that are significantly higher than the target rate set by the WHO [6].

If immunization against HPV becomes affordable to the most of Russian citizens and will be included in the Russian National Immunization Schedule or other administrative health programs, for instance, in any Zonal and Regional Health-Saving Programs, then at the start there may be a lack of vaccines. So, it is necessary to indicate territories where they should be delivered first. For this, in our opinion, it is necessary to determine territories with the highest rates of cervical cancer incidence and mortality, as well as a statistical correlation between them in their increasing. In accordance with these criteria we found in our previous research study that among State Entities located in Siberia, the Kemerovskaya Oblast, the Republic Buryatia and especially the Tyva Republic are in first need of cervical cancer prevention. These state entities have a high proportion of indigenous peoples and ethnic minorities [7,8].

The aim. Some regions of the Russian Arctic also have a significant proportion of indigenous peoples and ethnic minorities. Therefore, in this study, the goal was set - to find out whether a large vulnerability to cervical cancer is also typical for multiethnic territories of the Arctic, and to find out which State Entities, whose settlements are attributed to the land territories of the Arctic zone of the Russian Federation (AZRF), are in first need to carry out preventive measures in relation to cervical cancer, including immunization against HPV. AZRF includes settlements of Arkhangelskaya Oblast (AO), Murmanskaya Oblast (MO), republics Karelia (RKa), Komi (RKo) and Sakha (Yakutia) (RSYa), as well as Krasnoyarski Krai (KK), Chukotski Autonomous Okrug (ChAO), Yamalo-Nenetski Autonomous Okrug (YaNAO) and Nenetski Autonomous Okrug (NAO) [9]. Objectives of the research study were to compare cervical cancer incidence (CCI) rates of these SEs with the all-Russian, and also to conduct analysis to identify SE(s) with the most negative situation in terms of the highest CCI rates and the highest values of the CCI increase from baseline.

Materials and methods. The CCI rates were extracted from the books of the Moscow Research Oncological Institute named after P.A.Herzen - a branch of the Federal State Budgetary Institution "National Medical Research Center of Radiology" of the Ministry of Health of Russia. The books issued from 2012 to 2020 on the Website for medical and pharmaceutical workers "ONCOLOGY.ru". The CCI rates per 100 thousand populations which were standardized in accordance with the world distribution of the population by age (age-standardized incidence rate, ASIR) were used for the comparative assessment [10].

The CC ASIRs of the AO, the ChAO, the YaNAO, the NAO, the MO, the RKa, the RKo, the KK, the RSYA and the RF were analyzed in this research study. The retrospective time period was from 2011 to 2019, as the CCI data in the YaNAO have become available since 2011.

The cancer site is the cervix uteri (C53).

As the CC ASIRs did not have a normal distribution to identify differences in more than two SE's multiple ordinal data Friedman's two-way rank analysis was used. To identify differences between data of SEs Wilcoxon rank test was used. To identify paired differences in mean values T-test was used.

The values of the annual CCI changes from baseline (ABCi) were calculated as the ratio of the difference between the annual CC ASIRi (i - [2017; 2019]) and the CC ASIR in 2016 (ASIRo) to the value of the CC ASIR in 2016, which was taken as the baseline:

CCI ABCi = (CC ASIRi - CCI ASIRo) / CC ASIRo;

The values of the CC ASIR in 2016 were taken as the baseline, since only in this year separate data on CCI in the AO and the NAO became available. Until 2015 such data were presented together and so taken into account together too.

Differences were considered significant at $p \leq 0.05$. If $0.05 < p \leq 0.1$, differences were considered to have a tendency to exist.

Results. The CC ASIRs in the AO, the MO, the RKa, the RKo, the KK, the ChAO, the RSYa, the YaNAO, the NAO and Russia as a whole in the period 2011-2019 are presented in Table 1. As in the books the CCI data in the YaNAO

Table 1

Annual values of CC ASIRs in SEs whose settlements belong to the land territories of AZRF, in the period 2011-2019

Год	RF		AO with NAO		AO		MO		RKa		RKo		KK		ChAO		RSYa		YaNAO		NAO	
	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка
2011	13,70	0,12	15,52	1,41			11,01	1,37	35,67	3,00	17,16	1,74	14,94	0,88	22,14	9,06	16,68	1,70	15,27	2,01		
2012	13,90	0,12	15,90	1,43			10,33	1,32	24,61	2,49	15,71	1,62	16,10	0,91	36,99	11,80	16,58	1,69	17,83	2,85		
2013	14,17	0,12	16,15	1,42			11,21	1,44	22,72	2,39	17,41	1,70	17,29	0,94	24,86	9,42	20,30	1,84	11,41	1,76		
2014	14,47	0,12	18,89	1,56			17,15	1,76	24,57	2,46	16,53	1,65	19,73	1,00	20,91	7,47	19,59	1,83	15,26	2,35		
2015	15,01	0,12	17,84	1,53			19,80	1,92	22,90	2,43	16,48	1,69	20,62	1,03	22,90	8,13	19,20	1,79	22,88	3,06		
2016	15,45	0,12			18,32	1,63	16,26	1,70	22,58	2,52	17,13	1,72	18,90	0,99	21,30	7,62	22,85	1,94	20,39	2,59	8,01	5,85
2017	15,76	0,13			17,78	1,57	17,73	2,02	19,94	2,28	23,50	2,04	21,06	1,03	13,11	5,92	20,20	1,82	15,96	2,59	29,37	10,69
2018	15,80	0,12			23,69	1,85	20,76	1,94	20,06	2,23	16,77	1,79	21,49	1,03	9,01	5,20	21,57	1,89	12,53	1,94	31,38	9,61
2019	15,38	0,12			28,85	2,17	17,00	1,81	14,64	1,79	17,75	1,76	21,03	1,04	11,28	5,64	18,38	1,75	12,69	1,91	32,50	10,39

Note: See the explanation of abbreviations in Tables 1-2 and Fig.1-2 in the text

became available since 2011, and the AO and the NAO data were presented together until 2015 - their division occurred only in 2016, so we identified 2 time periods for conducting comparative analysis. The first observation period was 2011-2015 when the CCI data in the AO and the NAO was taken together and the period 2016-2019 that have separated data from the AO and the NAO.

Friedman's two-way rank analysis during the observation period 2011-2015 revealed the heterogeneity of the CC ASIRs among all SEs ($p = 0.000$), while in the period 2016-2019 there was only a tendency to have the heterogeneity ($p = 0.065$). But, when we excluded 2016 from the studied time period, so the period changed to 2017-2019, the analysis revealed the CC ASIRs heterogeneity with the required significance ($p = 0.006$). Therefore, as a result, the period 2017-2019 was highlighted for comparative analysis.

The CC ASIRs average ranks of SEs whose settlements belong to the land territories of the AZRF during these time periods are shown in Figure 1.

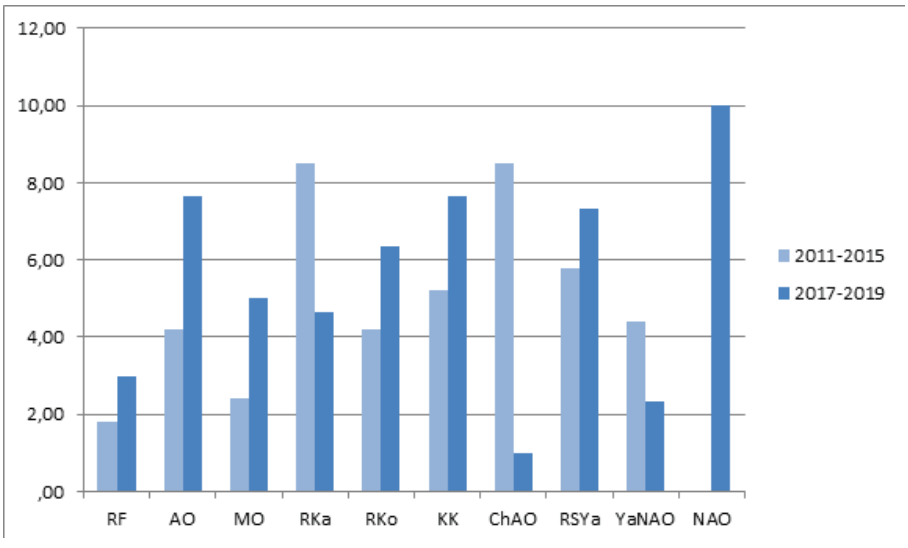

Fig 1. CC ASIRs average ranks of SEs whose settlements belong to the land territories of the AZRF

Multiple and paired rank analyzes allowed us to identify SEs, with the maximum CCI rates in the period 2011-2015, and that were the ChAO and the RKa. No differences in their CC ASIRs were revealed ($p = 0.715$). The CC ASIRs in the ChAO and in the RKa exceeded the CC ASIRs in the AO with NAO, the MO, the RKo, the KK, the ChAO, the RSYa, and the YaNAO ($p = 0.043$ of the rank analysis in pairs of listed SEs with ChAO; $p = 0.043$ in pairs of listed SEs with the RKa).

In the period 2017-2019 the maximum CCI rates in a group of all SEs were found in a subgroup contained the AO, the NAO, the RKo, the KK and the RSYa, their CC ASIRs were homogeneous ($p = 0.155$ of multiple rank analysis). As a result of the CC ASIRs paired rank analysis no differences were recorded in this subgroup either (p did not reach the required significance in any CC ASIRs pair of these SEs). However, it should be noted that the CCI rates in the NAO was near to have the tendency to be maximum in the group ($p = 0.109$ of the CC ASIRs rank analysis in pairs of rest eight SEs with NAO), while the CCI rates in the AO, the RKo, the KK and the RSYa exceeded with the same significance a fewer number of SEs: the CCI rates in the KK and the RSYa exceeded the rates of four SEs such as the MO, the RKa, the ChAO and the YaNAO, whereas the CCI rates in the AO have exceeded the rates of three SEs such as the MO, the ChAO and the YaNAO, while the CCI rates in the RKo have exceeded the rates of two SEs such as the ChAO and the YaNAO.

In 2011-2015 in six territories out of eight - in the AO with NAO, the RKa, the RKo, KK, ChAO and the RSYa, the CC ASIRs exceeded all-Russian ($p = 0.043$ of the CC ASIRs rank analysis in all pairs of these territories with the RF). The CC ASIRs of the MO and the YaNAO did not have significant differences with the all-Russian ($p = 0.686$ of the rank analysis in pair MO-RF and $p = 0.225$ in pair YaNAO-RF).

In 2017-2019 in six SEs out of nine – in the AO, the NAO, the MO, the RKo, the KK and the RSYa the CC ASIRs were near to have the tendency to exceed the all-Russian ($p = 0.109$ of the CC ASIRs rank analysis in all pairs of these SEs with RF). The CC ASIRs in the ChAO was near to have the tendency to be lower than the all-Russian ($p = 0.109$ of the paired rank analysis), while the CC ASIRs in the RKa and the YaNAO did not have significant difference from the all-Russian ($p = 0.285$ of the CC ASIRs rank analysis of these SEs paired with the RF).

Thus in five SEs out of nine – in the AO, the NAO, the RKo, the KK and the RSYa, in 2011-2015 the CCI rates significantly exceeded the all-Russian, and exceeding has continued about as the tendency in 2017-2019. The CCI rates in 2011-2015 in the ChAO and the RKa being the highest among SEs selected for this study had exceeded significantly the all-Russian, but in 2017-2019 "gave up" its previous positions and did not differ

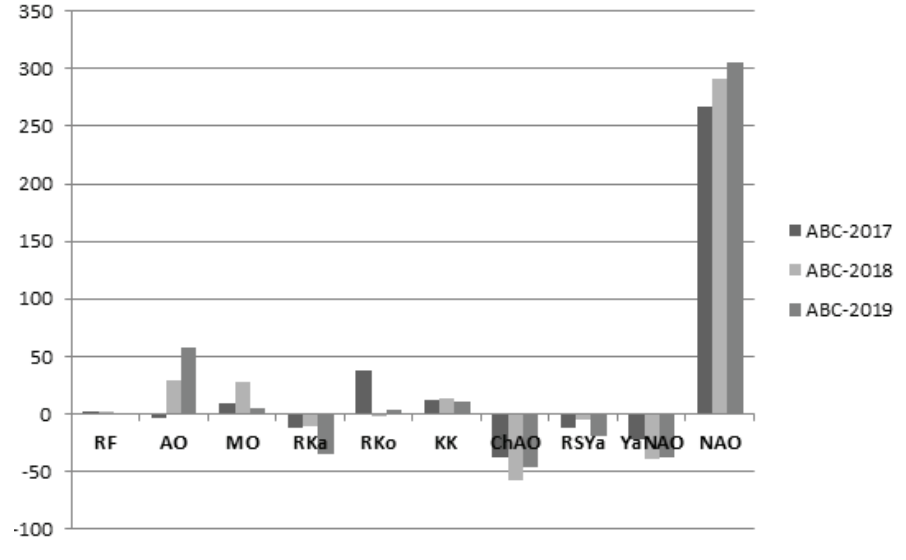

Fig 2. The expressed in percentage CCI ABCs in SEs whose settlements belong to the land territories of AZRF, in the period 2017-2019 versus to 2016

from the all-Russian. The CCI rates in the MO and the YaNAO did not differ significantly from the all-Russian in 2011-2015 and in 2017-2019.

