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ORIGINAL RESEARCH

A.A. Nikanorova, N.A. Barashkov, V.G. Pshennikova, S.S. Nakhodkin, S.A. Fedorova

SIGNS OF POLAR T3 SYNDROME IN YOUNG MEN IN YAKUTIA

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The aim of the study was to search for seasonal variations in the levels of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) in young men in Yakutia, where there are strong changes in climatic parameters in the winter-spring period (from -41.8°C to -0.2°C). Seasonal variations between winter and spring were found for fT3, where in winter its levels were lower – 6.48±0.31 pmol/L than in spring – 6.88±0.1 pmol/L (p=0.005). There were no statistically significant seasonal variations for TSH (U=97; p=0.914) and sv.T4 (U=47; p=0.112). Winter-spring seasonal variations of fT3 detected in this study there are signs of polar T3 syndrome in young men in Yakutia. To search for the causes of the detected seasonal variation, a correlation analysis of the levels of TSH, fT3 and fT4 was carried out depending on daylength and atmospheric air temperature. As a result, a correlation between fT3 and fT4 with the daylight (fT3: R=0.339, p=0.03; fT4: R=-0.346, p=0.01) and with air temperature (fT3: R=0.295, p=0.05; fT4: R=-0.296, p=0.04). No correlations were found with TSH levels (daylight: R=-0.06, p=0.69; air temperature: R=-0.09, p=0.559). Thus, the residents of Yakutia have signs of polar T3 syndrome, which can be associated with both a short light day and low atmospheric temperatures in winter. The results obtained may indicate an increase in the absorption of T3 at the tissue level when exposed to cold.

Keywords: thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), Yakutia, polar T3 syndrome.

Introduction. Since 1986, a series of papers has been published on changes in the homeostasis of hormones of the human pituitary-thyroid system during adaptation to a cold climate [1,5,11]. The first studies described seasonal changes in thyroid hormone levels, where a decrease in free triiodothyronine (fT3) levels was recorded after a 42-week residence at McMurdo Station in Antarctica, with significant changes in free thyroxine (fT4) levels and thyroid-stimulating hormone (TSH) was not detected [1,11]. A further study of the kinetics of peripheral levels of T3 showed that with prolonged exposure to cold, the rate of production of fT3 and the rate of removal of fT3 from the blood (clearance) increase, which increases the binding of T3 by various tissues [5]. Identified seasonal changes in the levels of hormones of the pituitary-thyroid system (in winter, the levels of fT3 decrease, the levels of TSH are normal/increase, fT4 are normal/decrease), called "polar T3 syndrome" [5]. Later studies by workers at other polar stations in Antarctica (the Great Wall and Zhongshan) also indicate the presence of seasonal changes in the pituitary-thyroid hormones typical of polar T3 syndrome [6]. In addition, signs of polar T3 syndrome have been identified outside Antarctica, among residents of cold regions, where winter temperatures fall below -40°C, and summer temperatures range from 0°C to +30°C (Finland, Russia) [14,17].

In this regard, the aim of this study is to search seasonal variations in the levels of TSH, fT3 and fT4 in the winter-spring period among the residents of Yakutia, where changes in climatic parameters are observed when the seasons change.

Materials and methods. The research sample comprised 92 Yakut men (with a mean age of 19.91±1.88 years). They presented no health issues at the time of the study, they independently filled out a questionnaire in which they indicated their gender, ethnicity and age. All participants gave written informed consent for participation in the study. Study was approved by the local Biomedical Ethics Committee at the Yakut Scientific Center of Complex Medical Problems, Siberian Branch of the Russian Academy Scientific of Medical Sciences, Yakutsk, Russia (Yakutsk, Protocol No. 16, and 13 December 2014).

Blood samples from the men we studied were carried out from December to May of 2014-2015. For each day of blood sampling, the average atmospheric temperature (°C) and the duration of daylight (hour, minute) were determined. Archived data on weather reports were used to determine the average air temperature (https://www.timeanddate.com). Using an online sunrise/sunset calculator (http://-www.sunrise-and-sunset.com/en/sun) determined the length of daylength.

Venous blood for the study was collected in the morning after an 8-hour fast from all participants. The levels of TSH (μU/ml), fT3 (pmol/L) and fT4 (pmol/L) in fasting blood serum were determined by time-resolution fluoroimmunoassay with using the kits "DELFIA hTSH Ultra", "DELFIA Free Thyroxine", "DELFIA Free Triiodothyronine" (PerkinElmer Inc., USA). The concentration of three hormones in the samples was measured at a wavelength of 450 nm on a VICTOR X5 Multilabel Plate Reader (Perkin Elmer Inc., USA). Normalization of the studied sample by TSH, fT3 and fT4, was carried out using an interquartile (Q1; Q3), so the normalization values were: TSH – 1.62-2.71 μU/ml (n=45), fT3 – 5.96-7.08 pmol/L (n=45), fT4 – 13.2-15.7 pmol/L (n=49).

Statistical analysis. The obtained data were analyzed using Statistica 13.5, a

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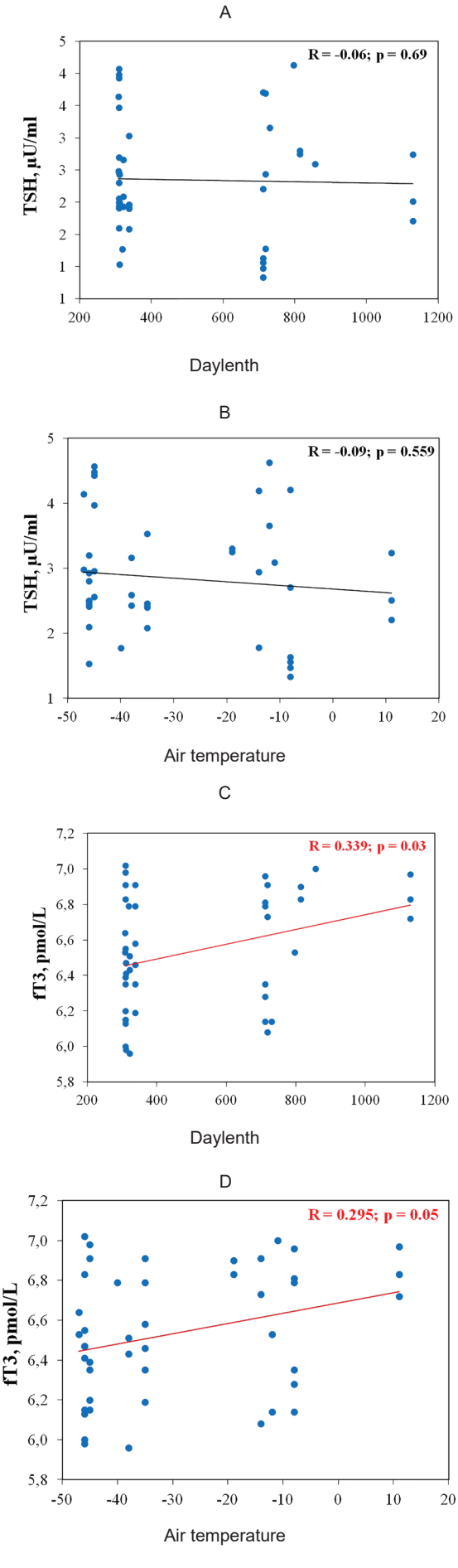
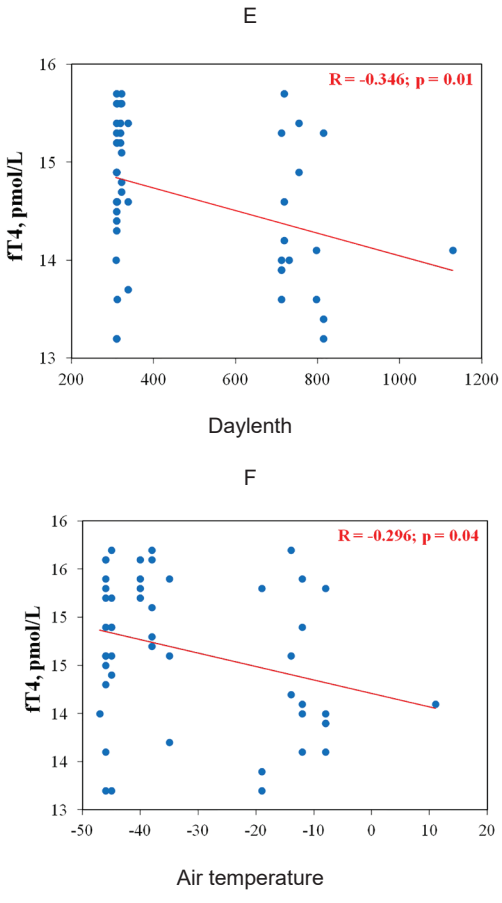
statistical software program (TIBCO Software Inc., Palo Alto, CA, USA). Quantitative results are reported as the mean ± standard deviation. The search for seasonal variations in hormone levels was carried out using the nonparametric Mann-Whitney U-test for small samples (n<100). To determine the dependence of hormone levels on air temperature and the daylight a Spearman correlation analysis was performed. The values of p<0.05 were considered statistically significant.

Results and discussion. *Seasonal variations in TSH, fT3 and fT4 in the "winter-spring" periods.* Comparative analysis of seasonal variations in the levels of hormones TSH, fT3 and fT4 was conducted between the periods "winter" (December-March) and "spring" (April-May) (Table). As a result of this analysis, seasonal changes were detected for fT3 (p=0.005), where in winter its levels were lower (6.48±0.31 pmol/L) than in spring (6.88±0.1 pmol/L). For TSH and fT4 no significant seasonal changes were found.

Our results are consistent with the data of Levy et al., [12] and Leonardo et al., [14] on seasonal variations in the levels of fT3, in residents of central Yakutia, where reduced levels of fT3 were recorded in winter, compared with summer. In addition, seasonal changes in the levels of hormones of the pituitary-thyroid system (TSH, fT4) were also found in children and adolescents from the Arctic regions of Yakutia [13]. Thus, residents of Yakutia have seasonal variations in the hormones of the pituitary-thyroid system, similar to the polar T3 syndrome.

Assessment of the effect of daylength and air temperature on the levels of TSH, fT3 and fT4. It is believed that seasonal changes in the levels of hormones of the pituitary-thyroid system are a consequence of exposure to low atmospheric temperatures, daylength or depression [5], but it is still not known what has a stronger effect on polar T3 syndrome. In this regard, we carried out a correlation analysis of TSH (n=45), fT3 (n=45) and fT4 (n=49) depending on the duration of daylight and air temperature (Figure). At the time of the study, from December to May, the air temperature warmed from -41.8°C to -0.2°C, and daylength increased from 5 hours to 15 hours. Correlation analysis of TSH levels revealed no dependence on daylength and air temperature (Figure A,B). However, we have identified two multidirectional correlations, where with an increase in daylight and an increase in air temperature, the fT3 increased (Figure C,D), and fT4, on the contrary, decreased (Figure E,F). It





Spearman's correlation analysis of TSH (A, B), fT3 (C, D) and fT4 (E, F) with daylight duration and atmospheric air temperature in men

Comparative analysis of seasonal variations in the levels of TSH, fT3 and fT4 between the periods "winter" and "spring"

Hormones	Winter	Spring	U-test	*p*
TSH, μU/ml	2,12±0,29 (n=40)	2,13±0,49 (n=5)	97	0,914
fT3, pmol/L	**6,48±0,31 (n=39)**	**6,88±0,1 (n=6)**	**34**	**0,005**
fT4, pmol/L	14,71±0,73 (n=45)	14±0,95 (n=4)	47	0,116

Note: Statistically significant differences are highlighted in bold (p<0.05)

is known that the thyroid gland produces approximately 80% of T4 and only 20% of T3, while the remaining 80% of T3 comes as a result of conversion from T4, using the type 2 deiodinase enzyme [10]. The results of this correlation analysis show that in winter (short daylight hours and low air temperature) the thyroid gland secretes more T4 than in the warm period, which may indicate the active work of the thyroid gland at this time of year. Thus, we have revealed that the signs of polar T3 syndrome can be affected by both the duration of daylight and negative atmospheric temperatures.

The mechanism of participation of T3 and T4 in nonshivering thermogenesis. The climate of Yakutia is characterized as sharply continental with a fairly long winter, where the air temperatures fall below -40°C. Therefore, in winter, high heat production is required to protect the body from hypothermia. Currently, it is well known that thyroid hormones, together with the adrenergic system, can participate in increasing heat production during nonshivering thermogenesis [4,8,18]. So, in Greenland, Inuit hunters, who were constantly exposed to the cold, had levels of fT3 was lower compared to urban residents who had more comfortable living conditions [19]. Thus, when exposed to cold, brown adipocytes begin to actively absorb fT3 from the blood and additionally convert T4 into T3 with the help of the type 2 deiodinase enzyme. Studies on rats have shown that brown adipose tissue is responsible for about half of the total systemic conversion of T3 from T4 [16], which increase 10-fold under cold exposure [7]. An increase in T3 levels in brown adipocytes enhances the expression of the uncoupling protein thermogenin, thereby increasing the heat production of nonshivering thermogenesis [9,15]. In this regard, we assume that the decrease in the levels of fT3 in the cold season compared with warm periods occurs due to an increase in the absorption of T3 by brown adipocytes in winter, to enhance the thermogenic response of brown adipose tissue in response to cold exposure. This assumption is consistent with the opinion of some authors [12,14] that a decrease in the levels of fT3 in winter (polar T3 syndrome) indicates an increased absorption of T3 at the tissue level during extreme cold. Recent studies have found indirect evidence of brown adipose tissue activity in adult Yakuts in the supraclavicular region [2,3], which may also indicate active uptake of T3 by various tissues, including brown adipocytes in the cold season.

Conclusion. The results of this study show the presence of seasonal variations in the levels of fT3 in the winter-spring period, where since December the levels of fT3 are falling, and since April they begin to rise. At the same time, the levels of fT4 and TSH remain normal. These data indicate the presence of signs of polar T3 syndrome in young men in the climatic conditions of central Yakutia. The search for the causes of the revealed seasonal variations showed that at the levels of fT3 can affect both the daylength and the air temperature. A decrease in the levels of fT3 in the cold season compared to warm periods may indicate an increase in the absorption of T3 at the tissue level.