The CCI ABCs expressed in percentage in SEs whose settlements belong to the land territories of AZRF, in the period 2017-2019 versus to 2016 are graphically presented in Figure 2.

The highest value of the CCI ABCs revealed in the NAO, there were the tendency to increase by 3.7 times in 2017 (0.05<p≤0.1 associated with T-test when we calculated differences in the CC ASIRs in this year compared to 2016) and significant increase by 4 times in 2018 and 2019 (p<0.05 associated with T-test). The increase by 1.3 times and 1.6 times recorded in the AO in 2018 and 2019 respectively (p <0.05 associated with T-test) and in the RKo - by 1.4 times in 2017 (p <0.05 associated with T-test). In the KK the tendency to increase by 1.13 times in 2018 were (0.05 <p≤ 0.1 associated with T-test).

The maximum values of the CCI decrease from baseline was noted in the YaNAO – by 1.6 times in 2018 and 2019 and in the RKa – by 1.5 times in 2019 (p<0.05 associated with T-test in all cases mentioned above). Also, a tendency to decrease in the CCI rates by 1.2 times was identified in the RSYa in 2019 (0.05<p≤0.1 associated with T-test). In the ChAO, despite the fact that the values of the CCI decrease from baseline were essential, and this values from year to year have been steadily decreasing – by 1.6 times in 2017, 1.9 times in 2018 and 2.4 times in 2019, the p value (associated with T-test) did not reach either significance neither having the tendency when differences in CC ASIRs in this years were calculated, y (p>0.1 associated with T-test).

In the rest of the years and in other SEs included in the study no changes in CCI from baseline were revealed.

In order to get a picture, we have compiled Table 2, which reflected the analyzed data. In it, we assigned 1 point to the presence of analyzed data, 0.5 point to the tendency towards its presence, and 0 to its absence. In the "CCI ABCs" column, 1 point corresponds to every year when the CCI rate had the increase from baseline, 0.5 points – to every year when the CCI rate had the tendency to the increase from baseline and the negative values correspond to the decrease from baseline. And as a result, among SEs, the whose settlements belong to the land territories of the Russian Arctic, the maximum final score reflecting the current situation regarding to CCI as the most negative was assigned to the NAO, whose population have a significant proportion of indigenous people and ethnic minorities.

Table 2

The sum of the analyzed data on CCI in SEs whose settlements belong to the land territories of the AZRF, 2011-2019

	AO	MO	Рка	Рко	КК	ChAO	RSYa	YaNAO	NAO
The maximum CC ASIR	1		1	1	1	1	1		1.5
CCI ABCs	2		-1	1	0.5		-0.5	-2	2.5
The maximum increase of CCI from baseline									1
The sum	**3**	**0**	**0**	**2**	**1.5**	**1**	**0.5**	**-2**	**5**

Conclusion. Our research study showed that for the population of SEs, whose settlements are attributed to the land territories of the Russian Arctic, as well as for the population of SEs, located in Siberia, the implementation of preventive measures against cervical cancer, including immunization against HPV, is an important task. CCI in 2011-2019 in all highlighted in this study SEs exceeded or was comparable with the all-Russian which in turn significantly exceeded the target rate established by the WHO - 4 cases per 100 thousand women per year. In addition, in five SEs – in the AO, the NAO, the RKo, the KK and the RSYa in 2011-2015 rates of CCI significantly exceeded the all-Russian with the tendency to exceeding in the period 2017-2019.

The most unfavorable situation in relation to CCI was revealed in the NAO, which is a home for a significant number of indigenous peoples and ethnic minorities. Of course, in order to gets a clearer picture for taking measures to prevent CC including immunization against HPV and for CC early detection in these territories further analysis is needed, especially, of CC mortality, and this will be our next research study.

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SCIENTIFIC REVIEWS AND LECTURES

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GUT MICROBIOME AND BREASTFEEDING OF CHILDREN

A review of the literature on studies of intestinal microflora in children is presented. Research in recent years demonstrates the importance of the impact of the gut microbiota on children's health. Contemporary ideas about the gut microbiome are considered. A brief description of the intestinal microflora composition and its impact on the health of the child is given.

Keywords: intestinal microflora, intestinal microbiome, microbiota, gastrointestinal tract, immune system.

Introduction. Currently, the intestinal microbiota is being thoroughly studied all over the world, as a significant influence of the state of the intestinal microflora on the health of children has been proven, and its dysfunction – dysbiosis leads to various pathological conditions.

This review presents the results of Russian and foreign studies on the state of the intestinal microbiome in young children.

Modern ideas about the gut microbiota appeared several years ago in connection with the emergence of molecular-genetic research methods, which made it possible to obtain new information about the composition of the intestinal microbiota in people of different ages. the formation of the intestinal microbiota in children is of a great interest, especially at an early age. In particular, this is caused by a change in the understanding of the microbiocenosis of various biotopes of the body and the appearance of previously unexplored bacterial species [3,5,10].

About thousand species of microorganisms live in the intestine, 90 percent of them are anaerobic [1,2,11,24,25,26].

According to the US National Institute of Health (NIH), only 10 percent of the cells that make up the human body are actually human cells, and the remaining 90 percent belong to bacteria inhabiting various human biotopes [3,4,15,16].

As you know, the intestine is the largest "immune organ" of a person, 80 percent of immunocompetent cells are located there. The formation of the intestinal microbiota is influenced by a number of factors, such as the gestation period, the method of delivery, the type of feeding. Unfavorable factors also have a great influence, especially in the early stages of ontogenesis, such as complicated pregnancy, violation of endoecology in the mother, changes in gestation, operative delivery, late application to the breast, artificial feeding, antibiotic therapy [2,16,19,28,29].

As a result of many studies, data indicating that microbial colonization expands rapidly after birth, and the composition of the microbiome varies especially strongly in early childhood have emerged. It was found that the microbiome in infancy contains vaginal, dermal, oral and fecal strains of the mother, while the intestinal microbiome of the child had the biggest similarity with the intestinal microbiome of the mother by 4 months of life [20,21,28,29].

In the postnatal period, the main influence on the composition of the intestinal microbiota is the method of feeding. Thus, breast milk contains a large number of bacteria, while the microbiota of breast milk is formed when microorganisms penetrate through the intestinal lymphoid tissue (enterological pathway) or by endocytosis due to increased permeability of the intestinal mucosa during childbirth. Probiotic bacteria predominate during breastfeeding, Enterobacteria predominate during artificial feeding [2,12,13,14].

Breastfeeding is believed to protect against the child from development of many diseases, including obesity, diabetes and autoimmune diseases such as asthma and allergies. According to a number of authors, the mechanism by which breast milk determines a child's predisposition to such diseases can be determined by a long-term effect on the intestinal microbiota [6,7,8,22,24]. In particular, as the only source of nutrition in the first 4-6 months of life, the composition of breast milk or formula determines the availability of nutrients for the intestinal microbiota in an infant, and can have a selective effect. The key difference between breast milk and artificial mixtures is the presence of prebiotics, oligosaccharides and antibodies that affect bacterial colonization. Breast milk contains bifidobacteria, streptococci, lactobacilli, which directly make up the microbiome of the baby's intestines. However, there is a great variability in the composition of breast milk depending on the state of health of the mother [27]. The composition of breast milk is dynamic, changes over time, and may also depend on the sex of the child or during illness. It remains to be determined whether the "main" group of breast milk components is responsible for the protective function. For premature infants, breast milk feeding mitigates some of the negative consequences affecting the formation of the intestinal microbiome [26,27].

Studies of the microbiota of young children have focused on the number and diversity of specific bacterial flora. In one of the studies, it was found that breastfed children have a large number of bifidobacteria, and the microbiome of children feeding on the mixture was more diverse [9,12,13]. Another study showed that with natural feeding in the intestinal microbiome of a child, the number of actinobacteria increases and the number of proteobacteria decreases than in children who are artificially fed [14]. In a prospective study, overweight children aged 7 years had a lower content of bifidobacteria and a higher colonization of Staphylococcus aureus in infancy, compared with children with normal weight. This study proved that immunoglobulins obtained from breast milk stimulate the immune function of the intestine and the composition of the intestinal microbiome, which provides additional evidence for the mechanisms linking breastfeeding with immunoprotection. It was also found that in a population at risk of malnutrition (insufficient intake of essential trace elements), lower levels of sialylated oli-

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gosaccharides in breast milk are associated with a slowdown in the growth of young children, and their inclusion in the diet of laboratory animals caused an increase in body weight. This confirms the association of body height and weight with the gut microbiome [10,11].

According to many authors, a number of additional studies are required, but the data obtained emphasize the period of early childhood as a critical period when microbial dysbiosis can lead to overweight in later life. The components of breast milk form the microbiome of the baby's intestine and can provide lifelong protection against obesity and other metabolic diseases [16].

Recent studies show that microbial transfer from mother to fetus already occurs in the womb. Microbes were found in the placenta, amniotic fluid, fetal cell membrane, umbilical cord blood and meconium [17].

Breastfeeding provides the newborn with its own microbiota, as well as prebiotic, immunological and other microbiota-forming compounds that can indirectly change the composition of colonization in the newborn. Therefore, the diverse composition of breast milk can be considered as a selective biofactor for achieving the diversity of the intestinal microbiota and, consequently, as a determining factor of health [21].

A number of studies have proven that breast milk contains 102-104 viable bacteria per milliliter, thus, it can directly affect the establishment of the neonatal microbiota [22]. Lactobacilli, staphylococci, enterococci and bifidobacteria are transferred through breast milk [21]. The microbiota of breast milk also develops during the entire period of breastfeeding. Thus, the colostrum microbiota is more diversed than later breast milk [15]. Colostrum contains a large number of staphylococci, lactic acid bacteria and streptococci [21]. A month after the birth of a child, the number of staphylococci decreases sharply, while lactic acid bacteria are still numerous. Breast milk oligosaccharides are structurally complex sugars, unique in composition. They are indigestible, do not provide energy, but serve as prebiotics, which are substrates for the fermentation processes of intestinal microbes, inducing their growth and activity of beneficial bacteria [22]. The composition of breast milk oligosaccharides is regulated by the genetic status of the fucosyltransferase-2 secretor and other factors, including the stage of lactation, maternal health and ethnicity [4]. In addition, oligosaccharides favor the growth of bifidobacteria [4,22,23]. The maturation of the breast milk microbiota occurs in parallel with the evolution of the intestinal microbiota of the newborn [7].

Translocation of microbes, microbial nucleic acids and bacterial lipopolysaccharides from the intestine into the bloodstream occurs regularly [26]. According to several authors, the origin of bacteria in breast milk is still being discussed. Some researchers suggest that breast milk bacteria originate from maternal skin, since some bacteria contained in breast milk are present on adult skin [18,20]. However, most studies suggest that translocation of maternal intestinal bacteria into the mammary gland is the main pathway. Dendritic cells and macrophages can capture live commensal bacteria from the intestinal lumen and transfer to mesenteric lymph nodes. From there, the bacteria can circulate to other organs, including the mammary glands [23]. Also, the method of delivery can affect the transfer of bacteria to the mammary glands. The same studies have proved that during cesarean section, the microbiota of breast milk is the most diverse, but contains fewer bifidobacteria [18,23].

The role of breast milk for the development of the baby's gut microbiota is very important and is the main tool for the development of the immune system.

Thus, a review of studies conducted on this topic shows that there is significant evidence of a connection between the composition of the baby's gut microbiome and the mother's breast milk. However, there are currently no large-scale studies on the possibilities of the influence of breast milk factors in the formation of the intestinal microbiota of a child. In the future, along with determining the dynamics of the microbiome over time, there is a need for randomized interventional studies that would study ways to regulate the formation of the microbiota of young children and possible subsequent programming of the immune response.

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PREDICTION OF THE RISK OF DEVELOPING DESTRUCTIVE FORMS OF ACUTE CHOLECYSTITIS

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The number of patients suffering from cholelithiasis continues to grow steadily all over the world. Acute cholecystitis is one of the most dangerous complications of cholelithiasis is. The mortality rate in this complication largely depends on the degree of destructive changes in the biliary tract and ranges from 4 to 26%. In addition to the high mortality rate, acute cholecystitis is characterized by a significant percentage of both preoperative and postoperative complications. At the same time, in acute cholecystitis, there are no clear recommendations that would allow making a timely correct decision on the tactics of patient management. Often, clinicians resort to conservative treatment and are late with the operation. Currently, we are looking for methods that would allow us to predict the risk of developing destructive forms of acute cholecystitis in a timely manner. In some cases, on the contrary, there is an underestimation of contraindications, especially in somatically burdened patients, and unjustified surgical activity. Along with this, there is no consensus on the timing of surgical intervention In this review, the main methods for predicting the development of destructive forms of acute cholecystitis are considered. The new stage of diagnosis of diseases and predicting complications is characterized by the introduction of various mathematical models in an inextricable relationship with the accumulated diagnostic knowledge. Various methods are proposed based on the creation of mathematical models and programs for predicting acute calculous cholecystitis in emergency patients. Numerous studies have been devoted to the development of a point system for predicting destructive processes in the gallbladder. The algorithm of using these methods in patients with acute cholecystitis is presented, as well as the prospects for further search for effective methods for predicting the destruction of the gallbladder, acceptable for use in a wide clinical practice. At the same time, the problem of predicting the risk of developing this complication remains relevant. There is a need to search for new methods that would allow predicting the risk of developing destructive forms of acute cholecystitis at an early stage of the disease and determining the most rational treatment tactics. The number of patients suffering from cholelithiasis continues to grow steadily all over the world. One of the most dangerous complications of cholelithiasis is acute cholecystitis. The mortality rate in this complication largely depends on the degree of destructive changes in the biliary tract and ranges from 4 to 26%. In addition to the high mortality rate, acute cholecystitis is characterized by a significant percentage of both preoperative and postoperative complications. At the same time, in acute cholecystitis, there are no clear recommendations that would allow making a timely correct decision on the tactics of patient management. Often, clinicians resort to conservative treatment and are late with the operation. Currently, we are looking for methods that would allow us to predict the risk of developing destructive forms of acute cholecystitis in a timely manner. In some cases, on the contrary, there is an underestimation of contraindications, especially in somatically burdened patients, and unjustified surgical activity. Along with this, there is no consensus on the timing of surgical intervention In this review, the main methods for predicting the development of destructive forms of acute cholecystitis are considered. The new stage of diagnosis of diseases and predicting complications is characterized by the introduction of various mathematical models in an inextricable relationship with the accumulated diagnostic knowledge. Various methods are proposed based on the creation of mathematical models and programs for predicting acute calculous cholecystitis in emergency patients. Numerous studies have been devoted to the development of a point system for predicting destructive processes in the gallbladder. The algorithm of using these methods in patients with acute cholecystitis is presented, as well as the prospects for further search for effective methods for predicting the destruction of the gallbladder, acceptable for use in a wide clinical practice. At the same time, the problem of predicting the risk of developing this complication remains relevant. There is a need to search for new methods that would allow predicting the risk of developing destructive forms of acute cholecystitis at an early stage of the disease and determining the most rational treatment tactics.

Keywords: cholelithiasis, acute cholecystitis, prognosis, destructive forms, cholelithiasis, diagnosis.

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Treatment of acute cholecystitis is a difficult problem for clinicians. This is primarily due to high morbidity and a significant percentage of deaths. In recent years, there has been a steady increase in patients with cholelithiasis all over the world and reaches 10-15% in the adult population. According to American researchers, 6.3 million men and 14.2 million women aged 20-74 years suffer from cholelithiasis in the USA [29]. In Italy, according to the results of

a multi-centralized study, the frequency of stone formation in the biliary tract reaches 9.5% in men and 18.8% in women [29]. Along with this, it was found that acute cholecystitis occurs in 10-20% of stone carriers, as one of the first manifestations of cholelithiasis [9,37,38]. According to various authors, the mortality rate in acute cholecystitis ranges from 4-26% [9,37,38]. At the same time, with increasing age of the patient, the number of adverse outcomes increases. In addition to high mortality, acute cholecystitis is characterized by a significant percentage of both preoperative and postoperative complications. Thus, in 5-6% of cases, patients develop purulent-inflammatory complications in the postoperative period [9,37,38]. With the increase in the incidence of cholelithiasis, there is a steady increase in the number of cholecystectomies [17,30,32,33]. The latter is considered the gold standard in helping patients with cholelithiasis. At the same time, for various reasons (the age of the patient, the presence of severe concomitant pathology, the equipment of the hospital, the experience of the surgeon, etc.), the tactics of managing patients with cholelithiasis varies markedly [9,32,33]. Surgical activity in cholelithiasis is quite high in world practice, which, according to most clinicians, is a justified measure. Thus, according to American researchers, about 400-500 thousand cholecystectomies are performed annually in the USA, and about 100 thousand in Germany [30, 34,36].

At the same time, in acute cholecystitis, there are no clear recommendations that would make it possible to make a timely correct decision on patient management tactics. Clinicians often resort to conservative treatment and are late with the operation. In some cases, on the contrary, there is an underestimation of contraindications, especially in somatically burdened patients, and unjustified surgical activity. Along with this, there is no consensus on the timing of surgical intervention [15]. This fact is due to the fact that there are no sufficiently reliable methods for predicting destructive forms of acute cholecystitis that would assess the risk of destructive changes in the biliary tract with high sensitivity and specificity [9, 17,33,38,37].

Currently, the main methods of diagnosis of acute cholecystitis are: ultrasound, computer and magnetic resonance imaging. Kiewet et al. [26] presents the results of a meta-analysis in which the sensitivity and specificity of the prognostic significance of different methods are characterized. Thus, according to metanalysis, ultrasound of the abdominal cavity has a sensitivity of 50 to 100%, and a specificity of 33 to 100% in the diagnosis and prediction of destructive forms of acute cholecystitis. Similar results were obtained in other studies [22,26,39]. It was found that traditional methods of examination of patients with acute cholecystitis have a sensitivity of 26-100%, specificity of 62-88.1%. At the same time, it was revealed that the positive and negative predictive value of traditional methods ranges from 35%-93.7%, while the global accuracy varies from 70,1-79% [18,21, 23,24,25,27].

It should be noted that the sensitivity of computed tomography ranges from 31-95%, and the specificity from 45-100% [1,2,6]. At the same time, it was found that according to various authors, the sensitivity of this method is 85% (95% CI 66-95%), specificity 81% (95% CI 69-90%) [26]. The head to head study indicates that the diagnostic accuracy of magnetic resonance imaging is comparable to the ultrasound method [1,2,6,26].

In addition to the methods described above, for the differential diagnosis of destructive forms of acute cholecystitis, the determination of the plasma absorption coefficient of infrared radiation in the range of 1543-1396 cm-1 is used. This study is carried out using the hardware and software system "Icarus". It was revealed that in all forms of acute cholecystitis, there is a significant decrease in the radiation absorption index in the range of 1543-1396 cm-1. Thus, with an absorption coefficient of 29.7 ± 1.1%, catarrhal cholecystitis is determined, with an absorption coefficient of 26.4 ± 1.6% - phlegmonous, 21.2 ± 1.8% - gangrenous, and with an absorption coefficient of 18.6 ± 0.5% - gangrenous perforative [11].

The diagnosis of destructive cholecystitis in children is difficult. The study by Sushko E.P. describes the use in the diagnosis of acute cholecystitis in children of the determination of antibodies in the reaction of suppression of hemagglutination with gallbladder tissue, it was revealed that during the formulation of the reaction of passive hemagglutination with an antigen from the extract of the tissue of the inflamed gallbladder an antibody titer of 1:32 was obtained. Such a change in the titer of antibodies is regarded as reactive cholecystitis [10].

The new stage of diagnosis of diseases and prediction of complications is characterized by the introduction of various mathematical models in an inextricable relationship with the accumulated diagnostic knowledge. Various methods based on the creation of mathematical models and programs for predicting acute calculous cholecystitis in emergency patients are proposed. In particular, a program of mathematical prediction of the development of destruction in acute cholecystitis is proposed, based on the study of a number of indicators in peripheral blood. At the same time, the method of support vectors, regression analysis, and the method of a direct non-cyclic graph are used. The following criteria were taken: bilirubin level, AST, leukocyte concentration, a number of indicators of the leukocyte formula (segmented leukocytes, monocytes, lymphocytes), ESR, results of organometry and histometry. The sensitivity of this mathematical program is 79% [7].

Numerous studies have been devoted to the development of a scoring system for predicting destructive processes in the gallbladder. In particular, the use of such parameters as: age more than 45 years (1.5 points); heart rate more than 90 per minute (1 point); male sex (2 points); leukocytosis more than 13 thousand (1.5 points); wall thickness more than 4.5 mm (1 point). Thus, a high probability of gangrenous cholecystitis was determined with a score of more than 4.5 [20,31].

Mustafin D.G. He described conducted a study aimed at finding patterns of change in clinical, laboratory and instrumental data using a new mathematical method based on modeling network neural substances. In this study, the following indicators were used as a basis: changes in tumor necrosis factor, a-2-glycoprotein, ferritin study in gallbladder tissues, bile microbiology, ultrasound and CT data of the gallbladder. As a result of this study, it was found that different forms of acute cholecystitis are characterized by certain changes in the studied parameters (wall thickening according to ultrasound, wall compaction according to CT, increased C-reactive protein and TNF-alpha) [8].

The study of ferritin in patients with acute cholecystitis as a diagnostic criterion for detecting destructive forms of acute cholecystitis is described in the work of Kchibekov. E. A. This method is based on the study of the level of ferritin in blood serum and gallbladder tissues. At the same time, the concentration of ferritin in the blood serum is 0-10ng / ml and in the tissues of the gallbladder 0-0.25 mg / l is taken as 1 point. At the same time, the level of ferritin in the blood serum of 70 ng /ml corresponds to 7 points, and in the tissues of the gallbladder of 0.75 ng / ml - 3 points. Further, the scores are added up and at a value of 10 points, they do not assume destructive cholecystitis, and at a value of 10 points

or higher, destructive cholecystitis [13].

Sibilev V.N.'s study indicates the effectiveness of computer infrared blood spectrophotometry, which allows confirming the diagnosis of acute cholecystitis and predicting the occurrence of destructive forms [11].

Features of diagnosis and prediction of acute cholecystitis forms according to ultrasound of the gallbladder are presented in a number of works. Polymorphism of ultrasound signs in patients with acute cholecystitis is indicated. A diverse picture is associated with both morphological changes and various microbial flora in the gallbladder. At the same time, the diagnostic significance of ultrasound was revealed in the so-called "erased" forms, when there are no changes from the peripheral blood. The leading ultrasound criterion is considered to be changes in the structure of the gallbladder wall [3]. It was also found that destructive cholecystitis is characterized by the following ultrasound criteria: a "double contour" symptom, the appearance of hyperechoic suspension, a "hanging" symptom, the presence of perivesical effusion [4]. Along with this, the effectiveness of determining ultrasound criteria (length, area and volume of the gallbladder) in conjunction with the assessment of blood flow (the value of the maximum systolic velocity (V max) and resistance indices (RI, PI) in the gallbladder wall in the diagnosis of acute cholecystitis is noted. It was found that as hypertension in the gallbladder increases, there is an increase in the extent and speed of blood flow in venous vessels, recorded by color duplex scanning. At the same time, an increase in the frequency of ultrasound criteria (the ratio of length to its transverse size) and Doppler parameters of blood flow (maximum systolic blood flow velocity and systolic-diastolic ratio of the Doppler spectrum of blood flow) allow us to judge intravesical hypertension [28].

Numerous studies have noted that the traditional use of ultrasound should be combined with other methods to increase the informative value of the study. As an additional method, point shear–wave elastography (pSWE) should be used. The use of this method increases the diagnostic accuracy of ultrasound up to 96.3%, and the specificity up to 95%. In addition to pSWE, microvascular imaging (SMI) can be used to increase the accuracy of ultrasound. This method is used to assess the microcirculatory bed and blood flow rate in liver tissues. It was found that the use of SMI increases the diagnostic accuracy of ultrasound up to 85% [4,12,28].

Along with this, a method of rapid diagnosis of destructive changes of the gallbladder in acute cholecystitis is proposed. The following four criteria are taken as a basis: palpable gallbladder; body temperature and heart rate; the level of leukocytosis and rod-shaped shift in the general blood test; the layering of the gallbladder wall and effusion around the gallbladder during ultrasound examination. It was found that in the absence of the listed 4 criteria and the presence of leukocytosis up to 12 thousand, catarrhal cholecystitis can be suspected. And if they are present, including leukocytosis of more than 12 thousand, heart rate values of more than 80 beats / min, phlegmonous cholecystitis is diagnosed [5].

Of particular importance for surgeons is the diagnosis and prognosis of clinically asymptomatic forms of acute cholecystitis. Among the works devoted to this problem, the use of immunochemical methods is of interest. Shikhragimov M.I. studied the concentration of lactoferrin in blood serum and saliva by enzyme immunoassay to diagnose and predict the latent form of acute cholecystitis. As a result of this study, an increase in the concentration of lactoferrin was found in patients with a latent course of destructive cholecystitis. It is noted that the assessment of lactoferrin concentration makes it possible to predict destructive forms and complications of acute cholecystitis [16]. The significance of the lactoferrin study is described by E.A. Kchibekov [13]. The invention of the latter evaluates the level of lactoferrin in the blood serum of patients with acute cholecystitis during hospital treatment. To clarify the diagnosis, it is proposed to rank the obtained concentrations of lactoferrin, take the value of 200 ng/ml as 1 point, with a value of 8-10 points, catarrhal cholecystitis is predicted, and with a value above 10 points, a destructive form [14].

Thus, it can be concluded that at the present stage, the diagnosis of destructive forms of acute cholecystitis is not difficult. At the same time, the problem of predicting the risk of developing this complication remains relevant. There is a need to search for new methods that would make it possible to predict the risk of developing destructive forms of acute cholecystitis at an early stage of the disease and determine the most rational treatment tactics.