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ASSESSMENT OF THE RELATIONSHIP OF LIPID METABOLISM INDICATORS AND PULMONARY HYPERTENSION IN THE INITIAL PERIODS OF MYOCARDIAL INFARCTION IN MEN UNDER 60 YEARS OLD

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Pulmonary hypertension (PH) is an understudied but significant complication of myocardial infarction (MI). Currently, there are no diagnostic algorithms that can predict the development of PH in the setting of myocardial infarction, which requires the development of prediction models based on the results of routine examination, for example, lipid profile. The purpose of the research was to study the parameters of lipid metabolism in men with PH that developed against the background of MI and their impact on the risk of developing PH. The results of examination of men aged 32-60 years with verified MI were studied. According to the level of mean pulmonary artery pressure (MPAP) determined by echocardiography, patients were divided into two groups: the study group (with a MPAP level of more than 20 mm Hg at the end of the third week of MI) and the comparison group (with a normal MPAP level at the end of the third week of MI). The studied indicators were compared based on the Mann-Whitney, Wilcoxon, and Chi-square tests; correlations were performed using the Spearman method. It was found that patients in the study group had lower levels of the atherogenic coefficient (AC) and the total cholesterol/high-density lipoprotein (TC/HDL) index at the end of the third week of MI. Levels of triglycerides (TG) < 1.3 mmol/l and very low density lipoprotein (VLDL) ≥ 1.2 mmol/l, TC/HDL indices < 6.0 and LDL/HDL < 3.2 in the first 48 hours, LDL <2.4 mmol/l, AC value <5.0, TC/HDL indices <6.0 and LDL/HDL <3.2 at the end of the third week of MI influence the risk of developing PH in the subacute period of MI. Correlations have also been established between the level of MPAP and lipid profile parameters. It is advisable to use the obtained results when developing a model for predicting the development of PH against the background of MI.

Keywords: pulmonary hypertension, myocardial infarction, lipid metabolism, mean pulmonary artery pressure, heart failure, men, young and middle age.

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Introduction. Diseases of the cardiovascular system currently dominate the structure of causes of mortality throughout the world, and myocardial infarction (MI) remains one of the most significant among them [12]. The prognosis of a patient with MI largely depends on the presence and severity of complications, among which it is worth highlighting pulmonary hypertension (PH) [1]. This syndrome is characterized by a predominantly asymptomatic course, which leads to its detection only at the stage of development of irreversible changes in pulmonary hemodynamics, aggravating the course of MI and contributing to an increase in mortality [17]. Timely diagnosis of PH in MI will allow identifying patients at high risk of its development for dynamic monitoring and timely implementation of preventive and therapeutic measures. It is advisable to base forecasting models on routine diagnostic methods that do not require additional time and economic

costs. It is assumed that one of them may be the determination of the lipid profile, and therefore it is advisable to study the influence of its parameters on the course of PH in MI. The importance of lipids and lipoproteins for the development and course of lung pathology, including PH, is currently being actively studied. The influence of apoliproteins E and A I on the pathogenesis of bronchial asthma, cancer, fibrosis and emphysema, as well as PH [4,16]. It is believed that the development of PH in the setting of MI is caused mainly by left ventricular (LV) systolic dysfunction, which, in turn, is associated with apolipoprotein levels [9].

Aim. To consider patterns of changes in lipid metabolism in men under 60 years of age with MI complicated by the development of PH in its subacute period, from the point of view of their role in the formation of this complication and use as its predictors.

Material and methods. The study involved men aged 32-60 years with type I MI according to the IV universal definition (2018). It excluded cases of decreased glomerular filtration rate of 29 or less ml/min/1,73 m2 (CKD-EPI, 2011), congenital anomalies of the development of coronary arteries and their consequences, coronaritis, infectious endocarditis, thrombophilia and true polycythemia, hemorrhagic diathesis, viral hepatitis B and C, HIV infection, liver cirrhosis, diseases connective tissue against the background of continuous immunosuppressive therapy, endocrine diseases (except diabetes mellitus), malignant neoplasms, with hemoglobin levels less than 130 g/l, the number of leukocytes less than $3.0*10^9$/l and platelets – less than $100*10^9$/l. The study was approved by the Independent Ethics Committee at the Military Medical Academy named after S.M. Kirov (Protocol No. 258 dated December 21, 2021).

Patients received examination and treatment within the framework of approved clinical guidelines. Transthoracic echocardiography (ECHO-KG) performed according to protocols for patients in the acute period of MI [6,8], including noninvasive assessment of mean pulmonary artery pressure (MPAP) (A. Kitabatake, 1983 - calculation of the ratio of acceleration time (time to reach maximum flow velocity) to the time of ejection of the right ventricle (right ventricular ejection time – RVET)) [15] and lipidogram assessment [3] were performed twice: in the first 48 hours of MI and at the end of the third week of this disease.

The study group (I) included 102 patients (51.0 ± 7.0 years) with PH (MPAP less than 20 mm Hg at the first measurement and exceeding this value at the second measurement). The comparison group (II) was formed from 468 patients (51.4 ± 6.0 years, p = 0.9) without PH (MPAP less than 20 mmHg at the second measurement point). The value of total pulmonary resistance (TPR) was obtained by calculation using the formula: TPR = ((MPAP – 5) × 80) /CO, where TPR is the total pulmonary resistance (din×s×cm-5), MPAP is the average pressure in the pulmonary artery (mmHg), CO is the cardiac output (l/min) [7].

The studied groups of patients did not differ significantly in the characteristics of MI (localization, sequence, presence of a Q wave), the presence of concomitant pathology (obstructive pulmonary diseases, diabetes mellitus, metabolic syndrome), as well as coronary angiography parameters (number of affected vessels, length of stenoses, myocardial revascularization). When assessing disturbances in local myocardial contractility, no differences were found in the lesion segments in the studied groups. All patients received drug therapy in accordance with approved clinical guidelines [5]. Patients included in the study did not take lipid-lowering drugs before the development of MI.

Among the lipid parameters in the blood serum of the examined patients, we determined the concentration of total cholesterol (TC), very low density lipoproteins (VLDL), high density lipoprotein (HDL) and low density lipoprotein (LDL), and triglycerides (TG). We also calculated the coefficient (CA = (TC- LDL)/HDL) and indices (TC/ HDL, LDL/ HDL) of atherogenicity [3].

Comparisons between groups of quantitative variables were performed using the Mann-Whitney method. The dynamics of quantitative parameters between measurement points were assessed using the Wilcoxon test. To calculate the absolute (AR) and relative (RR) risk of the occurrence of PH at the end of the subacute period of MI, taking into account the values of lipid metabolism parameters, the Pearson Chi-square test was used. Analysis of correlations between indicators of lipid metabolism and levels of MPAP and TPR was performed according to Ch. Spearman (r). A p value less than 0.05 was considered statistically significant.

Results. When comparing the parameters of lipid metabolism in the first hours, they drew attention to the fact that in patients of the control group (II), in contrast to the studied group (I), higher values of TC (I: 5,6 ± 1,3 (1,92-8,46); II: 5,7 ± 1,3 (1,90-10,32) (mmol/l), p = 0,7), TG (I: 2,3 ± 1,5 (0,57-6,80); II: 2,6 ± 2,0 (0,35-13,80) (mmol/l), p = 0,4), LDL (I: 3,8 ± 1,2 (0,30-6,00); II: 3,9 ± 1,3 (0,92-8,62) (mmol/l), p = 0,6), and also CA (I: 4,9 ± 2,3 (0,70-11,40); II: 5,1 ± 2,0 (0,38-12,60), p = 0,3) and LDL/HDL index (I: 4,3 ± 2,1 (0,27-11,38); II: 4,4 ± 2,0 (0,75-12,68), p = 0,7). However, they did not reach a reliable level.

When studying lipid metabolism parameters in the subacute period of MI (end of the third week of MI), lower values of CA (Fig. 1a) and TC/HDL (Fig. 1b) were revealed in the study group compared to the control group. These changes are probably associated with the initiation or intensification of lipid-lowering therapy, as well as with the involvement of lipids in the processes of peroxidation in the inflamed zone, which are more pronounced against the background of the development of PH [19].

It is worth noting that the low content of atherogenic fractions of OH is recognized, among other things, as a marker of an unfavorable prognosis of MI. [2].

It has been established that the risk of developing PH at the end of the subacute period of MI is influenced by the following indicators determined in the first 48 hours of MI: levels of TG < 1,3 mmol/l (RR: 1,75; p=0,02) и VLDL ≥ 1,2 mmol/l (RR: 2,01; p=0,03), values of indices TC/HDL < 6,2 (RR: 1,72; p=0,03) and LDL/HDL < 2,4 (RR: 0,35; p=0,04). The influence of these factors on the AR value is presented in Figure 2a.

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It has been established that the risk of developing PH at the end of the subacute period of MI is influenced by the following indicators determined in the first 48 hours of MI: levels of TG < 1,3 mmol/l (RR: 1,75; p=0,02) и VLDL ≥ 1,2 mmol/l (RR: 2,01; p=0,03), values of indices TC/HDL < 6,2 (RR: 1,72; p=0,03) and LDL/HDL < 2,4 (RR: 0,35; p=0,04). The influence of these factors on the AR value is presented in Figure 2a.

At the end of the third week of MI, the following parameters turned out to be significant for the risk of developing PH in the subacute period: level of LDL < 2,4 mmol/l (RR: 2,78; p=0,02), values of CA < 5,0 (RR: 4,57; p=0,0002), as well as the values of TC/HDL indices < 6,0 (RR: 4,57; p=0,0002) and LDL/HDL indices < 3,2 (RR: 2,61; p=0,03). The influence of these factors on the AR value is presented in Figure 2b.

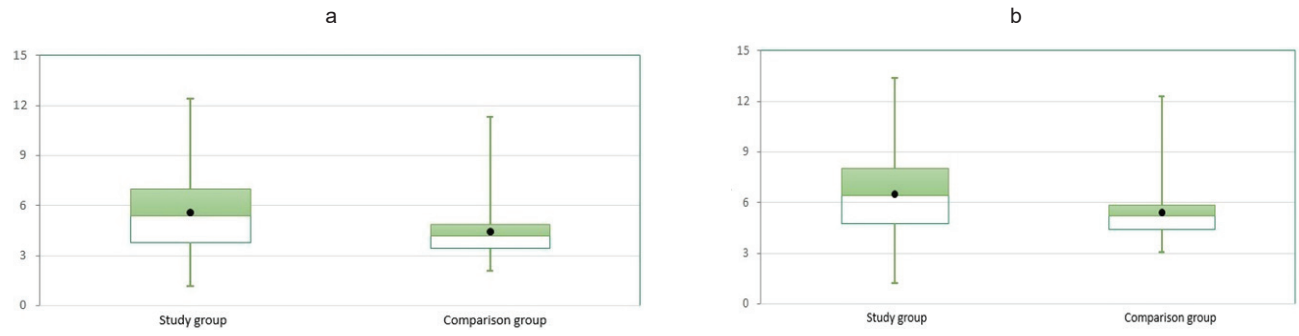

Fig. 1. Significant differences (p=0.006) in the values of CA (a) and the TC/HDL index (b) in the studied groups, determined at the end of the third week of MI. Designations used in the figure: dot – arithmetic mean, horizontal segment – median, rectangle – intraquartile range, vertical segments – minimum and maximum values

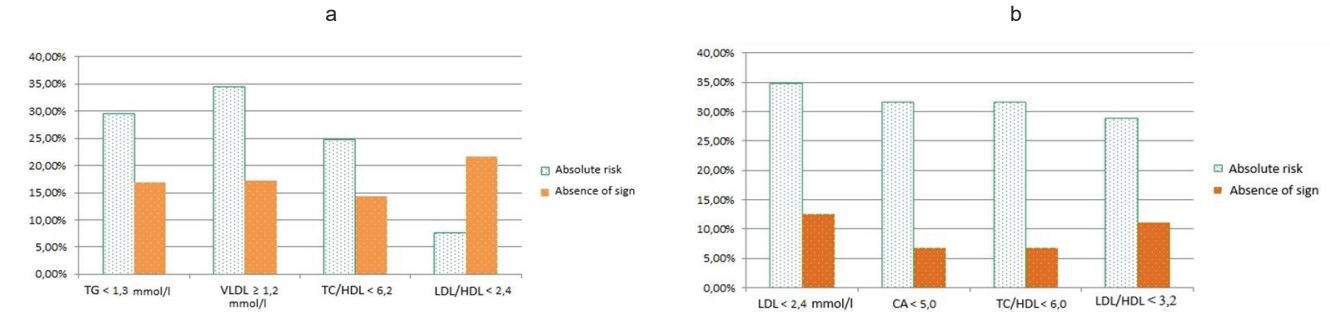

Fig. 2. Significant influence of lipid metabolism parameters obtained at the first (a) and second (b) measurement points on the absolute risk (AR, %) of developing PH in those examined

When analyzing the dynamics of lipid profile parameters in the studied groups, multidirectional changes in the concentrations of TC, CA, TG, HDL, as well as the TC/HDL index were noted between the measurement points (Fig. 3). Similar dynamics in both studied groups were revealed in relation to the LDL/HDL index, LDL and VLDL levels (Fig. 3). The most pronounced increase was noted for the level of VLDL both in the study group and in the comparison group (Fig. 3).

As can be seen from Figure 3, patients in the comparison group are characterized by less pronounced dynamics of lipid profile indicators, as well as lower levels of atherogenic fractions, which may be explained by the involvement of lipids in oxidation processes involved in the pathogenesis of PH [19].

Table 1 presents data on the presence of significant correlations between indicators of lipid metabolism and the value of MPAP during the first 48 hours (a) and the end of the third week of MI (b) in the group of patients with PH.