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POINT OF VIEW

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THE DIAGNOSTIC METHOD FOR MAXILLA CONSTRICTION BIOMETRIC PARAMETERS DUE TO THE HARD PALATE VAULT HEIGHT IN CHILDREN AND ADOLESCENTS WITH VARIOUS DEGREES OF SEVERITY OF CONNECTIVE TISSUE DYSPLASIA

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Today, there is a high prevalence of connective tissue dysplasia (CTD) among children and adolescents. It manifests as general and local phenotypic features. Among its local manifestations, gothic palate and dentoalveolar anomalies are most frequently diagnosed. We have developed a new device for measuring the maxilla constriction at different CTD severity and a method for determining the maxilla constriction at congenital deformities of the hard palate in children at different CTD severity. The use of this device and method in identifying local (organs and tissues of the oral cavity) CTD signs contributes to more rapid adoption of comprehensive therapeutic and preventive actions to restore constrictions and maxillofacial anomalies of the upper jaw without complex clinical and diagnostic measures.

Keywords: connective tissue dysplasia, phenotypic features, maxilla, gothic palate, dental deformity, treatment, prevention.

Introduction. Nowadays the dental anomalies frequency among schoolchildren is determined as a high level [4, 23, 26]. At the same time, a wide range of pathogenesis and etiological factors cause certain difficulties in solving the problems of their treatment and prevention [8, 30]. Meanwhile, the dentoalveolar system anomalies are considered as an isolated pathology, as well as multifactorial, environmental and genetic diseases [11, 20, 24]. CTD belongs to the heterogeneous group of pathologies associated with hereditary factors, where their phenotypic features are related to this pathology [1, 2, 10, 21, 25]. At the same time, the common CTD manifestations of phenotypic features are associated with changes in connective tissue metabolic processes that contribute to the development of pathological processes of the musculoskeletal system, circulatory organs and abdominal cavity, etc. [3, 9, 19, 22, 31].

It should be noted that the connective tissue, with its constituent components is the basis for the organs and tissues of the dentoalveolar system, and make their complete functioning [6, 7, 12, 27]. At the same time, local CTD manifestations contribute to a decrease in dental caries resistance and an increase in pathological processes of periodontal tissues, anatomical deformation of the hard palate, dental anomalies, temporomandibular joints, etc. [5, 13, 14, 28]. Meanwhile, the dental aspects of this problem have not been studied sufficiently today, where it has been established that one of the CTD markers is the gothic palate, which determines the nature of morphofunctional changes in the dentoalveolar system [15, 16, 17, 18, 29]. The research improving the treatment, prevention and rehabilitation of local CTD manifestations in children and adolescents has theoretical, scientific and practical significance in dentistry.

The aim of the research is to determine the degrees of dentition constriction on the basis of a comprehensive clinical and biometric study of anatomical maxilla deformities taking into account congenital deformities of the hard palate in children and adolescents with different degrees of connective tissue dysplasia severity.

Materials and methods of the study. We have carried out a survey of 956 children and adolescents aged from 12-15 years old with congenital connective tissue differentiation disorders. The examination included educational establishments of the Republic of Sakha (Yakutia):

– Yakutsk schools (School No. 5, School № 2, School № 35, Yakutsk City Lyceum, Yakutsk City Gymnasium, School № 26, Gymnasium № 8, School № 9).

– Village Pokrovsk, Khangalassky ulus (district) (Schools No. 1 and No. 2.)

– villages Mokhsogollokh, Tekhtyur, Oktemtsy, Chapaevo, Nemugyuntsy, Kyl-Bastakh, Oy and Ulakhan-An.

The CTD severity was interpreted by T. Milkovska-Dmitrova and A. Karkashev's method (1985). The CTD severity in the examined children and adolescents was calculated according to the sum of scores: the sum of scores does not exceed 12 in a mild degree, 23 - in a moderate degree, and 24 or more - in a severe degree. The depth of the hard palate vault in case of deformities was diagnosed by a well-known device for measuring the height of the hard palate vault [15].

A biometric study of the hard palate vault height with different CTD severity degrees was carried out, in 629 at dental consultation and in 327 jaw models according to the method of Ushnitsky I.D., Nikiforova E.Yu., Ammosova A.M. (2018) [16]. Cast models of the jaws were obtained at dental consultation, then biometric measurements were performed at

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Dependence of the narrowing of the upper jaw on the severity of connective tissue dysplasia (mm)

Indicators of narrowing of the upper jaw are mild	Mild degree (the depth of the height of the arch of the hard palate is up to 18.0+0.02 mm)		Moderate degree (depth of the firmament arch height from 19.0+0.04 up to 27.0+0.3 mm)		Severe degree (depth of the firmament arch height from 28.0 +0.03 up to 32.0+ 0.02 mm)	
	distance between premolars	distance between molars	distance between premolars	distance between molars	distance between premolars	distance between molars
Minimum values	-9.87±0.46	-10±0.47	-12.2±0.36	-14±0.18	-9.5±0.59	-17.12±0.74
Maximum values	+5.51±0.38	+7.69±0.40	+3.53±0.11	+6.13±0.15	-5.24±0.53	-3.37±0.82
Average values	-2.57±0.13	-2.16±0.15	-2.90±0.17*	-2.57±0.24*	-6.69±0.47**	-6.58±0.43**

Note. Statistical significance of differences in the narrowing of the upper jaw in DST: * - mild and moderate severity; ** - moderate and severe severity.

the Department of Therapeutic, Surgical, Orthopedic Dentistry and Pediatric Dentistry of the Medical Institute of M.K. Ammosov North-Eastern Federal University and Yakutsk Specialized Dental Center. Morphometric studies of anatomical deformities of the hard palate were performed by a special device for measuring the height of the hard palate vault [15], the upper jaw was performed on diagnostic models using a special caliper having fixed and movable jaws for measuring external dimensions made in a truncated plate form, which are designed for fixing removable intraoral pads for fixed and movable measuring jaws (patent № 205333 dated 09.07.2021). To obtain objective data, we used Pont-Linder-Hart's method for determining the width of dental rows in children and adolescents, where we found the relationship between the total values of the mesiodistal incisors and the width of the dental row in the area of the first premolars and molars. Further, we interpreted the obtained data of maxillary constriction depending on the parameters of the hard palate vault height at different CTD severity.

The research was regulated by the basic documents of organization of scientific research in Russia.

Statistical analysis of the results was carried out with a package of programs "SPSS" version 22, license "IBM SPSS 22", as well as Pearson correlation analysis (r) and factor analysis by Varimax method.

Results and discussion. The data showed the presence of some peculiarities. Thus, our biometric studies established the variability of morphological deformities of the maxilla constriction depending on the hard palate vault height in different degrees of CTD severity in the examined age groups of children. According to the frequency of its various severity, the average degree prevailed (55,12±1,05%), followed by the mild form - 32,05±1,59%, and the lowest indices were found at the severe degree - 12,83±2,04%.

The hard palate vault height was measured by our own device [15] according to successive technological steps. If cast diagnostic models were used, the height of the hard palate vault was measured with the use of our device. For this purpose, a bar was placed between the second premolars and the first molars of the upper jaw to create a horizontal reference point and the measuring ruler was advanced to the stop (to the deepest [high] point of the hard palate vault).

Analysis of the results indicates the presence of some features of maxillary constriction depending on the CTD severity, taking into account the depth of change in the hard palate vault (Table). Thus, when the depth of the gothic palate is pronounced in the examined schoolchildren with mild CTD, the indexes of variability in the upper jaw constriction by measuring points between premolars is 15,38± 0,08 mm and molars is 17,69± 0,07 mm. Whereas, the average values respectively characterized maxillary constrictions within -2,57± 0,13 and -2,16± 0,13 mm. Meanwhile, the dynamic changes in the studied parameters became more pronounced, where the values of the distances between premolars and molars were at the level of numerical values 15,73± 0,08 and 20,13± 0,06 mm in CTD moderate severity. At the same time, the mean values were -2,90 ± 0,17 and -2,57± 0,24 mm, which when compared with the mild degree have significant differences (P<0.05). Children with severe CTD pronounced changes in the height of hard palate vault accompanied by significant deformities of the maxillary dentition in the form of its pronounced deformities. Thus, between the measuring points on premolars and molars, there were 14,74± 0,07 and 20,49± 0,11 mm, and their mean values were 6,69± 0,47 and -6,58± 0,43 mm respectively, which also had significant differences in comparison with data of average severity (P<0,05).

The data of the biometric measurements results determine the maxilla constrictions due to the hard palate vault height at different degrees of CTD severity in children and adolescents. In addition, the use of the developed method in identifying local (organs and tissues of the oral cavity) CTD manifestations contributes to a more rapid adoption of comprehensive therapeutic and preventive actions to restore constrictions, maxillofacial anomalies and deformities of the upper jaw without complex clinical and diagnostic measures.

Pearson correlation analysis revealed the relationship between the gothic palate and bite disorder (r=0.81), changes in tooth position and dentition deformity (r=0.59). In addition, the relation presence between the gothic palate and upper jaw constriction in CTD among children and adolescents was confirmed by the results of factor analysis using the Varimax method.

Conclusion. We have obtained the results of measuring the maxilla constriction for the first time depending on the depth of the hard palate vault in schoolchildren with various CTD degrees. It forms the basis for timely planning and organization of comprehensive dental care improving the diagnosis, treatment and prevention of morphological maxilla deformities in this pathology, involving specialists in various fields.

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A CASE OF WAARDENBURG SYNDROME TYPE II CAUSED OF NONSENSE VARIANT OF THE MITF GENE IN THE CONTEXT OF THE EPIGENETIC MOSAICISM HYPOTHESIS

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Keywords: Waardenburg syndrome, iris heterochromia, MITF, epigenetic, mosaicism.

Waardenburg syndrome (WS) represents a very rare autosomal dominant disease. The prevalence of WS is estimated at 1 per 42,000 among the European population and people with congenital hearing loss 2-5% [3; 8; 5; 7; 9]. It is known that the most common causes of WS are mutations in the *PAX3*, *MITF*, *SOX10* and *SNAI2* genes [10; 12]. WS is divided into four types depending on phenotypic manifestations: WS type I (OMIM 193500); WS type II (OMIM 193510); WS type III Waardenburg-Klein syndrome (OMIM 148820); WS type IV – Waardenburg-Shah syndrome (OMIM 277580). Common phenotypic manifestations for all types of WS are hearing loss, impaired skin, hair and iris pigmentation, decreased visual acuity, changes in certain skeletal bones and weakened immune system. It is a well-known fact that clinical phenotypes of WS are extremely variable. In the case of WS, the literature often describes cases of significant phenotypic differences even between affected members of the same family carrying the same mutation [6]. Previously, the phenotypic variability of lesion observed in WS was associated mainly with the influence of modifier genes. Thus, a modifying effect of the *LEF-1* gene on *MITF* gene expression has been shown among patients with WS type II [11]. However, in 2021 R. Happle, based on clinical features of patients with asymmetric lesions of the sensory organs – sight and hearing – the hypothesis of a possible epigenetic influence on the phenotypic variability of WS was put forward [4]. A classic example of the role of epigenetic factors is imprinting in autosomal dominant diseases: Angelman syndrome ("off" maternal allele) and Prader-Willi syndrome ("off" paternal allele); in relation to WS [1], such hypothesis was first proposed.

In Yakutia in 2019, a clinical case of type II WS was described, in which a patient had iris heterochromia with a sectoral site of normal pigmentation on the affected iris, and asymmetric hearing loss (unilateral deafness) [2]. The described clinical case with of a patient with type II WS, with asymmetric lesions the sight and hearing organs is more in favor of the hypothesis of epigenetic mosaicism the proposed by R. Happle [4], than in favor of the hypothesis of the influence of modifier genes [11]. In our opinion, in cases of epigenetic mosaicism, uneven damage to sensory organs is theoretically more likely, than with the epigenetic influence of modifier genes, since in this case we would observe a more uniform damage (for example, bilateral damage to the organs of vision and hearing). Thus, despite WS is well-studied, the new hypothesis of epigenetic mosaicism in WS requires further study and suggests that new evidence of epigenetic control in other cases of irregular gene expression is needed.

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CLINICAL CASE

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A CLINICAL FOLLOW-UP OF A 5-YEAR OLD CHILD WITH SOPH-SYNDROME

A rare case of genetically caused SOPH-syndrome is described in a 5-year old Yakut child. Characteristic features of the follow-up, diagnosis and monitoring over the patient are noted here.

Keywords: SOPH-syndrome, short stature, Pelger-Huet anomaly of leukocytes, atrophy of the optic nerves, children, Yakutia.

Introduction. Rare autosomal recessive, X-linked recessive and autosomal dominant congenital pathology cases are accumulated in indigenous people of the Republic of Sakha (Yakutia), namely in the Yakuts [1,2,5]. N.R. Maksimova, MD, described new cases of genetic disorder in the children population of the Republic of Sakha (Yakutia), namely SOPH-syndrome. The children with such syndrome are born with normal body weight and height, but by the age of 6-7 months optic nerve atrophy and reduced weight and height, as well as the reduction of immunocompetent cells subpopulations, which result in immunodeficiency, are noticed [3,4]. Analysis of catamnesis of the SOPH-syndrome patients and their dynamic follow-up will allow introducing clinical recommendations for monitoring such patients.