In addition, in the patients of the study group, a direct correlation of medium strength ($r = 0.39$, $p < 0.001$) was established between the level of HDL in the acute period of MI and the value of TPR in the first hours of MI, as well as a direct correlation of medium strength ($r = 0.39$, $p < 0.05$) between the concentration of VLDL in the first hours of MI and the value of TPR in the subacute period of MI. The presence of these correlations further indicates the contribution of lipid metabolism to the formation of PH. An increase in TC, mainly due to atherogenic fractions, in parallel with an increase in pressure in the pulmonary artery, is most likely due to the depletion of the HDL pool, involved as an anti-inflammatory agent under conditions of oxidative stress in PH [19].

Discussion. Systolic and diastolic dysfunction as early manifestations of heart failure are considered to be the main causes of clinical PH associated with diseases of the left heart [13]. It is assumed that mechanical resistance due to high pressure in the pulmonary veins is one of the main causes of PH in cases of ischemic cardiomyopathy with systolic dysfunction of the left ventricle [13]. When cardiac function declines, vascular remodeling of the pulmonary vessels in response to prolonged high pressure stimulation is thought to lead to PH [13]. However, the main pathological mechanisms and specific processes remain unclear [13]. It is believed that elucidating the relationship between MI and the development of PH may lead to a better understanding of potential risk factors and improved treatment of this complication [13]. The results of the present study confirm the influence of lipid profile parameters on pulmonary hemodynamics. The literature describes mechanisms for the implementation of the relationship between lipids and MPAP using exosomes [22], filled with regulatory microRNAs [14], which realize their action through a number of pathways (inflammatory reactions, cell migration, proliferation, apoptosis, autophagy, including mitochondrial [20], and epithelial-mesenchymal transition) [20]. They also involve transforming growth factor beta [10], oxidized variants of lipoproteins and enzymes of this oxidation [22], as well as apolipoproteins A1 and E [3,15]. Most of them have proven importance not only in the pathogenesis of PH, MI, but also diabetes mellitus and other types of cardiovascular pathology (atherosclerosis, heart failure, ischemia-reperfusion injury of the myocardium) [11,20]. In metabolomic studies of plasma during treatment of patients with PH with metformin, lipid derivatives are the most altered [18]. It is also known about the contribution of atherogenic lipid fractions to the formation of idiopathic venous thromboembolism and PH [21]. The results of the study also prove the influence of lipid metabolites on the development of PH in MI, which requires further detailed study of them as markers for predicting the development of this complication.

Table 1

Changes in lipid metabolism parameters in the compared groups between observation points (p – significance level)

Indicator	Study group		Comparison group	
	Dynamics, %	p	Dynamics, %	p
TC	- 4.8	<0.0001	+ 1.2	<0.0001
TG	+ 0.7	0.0002	- 7.7	<0.0001
LDL	+ 21.9	0.0003	+ 48.1	<0.0001
VLDL	+ 176.5	<0.0001	+ 260.4	<0.0001
HDL	+ 1.1	0.0004	- 6.8	<0.0001
CA	- 10.8	0.0002	+ 8.9	<0.0001
TC/HDL index	- 13.7	0.0004	+ 3.3	<0.0001
LDL/HDL index	+ 11.4	0.0003	+ 51.1	<0.0001

Table 2

Reliable correlations between the parameters of lipid metabolism and MPAP of the first (a) and repeated (b) measurement points in the study group

а		б	
Indicator	r	Indicator	R
TG (1), p<0.05	-0.29	TC (2), p<0.05	0.33
VLDL (1), p<0.05	-0.33	LDL (2), p<0.001	0.73
TG (2), p<0.05	0.6	LDL/HDL (2), p<0.001	0.74

Note. 1 - indicators obtained in the first 48 hours of MI, 2 - indicators at the end of the third week of the disease; r - correlation coefficient; p – significance level

Conclusion. In PH that develops after MI in men under 60 years of age, lower CA and TC/HDL are recorded during the period of its first manifestations. The risk of developing PH after MI increases with levels of TG < 1,3 mmol/l, VLDL ≥ 1,2 mmol/l, TC/HDL < 6,2 и LDL/HDL < 2,4 during the first 48 hours of MI, LDL < 2,4 mmol/l, CA < 5,0, TC/HDL < 6,0 и LDL/HDL < 3,2 at the end of the third week of MI. Reliable relationships have been established between indicators of lipid metabolism and pulmonary hemodynamics. The data obtained are promising for modeling the risk of PH after MI in young and middle-aged men.

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ASSOCIATION OF POLYMORPHISM rs1495741 *NAT2* GENE WITH INFLAMMATORY LIVER DISEASE DEVELOPMENT UNDER EXPOSURE TO EXTERNAL FACTORS

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Slow acetylation of substrate is associated with drug-induced liver damage and transformation of viral and alcohol hepatitis in cirrhosis. Increasing xenobiotic load is a significant factor in development of metabolic associated liver diseases. This interaction between genotype and environment should be studied to reveal disease pathogenesis. We analysed polymorphism rs1495741 genotypes in control group and in patients with cryptogenic liver cirrhosis and non-alcohol fatty liver disease to evaluate association of acetylation type with liver disease development. As part of the study, patients filled the questionnaire to assess xenobiotic load. The rs1495741 polymorphism was detected by real-time PCR. Significant differences were revealed in the criptogenic liver cirrhosis and non-alcoholic fatty liver disease groups in patients consuming fried and smoked foods (OR: 5,49 at p<0,05); in combination with older age (>55) the risk increases by 7.57 times (p<0,05). However, no association of the rs1495741 polymorphism with the development of liver diseases was identified.

Keywords: N-acetyltransferase 2, polymorphism, cryptogenic liver cirrhosis, non-alcoholic fatty liver disease.

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Introduction. One of the causes for high mortality in the Russian Federation is the liver cirrhosis, associated with hepatitis virus infection and alcohol abuse. Previously, in approximately 10% of cases, it was not possible to identify the etiological cause of the disease, which led to a diagnosis of cryptogenic liver cirrhosis (CLC). The development of molecular genetic diagnostics in combination with laboratory and instrumental methods has led to a decrease in the proportion of CLC in the structure of cirrhosis [4]. In addition, studies have shown that most people with CLC are likely to have an outcome of active fibrosis in non-alcoholic steatohepatitis, a severe form of non-alcoholic fatty liver disease (NAFLD) [18].

Currently, the population is faced with a variety of foreign chemicals (xenobiotics): pharmaceuticals, household chemicals and products of human economic activity, including food additives. The liver plays the main role in the neutralization and biotransformation of xenobiotics. One of the enzymes in the second phase of detoxification is N-acetyltransferase 2 (NAT2), which is involved in the acetylation of arylamines and hydrazines [9]. The enzyme gene is localized on chromosome 8 (8p22) and has several single nucleotide polymorphisms (SNP), the combination of which led to the existence of two haplotypes, slow and rapid acetylation, in the population [8]. The *NAT2* genotype can be identified by SNP detection in polymerase chain reaction (PCR) or gene sequencing. The simplest and the most sensitive methods is real-time PCR genotyping of tagSNP (rs1495741), which correlates with acetylation type [2, 5].

Scientists described the role of slow acetylation alleles in the development of drug-induced hepatitis when using anti-tuberculosis drugs. It is known that rapid acetylation alleles are associated with a high risk of transformation of hepatitis into cirrhosis and hepatocellular carcinoma (HCC) in the presence of provoking environmental factors in patients with chronic viral and alcoholic hepatitis [10, 12, 13]. Considering that the expression of NAT2 has the highest level in the liver, it can be assumed that, depending on the rate of acetylation, toxic substances accumulate in liver cells, which form a focus of chronic inflammation under conditions of constant increased load of xenobiotics [19]. Taking into account the increasing influence of exogenous chemicals on the human body, it seems relevant to study the role of gene polymorphisms that determine the activity of xenobiotic metabolic enzymes in the development of CLC and NAFLD.

The aim of this study is to evaluate

the influence of external factors (age, gender, smoking, regular consumption of fried and smoked foods) and genetically determined type of acetylation on the risk of developing CLC and NAFLD under conditions of high xenobiotic load.

Materials and methods. The study included 47 patients who signed informed voluntary consent and had liver disease: CLC or NAFLD. Healthy individuals without a history of liver cirrhosis (N=17) were selected as controls. As part of the study, patients were surveyed in groups to assess xenobiotic load (smoking, including electronic devices, frequent consumption of fried and smoked foods 5 times or more in a week, the presence of harmful factors at work). This study was approved by the Ethics Committee of ISMU (protocol No. 1 of the Ethics Committee of ISMU dated April 9, 2023).

Buccal epithelium was used as the material for the study. Rs1495741 polymorphism genotype was determined in the Research Institute of Biomedical Technologies of the Irkutsk State Medical University according to the method described earlier [2].

Statistical analysis was carried out by the R programming language for statistical data processing and graphics [14]. The sample size was not previously calculated. Differences in age in the groups were determined by the Mann-Whitney test for small samples; gender differences were calculated by Fisher's exact test. The distribution of allele and genotype frequencies was compared with the expected distribution according to the Hardy-Weinberg law by the Chi-square test. The odds ratio (OR) for disease development under the influence of factors was calculated by Fisher's exact test with confidence interval (CI) 95%. The rs1495741 polymorphism genotype association with the disease development was calculated in the SNPassoc package [17]. Differences between groups were considered significant at p<0,05.

Results. The average age of patients in the clinical group is 60,68 (56,79 - 64,57) years, in the control group it is 49,23 (43,96 - 54,51) years (Table 1). The age of patients was significantly higher in the clinical group compared to the control group (Mann-Whitney test W=615,5, p=0,001037). There were no significant differences between the groups by gender (Chi-square=0,0647, p=0,799). The small sample size should be noted, which is caused by incomplete questionnaires of patients included in the groups.

Despite the small sample size, the distribution of genotype and allele frequencies in the groups does not differ from expected, according to the Hardy-Weinberg law (Chi-square, p>0.05) (Table 2), and are similar to the frequencies observed in the European population (1000 Genomes Project, p>0.05).

When comparing the genotype frequencies of the rs1495741 polymorphism in the groups, no significant association of slow or rapid acetylation genotypes with the development of NAFLD or CLC was found (Table 2).

To assess the effect of environmental factors on the disease development, we used Fisher's exact test at a confidence level of 95%. As a result, in the group of people who consume fried and smoked foods 5 or more times in a week, the risks of the disease development are significantly higher by 5,5 times compared to the control group (p = 0,004) (Table 3).

According to the differences in age between the clinical and control groups, we constructed a logistic regression model that included the following factors: age over 55 years, consumption of fried and smoked foods more than 5 times a week, and the rs1495741 polymorphism. As a result, the rs1495741 *NAT2* genotype was not considered as a significant predictor and was removed from the model. The final model included the effects of age and fried food consumption (p=0,0001). After assessment of predictor value, we found that the chances of developing inflammatory liver diseases increase by 7.57 times when consuming fried and smoked foods in combination with age >55 years (Table 4).

Discussion. Among the environmental factors, the consumption of fried and smoked foods (more than 5 times in a week) has the greatest importance in the development of metabolic liver diseases. The chances of disease development are 5.5 times higher in the case group compared to controls; in combination with age >55 years, the chances increase by 7.57 times. The small sample size should be noted, which may indicate randomness of the obtained results and the sample size should be increased. In addition, there are differences in age between the groups, which arose due to the peculiarities of the patient sampling: the group included patients with a newly diagnosed liver cirrhosis and patients of an

Table 1

Distribution of patients by gender and age in the groups

Characteristic	Control (CLC–, NAFLD–)	Case (CLC+, NAFLD+)	P value
Age, M±m (95% CI)	49.23±2.69 (43.96 – 54.51)	60.68±1.98 (56.79 – 64.57)	0.001037
Women	11	32	0.799
Men	6	15	
Total	17	47	

Table 2

Distribution of frequencies of genotypes and alleles of polymorphism rs1495741 in the studied group

Group	Genotype frequency. absolute (relative)			Allele frequency. absolute (relative)		Hardy-Weinberg equation. p value
	AA	*AG*	*GG*	*A*	*G*	
Control	9 (0.529)	7 (0.412)	1 (0.059)	25 (0.735)	9 (0.265)	1
Case	20 (0.4255)	20 (0.4255)	7 (0.149)	60 (0.638)	34 (0.362)	0.5454
Odds ratio (95% CI)	1.00	1.29 (0.4 – 4.13)	3.15 (0.34 – 29.53)	1.57 (0.62 – 4.28)		AIC=78.9
p value for OR	0.5383			0.3977		

older age group who had previously been observed with a diagnosis of NAFLD.

It is known that heterocyclic aromatic amines are formed during frying and smoking foods. They are absorbed in the intestine and then metabolized in the liver under the action of enzymes of the first and second phases of detoxification. During the first phase of biotransformation, under the influence of the cytochrome P450 system, active carcinogens with genotoxic effects can be produced. These active metabolites are subsequently inactivated by the NAT2 enzyme [3, 6, 7]. Thus, individuals with a slow acetylation pattern have a higher chance of accumulating active toxic metabolites leading to liver damage. As a result, an inflammation is formed, which, under conditions of constant exposure to xenobiotics, leads to chronic liver damage with further transformation into fibrosis and cirrhosis. Consumption of fried foods is associated with higher risk for the progression of fibrosis in NAFLD and the development of HCC with red meat consumption [13, 15, 16]. The main pathogenetic role belongs to saturated fats and trans fats deposited in the liver. It is possible that heterocyclic aromatic amines activated by the cytochrome system are slowly metabolized by the NAT2 enzyme and accumulate in hepatocytes, which also makes a significant contribution to the development of steatohepatitis, subsequent fibrosis and liver cirrhosis. According to our results, the chances of developing liver diseases under conditions of regular consumption of fried and smoked foods increases by 5,5 times, but no reliable results have been found on the association of slow or rapid acetylation type with the development of metabolic-associated liver diseases. But in the control group, only one patient had a genotype associated with the rapid acetylation type, which does not allow us to reliably determine the role of acetylation in the development of liver diseases under the influence of environmental factors. Therefore, it is necessary to increase the number of individuals with the rapid acetylation type in the control group. However, in Russia, the frequency of the rapid acetylation genotype varies from 0,05 to 0,5 depending on the region [1, 11]. This factor significantly affects the probability of the presence of volunteers with the rapid acetylation type in the sample.