A clinical case: A family applied for medical assistance to the Perinatal Center of the Republican hospital #1 (National health center of Yakutsk) in December 2017 complaining of frequent respiratory viral infections, visual impairment, retarded physical and speech developments.

The life history of the patient shows that the girl was born in 2016 in the Yakut family from the second pregnancy. The pregnancy was characterized by isthmic cervical insufficiency with threat of pregnancy loss. There was cephalic presentation in time for labor. The birth weight was 3450g, height 53cm. The Apgar scores were 8/9. There was loud cry, and the neonate was breast fed immediately after delivery and laid on the mother. The girl was breastfed until 1 year and 6 months. Psychomotor development: she holds up her head since 1month, rolls from 4 months, speaks from 13 months and walks from 16 months. She was infected with acute viral respiratory infections, pneumonias, laryngotracheitis, and bronchitis. There were no traumas.

The case history shows reduction of the markers of weight and height, frequent cases of acute viral respiratory infections from the age of 1, the girl was infected with acute pneumonia two times within one year period.

On examination the disease severity was classified as moderate. The physical development is retarded, as well as her speech and psychological development. The girl is malnourished. Cutaneous covering and visible mucous membranes are pale. The skin elasticity is between the normal level. Subcutaneous adipose tissue is mildly expressed. Muscular elasticity is decreased. The pharyngeal tonsils and the soft palate are pink. The chest is of a correct shape, it is not deformed. Respiration is vesicular without wheeze. The heart sounds are rhythmic and clear. The abdomen is soft and painless. The liver and the spleen are within the norm.

According to the test results: The full blood count, taken in 11.01.2018, showed hypochromic anemia. Lymphopenia. Leukopenia. Pelger-Huet anomaly of leukocytes.

Biochemical blood test results, taken in 11.01.2018, showed decrease in the globulin fraction. The immunogram, taken in 22.01.2018, showed IgA 0.1 mg/mL (0.21-2.82g/L), IgM 0.49 mg/mL (0.47-2.40 mg/mL), IgG 1.7 mg/mL (4.83-12.26mg/mL), CD3+81.0% (62-69%), CD4+46.0% (28-76%), CD8+32.0% (4-45%), CD3+CD8+ 1.44% (30-40%), CD19+12,0% (reference ranges 21-28%), CD25+ 7.0% (reference ranges 7-10%), CD3+HLA-DR+ 2.0%, CD16+CD56+ 6.0%. The clinical decision: decrease of contents of A immunoglobulin, G immunoglobulin and cytotoxic lymphocytes CD 3+CD8+.

The electrocardiogram from 12.01.2018 revealed sinus arrhythmia, expressed by bradycardia. Heart rate was 112-91 beats per minute. The electrical axis of the heart was normal. The intraventricular conduction was disturbed. The ventricular repolarization was also disturbed.

The color Doppler ultrasound from 18.02.2020 showed an open oval window of 0.23-0.26 cm. Ectopic tying of the chords of the mitral valve was with minimum regurgitation. A left ventricular trabecula is revealed. The cavities of the heart are not enlarged.

The X-ray exam (18.01.2018) showed the bone age of 2-2.5 years.

The examination by the ophthalmologist (17.01.2018) revealed partial atrophy of the optic nerves.

The consultation with the geneticist (18.02.2018) revealed genealogical anamnesis, which showed no complications caused by the monogenic disorder, the parents are phenotypically healthy.

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Phenotype: a real height is 76cm, (expected height is 86.8cm).

A real weight at the age of 1 year and 10 months is 9 kg instead of 12 kg normally. The BMI is -14.587. The gait is not affected. The constitution is proportional. Nanism. Insufficiency of the body weight is expressed, the skin is clean, pale and elastic. Skin turgor is decreased, the skin is soft and cutis laxa type, and there is a hyperpigmented lesion on the feet. The facial features are small and unexpressed, mild exophthalmos and high pitch voice are noticed. The auricles are not affected and localized typically. The left side of the chest is protruded. The arms and the legs are symmetrically short, and there is micromelia of the hands and feet. The abdomen is slightly enlarged. The liver and the spleen are not affected. The external genitalia are of the female type.

The geneticist administered DNA test to specify diagnosis. A homozygous carrier for the 5741G>A mutation in NBAS gene, causing SOPH syndrome with autosomal recessive type of inheritance, was revealed.

Clinical diagnosis: SOPH-syndrome with nanism, Pelger-Huet anomaly of leukocytes with primary immunodeficiency (Q87.1) is diagnosed. There is a partial congenital atrophy of the optic nerves of the both eyes. Minor anomaly of the heart is noticed with an open oval window of 0.23-0.26cm. There is an ectopic tying of the chords of the mitral valve with minimum regurgitation. Left ventricular trabecula is revealed.

Recommendations: Regular check-ups at the local pediatrician, cardiologist, allergologist and immunologist are recommended to follow up a proband and a family at the medical genetic consultation center. 50 drops of Elkar 30% 3 times a day lasting for a month is administered, the course of treatment is recommended to repeat in 6 months. Likopid 1mg is recommended to be taken once a day lasting for 10 days. Polyvitamins should be taken for a month three times within one year period. Electrocardiogram should be controlled 2 times a year. Echocardiogram should be controlled in 2-3 years. The diet rich in proteins and vitamins is recommended. Sanatorium-and-spa treatment and together with general health improving procedures are recommended.

In 2018 the child was considered as a disabled.

The following two years the child felt well and suffered respiratory and viral infections only two times.

Table 1

Dynamics of the physical development in the SOPH-syndrome child

Date	Age	Weight of the SOPH-syndrome child	Normal weight	Height of the SOPH-syndrome child	Normal height
2018	1year,10 months	9	12	76	86.8
2020	3 years	12	14.85	87.0	97.27
2021	5 years	15.5	18.48	95.6	109.0

Table 2

The immunogram dynamics in the SOPH-syndrome child

Дата	IgA mg/mL	IgA mg/mL	IgA mg/mL	CD3+%	CD4+%	CD8+%	CD4+CD8+%	CD19+%	CD25+%	CD3+HLA-DR+%
11.12.2018	0.1	0.49	1.7	81	46	32	1.43	11.0	7.0	2.0
1.02.2020	0.1	0.52	1.8	86	46	34	1.44	12.0	7.5	2.1
08.02.2021	0.1	0.55	1.85	82	48	36	1.56	13.0	7.7	-

The dynamics of the physical development is represented in the table.

In 2020 the following features were revealed as real weight 12 kg (normally it should be 15 kg); real height 90.7 cm (normally it should be 96.8cm). In 2021 real weight of the patient was 15.5 kg (normally it should be 18.48kg), real height 96.6 cm (normally it should be 109.0).

For the period of 4-year follow-up the patient showed hypochromic anemia, lymphopenia and leukopenia according to the results of the full blood counts, Pelger-Huet anomaly of the leucocytes.

The table 2 shows the dynamics of sharp decrease in immunoglobulin A, immunoglobulin G, decrease in the number of cytotoxic lymphocytes CD3+CD8+.

The patient feels well at the moment. In 2021 she was vaccinated with Grippol, she did not suffer from the acute respiratory infectious diseases during a year.

Conclusion: The clinical manifestations of SOPH-syndrome, a rare congenital disease, are short stature of the child, atrophy of the optic nerves, Pelger-Huet anomaly of leucocytes. Besides these manifestations primary immunodeficiency was revealed. The dynamic follow-up of the children with rare congenital disorders in the Republic of Sakha (Yakutia) allows developing certain clinical recommendations.

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A CLINICAL CASE OF PRIMARY MALIGNANT FIBROUS HISTIOCYTOMA OF THE HEART

Sarcomas are common malignant tumors of the heart. Malignant fibrous histiocytoma is one of the rare forms of heart sarcomas, morphologically diagnosed by cytological and immunohistochemical studies.

The article presents a clinical case of primary malignant fibrous histiocytoma of the heart from the practice of the cardiology department of the Yakutsk Republican Clinical Hospital. The tumor was located in the right ventricle, which is rare and the clinical picture was dominated by symptoms of chronic pulmonary embolism with hypertension. On echocardiography and computed tomography, the volumetric lesion was regarded as a thrombus. Autopsy and histological examination revealed malignant fibrous histiocytoma of the heart. The complexity of the diagnosis was associated with the nonspecific polymorphic clinical picture and the different structure of the neoplasm itself.

Keywords: cardiac tumors, malignant fibrous histiocytoma, pulmonary thromboembolism, chronic thromboembolic pulmonary hypertension, pulmonary trunk, right ventricle, clinical case, malignant neoplasms, diagnosis, clinical case.

Introduction: primary cardiac tumors are very rare, compared with secondary ones, of all autopsies they are detected in approximately 0.001-0.28% [1]. The reason for the rare development of cardiac tumors is believed to be that there are features in myocardial metabolism, such as rapid blood flow inside the heart and limited lymphatic connections in the heart [2].

Benign, among primary cardiac tumors are three times more common than malignant. Cardiac sarcomas are malignant tumors that often develop at the age of 30-50 years, on average at 40 years [1,2]. In men, they occur with a frequency of 65-75%, respectively more than in women [6].

The clinical picture depends on the localization and on the type of tumor; it is manifest by symptoms not only from the heart, but also from other systems and organs. Only in 3-10% of cases they are detected by clinical signs [3,6]. They can usually resemble signs of common heart disease: a variety of chest pains, syncope, arrhythmias, heart murmurs, conduction disturbances, pericardial effusion, or cardiac tamponade. The nature of the symptoms observed in cardiac tumors is most closely related to the localization of the tumor [7,8]. Circulatory failure is the most common manifestation of primary cardiac tumors. It occurs when the tumor is large and is caused by the mobility of the tumor in the heart chamber, causing disturbances in the flow or outflow of blood. If the myocardium is damaged by a tumor, its contractile function may be impaired, which also leads to congestive heart failure [6].

From obstruction by a tumor of the atrioventricular opening in 30% of patients, sudden death occurs, and in the rest, more often the cause of death is progressive heart failure and embolic complications [4,7].

Detection of a volumetric neoplasm in the cavity or layers of the heart and positive biopsy results are the main diagnostic signs of cardiac tumors [9].

Malignant fibrous histiocytoma is characterized by intracavitary growth, accompanied by obstructive and constitutional symptoms. The most common tumor localization is the left atrium, but the tumor can also grow in the right atrium and right ventricle [4,5]. Since most malignant primary cardiac tumors have a crumbling intracavitary surface, blood clots can form on uneven surfaces. Accordingly, tumor embolism of the pulmonary artery, as well as obstruction of the left heart, can lead to pulmonary hypertension [8,9]. In 11-24% of cases, malignant fibrous histiocytoma is detected among sarcomas [10]. Metastasis to other internal organs is rare.

The main radical treatment method is surgical removal of the primary tumor [8].

The prognosis for malignant neoplasms of the heart is unfavorable, patients die within 6 - 12 months after the onset of the first clinical symptoms [7, 10].

Description of the clinical case: we present a clinical case from the practice of the cardiology department of the Yakutsk Republican Clinical Hospital.

Patient Z., 46 years old, a resident of the village, upon admission complained of shortness of breath at the slightest physical exertion, weakness, loss of consciousness.

From the anamnesis it is known that from time to time he was bothered by compressive pains in the region of the heart, which healed on their own. He did not seek medical help. Later, the pain began to appear more often, shortness of breath during physical exertion began to disturb. I went to the local hospital. Auscultation revealed a murmur in the heart, diagnosed with a heart defect. To clarify the diagnosis, he was sent to the Yakutsk Republican Cardiological Dispensary, where, after examination, he was diagnosed: chronic pulmonary embolism. Secondary pulmonary hypertension of 1 degree. CCPF 2 A, FC II. Right ventricular thrombus. An extract was sent to the Federal State Budgetary Institution National Medical Research Center named after Academician E.N. Meshalkin, Ministry of Health of the Russian Federation, Novosibirsk. On the recommendation, he took warfarin under INR control, amlodipine 2.5 mg. In connection with the deterioration of his condition within 6 months, in the form of an increase in shortness of breath, which began to appear at the slightest physical exertion, he was sent again to the Yakutsk Republican Cardiological Dispensary. During physical exertion - climbing on foot to the 8th floor (the elevator did not work), fainted. Delivered by ambulance to the cardiology department of the Yakutsk Republican Clinical Hospital.

Upon admission: the general condition

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Fig.1. Echocardiography with formation in the right ventricle

is severe. Consciousness is clear. Active position. The skin is clean, pale. Rashes, no hemorrhages. Skin turgor is preserved. Visible mucous membranes are clean and pale. Nasal breathing is free. On auscultation in the lungs, breathing is hard, no wheezing. Respiratory rate - 20 per min. SpO2 - 94%. Heart sounds are weakened, the rhythm is correct. Diastolic murmur over the tricuspid valve, accent of the second tone over the pulmonary artery. BP - 100/80 mm Hg, heart rate - 96 per min. The abdomen is soft and painless on palpation. The liver is not enlarged, painless. The chair is not broken. Free, painless urination. The urine is light. No peripheral edema.