Thus, increased consumption of fried and smoked foods more than 5 times a week should be considered as a risk factor for the development of metabolic-associated liver diseases especially in association with elder age over 55 years.

Table 3

Effect of environmental factors on the development of liver diseases

Factor	Control	Case	Odds ratio (95% CI)	P value
Smoking				
No	15	39	1.00	1
Yes	2	8	1.53 (0.26 – 16.41)	
Fried and smoked food				
No	12	14	1.00	0.004
Yes	5	33	5.49 (1.47 – 23.89)	

Table 4

Factors included in the model and their role in the development of liver diseases

Factor	Coefficient	Odds ration (95% CI)	P value
Age >55 years	2.0246	7.57 (3.79 – 14.63)	0.00436
Fried and smoked food consumption	2.0246	7.57 (3.79 – 14.63)	0.00436
Constant	-0.9993	–	0.09725

Increasing the groups, as well as including patients from other regions of Russia in the study, will allow us to assess the significance of genotype associated with acetylation rate and role of different environmental factors. Non-infectious liver diseases are multifactorial diseases, therefore, determining the genotype in combination with multifactorial analysis will improve the effectiveness of treatment and prevention, which is a relevant area in personalized medicine.

The work was carried out within the framework of the state assignment of the Ministry of Health of the Russian Federation (topic No. 121031000062-2 Study of the role of NAT2 polymorphism in the development of cryptogenic liver cirrhosis under conditions of xenobiotic load).

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SLEEP STRUCTURE IN ADULTS WITH RECURRENT EPILEPTIC SEIZURES OF REMOTE SYMPTOMATIC ETIOLOGY

A video-polysomnographic study of the structural characteristics of night sleep was carried out in 157 patients with a first-time unprovoked tonic-clonic seizure. The main group included patients with remote symptomatic seizure (RSS). Over the course of three years, 60 individuals had recurrent attacks; 38 patients had no recurrence of attacks during the observation period. The comparison group included 59 MRI- and EEG-negative patients. Patients with recurrent RSS had lower sleep efficiency, longer rapid eye movement phase, sleep fragmentation, wake after sleep onset, and more frequent awakenings from sleep (number of awakenings) versus patients with a single RSS and the comparison group. The identified changes demonstrate deeper disturbances in sleep architecture in patients with recurrent RSS and can be taken into account in prognostic counseling of this category of patients.

Keywords: remote symptomatic seizure, sleep structure.

Introduction. Remote symptomatic seizures (RSS) refer to unprovoked epileptic seizures that occur in the setting of previous structural brain injury [14]. The risk of relapse of RSS is often high, but the clinical indicator of the onset of epilepsy in adults continues to be a repeated epileptic seizure [28]. According to various researchers, the likelihood of relapse of RSS depends on the etiology and concomitant diseases [4, 7, 19], significantly increasing when epileptiform activity is detected [10]. It is well known that the probability of recording epileptiform discharges increases when recording the bioelectrical activity of the brain during sleep [2, 11]. Sleep and epilepsy are pathogenetically interrelated cyclic processes [12]. Epileptiform activity alters sleep structure, and sleep disturbance is one of the main risk factors for recurrent seizures [15]. According to recent data, epilepsy is characterized by a characteristic change in polysomnographic (PSG) indicators in the form of a reduction in the REM sleep phase and an increase in the number of spontaneous awakenings during sleep [26]. The study of PSG sleep indicators, potential markers of epileptogenesis that can predict the recurrence of epileptic seizures and influence treatment tactics in patients with remote symptomatic etiology is a relevant task, currently underrepresented in the available literature.

The study aim was to study the macro-architecture of night sleep during relapse of RSS in adults.

Materials and Methods. The study included 157 patients with a first-time unprovoked tonic-clonic seizure who were followed up by an epileptologist from 2008 to 2020. Neurophysiological investigation was carried out in the laboratory of video-EEG monitoring of the Department of Neurology and Neurosurgery of the Federal State Budgetary Educational Institution "Siberian State Medical University". The main group included patients with a first-time epileptic seizure with a focal onset, classified as RSS. Clinical inclusion criteria: anamnestic evidence of previous neurological diseases or traumatic brain injury confirmed by neurological examination, structural changes on MRI, age from 18 to 55 years, follow-up for three years, absence of epileptic seizures within 10 days before the study. Clinical exclusion criteria: repeated epileptic seizure, antiepileptic therapy [27], acute neurological pathology, acute physical conditions and exacerbations of chronic physical diseases [27], gravidity period and lactation, mental disorders, epileptiform activity on the EEG. During the observation period, 60 persons had recurrent seizures and, in accordance with the criteria [1], the onset of epilepsy was diagnosed. These patients made up group A. In 38 patients, attacks did not recur during the observation period (group B). The comparison group included 59 MRI- and EEG-negative patients with a first-time epileptic seizure with an unspecified onset (group B).

The characteristics of the individuals included in the study are presented in Table 1. The study groups were comparable in sex, age and lobar localization of epileptogenic damage to the cerebral cortex.

Neurophysiological study protocol. All patients underwent a video-polysomnographic study, including electroencephalography (in leads F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2 using the standard arrangement of electrodes according to the 10–20 system), electrooculography (2 channels), electrocardiography (1 lead), electromyography from the mentalis (2 channels), using the Neuron-Spectrum-4VP device from Neurosoft during physiological night sleep. Visual determination of sleep stages was performed according to the standard criteria of the American Academy of Sleep Medicine [8]. After identifying the stages and phases of sleep, the generally accepted parameters characterizing the structure of sleep were calculated [3]: total recording time (TIB - time in bed), total sleep duration (TST - total sleep time) - the total duration of all stages and phases of sleep, sleep latency (SOL – sleep onset latency) – time from turning off the light to the onset of the first period of sleep in minutes, sleep efficiency (SE – sleep efficiency) – percentage of TST from TIB, REM sleep latency (RL – rapid eye movement sleep latency) – time from falling asleep before the onset of the first epoch of rapid eye movement (R) in minutes, the relative duration of each stage of slow-wave sleep (nREM): the first stage - N1, the second stage - N2, the third stage - N3 and R in relation to TST as a percentage, the relative duration of wakefulness within sleep (WASO – wake after sleep onset) – in the interval from falling asleep to morning awakening (TIB-SOL) as a percentage, the number of spontaneous awakenings from sleep (NWake – number of awakenings) and overall sleep fragmentation (SSI – stage shift index) [13] in terms of 1 hour of sleep in absolute units. To estimate the number of awakenings in the nREM stages, we counted the number of actual transitions from N1, N2 and N3 to the wakefulness stage (W) [17] in the period from falling asleep to morning awakening. The normalized frequency of awakenings was calculated in relation to the sum of all transitions in W as a percentage [16]. Statistical processing was performed using the Statistica 6.0 package. The study used nonparametric comparison methods (Mann–Whitney, Kruskal-Wallis test), for evaluation of inter-group differences in the case of multiple comparisons we used Bonferroni correction [27]. A significance level of $p<0.05$ was accepted as reliable. Data are presented as medians (Me) and quartiles (q1; q3) – Me (q1; q2).

Results. Indicators characterizing the night sleep macrostructure are shown in Table 2. In patients from group A, the duration of TST was statistically significantly [27] reduced compared to group C, and the onset time R was increased, but these indicators did not differ among patients with focal seizures. The total recording time, sleep latency and nREM structure were comparable in the study groups, however, the relative duration of the REM sleep phase in group A was statistically significantly less than in group C. The duration of R in group B was also longer than in group A, however the differences did not reach the level of significance.

SE values in patients from group A were statistically significantly lower than the corresponding indicator in groups B and C (Figure 1).

The decrease in sleep efficiency among subjects of this group was accompanied by a significant increase in the relative duration of WASO.

Patients in group A had higher sleep fragmentation compared to the other groups (Table 3). The number of spontaneous awakenings per hour of sleep in patients from group A also statistically significantly exceeded the values of the corresponding indicators in the other groups.

When comparing the number of awakenings per hour in the stages of

Table 1

Clinical characteristics of individuals included in the study

Indicator	A (n=60)	B (n=38)	C (n=59)	p K-W test
Age, years (Me(q1; q2))	37.5(26;45)	34(26;50)	29(25;41)	0.2
Sex, f (m) - abs. numbers	15/45	10 /28	19 /40	0.6
Localization (MRI) according to the lobes of the brain - abs. numbers (%)				
Frontal	27 (45.0)	17 (44.74)		0.7
Temporal	24 (40.0)	14 (36.84)		
Parietal	7 (11.67)	5 (13.16)		
Occipital	2 (3.33)	2 (5.26)		
Note. K-W test – Kruskal-Wallis test				

Table 2

Commonly accepted polysomnographic indicators in the study groups

Indicator	Groups			p K-W test
	A	B	C	
TIB, min	397.43 (357.21;433.02)	396.26 (346.32;428.23)	406.26 (365.1;439.89)	pA-B 0.483
TST, min	333.08 (271.64;380.81)	355.14 (304.4;393.72)	374.92 (321.18;399.68)	pA-B 0.024 pA,B 0.008
SOL, min	7.67 (3.73;19.68)	6.18 (2.53;20.47)	7.37 (3.38;21.07)	pA-B 0.56
RL, min	86.57 (66.69;125.77)	85.23 (63.78;119.45)	73.28 (56.2;102.52)	pA-B 0.074
N1, %	21.3 (13.41;28.67)	17.8 (11.79;24.56)	17.02 (13.17;25.17)	pA-B 0.243
N2, %	42.85 (35.85;48.37)	41.02 (33.64;44.94)	43.84 (33.93;49.56)	pA-B 0.681
N3, %	22.56 (15.93;27.24)	24.12 (18.41;30.66)	20.52 (14.66;28)	pA-B 0.166
R, %	13.2 (10.56;15.47)	16.24 (10.95;18.28)	17.37 (16.2;19.9)	pA-B 0.0001 pA,B 0.00001

Note. The values of sleep indicators are given in minutes as medians (Me) and quartiles (q1; q3) – Me (q1; q2); K-W test – Kruskal-Wallis test pA-C – differences between all compared groups, pA-B – differences between groups A and B, pB-C – differences between groups B and C, pA-C – differences between groups A and C

slow sleep (Figure 2), a statistically significant increase in these indicators was revealed in the stages [21] of slow sleep in group A compared to group B, in [22] N1, N2 compared to group C. The relative number of transitions to the waking stage from N3 in group A exceeded the value of the corresponding indicators in groups B and C, but the differences did not reach the level of significance.

Discussion. Sleep is a complex neurodynamic self-regulating process and its changes in patients with new-onset RSS may be associated with subclinical epileptogenic restructuring of neural networks and, according to [23], analysis of patients with epileptic seizures who are not taking antiepileptic therapy can reveal changes in sleep architecture, associated to a greater extent with the influence of the pathogenesis of the disease.

In patients with recurrent RSS, there was a decrease in the total duration and efficiency of sleep, but the latency and structure of slow-wave sleep did not differ in the study groups. In general, sleep efficiency is an integral indicator that depends on the time of falling asleep and the duration of wakefulness during sleep. In the group of patients with recurrence of focal attacks, the relative duration of wakefulness within sleep and the overall fragmentation of sleep were higher, which characterizes the instability of sleep maintenance processes in this group of patients. The findings echo the changes identified [9] in sleep macro-architecture in adult patients with the onset of focal epilepsy and, according to the authors, can be explained by neurotransmitter disorders caused by epileptogenesis, leading to disruption of sleep regulation.

Clinical studies carried-out to date have shown that patients with epilepsy are characterized by an increase in the time of onset of the REM sleep phase, and the duration of this phase becomes shorter [25].

In the cohort of patients with the debut of focal epilepsy, a reduction in REM sleep was observed, however, latency values of this phase did not differ in the groups of comparison

A number of studies demonstrate variability in the duration of REM sleep depending on drug control of seizures and the effectiveness of surgical treatment of focal epilepsy [21, 27]. In patients with a follow-up onset of epilepsy, the duration of the REM sleep phase was shorter compared to patients with a single RSS, but the differences did not reach a statistically significant level.

It is now known that neurodynamic processes occurring in slow-wave sleep can promote the propagation of epileptiform activity, on the contrary, suppress the REM sleep phase [22].

It is assumed that the persistently detected phenomenon of REM sleep reduction in patients with epilepsy is not directly pathophysiologically related to the epileptic process, but is probably secondary to the disturbance in the dynamics of the change and duration of slow-wave sleep stages caused by epileptogenesis, which is manifested by increased fragmentation and frequent awakenings [18].

The overall fragmentation and the number of spontaneous awakenings during sleep in patients with recurrent RSS were higher compared to other groups, which from a modern point of view can be considered as a potential neurophysiological marker of an increased risk of recurrent epileptic seizures in this group of patients with unprovoked seizures.

Table 3

Number of spontaneous awakenings during sleep and overall sleep fragmentation in the study groups

Indicator (number of events an hour)	Groups			p K-W test	p M-W U Test
	A	B	C		
SSI	8.55 (6.5;12.71)	6.35 (4.34;9.07)	6.51 (4.27;9.03)	0.002	A>Б* A>B*
N of awakenings	1.75 (0.95;2.94)	0.82 (0.42;1.52)	0.88 (0.37;1.87)	0.001	A1>Б** A>B*

Note. Sleep indicators values are presented as medians (Me) and quartiles (q1; q3) – Me (q1; q2); K-W test – Kruskal-Wallis test; M-W U Test – Mann-Whitney U Test; **p< 0.001 and *p< 0.01 (Mann-Whitney U Test).

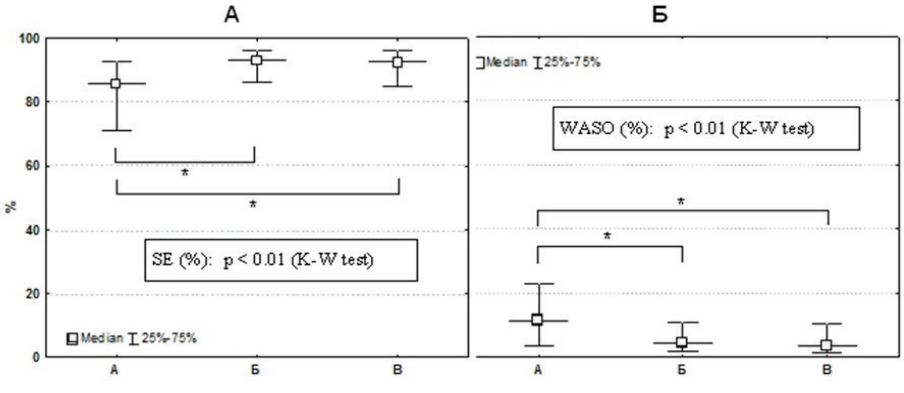

Fig. 1. Note. Sleep indicators values are presented in % as medians (Me) and quartiles (q1; q3); K-W test – Kruskal-Wallis test; p – level of reliability of differences; *p< 0.01 (Mann-Whitney U Test); А – SE (%): TST / TIB in %, И – WASO (%): WASO/(TIB-SOL) in %.
Sleep efficiency and duration of wakefulness during sleep in the study groups.

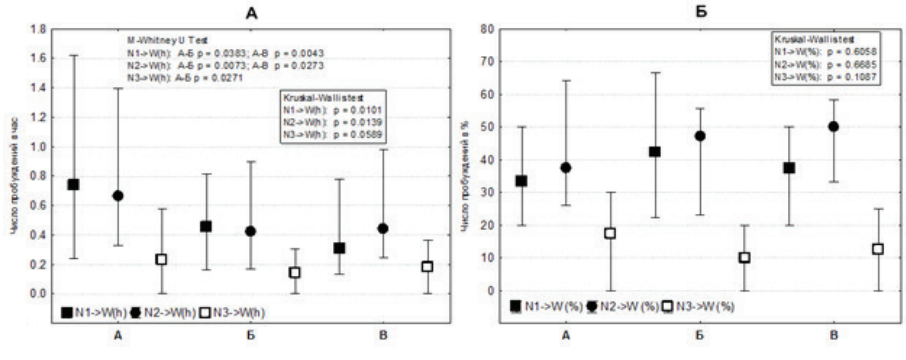

Fig. 2. Absolute (per hour) and relative (in %) number of awakenings at the stages of slow-wave sleep in the study groups: A – number of awakenings per hour: N1->W(h) - out of stage N1, N2->W(h) – out of stage N2, N3->W(h) – out of stage N3; B – relative number of transitions into the stage W out of definite stage of slow sleep in % in relation to the sum of all awakenings: N1->W(%) – out of stage N1, N2->W(%) – out of stage N2, N3->W(%) – out of stage N3.

Recent experimental model-based analysis of post-traumatic epilepsy in rats has demonstrated the need for stage differentiation when assessing PSG indicators characterizing sleep continuity [6]. According to the authors, a higher frequency of transitions from delta sleep to wakefulness can be considered a prognostic marker of post-traumatic epileptogenesis.

In patients with recurrent RSS, the absolute and relative frequency of awakenings from the deep stage of slow-wave sleep tended to exceed the value of the corresponding indicator compared to other groups.

According to the modern clinical paradigm, timely initiation of antiepileptic therapy is a necessary condition for achieving disease remission [25], and freedom from seizures correlates with normalization of sleep architecture [24].

According to J.L. Moore, D.Z. Carvalho, E.K. St. Louis, C. Bazil [20], the systematic study of two inextricably interacting neurodynamic processes of sleep and epilepsy is an urgent clinical task. The data obtained in the present study indicate that in patients with recurrent RSS, sleep consolidation and continuity are more affected, which is manifested by more frequent awakenings and sleep fragmentation.

Conclusion. The identified changes may characterize the disruption of chronobiological sleep regulation associated with subclinical epileptogenesis and be taken into account in prognostic counseling of patients with remote symptomatic seizures when assessing the prognosis of the disease and developing programs for personalized rehabilitation and prevention of relapse of epileptic seizures in this category of patients.

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INDICATORS OF QUALITY OF LIFE IN SCHOOLCHILDREN WITH ABDOMINAL PAIN IN THE ASSESSMENT OF CHILDREN AND THEIR PARENTS IN ETHNIC POPULATIONS OF TYVA

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Aim. To study and compare indicators of quality of life in schoolchildren with abdominal pain in the assessment of children and their parents in the ethnic populations of the Republic of Tyva.

Material and Methods. In the Republic of Tyva, schoolchildren aged 7-18 years of the indigenous population (312 Mongoloids - Tuvans) and alien population (136 Caucasians) were examined using a cross-sectional method. Gastroenterological complaints and demographic information were recorded. To assess the quality of life of children, adapted Russian parent (CHQ-PF28) and child (CHQ-PF45) versions of the Child Health Questionnaire (CHQ) were used. The questionnaire allows you to assess various areas of a child's life. The studies were approved by the ethics committee and the consent of the patients (their parents) was obtained.

Results. A decrease in the quality of life was established in schoolchildren of both ethnic populations in the presence of abdominal pain, both in their own assessment and by their parents. This applies to the general state of health, and specifically to the state of physical, mental health, as well as the emotional sphere. At the same time, in the Tuvan population, when schoolchildren assessed their quality of life, in contrast to their parents, a decrease was noted on scales related specifically to indicators of mental and physical health. It is noteworthy that the decrease in quality of life indicators in the assessment of children is more significant than in the assessment of parents, and affects a wide range of questionnaire scales in both ethnic populations of schoolchildren in Tyva. At the same time, children with abdominal pain are severely limited in communication with peers, both due to emotional and physical problems, and often experience a constant feeling of anxiety and depression. The latter is not properly reflected in the results of the analysis of parental quality of life questionnaires.

Conclusion. The peculiarities of the frequency of family deprivation in ethnic populations have been established.

Keywords: quality of life, CHQ, abdominal pain, children, ethnicity, Tyva.

Abdominal pain is an acute problem in pediatric practice due to its widespread prevalence, reaching 13.5% [10]. In childhood, abdominal pain dominates, having different localization and mostly related to various nosological forms of functional pathology of the gastrointestinal tract: functional abdominal pain syndrome, functional dyspepsia (FD), irritable bowel syndrome (IBS), etc. [10, 14, 15].

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There is convincing evidence linking the appearance of abdominal pain with various causes, which characterizes the multifactorial nature of their formation. Factors with the most pronounced negative impact on the development of abdominal pain in children include psychotraumatic factors, psychological disorders, errors in diet, etc. [10, 14, 16]. Often, abdominal pain present in childhood transforms into chronic pain. This circumstance dictates special attention to the problem [10].

In turn, abdominal pain is a factor with a pronounced negative impact on the quality of life of children. Quality of life is a multidimensional reflection of both physical and mental health and social functioning of an individual [6, 10]. At the same time, in children with abdominal pain, a decrease in the quality of life can be caused by both an immediate health problem and psychosocial distress, in relation to which the pain syndrome is secondary. A recent meta-analysis highlighted another problem that exists in children with chronic abdominal pain, which is interpreted as pain catastrophizing [10]. This condition is particularly closely associated with a decrease in the child's quality of life. At the same time, it is characterized by prediction and expectation of something bad, and a feeling of helplessness [5, 6]. What matters is the level of stress resistance, determined by the physiological characteristics of the body's regulatory processes with a genetic basis. This affects both the prevalence of abdominal pain in children and their catastrophizing.

However, each disease can cause unique and individual-specific problems. Many researchers agree that monitoring the quality of life in pediatric practice is not only capable of verifying the effectiveness of preventive, therapeutic and rehabilitation programs, but also makes it possible to develop sound recommendations for improving the system of providing medical and social care to children [12, 17].

Aim. To study and compare indicators of quality of life in schoolchildren with abdominal pain as assessed by children and their parents in the ethnic populations of the Republic of Tyva.

Materials and methods. Schoolchildren in the populations of the indigenous and alien populations of the Republic of Tyva (Mongoloids - Tuvinians and Caucasians) were simultaneously examined using a cross-sectional method. The age of the children ranged from 7 to 18 years. A total of 448 children were examined:

indigenous population (Mongoloids - Tuvans) - 312 schoolchildren (7-11 years old - 187 and 12-17 years old - 125 people; boys - 127, girls - 185 people); alien population (Caucasians) - 136 schoolchildren (7-11 years old - 58 and 12-17 years old - 78 people; boys - 62, girls - 74 people). Standard questionnaires were filled out, recording gastroenterological complaints in the child and demographic information: age, gender, ethnicity.

The criteria for excluding children from the study were the presence of acute inflammatory diseases during the last month; chronic diseases in the acute stage; functional failure of organs and systems of the body; mental, intellectual disabilities and language barriers among the subjects.

To study and interpret the quality of life and health status of children, adapted Russian parental (CHQ-PF28) and child (CHQ-PF45) versions of the Child Health Questionnaire (CHQ) [7, 8], which is an instrument approved by the International Center for the Study of Quality of Life, were used and is recommended for use in scientific research to assess the quality of life of children [3]. Using the questionnaire, you can assess various areas of a child's life. These are "General health assessment", "Physical activity", "The role of emotional and behavioral problems in disability", "The role of physical problems in disability", "Pain/Discomfort", "Behavior", "Mental health", "Self-assessment", "Changes in health", "Emotional impact on parents", "Limitation of parents' free time", "Family activity", "Family cohesion". Quality of life indicators were calculated using a 100-point system. A decrease in score indicators is associated with a lower level of the child's quality of life. The study was conducted after the parents signed the informed consent. The research work was approved by the ethics committee and carried out within the framework of the state scientific theme of the Federal State Budgetary Institution Federal Research Center KSC SB RAS ("Research Institute of Medical Problems of the North").

To carry out statistical analysis of the study data, SPSS (version 23.0; IBM, Inc.) and Microsoft Excel 2010 were used. Quantitative data were described using the arithmetic mean (M) and standard deviation (SD). The significance of differences in traits was analyzed using Mann-Whitney tests for independent samples and Wilcoxon signed rank tests for related samples. Statistical significance of differences in characteristics was assessed at $p<0.05$.

Research results and discussion. In parent assessments using the CHQ questionnaire, quality of life scores for Caucasian schoolchildren with abdominal pain were reduced compared to children without complaints (Table 1). Specifically, a decrease in indicators on the "General health assessment" scale ($p = 0.001$) and on the "Pain/Discomfort" scale ($p = 0.001$) was established. This indicates that the presence of severe or frequent abdominal pain is a factor that causes significant concern for parents. In addition, in children with abdominal pain, according to the parent questionnaire, there was a decrease in indicators on the "Behavior" scale, consisting of immature, sometimes aggressive behavior of the child ($p = 0.008$); on the "Mental health" scale, as well as on the "Family cohesion" scale ($p = 0.003$), which indicates a lack of ability in the family to get along with each other and negotiate.

At the same time, in the assessment of schoolchildren themselves with abdominal pain in the Caucasian population, more significant negative deviations in indicators on the scales of the CHQ quality of life questionnaire for children were noted, relative to children without complaints. This concerned such scales as "General health assessment" ($p = 0.001$), "Pain/Discomfort" ($p = 0.001$), "Behavior" ($p = 0.001$), "Mental health" ($p = 0.001$) and "Family cohesion" ($p = 0.086$), according to which, in their assessment, like their parents, there was a decrease in indicators. But, in addition, in children with pain, when assessing the quality of life, lower scores were obtained than in children without complaints on such a scale as "Family activi-

Table 1

Indicators of quality of life in schoolchildren with abdominal pain in the Caucasian population of Tyva as assessed by children and their parents using the scales of the Child Health Questionnaire

CHQ version	CHQ scales	With abdominal pain (n=66)		Without abdominal pain (n=70)		P
		M	SD	M	SD	
Parent version	1. General health assessment	44.3	17.4	60.7	22.8	0.001
	2. Physical activity	91.1	19.0	93.9	16.0	0.371
	3. Role of emotional problems in limited life activity	81.5	27.3	87.7	23.3	0.166
	4. Role of physical problems in limited life activity	87.1	25.3	90.7	21.4	0.401
	5. Pain/Discomfort	60.6	18.6	79.3	14.8	0.001
	6. Behavior	61.3	16.4	69.3	13.5	0.008
	7. Mental health	78.5	26.3	87.0	22.5	0.029
	8. Overall comprehension of health	56.2	24.9	57.3	22.7	0.970
	9. Changes in health condition	61.7	23.7	62.3	19.9	0.819
	10. Emonional influence on parents	43.4	32.0	51.3	30.8	0.144
	11. Free time limitation	82.5	25.5	81.6	27.6	0.838
	12. Family cohesion	76.4	18.4	85.2	20.2	0.003
Children's version	13. General health assessment	48.1	21.6	64.3	25.0	0.001
	14. Physical activity	89.7	19.0	91.8	16.7	0.318
	15. Role of emotional problems in limited life activity	71.9	25.6	78.6	20.5	0.177
	16. Role of physical problems in limited life activity	79.7	28.0	85.1	26.1	0.224
	17. Pain/Discomfort	58.3	23.8	77.5	19.6	0.001
	18. Behavior	66.8	11.8	74.2	9.3	0.001
	19. Mental health	66.9	14.9	75.0	11.3	0.001
	20. Self-assessment	73.1	20.5	78.3	19.0	0.119
	21. Overall comprehension of health	65.6	24.3	73.5	19.5	0.087
	22. Changes in health condition	60.8	23.0	63.8	20.8	0.391
	23. Family events	69.7	16.4	77.3	20.2	0.008
	24. Family cohesion	78.5	20.8	84.3	19.4	0.086
P1-13		0.085		0.200		
P2-14		0.302		0.171		
P3-15		0.010		0.013		
P4-16		0.022		0.059		
P5-17		0.363		0.330		
P6-18		0.006		0.002		
P7-19		0.001		0.001		
P8-21		0.023		0.001		
P9-22		0.648		0.378		
P12-24		0.572		0.527		

ty" (p = 0.008). It should also be emphasized that children with abdominal pain additionally had a pronounced tendency to decrease on the "General perception of health" scale (p = 0.087).