Laboratory tests: a general blood test and a general urine test without pathological changes, in the biochemical blood test, an increase in CRPhs was noted - 14.3 mg / l, creatinine - 146 mmol / l; D-dimer was within the normal range of 186 ng / ml, INR over time from 1.6 to 3.2.

Instrumental studies: chest X-ray - in the lungs without focal and infiltrative changes.

ECG shows sinus tachycardia 109 beats per minute. Incomplete right bundle branch block. Signs of chronic cor pulmonale. Pulmonary embolism.

Echocardiography: aorta 36 mm, not dilated, not changed. The leaflets of the aortic valve are thin. The left atrium is not dilated (28x35mm), the left ventricle is not dilated (EDD - 39mm, ESD 23mm), the right ventricle is expanded (40mm), the right atrium is expanded (58x53 mm). Pulmonary trunk 21 mm. The valves of the pulmonary trunk are compacted with fibrosis, deformed. Pressure gradient 7.3 mm Hg. The leaflets of the tricuspid valve are thin, regurgitation of the II-III degree. On the anterior wall of the right ventricle, there is a fixed hyperechoic formation with a diameter of 52.9x29 mm, color doppler mapping "0" of blood flow. A blood clot from the right ventricle descends to the valve leaflet, partially covering it. Fluid in the pericardium. EF 72% satisfactory (Fig. 1).

Computed tomography of the chest and mediastinum with a bolus injection of contrast medium - CT for signs of a thrombus in the right ventricle, pulmonary trunk, partly in the left pulmonary artery. Thromboembolism of small branches of the pulmonary artery (small wedge-shaped foci with indistinct contours along the S1-2 projection of the left lung and S8 of the right lung) is not excluded. Parietal calcifications on the pulmonary trunk. CT - signs of hydropericardium. Diffuse parenchymal changes in the liver.

In the department, the patient's condition remained consistently grave. Received treatment: warfarin 5 mg under INR control, amlodipine 2.5 mg, inspra 25 mg, digoxin 0.125 mg, sildenophil 75 mg per day. In the department he was consulted by an angiosurgeon, diagnosed with thrombosis of the right ventricle, pulmonary trunk, left pulmonary artery and by a cardiac surgeon, diagnosed with pulmonary embolism. Thrombosis of the pulmonary trunk, left pulmonary artery. Right ventricular thrombus. High-grade pulmonary hypertension. It was recommended to send the patient to federal centers of cardiovascular surgery when stabilizing

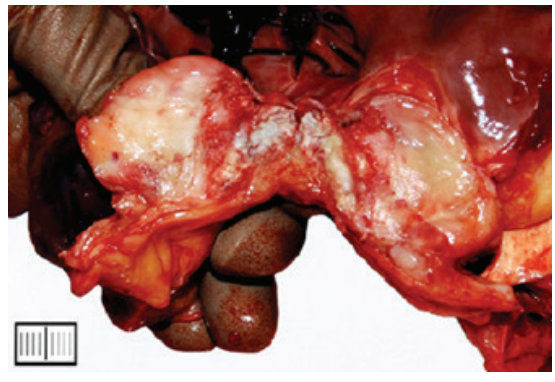

Fig. 2 Malignant fibrous histiocytoma in the right ventricle.

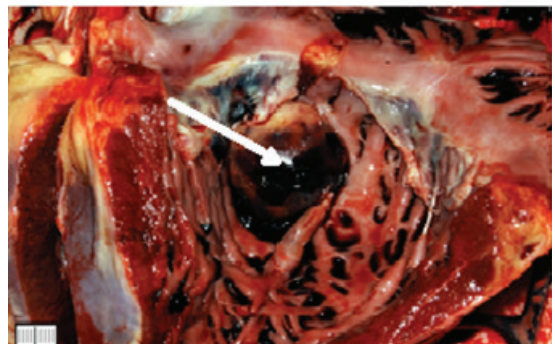

Fig. 3 Thrombus on the tumor

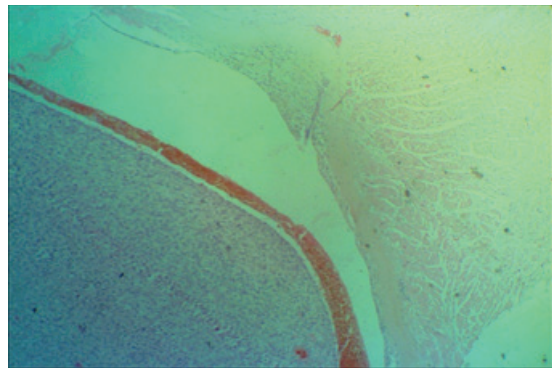

Fig. 4 Malignant fibrous histiocytoma of the right ventricle.

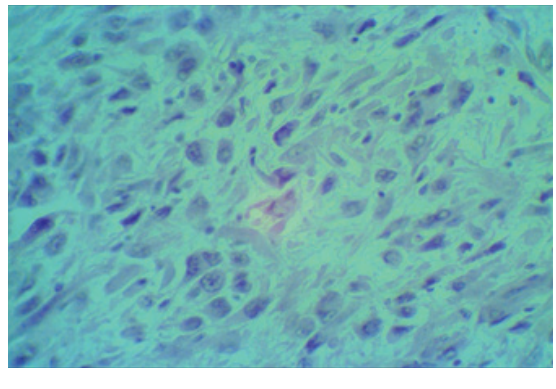

Fig. 5 Germination of malignant fibrous histiocytoma into the myocardium

the patient's condition due to the lack of the possibility of performing surgical treatment in full in the conditions of the cardiac surgery department of the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Hospital No. 1 - National Center of Medicine". By the decision of the council, an extract was prepared and sent to the Federal State Budgetary Institution National Medical Research Center of Cardiology of the Ministry of Health of Russia, Moscow. Based on complaints, anamnesis data, laboratory and instrumental studies, a clinical diagnosis was made: recurrent pulmonary embolism. Right ventricular thrombus. Chronic thromboembolic pulmonary hypertension of severe severity. Complication of the underlying disease: chronic cor pulmonale. CHF 2A FC III NYHA. Lung infarctions S1-2 on the left, S8 on the right. Syncope condition. Cardiogenic liver fibrosis. Concomitant diseases: chronic bronchitis, without exacerbation

In the department, his condition worsened, shortness of breath increased and there was an episode of syncope, in connection with which he was transferred to the intensive care unit. Due to the progression of heart and respiratory failure, the patient died.

Autopsy and histological examination revealed malignant fibrous histiocytoma of the anterior wall of the right ventricle (at the outlet of the right ventricle) and proximal pulmonary artery with invasion into the myocardium and posterior left pulmonary artery valve with parietal thrombosis (Fig. 2,3,4,5). The cause of death was pulmonary embolism.

Conclusion: tumors that grow in the heart cavity need differentiation between themselves and other masses in the heart cavity, for example, with blood clots. In this clinical case, echocardiography and computed tomography were performed, where the mass was regarded as a thrombus. Autopsy and histological examination revealed malignant fibrous histiocytoma of the heart.

Obviously, the discrepancy in the diagnosis was due to the difficulty of diagnosing primary cardiac tumors associated with a nonspecific polymorphic clinical picture and a different structure of the neoplasm itself.

The described clinical case is an example of a pathology with a rare localization of a heart tumor. The presence of masses with a clinic for thromboembolism and pericardial effusion should be alarming in terms of oncology with an expanded patient examination plan.

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PRENATAL DIAGNOSIS OF CAUDAL REGRESSION AT 15 WEEKS OF GESTATION

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УДК 616-007.74

A case of prenatal diagnosis of caudal regression syndrome at 15 weeks of gestation is presented. Ultrasound markers, the stages of prenatal ultrasound diagnostics - taking into account the involved external factors - are described. The diagnosis is based on the basic clinical signs characteristic of this syndrome. Due to the severe form of the caudal regression syndrome, the family decided to terminate the pregnancy. Pathomorphological and postmortem X-ray examination of the abortus confirmed the echographic changes detected in the prenatal period.

Keywords: fetus, caudal regression syndrome, ultrasound prenatal diagnosis, postmortem X-ray examination.

Introduction. Rare congenital malformation of the distal part of the spine and lower extremities in the fetus was first described by Hohl in 1852, and then by Duhamel in 1961 [10]. Caudal regression syndrome (CRS) occurs with a frequency of 1:60,000 to 1:100,000 pregnancies [3].

The defect develops sporadically in the embryo, up to the 28th day of pregnancy, and is associated with a developmental disorder of the main somatic vessels, with abnormal blood circulation in the caudal parts of the embryo, followed by a disorder in the development and layering of the organs of the lower body and the formation of combined anomalies of the cardiovascular, respiratory, gastrointestinal, genitourinary, nervous, musculoskeletal systems [1,2].

The vascular genesis of CRS is confirmed by the data of other authors [1,13]. Thus, fetuses with caudal regression develop a disorder of embryonic angiogenesis, which leads to the arterial steal syndrome, in which blood flow is redirected from the lower parts of the embryo to the chorion, which leads to the development of multiple malformations of the lower extremities. In the overwhelming majority of fetuses with CRS, the umbilical cord arteries connect directly with the superior mesenteric arteries, forming aberrant collateral vascularization [1,13]. Women with overweight, latent or explicit form of diabetes mellitus or who have been exposed to teratogenic factors (high radiation background, hyperthermia in early pregnancy and in the pre-pregnancy period, exposure to retinoids, sulfanilamides, organic solvents, cadmium, ochratoxin A, diethylpropion) during pregnancy have a high probability of developing embryos with caudal regression syndrome [4].

This congenital malformation in most cases is combined with a number of anomalies of the central nervous system (holoprosencephaly, Arnold-Chiari syndrome, secondary hydrocephalus, myelomeningocele), the cardiovascular system (ventricular septal defect), the gastrointestinal tract (tracheoesophageal fistula, duodenal atresia, anus atresia) and the genitourinary system (ureterohydronephrosis, bladder exstrophy, rectoureteral and rectovaginal fistulas, horseshoe kidney, hypospadias, urethral atresia, external genitalia transposition) [5-9].

In a mild case of spinal column involvement in the pathological process, the fetus may lack only the coccyx, or sacral and lumbar vertebrae - up to the absence of lower thoracic vertebrae - with a severe form of lesion. The specific change of individual vertebrae in the form of a "butterfly" or a "wedge" shape caused by an incomplete anterior or posterior cleft of the vertebral arch, which is due to insufficient fusion of individual ossification centers, is also described [6,9,11].

The prognosis for CRS depends on the degree of lesion and in its severe forms it is unfavorable.

The first and most complete classification of CRS was proposed by Renshaw in 1978, who described four variants of the defect [12]:

Variant I - a unilateral lesion, with the preservation of all joints with deformation and asymmetry of the pelvic ring, and lumbar scoliosis. There may also be clubfoot (equinovarus deformity of the feet) and neurological disorders in the form of loss of sensitivity.

Variant II is an incomplete bilateral lesion with an anomaly of the vertebrae ("butterfly-shaped", "wedge-shaped" and semi-vertebrae), with paresis and paralysis of the lower extremities.

Variant III is fragmentary lumbar and complete sacral agenesis, in which the iliac bones are connected to the lateral surfaces of the existing last vertebra, forming a "shield-like" fusion of the iliac bones. In this variant, dislocations of the femoral bones, contractures of the knee joints and clubfoot are observed.

Variant IV is selective lumbar and complete sacral agenesis, when the lower part of the present vertebra is installed above the "shield-like" articulation of the hypoplasized iliac bones, which causes complete instability of the pelvic spine. Movements in the hip joints are limited due to contractures, pterygiums are detected in the popliteal fossa, and pronounced clubfoot of the feet is observed. As a result of the described changes, the patient is constantly in the "frog pose" [12]

Here is a description of the clinical case of prenatal ultrasound diagnosis of an extremely rare fetal malformation.

Patient R., 32 years old. She was registered at the health center from the 5th week of pregnancy. This is her second pregnancy. Her husband is 32 years old, smokes. The married couple is not related. Spouses have no occupational hazards.

During the pre-gravidar period, the patient took medicine of the nitrofuran class and notes contact with organic solvents during the same period. Genealogical history is not burdened. Chronic diseases - obesity of the 1st degree, chronic cystitis. This pregnancy proceeded with the threat of termination of pregnancy in

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the 1st trimester due to a viral respiratory infection, also at 16 weeks the patient suffered a novel coronavirus infection COVID-19, on an outpatient basis, without complications.

The studies were carried out on the Mindrey-7 ultrasound device using C5-3, V10-4 MHz convexic sensors, and on the Voluson - E10 device, with RM6C, RIC 6-12 D sensors.

During ultrasound imaging at the age of 13 weeks of pregnancy, challenging due to the pronounced subcutaneous fat layer of the anterior abdominal wall, a slight increase in the echo-shadow of the fetal stomach and the absence of an image of the fetal kidneys in a typical place attracted attention. The coccygeal-parietal size of the fetus at the age of 13/2 weeks was 68.2 mm, which corresponded to the age of 13/0 weeks. An attempt at a detailed study using a transvaginal sensor did not clarify the picture due to the unfavorable position of the fetus and low motor activity, uncharacteristic for this period of pregnancy. The patient was invited for an additional examination.

According to the results of combined prenatal screening, in the 1st trimester of pregnancy, the risks of aneuploidy were distributed as follows: for Down syndrome - 1:6128, for Edwards and Patau syndromes - less than 1:20,000 (RARP - a - 0.71 Mom, b - hCG - 0.98 Mom).

During repeated examination, at the time of 15/6 weeks of pregnancy, the lumbar and sacral spine were not clearly defined, the dimensions of the fetal stomach were 17x8x10 mm compared to the normal size of up to 12x5x8 mm;(fig.1) it seemed that both kidneys were on the left (the right kidney was in heterolateral pelvic dystopia - Fig. 2). In the lower parts of the anterior abdominal wall, almost in the perineal region, a "low abdominal bulge" was detected - an exstrophed bladder, to the upper part of which the umbilical cord was attached. At the same time, biological sex of the fetus could not be clearly determined. The lower limbs were defined in a fixed, bent position. Motor activity in the lower extremities was not defined. Due to the bent position of the fetus, the area of the anterior abdominal wall could not be clearly visualized.

Based on the information above, with the conclusion that this echographic picture corresponds to the caudal regression syndrome, the pregnant woman was sent for consultation to the Medical genetics Center, where the initial diagnosis was confirmed at 17/2 weeks. Additionally, fetal VSD (ventricular septal defect), increased fetal gastric echo-shadow, heterolateral pelvic dystopia of the right kidney, a single umbilical artery, bilateral clubfoot were detected.

Without prenatal karyotyping and according to the collegial conclusion of the Prenatal consilium, taking into account the decision of the family, the patient is directed to termination of pregnancy due to severe malformations and an unfavorable prognosis, with mandatory pathoanatomic verification.

Pathoanatomic data. Male abortus, weighing 303 g, height 20 cm (Fig.3). An external examination revealed: the trunk is shortened, the lower extremities of the fetus are in the "frog pose", a defect of 18x17 mm is defined on the anterior abdominal wall under the umbilical ring, from where the bladder wall and intestinal loops are prolapsed (cloaca exstrophy). The lower limbs are bent at the hip and knee joints, the feet are rotated inward. The bilateral popliteal pterygium, more pronounced on the left, is determined (Fig.4)

Cardiovascular system: a defect of

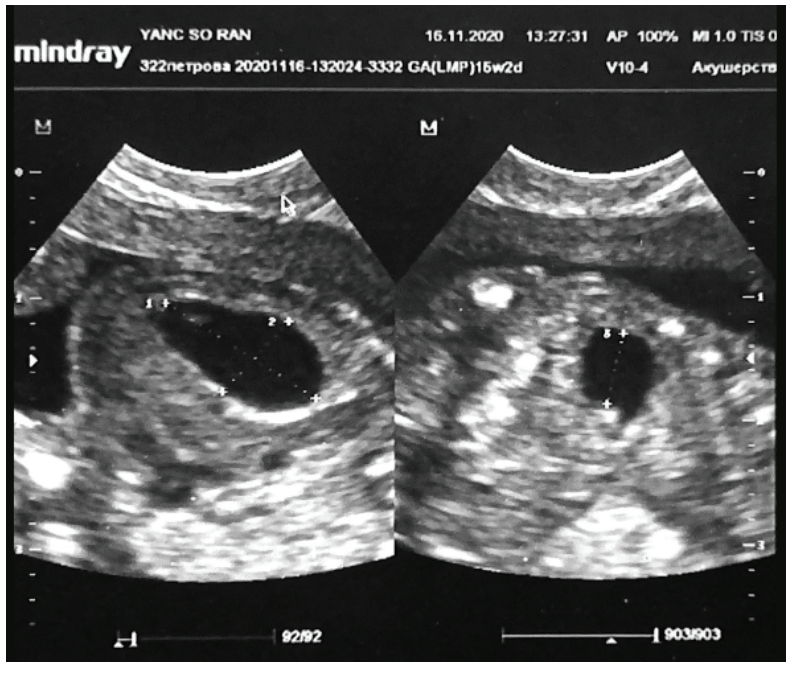

Fig.1. Enlarged echotene of the fetal stomach

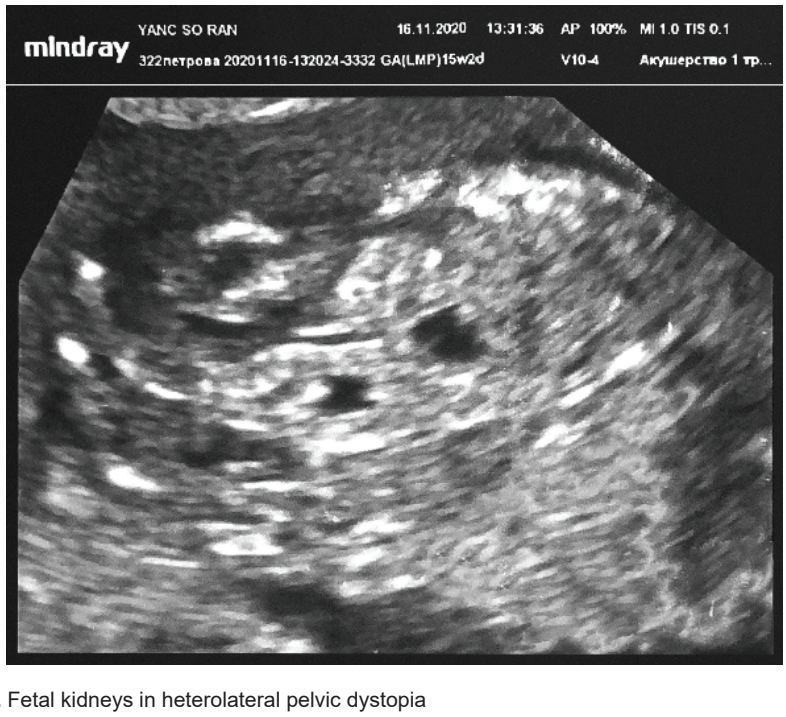

Fig.2. Fetal kidneys in heterolateral pelvic dystopia

the interventricular septum in the muscular part, 3 mm wide, is determined. The stomach is enlarged in size, duodenal atresia is determined. Both kidneys are located on the left, one of them in the pelvic cavity. Spine: the lumbar and sacral spine are not defined (Fig.5), the pelvic ring is not formed, the iliac bones are separate. Extraembryonic structures: placenta with signs of premature maturation, single artery of the umbilical cord.

Postmortem X-ray examination data: multiple bone anomalies are determined: 9 thoracic vertebrae, from the 6th to the 9th vertebrae of the "butterfly" shape, 9 thinned ribs on both sides. The lower thoracic, lumbar vertebrae, sacrum and coccyx are absent (Fig.6). The lower branches of the pubic bones and the rest of the pelvic bones are not clearly differentiated. Bones of the upper extremities are of the usual shape and size. The bones of the lower extremities - femoral and tibial are reduced in size, the fibulae are not differentiated. In both feet, 5 metatarsal bones are determined.

Conclusion. Prenatal ultrasound diagnosis of syndromic pathology is based on multiple systemic pathognomonic signs. In the case of caudal regression syndrome, it is the absence and change of vertebral bodies at the level of the lumbar and sacral divisions, the disturbed structure of the pelvic ring bones, characteristic disorders of the development of the lower extremities, malformations of the cardiovascular system, gastrointestinal tract and genitourinary system and concomitant disorders of the development of extraembryonic structures. The syndromic diagnosis is indirectly indicated by both the pre-pregnancy period and the course of pregnancy in the early stages: taking teratogenic drugs and exposure to organic solvent vapors.

In the case described by us, the diagnosis was suspected at the first screening study conducted at 13/2 weeks on an ultrasound machine of an average, non-specialized level, and finally formed and exposed at the first, outpatient, prenatal examination level, at 15/6 weeks of pregnancy. The changes described during ultrasound examination in the prenatal period and confirmed pathomorphologically and postmortem radiography fit into the IV variant of the caudal regression syndrome according to the Renshaw classification [12].

For a more complete verification of the syndromic diagnosis during pathoanatomic examination, additional participation of specialists - pediatricians, neurosurgeons, cardiologists, orthopedists, urologists is desirable.

Fig.3. Male abortus, weighing 303 g, height 20 cm

Fig.4. Popliteal pterygium

Fig. 5. View of abortus from the back

Fig.6 Postmortem radiography in direct projection

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A CLINICAL CASE OF ACUTE CORONARY SYNDROME WITH ECG-ST-LIFTING COMPLICATED WITH CARDIOGENIC SHOCK

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Acute coronary syndrome is the most common cause of cardiogenic shock and urgent reperfusion therapy is essential. The article presents a clinical case of acute coronary syndrome with an electrocardiogram ST segment elevation complicated by cardiogenic shock. Timely reperfusion therapy - percutaneous intervention on the infarction-associated antero-descending coronary artery, made it possible to improve the prognosis and outcome of acute myocardial infarction with acute heart failure Killip class IV.

Keywords: acute coronary syndrome, myocardial infarction, cardiogenic shock, percutaneous intervention.

Introduction. Acute myocardial infarction (AMI) is considered the most common cause of cardiogenic shock (CS) and more often observed in patients with acute myocardial infarction with ST segment elevation (STEMI) compared with patients with acute myocardial infarction without ST segment elevation (NSTEMI) electrocardiogram. According to statistics, cardiogenic shock (CS) occurs in 5-7% of patients, and is accompanied by unfavorable outcomes in 40-60% of cases. Nosocomial mortality in this category of patients has decreased from 70-80% in 1970 to 40-60% at present, however, CS remains the main cause of death among patients hospitalized with AMI. Cardiogenic shock, being a terminal condition, in 75% of patients is caused by left ventricular failure, in 10% - by mechanical damage to the heart and in 3% - by right ventricular failure, leads to generalized tissue hypoperfusion, irreversible cellular damage and, if adequate care is not provided, to death [1-3].

One of the main factors responsible for the high mortality in CS, which developed against the background of AMI, is the long duration of the period during which the patient was in a state of shock, since in such cases the syndrome of multiple organ dysfunction develops. Consequently, it became obvious that CS caused by AMI is a complication of heart disease, in which many organs are affected, which largely determines the need for intensive therapy. Current recommendations postulate urgent percutaneous intervention (PCI) for patients with ST-segment elevation myocardial infarction and CS [4].

Thus, taking into account the urgency of the problems associated with the development of acute coronary syndrome complicated by cardiogenic shock and the importance of timely reperfusion therapy, we present as a clinical example the case history of a patient treated at the Regional Vascular Center in Yakutsk.

Patient G., 58 years old, was delivered at 00:02 on April 1, 2021 to the admission ward of the department of anesthesiology, resuscitation and intensive care (DARIC) №2 of the Regional Vascular Center of the Republican Hospital № 2-Center for Emergency Medical Aid by the team of the ambulance station (SSMP).

It is impossible to collect complaints and anamnesis from the patient's words during hospitalization due to the severity of the patient's condition. According to his wife, patient G. on March 31, 2021, before going to bed, did not show any complaints, at 11:10 p.m. she found him unconscious in bed, the patient did not react to external stimuli, called the SSMP team at 11:15 p.m. Upon arrival, the patient experienced clinical death, exposure 12 minutes, ECG elevation of the ST segment along the anterior wall, body temperature 36.5 ° C, BP 60 / 40 mm Hg, heart rate 93 beats per minute. SpO2 97%. Cardiopulmonary resuscitation was performed. Closed heart massage 30:2. Relanium 2.0 ml, Fentanyl 2.0 ml, Heparin 4000, S. Dopamine 5.0 ml.

Later, when the patient's condition stabilized, a medical history was collected: previously, IHD, PICS, CVA, he denies syncope. BP does not control, rarely rises to 160/100 mm Hg, adapted to BP 120/80 mm Hg. Previously, pain in the region of the heart was rarely disturbed, without a clear connection with physical activity, he did not go to doctors about this, he is not registered with D. He does not take medications all the time.

When examined in the admission ward, the patient's general condition was regarded as extremely serious, due to the underlying disease. Coma Consciousness + Medsedation. The skin and visible mucous membranes are clean, pale, no peripheral edema. Breathing - mechanical ventilation through the Ambu bag, auscultation in the accessible sections is hard, wheezing is wired, moist, weakened in the lower sections on both sides. When examining the cardiovascular system, heart sounds are rhythmic, muffled. No noise. HR-104 per minute, AP-80/50 mm Hg. Saturation-97%. From the gastrointestinal tract: the abdomen is enlarged due to the subcutaneous fat, participates in the act of breathing, palpable soft. The liver and spleen are not enlarged. Stool, urine output is unknown.