When comparing indicators on the scales of parental CHQ questionnaires, lower indicators were obtained than in the assessment of the children themselves on the "General perception of health" scale (p = 0.023). In addition, parents more often paid attention to the immature, sometimes aggressive behavior of their children, as evidenced by lower scores on the "Behavior" scale (p = 0.006). Then, in assessing the quality of life of children with abdominal pain themselves, unlike parents, there was a decrease in indicators on the scales "Role of physical problems in limiting life activity" (p = 0.022), "Role of emotional problems in limiting life activity" (p = 0.01) and "Mental health" (p=0.001). All this indicates that children have problems communicating with peers, which is reflected in their behavior and is accompanied by aggression and immature, sometimes criminal behavior.

In the Tuvan population, in the assessment of parents of the quality of life of schoolchildren with abdominal pain, deviations are observed mainly on similar scales as in the Caucasian population (Table 2). This concerned the following scales: "General health assessment" (p=0.001), "Pain/Discomfort" (p=0.001), "Behavior" (p=0.019), "Family cohesion" (p=0.008). Additionally, in the assessment by parents of the quality of life of their children in the Tuvan population, in contrast to the Caucasian population, a decrease was noted on the scales "Physical activity" (p = 0.001), "General perception of health" (p = 0.054) and "Changes in health status" (p =0.001).

At the same time, in the Tuvan population, in the assessment of schoolchildren themselves with abdominal pain, a more significant decrease in their quality of life was noted. On almost all scales of the children's CHQ questionnaire, they had a decrease in scores compared to children without abdominal pain. The decrease in indicators affected almost all scales. These scales are: "General assessment of health" (p=0.001), "Physical activity" (p=0.004), "The role of emotional problems in limiting life activity" (p=0.047), "The role of physical problems in limiting life activity" (p=0.004), "Pain/Discomfort" (p=0.001), "Behavior" (p=0.001), "Mental health" (p=0.021), "Changes in health status" (p=0.001), "Family activity" (p =0.001), "Family cohesion" (p=0.002). In addition, they showed a tendency to decrease on the "Self-assessment" scale (p = 0.062).

Table 2

Indicators of quality of life in schoolchildren with abdominal pain in the Tuvan population of Tyva as assessed by children and their parents using the scales of the Child Health Questionnaire

CHQ version	CHQ scales	With abdominal pain (n=181)		Without abdominal pain (n=131)		P
		M	SD	M	SD	
Parent version	1. General health assessment	49.3	20.3	64.7	23.0	0.001
	2. Physical activity	86.1	25.6	92.6	19.5	0.001
	3. Role of emotional problems in limited life activity	84.6	23.7	84.8	23.1	0.991
	4. Role of physical problems in limited life activity	89.6	21.0	89.5	21.4	0.978
	5. Pain/Discomfort	67.5	20.3	80.6	17.4	0.001
	6. Behavior	71.6	15.8	76.1	15.3	0.019
	7. Mental health	92.0	16.2	89.7	21.1	0.982
	8. Overall comprehension of health	52.6	26.7	58.8	25.7	0.054
	9. Changes in health condition	62.1	24.5	73.4	24.0	0.001
	10. Emonional influence on parents	47.4	30.5	48.0	33.9	0.807
	11. Free time limitation	75.7	31.3	77.8	30.2	0.487
	12. Family cohesion	78.2	18.2	83.9	17.2	0.008
Children's version	13. General health assessment	52.1	20.6	63.9	24.6	0.001
	14. Physical activity	83.5	25.4	89.8	21.2	0.004
	15. Role of emotional problems in limited life activity	79.4	23.0	84.5	20.6	0.047
	16. Role of physical problems in limited life activity	76.9	30.7	86.0	27.6	0.004
	17. Pain/Discomfort	66.9	22.7	80.9	20.0	0.001
	18. Behavior	71.9	12.2	76.9	10.5	0.001
	19. Mental health	70.6	13.5	74.3	14.1	0.021
	20. Self-assessment	80.4	20.2	84.9	17.7	0.062
	21. Overall comprehension of health	62.3	19.7	66.1	22.7	0.114
	22. Changes in health condition	61.9	23.5	72.8	23.7	0.001
	23. Family events	70.6	21.0	81.6	20.1	0.001
	24. Family cohesion	77.0	20.2	83.7	20.5	0.002
P1-13		0.053		0.899		
P2-14		0.084		0.014		
P3-15		0.053		0.926		
P4-16		0.001		0.083		
P5-17		0.787		0.826		
P6-18		0.681		0.704		
P7-19		0.001		0.001		
P8-21		0.001		0.055		
P9-22		0.943		0.862		
P12-24		0.504		0.901		

At the same time, in the assessment of parents, in comparison with the assessment of schoolchildren, in the Tuvan population, a decrease in indicators was noted on scales that affect only general issues of children's health. These are the scales "General assessment of health" (p=0.053) and "General perception of health" (p=0.001). Whereas in the population, when schoolchildren assessed their quality of life, unlike parents, a decrease was noted on scales related specifically to indicators of mental and physical health. These are the scales "The role of emotional problems in limiting life activity" (p = 0.053), "The role of physical problems in limiting life activity" (p = 0.001), "Mental health" (p = 0.001). All this indicates that children with abdominal pain are severely limited in communication with peers, both due to emotional and physical problems. At the same time, children often experience constant feelings of anxiety and depression.

Thus, in the Republic of Tyva, schoolchildren with abdominal pain syndrome, both in their own assessment and by their parents, experience a decrease in quality of life. Studying the latter makes it possible to analyze comprehensive aspects of a child's life. The results indicate that a decrease in the quality of life in children with complaints of abdominal pain also concerns the general state of

health, specifically the state of physical, mental health, as well as the emotional sphere. It has been established that they have significant limitations in communicating with peers, both due to emotional and physical problems. It is noteworthy that the decrease in quality of life indicators in the assessment of children is more significant than in the assessment of parents, and affects a wider range of scales of the CHQ questionnaire in both ethnic populations of schoolchildren in Tyva. At the same time, children with abdominal pain often experienced constant feelings of anxiety and depression. The latter is not properly reflected in the results of the analysis of parental quality of life questionnaires. This probably indicates a lack of proper attention to the child's problems or the presence of a negative psycho-emotional climate in the family. This factor can act as a trigger for abdominal pain in a child, resulting from psychosocial distress, which has been found to be closely associated with functional disorders in the body [5, 6]. Thus, in the overwhelming majority of cases, abdominal pain syndrome among schoolchildren in Tyva is caused by functional disorders [1]. Moreover, under the guise of abdominal pain, they often have psychosomatic diseases (up to 65.0%), which require consultation with a psychologist and psychiatrist [5]. It has also been established that psychosocial distress is more closely associated with a decrease in quality of life than physical (organic) health problems [6].

Abdominal pain in children is often prospectively associated with its catastrophization (somatization) and is associated with the occurrence of psycho-emotional abnormalities. In this situation, children experience increased suspiciousness, a sense of defenselessness, anxiety, and depression [6, 12, 13]. In this regard, another problem emerges for the children of Tuva. This problem is depressive states, which in the Republic is characterized by particular severity due to the most negative indicators of child suicide in the Russian Federation [4].

At the same time, it was found that in the Tuvan population, estimated indicators of quality of life in schoolchildren with abdominal pain affect a larger number of scales, on which there is a decrease in indicators. To a certain extent, this can be ensured by the participation of genetic influence (functional characteristics of the digestive organs, nervous system - forming the level of stress resistance, the level of adaptation to environmental living conditions) [10, 11]. Thus, indigenous adolescents of the northern regions have peculiarities of the emotional sphere, consisting in a tendency to despondency, increased suspiciousness and a feeling of insecurity [4].

A large role in the occurrence of functional disorders in the body is given to the psychological climate in the family. In ethnic populations there may be a unique influence of factors that shape the psychological climate in the family. These are the education of parents, the quantitative composition of the family, the sanitary and hygienic standard of living of the family, the specifics of relationships and behavioral reactions in the family, dietary habits, etc., which are largely related to the ethnocultural characteristics of populations [2, 9]. All this, undoubtedly, is reflected in the level of resistance to various types of stress.

Comparison of quality of life indicators based on the assessment of the children themselves and their parents, in our opinion, is an informative tool for identifying psychological problems in schoolchildren with abdominal pain, which will reveal the presence of intra-family problems in the child and his "Family deprivation". The latter, namely the lack of proper contact between the child and the parent, is emphasized by the fact that in both populations, in assessing the quality of life by both the parents and the children themselves with abdominal pain, there was a decrease in values on the "Family cohesion" scale. The results of the study, in addition, indicate that children with abdominal pain are severely limited in communication with peers, both due to emotional and physical problems. This circumstance, obviously, can intensify their constant feelings of anxiety and depression. In this case, the child is left alone with his problems.

There is a point of view about the high effectiveness of using integrative assessments of quality of life in the analysis of treatment results, the course and prognosis of specific pathological conditions [17]. It seems that a comparative assessment of quality of life indicators using the scales of the CHQ questionnaire allows us to obtain data on the psychological and communicative relationships of family members. This, in turn, makes it possible for the majority to understand the cause of chronic abdominal pain. In addition, it allows us to develop a strategy and tactics for managing such patients by eliminating or mitigating the influence of negative intrafamily factors. It is necessary to more often involve psychologists and psychiatrists in the treatment of children with abdominal pain syndrome to isolate the contribution of psychosocial distress and the somatic component in the occurrence of complaints.

Conclusion. Thus, among Tyva schoolchildren, the presence of abdominal pain syndrome is associated with a decrease in the quality of life, both as assessed by the children themselves and their parents. Lower quality of life indicators were determined by the assessment of children themselves, especially indigenous schoolchildren, which affect almost all scales of the CHQ questionnaire. Tuvans have extremely pronounced differences in quality of life indicators when assessed by parents and children. At the same time, Tuvans with abdominal pain experience depressive symptoms, which are often disguised as behavioral disorders of the child.

Assessment of quality of life is an informative tool in assessing both the somatic and mental components in the formation of abdominal pain and can be recommended for wider use in practice.

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IN-VITRO EVALUATION OF THE ANTIOXIDANT ACTIVITY OF AQUEOUS AND ETHANOL EXTRACTS OF *VACCINIUM VITIS-IDAEAE L.* LEAVES

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Biologically active substances in lingonberry leaves (*Vaccinium vitis-idaeae L.*) have antioxidant properties. This study selected the optimal extraction method to obtain extracts with a high content of biologically active components with antioxidant activity from the leaves of *Vaccinium vitis-idaeae growing* in Yakutia. The data obtained allow us to conclude that biologically active substances isolated by alcoholic extraction from the leaves of *Vaccinium vitis-idaeae* can be used in medicine to find approaches to regulating pro-oxidant processes in the human body under various pathological conditions.

Keywords: lingonberry, biologically active substances, gravimetric method, model system.

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Introduction. For the treatment and prevention of new viral diseases, there is a need to search for new drugs. Plant-origin preparations with a high content of biologically active substances (BAS) are highly interesting due to their safety, availability, and renewal of biological resources. The quantitative and qualitative content of BAS of plant raw materials depends on natural conditions [6]. For example, the accumulation of BAS by plants can be influenced by the following factors: growing region conditions, cultivation method, weather conditions, maturation stages, soil, and extraction method [4, 5]. Thus, the harsh and unique abiotic factors of the plant growing environment in Yakutia contribute to the active accumulation of biologically active compounds in plants during a relatively short growing season.

In pharmaceutical practice, the most interesting are medicinal plants containing phenolic compounds with pronounced antioxidant properties.

Common lingonberry (Vaccinium vitis-idaeae L.) is a perennial shrub belonging to the Heather family (Ericaceae). Vaccinium vitis-idaeae grows in coniferous and mixed forests, in the mountain and plain tundras, and sometimes on peat bogs. The entire aboveground part of Vaccinium vitis-idaeae is used as a medicinal raw material: shoots, leaves, and berries. In 2018, common chasteberry was included in the State Pharmacopoeia of the Russian Federation (XIV edition). In medicine, the leaves of Vaccinium vitis-idaeae are used as a diuretic, antimicrobial, and anti-inflammatory agent.

According to literature data, components of Vaccinium vitis-idaeae exhibit anti-inflammatory, neuroprotective, hypoglycemic, antioxidant, and antitumor properties, which are determined by the

presence of biologically active substances of different natures [7, 8, 9]. Vaccinium vitis-idaeae leaves have been shown to contain phenolic glycosides such as arbutin, methylarbutin, vaccinin, hydroquinone, organic acids, including gallic, tartaric, ellagic, cinnamic, ursolic acids and flavonoids represented by quercetin, quercitrin, isoquercitrin and quercetin-3-arabinoside, including tannins and catechins [11].

The study aims to find an optimal extraction method for obtaining extracts with a high content of biologically active components with antioxidant activity from the leaves of Vaccinium vitis-idaeae growing in Yakutia.

Material and methods. The work was carried out in the laboratory of pre-cancerogenesis and malignant tumors of the Department of Epidemiology of chronic non-infectious Diseases, Yakut Science Centre of Complex Medical Problems, within the framework of the research work "Regional features of biochemical, immunological and morphological parameters in the indigenous and native population of the Republic of Sakha (Yakutia) in norm and pathology.

Plant raw materials and preparation of extracts. Ethyl and aqueous extracts of Vaccinium vitis-idaeae leaves were used in this study. Plant raw materials were collected during the fruiting phase (August-September) in Namsky District of the Republic of Sakha (Yakutia). The leaves were dried naturally at room temperature without access to direct sunlight. After the drying stage, the plant material was subjected to grinding on a vibrating ball mill "GT-200" ("GRINDER"). Extraction was carried out by single maceration for 60 minutes at a temperature of 60 C. Distilled water and ethyl alcohol in different concentrations from 20 to 95%, in increments of 10%, were used for extraction. By weight, the ratio of dried raw material of Vaccinium vitis-idaeae leaves and water/alcohol extractant was 1:10. The obtained extracts were centrifuged, then the soluble fraction of the extract was passed through a filter with a pore diameter of 0.22 μm ("Membrane Solutions").