Based on complaints and anamnesis of the disease, physical examination, ECG result, a preliminary diagnosis was made: Main: ACS with ST segment elevation along the anterior wall from 31.03.2021, Condition after clinical death, exposure 12 min. Background disease: Hypertension 3, risk of CVC 4. Complication of the main diagnosis: AHF 4 FC according to Killip. Cardiogenic shock. Concomitant diagnosis: Aortic atherosclerosis, AK, MK. GFR (CKD-EPI): 57 ml / min

The patient underwent an urgent assessment of laboratory data, coronary angiography (CAG), electrocardiography

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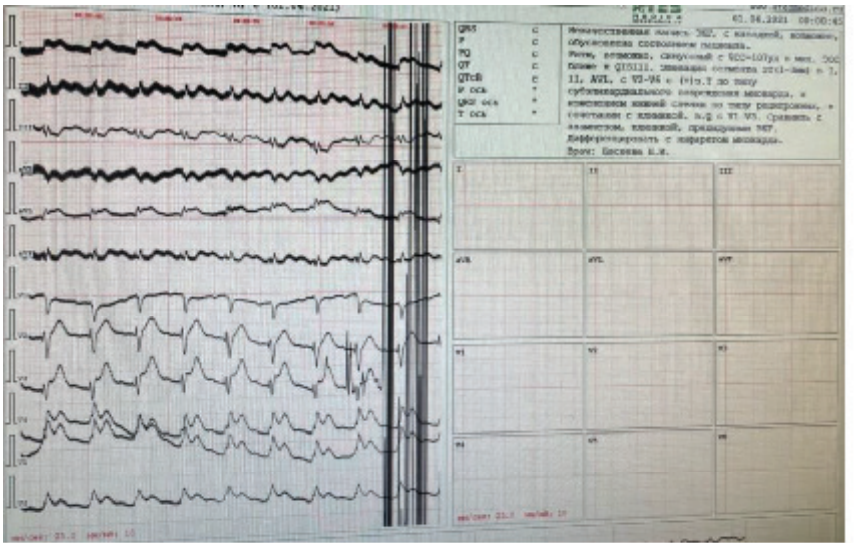
(ECG), ECHO-cardiography (ECHO-CG), followed by transfer to DARIC №2 RVC.

According to the general blood analysis upon admission, leukocytosis up to 19x10e9 /l, relative s /n neutrophilia up to 83.6%, relative lymphocytosis up to 43.7%, an increase in ESR up to 44 mm / h. Increase in cardiospecific enzymes - highly sensitive troponin I: the first - 0.669 ng / ml, the second - 13.2 ng / ml. According to biochemical blood analysis, a moderate decrease in proteins to 57 g / l, hyperbilirubinemia to 29.7 μmol / l, an increase in direct bilirubin to 7.5 μmol / l, hyperglycemia to 15.7 mmol / l, an increase in urea to 11.7 mmol / l, creatinine levels to 142.1 mmol / l, transaminase: ALT up to 207 U / l, AST up to 269 U / l. The coagulogram showed an increase in the level of fibrinogen up to 5.94 g / l.

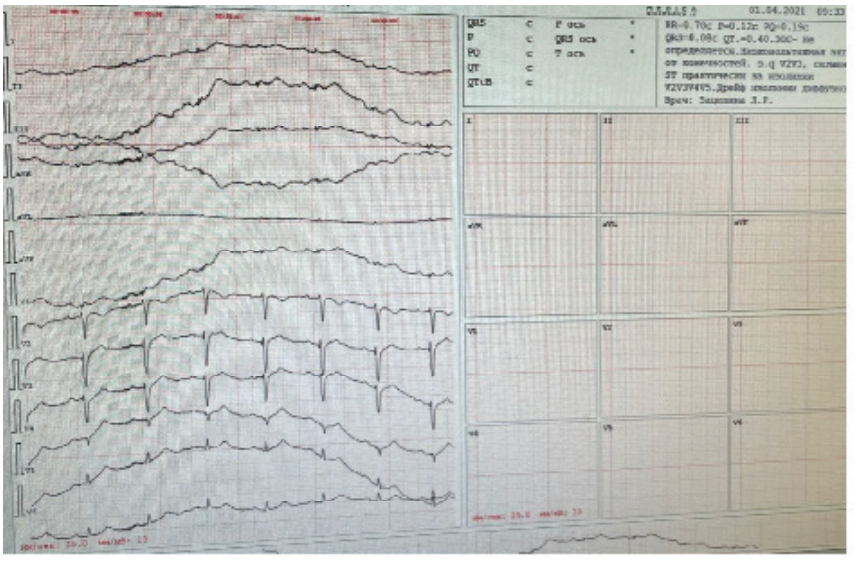
ECG: sinus rhythm with heart rate = 107 beats per minute. EOS is closer to QISIII. Changes along the anterior wall with seizure of the lateral wall - ST segment elevation (1-3 mm) in I, II, AVL, c V2-V6 with (+) h.T according to the type of subepicardial myocardial injury, and changes in the lower wall according to the reciprocal type, h.Q c V1-V3 (ECG № 1)

Patient G. at 00:20 was urgently submitted to the SKAG, according to which the conclusion was obtained: Right type. Stenosis of PNA in p/s 90%, m/s 40%, and it was decided to perform stenting of ADA under the cover of NFH. The operation was performed - transluminal balloon angioplasty and stenting of ADA DES - with Resolute Integrity 3.5x22mm stent (10 atm). Control angiography - a good angiographic result, the stent is fully deployed, there are no signs of dissection or thrombosis, TIMI III blood flow.

a



b



ECG result: a - on admission; b - after surgery

At 01.00 the patient on a gurney, accompanied by the anesthesia team, was transported from the X-ray operating room, transferred to the supervision of the resuscitator on duty. For the purpose of sedation and synchronization with the ventilator, the following was prescribed and administered: sol.Propofoli 1% 1000 mg (5 ampoules) through a perfuser with an initial rate of 8 ml / hour. The condition is extremely serious, due to systemic dysfunction with a predominance of cardiovascular failure (cardiogenic shock, myocardial ischemia), early postresuscitation period: cerebral failure as a result of acute hypoxia, ischemic damage to the kidneys, liver, gross violations of the acid-base composition of the blood and electrolyte disturbances, early postoperative period. Consciousness coma 1 (GCS 8 points) + medsedation. The skin is clean, pale, no peripheral edema. Breathing through the Ambu IT bag with subsequent transfer to the "Puritan Bennet" ventilator in forced A / C - RS mode with parameters up to 700 ml MOD 8.4 l / min PEEP 5 cm water column CO2 50%. On auscultation, breathing is hard, weakened in the lower sections, moist rales in the lower and middle sections are single, on both sides. According to TBT, scanty serous sputum. Heart sounds are rhythmic, muffled. Heart sounds are rhythmic, muffled. Hemodynamics are unstable, on vasopressor support of Dopamine at a dose of 7-10 mg / kg / min. AD-106/63 mm Hg Heart rate 122 per minute, Saturation - 97-99%. Diuresis through a catheter. Treatment was prescribed: with antiarrhythmic purpose, p. Cordaron 300 mg intravenously drip, taking into account metabolic acidosis of sodium hydrogencarbonate 200 ml, taking into account hyperglycemia: Insulin 9 units SC under glycemic control, in order to correct electrolyte disturbances NaCl 0.9% ml + KCl 4% 50 ml IV drip. Heparin infusion through the perfuser continues. Echocardiography (01.04.2021) revealed a slight induration of the aorta. Small asymmetric left ventricular hypertrophy. The maximally hypertrophied area of the left ventricular myocardium is the interventricular septum. LV diastolic function is impaired according to type 1 Mitral regurgitation of the minimum degree. Slight expansion of the left atrium. At the time of the study, there was a violation of local contractility in the form of hypokinesis of the basal anterior segment, the middle antero-septal, and the middle anterior segment. Glob-

al LV systolic function, normal, EF 55% (Simpson).

Based on the history, physical examination, laboratory and instrumental data, the result of SCAG: PNA - stenosis s/c 90% with the presence of a thrombus, positive cardioenzymes (troponin I 13.2 ng / ml), a clinical diagnosis was made:

Main: ischemic heart disease. Myocardial infarction in the antero-widespread area with the formation of the Q wave from 03/31/21. Condition after clinical death, exposure 12 min.

Operations:

1) SKAG from 01.04.21: Right type. ADA stenosis in p/s 90%, m/s 40%. Stenting of ADA for stenosis. DES Resolute Integrity 3.5x22mm.

2) Catheterization of the central vein.

3) ALV 01-02.04.2021

Background disease: Hypertensive disease, stage III. Controlled AG. Risk of CVC 4 (male sex, atherosclerosis, dyslipidemia, left ventricular hypertrophy).

Complication of the main diagnosis: AHF IV FC by Killip upon admission. Cardiogenic shock. CHF with intact EF (S55%) II A stage. FC III by NYHA/

Moderate posthypoxic encephalopathy. Ischemic damage to the kidneys, liver in the stage of regression. Chest contusion. Community-acquired bilateral hypostatic pneumonia, moderate severity in the stage of resorption.

Concomitant diagnosis: Atherosclerosis of the aorta, aortic valve, mitral valve. CKD 2st. GFR 88 ml / min.

On the ECG from 01.04.2021 09.33 ST segment is almost on the isoline (ECG №2).

To assess the level of consciousness on 02.04.2021, sedation was turned off. The patient is conscious. 04/02/2021 tracheal extubation was performed. Breathing is efficient. The general condition as of 02.04.2021at 16:00 is extremely difficult, with positive dynamics. Consciousness is clear, the pupils are equal, there are no paresis. Pale pink skin, hematomas at the injection sites. Visible mucous membranes of normal color, clean. Body temperature 36.7 ° C. Breathing is independent, even with a respiratory rate of 20 per minute, SpO2 97% against the background of insufflation of humidified O2 through binasal cannulas, auscultatory hard, weakened in the lower parts, with moist rales. Heart sounds are rhythmic, muffled. Hemodynamics against the background of Dopamine infusion at a dose of 10 mg / kg / min. BP 112/82 mm Hg, Heart rate 94 / min. CVP 70 mm water st. Urination by catheter, yellow, 500.0. No peripheral edema.

The postoperative period was uneventful.

02.04.2021 with dynamic observation, the general condition is consistently severe. Consciousness is clear, the pupils are equal, there are no paresis. Breathing is independent, even, with a respiratory rate of 20 per min., SpO2 97% against the background of insufflation of humidified O2 through binasal cannulas, auscultatory hard, weakened in the lower parts, with moist rales. Heart sounds are rhythmic, muffled. Hemodynamics against the background of Dopamine infusion at a dose of 10 mg / kg / min. BP 98/70 mm Hg, Heart rate 84 / min. CVP 100 mm water st.

03.04.2021 Dopamine infusion is disabled, hemodynamics is stable. Taking into account the stabilization of the patient, he was transferred to the general ward of the emergency cardiology department of the RVC.

On April 6, 2021, daily ECG monitoring was carried out for 10:29 hours at 3 holes. The main sinus rhythm with an average daily heart rate of 71 beats per minute. Max heart rate = 100 beats per minute (16:54), min heart rate = 62 beats per minute (23:29). Against the background of this rhythm, there were registered: single polyfocal, monomorphic supraventricular extrasystoles in total - 57. P-Q = 0.20 sec, Q-Tc = 0.42 sec. In otv. Y, the inversion of the T wave is recorded. Heart rate less than 35 beats per minute. pauses R-R more than 2500 msec. not registered. Sinus rhythm was recorded according to CMECG data. Signs of ischemic heart disease. Supraventricular extrasystole.

According to echocardiography from 04/09/2021 in dynamics: EF 55%, impaired local contractility in the form of a slight hypokinesis of the middle anterior segment. ECG dynamics of Q (+) myocardial infarction.

The following drug treatment was carried out: p. Heparin 5000 Un 4 times a day with an anticoagulant purpose, Clopidogrel 75 mg orally 1 t/d with an antiplatelet purpose, Aspirin 125 mg. orally 1 t/d with antiplatelet purpose, t. Metoprolol tartrate 25 mg orally 2 t/d with antiarrhythmic purpose, Atorvastatin 20 mg, further, to stabilize transaminase indicators (13.04.21, ALT 24 U / L, AST 15 U / L), it is recommended to increase the dose to 80 mg orally 1 t/d with hypolipidemic, pleiotropic purpose, Pantoprazole 20 mg orally 1 t/d with gastroprotective purpose, methionine 500 mg. inside 3 t/d with a hepatoprotective purpose, to stabilize blood pressure, ACE ingestion is recommended.

As a result of the treatment, the patient's condition stabilized. The patient spent 3 days at the DARIC №2, 12 days at the Department of Emergency Cardiology.

Considering the emergency myocardial revascularization during the first 2 hours after the development of ACS with ST segment elevation of the electrocardiogram, positive dynamics, disappearance of anginal pain, initial physical rehabilitation, improvement of exercise tolerance, stabilization of hemodynamics, it was decided to write out patient G. for further rehabilitation treatment in treatment and rehabilitation center of the Republican Clinical Hospital №3.

Conclusion. Acute coronary syndrome is the most common cause of cardiogenic shock and urgent reperfusion therapy is essential. The presented clinical case describes an example of the treatment of AMI complicated by cardiogenic shock, where timely reperfusion therapy - percutaneous coronary intervention on the infarction-associated anterior descending artery - improved the prognosis and outcome of acute myocardial infarction with acute heart failure FC IV according to KILLIP. With CS, there is a marked decrease in cardiac output and insufficient perfusion of vital organs. In this connection, patients in a state of CABG need careful monitoring and the use of active hemodynamic support through the administration of vasoconstrictors, drugs with a positive inotropic effect and / or using mechanical devices to support hemodynamics.

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