Determination of extractive substances content. For general quantitative analysis of extractive substances and identification of conditions that have the maximum extraction, the amount of biologically active components and ballast substances were determined depending on the type of extractant used.

Quantitative determination of the content of extractive substances was carried out gravimetrically, according to the method described in the state pharmacopeia "1.5.3.000615", using lyophilization. After extraction, ethyl, and aqueous extracts were transferred to accurately weighed containers for drying. Lyophilization of extractables was carried out on a Free-Zone (Labconco) lyophilic dryer (150Pa, -52 °C) until complete sublimation of the solvent. The weight of the extract before and after lyophilization was measured to determine the total mass of the extractable.

The content of extractive substances was calculated according to the formula specified in the method "Determination of extractive substances content in medicinal plant raw materials and medicinal plant preparations."

Determination of the antioxidant activity of aqueous and alcoholic extracts. To evaluate the antioxidant activity (AOA) of the studied extracts, we used the standard technique of lipid peroxidation (LPO) on the model system of yolk lipoproteins (YLP) [2]. Oxidation of unsaturated fatty acids was initiated by adding iron (II) sulfoxide. Optical density was measured at a wavelength of 530 nm on a Cary 100 UV-Vis spectrophotometer (Agilent Technologies). Antioxidant activity (X) was calculated in percent by the formula:

$$X = \frac{Ek - Eo}{Ek} \times 100,$$

Ek - optical density index in the control sample without Vaccinium vitis-idaeae leaf extract; Eo - optical density index in the experimental sample.

In this study, statistical processing of the obtained data was done using the software "SPSS Statistics" (version 27.0.1). The normality of the distribution of the data set was checked using the Kolmogorov criterion. Data sets with normal distribution were compared using Student's t-criterion, and data differing from normal distribution were compared using the Mann-Whitney statistical U-criterion. The significance level for accepting the null hypothesis was accepted at $p<0.05$.

Results and Discussion. In a study by Bujor et al. (2018) using a method to evaluate antioxidant activity by the ability of the studied objects to reduce the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), it was shown that the antioxidant properties of BAS of alcoholic extracts isolated from the leaves are higher than those from the fruits of Vaccinium vitis-idaeae [10]. This study suggests that the leaves of Vaccinium vitis-idaeae are a valuable biological raw material with a unique qualitative and quantitative composition of BAS. In this regard, we studied the antioxidant properties of aqueous and alcoholic extracts of Vaccinium vitis-idaeae leaves.

Determination of the content of extractable substances after filtration, through a membrane with a pore size of 0.22 μm, of aqueous and alcoholic extracts of Vaccinium vitis-idaeae leaves showed that with increasing concentration of ethyl alcohol in the extractant, the yield of the total content of active and ballast substances decreases. According to literature data, the leaves of Vaccinium vitis-idaeae of Central Yakutia contain up to 9.5% arbutin, up to 35% tannins, and ascorbic acid - 27% [1]. The study's results to determine the content of extractable substances confirm that the extractable substances of Vaccinium vitis-idaeae leaves are mainly represented by water-soluble compounds: simple phenols, carbohydrates, tannins, and organic acids.

The antioxidant activity of Vaccinium vitis-idaeae leaf extracts was investigated on a model system of yolk lipoproteins. The model system has a constant lipid

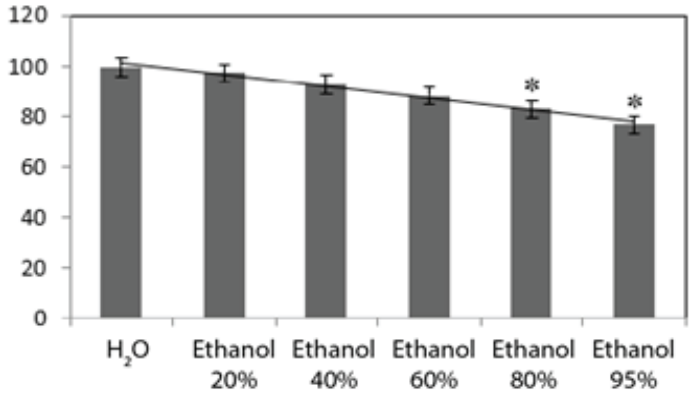

Fig. 1. The content of extractive substances in aqueous and ethyl extracts of *V. vitis-idaeae* leaves. The ordinate axis shows the content of extractive substances expressed in percent. The abscissa axis shows the type of extractant used; * - $p<0.05$.

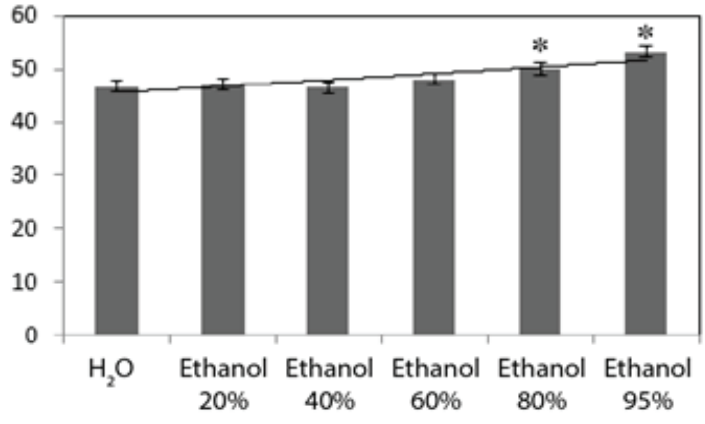

Fig. 2. Total antioxidant activity of aqueous and ethyl extracts of *V. vitis-idaeae* leaves in the model system of yolk lipoproteins. The ordinate axis shows antioxidant activity expressed in percent. The abscissa axis shows the type of extractant used; * - $p<0.05$.

composition. It contains two lipid-protein complexes, corresponding to the lipid and protein composition of very low and low-density human blood plasma [2]. When diluted in phosphate buffer, egg yolk phospholipids form bilayer micelles - liposomes. In this system, oxidation occurs on the surface of liposomes carrying a charge on the polar heads of phospholipids. The acceleration of free-radical oxidation processes accompanies the introduction of iron (II) sulfoxide into the system, while spontaneous oxidation in this model is extremely insignificant. The introduction of antioxidants into the model system inhibits the intensity of peroxidation processes. Consequently, the model system of yolk lipoproteins can determine the studied objects' antioxidant properties (plant extracts, biological fluids).

Our study's results showed that the extracts' antioxidant properties tend to increase depending on the increase in ethyl alcohol concentration. It was observed that the increase in antioxidant properties of the extracts starts from 60% alcohol extract and further.

Alcoholic extraction of Vaccinium vitis-idaeae leaves allows more intensive extraction of active substances (phenols, flavonoids, and catechins) from the object of study. Interesting are the works conducted by Raudone et al., where the authors showed that alcoholic extracts of Vaccinium vitis-idaeae leaves are characterized by a high content of phenolic substances, and the antioxidant activity of the extracts depends on their composition [3]. Preliminary data allow us to conclude that unique biologically active components isolated by alcoholic extraction from Vaccinium vitis-idaeae leaves can be used in medicine to find approaches to regulate pro-oxidant processes in the human body in various pathological conditions.

Conclusion. The obtained data indicate that the extraction of biologically active phenolic compounds from Vaccinium vitis-idaeae leaves is more intensive in 95% ethyl alcohol compared to aqueous and other aqueous-alcohol solutions, as evidenced by the increase in the total antioxidant activity carried out on the model of yolk lipoproteins.

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A RARE VARIANT OF c.7636C>T p.(Gln2546*) OF THE *MYO15A* GENE IN TWO PATIENTS FROM BURYATIA WITH SENSORINEURAL DEAFNESS

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In the world the role of pathogenic variants of the *MYO15A* gene in the etiology of hearing loss has not been sufficiently studied, since the large size of the gene (66 exons, 71 kb) suggests the search for pathogenic variants using NGS technologies, which are not yet sufficiently used in routine practice. In this regard, it is relevant to study the role of pathogenic variants of the *MYO15A* gene in the etiology of non-syndromic forms of hearing impairments. The purpose of this work is to describe the rare pathogenic variant c.7636C>T p.(Gln2546*) in the *MYO15A* gene, found in a homozygous state in two siblings with prelingual profound sensorineural hearing loss from a Buryat family. Previously, this variant was found only in one patient in a compound-heterozygous state with another nonsense variant in the *MYO15A* gene in Brazil and described as pathogenic. Detection of variant c.7636C>T p.(Gln2546*) in a homozygous state in Buryat siblings may indicate either a rare case of endogamous marriage or a wider distribution of this variant in the Lake Baikal region.

Keywords: autosomal recessive deafness (DFNB3), *MYO15A* gene, variant c.7636C>T p.(Gln2546*), Republic of Buryatia.

In Russia, according to the results of audiological screening of newborns in 2013, the diagnosis of hearing loss was confirmed in 3 of 1000 newborns, of which deafness was detected in 0.6 cases per 1000 newborns [1]. Half of all cases of hearing impairment are believed to have a hereditary etiology, and most of them (70%) are non-syndromic. Currently, more than 120 genes are associated with the nonsyndromic form of hearing loss, of which about 70 genes [https://hereditaryhearingloss.org/recessive-genes the link is active at the time of 27.01.2023] are associated with autosomal recessive forms [8]. One of the first genes to be associated with autosomal recessive hearing disorders were *GJB2* (DFNB1A, OMIM #121011), *MYO7A* (DFNB2, OMIM #276903) and *MYO15A* (DFNB3, OMIM #602666). However, currently, of these three genes, the most well-studied are the *GJB2* gene (2 exons) in non-syndromic forms [7] and the *MYO7A* gene (56 exons) in Usher syndrome [6]. Since the *MYO15A* gene is associated with a non-syndromic form of hearing loss (a less specific phenotype than Usher syndrome) and has a fairly large size (66 exons), its role in the etiology of hearing loss in the world has been studied to a lesser extent. Currently, most pathogenic variants in the *MYO15A* gene have been detected using NGS technologies. The *MYO15A* gene is localized on the 7th chromosome (17p11.2) and encodes an unconventional myosin 15A consisting of 3530 amino acid residues [8]. Myosin 15A is expressed at the tips of the stereocilia of snail hair cells [2] and is necessary for their elongation, as well as for the delivery of molecules to the tips of the stereocilia [17].

In Russia, among 226 *GJB2*-negative patients with hearing impairments, two causative variants c.6046+1G>A (donor splicing site) and c.8910del p.(Val2971fs*63) were found in one patient in the *MYO15A* gene in a compound heterozygous state [15]. The mutational contribution of the *MYO15A* gene among Russian patients was less than 1% [15]. However, recently two more causative variants of c.3576G>A p.(Trp1192Ter) and c.5192T>C p.(Phe1731Ser) were found in one patient from North Ossetia in the *MYO15A* gene [12].

Thus, the molecular genetic search for causative variants of the *MYO15A* gene in cohorts of patients with non-syndromic forms of hearing loss and deafness is relevant, which will contribute to the development of our understanding of the role of this gene in the etiology of hearing loss. In this regard, the purpose of this work is to describe the variant c.7636C>T p.(Gln2546*) in the *MYO15A* gene, found in a homozygous state in two siblings from a Buryat family.

Materials and methods. *Sample of the study.* Two different-sex siblings with hearing impairments from the same Buryat family were studied, their ages at the time of the study were 69 and 65 years. The surveys provided in the framework of this research were conducted after obtaining informed written consent from the participants. This study was approved by the local Committee on Biomedical Ethics at Yakut Scientific Center of Complex Medical Problems in 2019 (Yakutsk, Protocol No. 7 of August 27, 2019).

Clinical and audiological analysis. The study of hearing was carried out using threshold tonal audiometry with the audiometer "AA222" ("Interacoustics", Denmark) for air and bone conduction at frequencies of 0,25, 0,5, 1,0, 2,0, 4,0, 8,0 kHz. The degree of hearing loss was as-

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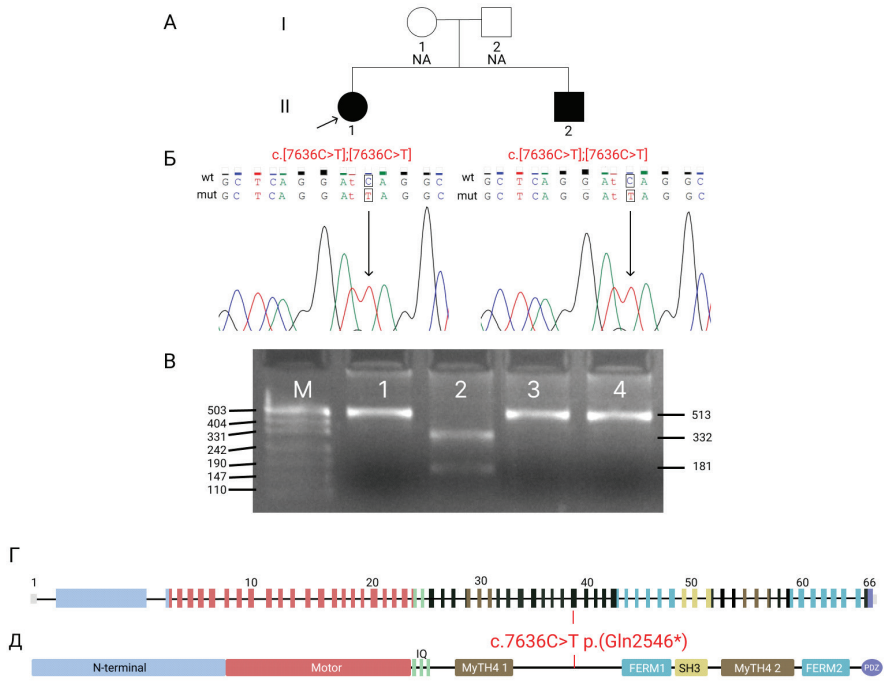
sessed by the average threshold of audibility in RDH0.5; 1.0;2.0;4.0 kHz according to the classification adopted by WHO: I degree - 26-40 dB, II degree - 41-55, III degree - 56-70, IV degree - 71-90, deafness - >90 dB.

Molecular genetic analysis. Genomic DNA was isolated from the peripheral blood leukocytes using the phenol-chloroform method. Massively parallel sequencing (MPS) was performed in one *GJB2*-negative patient with a burdened hereditary history (proband was a 69–year-old woman). MPS of genomic DNA sites corresponding to exons and splicing sites of genes associated with hereditary hearing loss (158 genes) was carried out on a HiSeq 1500, Illumina sequencer with HiSeq Rapid SBS Kit v2 reagents. The median exome coverage is 110x. Sequencing data processing was performed using an automated algorithm that included the alignment of readings to the reference sequence of the human genome (GRCh37/hg19).

Search for pathogenic variant c.7636C>T p.(Gln2546*) in the 39 exon of the *MYO15A* gene was performed in brother proband (sibs, 65 years old) using PCR-RFLP analysis. To amplify fragments in the 39 exon of the *MYO15A* gene (513 bp), primers (F) 5'-CCTGTTCTCCACAGAAACCCC-3' and (R) 5'- AACCCAGTAAGCTGGTGGGC – 3', selected using the Primer BLAST program, were used. *AclW* I endonuclease with GGATC(N)4↑ restriction site was used for restriction. Verification of the results of PCR-RFLP analyses was carried out by Sanger sequencing.

Results and discussion. Massively parallel sequencing was performed in one patient with an identified burdened hereditary history (hearing parents, deaf sibs) who did not have causative variants in the *GJB2* gene. As a result, the nonsense variant c.7636C>T p.(Gln2546*) (rs765936685) was revealed in the 39 exon of the *MYO15A* gene in the homozygous state, previously known as pathogenic (fig.). This variant leads to the replacement of the amino acid glutamine with a stop codon at the 2546th amino acid position, which leads to premature termination of the translation of the polypeptide chain of myosin 15A. The presence of this variant was verified using PCR-RFLP (fig.) followed by Sanger sequencing (fig.). This variant was also found in the homozygous state of the proband's brother (fig.).

Option c.7636C>T p.(Gln2546*) in the Deafness Variation Database (DVD) is presented as pathogenic (https://deafnessvariationdatabase.org/gene/MYO15A 17:18054586:C>T). A total of 12666 variants are annotated in this database, of which 375 were pathogenic/probably pathogenic [18]. In the ClinVar and gnomAD databases, variant c.7636C>T p.(Gln2546*) was not present at the time of the study, probably because of the lack of a phenotypic description.



Identification of the pathogenic variant c.7636C>T p.(Gln2546*) of the MYO15A gene in the Buryat family and the structure of the MYO15A gene: A – a fragment of the Buryat family pedigree; B – chromatograms of the results of sequencing the 39 exon of the MYO15A gene with variant c.7636C>T p.(Gln2546*) in the homozygous state in the proband (indicated by arrow, II-1) and sibs (II-2). NA – genotype has not been clarified; C – electrophoregrams of PCR-RFLP analysis results: M – molecular weight marker pUC 19/Msp I, 1 – sample not treated with AclW I endonuclease (513 bp), 2 – control sample without variant c.7636C>T (preserved restriction site for AclW I – 332 bp and 181 bp), genotype - c.[wt];[wt], 3 and 4 – samples with variant c.7636C>T in homozygous state in proband and sibs (restriction site for AclW I – 513 bp is lost); D – structural organization of the MYO15A gene: 66 exons are represented in the form of rectangles; E – the location of the domains of the myosin 15A protein [13]

In this paper, the variant c.7636C>T p.(Gln2546*) in the *MYO15A* gene was identified in the homozygous state for the first time. Previously, this variant was detected only in one patient with bilateral hearing impairment in a compound heterozygous state with variant c.9319G>T p.(Glu3107*) in Brazil [16]. However, the description of the nature and degree and severity of hearing loss were not described in this study [16]. In our case, audiological analysis of hearing thresholds in the proband and her sibs revealed profound sensorineural hearing loss (bilateral deafness). The onset of hearing impairment is most likely either in early childhood or is congenital. Both siblings studied at the school of the hard of hearing and deaf, and in everyday life they use only sign language. Violations in other organs and systems were not observed.

Previously, the pathogenic variant c.2674A>T p.(Ile892Phe) of the *MYO15A* gene (DFNB3, 600316) in a homozygous state with a high frequency was detected on the island of Bali (Indonesia), where 2.2% of the population had severe/profound hearing loss [3, 5]. However, subsequent studies on the spectrum and frequency of causative variants in the *MYO15A* gene among hearing impaired patients in different regions of the world have shown that in the Middle East, there are also a greater number of variants in the homozygous state [10]. In contrary, in Europe, among patients with hearing impairments, there is a predominance of compound heterozygous variants of the *MYO15A* gene [10]. The authors suggest that the accumulation of homozygous variants in the Middle East is influenced by the customs of consanguineous marriages [10]. In addition, it is known that in

this region, the founder effect is present in the distribution of individual variants of the *MYO15A* gene (c.5807_5813delCCCGTGGG and c.9995_10002dupgccggcc in Turkey, c.1171_1177dupGCCATCT in Oman) [14, 4]. While in Europe, cases of the founder effect on variants of the *MYO15A* gene have not yet been described [11]. In our case, in Buryatia, we found a variant c.7636C>T p.(Gln2546*) of the *MYO15A* gene in a homozygous state, which may indicate either a rare case of endogamous marriage, or a wider distribution of this variant in the Lake Baikal region. Further studies are required to assess the contribution of this variant in etiology of the hearing loss in the Republic of Buryatia.

Conclusion. In this paper, a rare pathogenic variant c.7636C>T p.(Gln2546*) was first detected in a homozygous state in two patients with congenital profound hearing loss. The detection of this variant in a homozygous state in two siblings from a Buryat family may indicate either a rare case of endogamous marriage, or a wider spread of this variant in the Lake Baikal region which requires further research to assess the contribution of this variant to the etiology of hearing impairment in the Republic of Buryatia.

The work was carried out within the framework of the research of the YSC CMP "Study of the genetic structure and burden of hereditary pathology in the populations of the Republic of Sakha (Yakutia)» and the State assignment of the Ministry of Science and Higher Education of the Russian Federation (FSRG-2023-0003).

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DIAGNOSTIC AND TREATMENT METHODS

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THE EFFECTIVENESS OF THE INTRODUCTION OF A SYSTEM FOR THE PREVENTION OF STERNAL COMPLICATIONS IN CARDIAC SURGERY

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The aim of the study. To evaluate the results of the introduction of a system for the prevention of sternal infectious complications at the Federal Center for Cardiovascular Surgery in Khabarovsk in comparison with the traditional method of cardiac surgery.

Materials and methods. The authors conducted a comparative analysis of two treatment groups of cardiac surgery patients operated with sternotomy median access. The first group, 2712 patients operated according to the traditional method (2016-2018); the second group of patients, 2991 people, were treated using the method of prevention of sternal infectious complications (2019-2021). Attention was paid to the performance of bimammary bypass surgery, which is one of the leading risk factors for complications, while performing this type of bypass surgery increased in the second group.

Results. As a result of the introduction of systemic prevention of complications during cardiac surgery, the number of superficial complications, such as divergence of wound edges, skin necrosis, osteomyelitis of the sternum significantly decreased from 1.18±0.207 to 0.43±0.120% (t=3.11), there was also a tendency to decrease deep complications, namely sternomediastinitis - from 0.55± 0.142 to 0.23±0.088% (t=1.90).

Conclusion. The introduction of a system for the prevention of sternal complications in the work of cardiac surgeons during median sternotomy has reduced the incidence of postoperative sternomediastinitis and superficial complications. Therefore, in order to reduce infectious complications after cardiac surgery, it is advisable to introduce systemic prevention of sternal infection more widely into clinical practice.

Keywords: cardiac surgery, infectious complications, postoperative sternomediastinitis, thoracic surgery.

Introduction. The problem of post-operative sternomediastinitis and sternal osteomyelitis is urgent for all countries of the world where cardiac surgery is performed. Infectious complications of the anterior chest after this type of surgery range from 0.3% to 6.9% [1, 8]. Postoperative sternomediastinitis is not a short-term complication but it significantly worsens the course of the clinical case [7; 9], increases the early in-hospital mortality to 7% compared to patients without inflammatory changes in the sternum (1,8%) [4,5].

The cost of treatment of deep post-operative sternal infection is excessively high, [6], reaching up to $500,000 in specialized centers of the USA [10], which even with an infection rate of less than 1% is quite an impressive cost for any state.

Risk factors for the development of postoperative sternomediastinitis differ and are divided into preoperative, intra-operative, and postoperative [2]. Prevention of these complications makes it possible to reduce the incidence of post-operative sternomediastinitis in patients under consideration [3].

The aim of the study. To study the effectiveness of the infection prevention system introduced in cardiac surgical operations in Khabarovsk Federal Centre of Cardiovascular Surgery. Materials and methods. The analysis of treatment of two groups of cardiac surgical patients operated on by median sternotomy in Khabarovsk Federal Centre of Cardiovascular Surgery was carried out using a continuous method. The first group of 2,712 patients was operated on before the introduction of systemic prevention of postoperative complications (from 2016 to 2018); while the second group of 2,991 patients were operated on after the introduction of the above-mentioned system of prevention of post-operative complications (from 2019 to 2021). Concomitant somatic pathologies in the first group of patients that have been operated on were represented by diabetes mellitus (in 472 patients), by chronic obstructive pulmonary disease (in 141), obesity (in 678), atrial fibrillation (in 224), and chronic kidney disease (in 115 patients). The number of the same concomitant somatic pathologies in the second group of patients constituted respectively 408, 307, 735, 255 and 159 patients. Statistical processing of the data was carried out by variance analysis with calculation of the coefficient of contingency (chi-square); represented in Table 1.

In the two groups studied, statistical significance for qualitative indicators was determined using chi-square value ($\chi 2$) taking into account the pairing of rows and columns; while for quantitative indicators it was determined with a Student's test. Qualitative indicators were considered statistically significant based on conjugation tables; whereas for quantitative indicators, the results were considered statistically significant at $p<0.05$.

The direct method of standardization was used to analyze the somatic pathology in the two studied groups of patients operated on with transsternal longitudinal access.

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Table 1

Comparative characteristics of concomitant somatic pathology in patients undergoing cardiac surgery

Indicators	Patients operated before the introduction of systemic prevention of postoperative complications (n=2 712)	Patients operated after the introduction of systemic prevention of postoperative complications (n=2 991)	The conjugacy indicator ($\chi 2$)
Concomitant pathology in general:	1630	1864	3.72
The first group of pathology:	472	408	15.58
Diabetes mellitus	472	408	15.58
The second group of pathology	1158	1456	20.47
Obstructive pulmonary disease	141	307	50.38
Fatness	678	735	0.14
Chronic kidney disease	115	159	3.52
Atrial fibrillation	224	255	0.14

Table 2

The frequency of infectious complications depending on the presence of concomitant somatic pathology in patients after cardiac surgery

Indicators	Patients with complications before the introduction of systemic prevention (n=74)	Patients with complications after the introduction of systemic prevention (n=45)	The conjugacy indicator ($\chi 2$)
Concomitant pathology in general:	74	45	37.65
The first group of pathology:	18	9	12.17
Diabetes mellitus	18	9	12.17
The second group of pathology	56	36	58.93
Obstructive pulmonary disease	8	4	94.55
Fatness	21	14	6.34
Chronic kidney disease	19	14	14.27
Atrial fibrillation	8	4	5.56

To make the general comparison of the two studied groups of patients having different structure of concomitant somatic pathology more objective, Fisher's criterion was additionally applied.

The age of the patients of the first and second groups was comparable and constituted 62.8±7.4 and 62.8±8.7 years old respectively.

To reduce postoperative complications of an infectious nature after cardiac surgery using transsternal access, systemic prevention based on the principles Vogt PR, (2019) [14] was developed.

The leading factors in the systemic prevention of the development of postoperative complications were exclusion of iodine-containing solutions, preservation of the attachment of the xiphoid process to the surrounding soft tissues, exclusion of wax to stop bleeding, performing skeletonization of the internal thoracic artery during bypass surgery, suturing the sternum with Z-shaped USP7 monofilament sutures (Steelex Sternum Set), and early activation of patients in the postoperative period. At the same time, systemic antibiotic prophylaxis was used for cardiac patients that have been operated on (first dose before surgery; with the second dose being administered in case the operation lasted more than 6 hours).

The groups under study were analyzed in a continuous chronological order; the groups included all patients operated on consecutively in the two three-year periods studied. At that, spe-

Table 3

Postoperative complications in the observed patients during cardiac surgery before and after the introduction of systemic prevention

Indicators	Complications		Statistical significance of indicators
	Before the introduction of the prevention system (n=2 712)	After the introduction of systemic prevention (n=2 991)	
Postoperative complications, including:	1.73±0.25%	0.67±0.15%	t=3.65. p<0.05
divergence of wound edges, skin necrosis, osteomyelitis of the sternum	1.18±0.21 %	0.43±0.12 %	t=3.11. p<0.05
sternomediastinitis	0.55±0.14%	0.23±0.09%	t=1.90. p>0.05

cial emphasis was placed on bimammary coronary artery bypass, the performance of which has increased 10-fold in the last three years - from 57 to 582 surgical interventions.

47 and 20 patients with infectious complications after cardiac operations performed at Khabarovsk Federal Center of Cardiovascular Surgery were admitted for treatment to the Thoracic Surgery Department of the Khabarovsk Regional Clinical Hospital №1 named after Prof. S.I. Sergeev in 2016-2018 and 2019-2021 respectively. The analysis of concomitant pathologies in the patients admitted to the Regional Clinical Hospital №1 showed that the number of cases of somatic diseases per patient was 1.57 and 2.25 in the first and in the second study groups respectively.

The incidence of infectious postoperative complications depending on somatic pathology is shown in Table. 2.

Discussion and results. Diabetes mellitus characterized by an increased risk of developing infectious complications occurred 27% more often (which is of statistical importance) in the first group of patients studied as compared with the second group or 17,40±0,73% vs. 13,64±0,63%, p<0,001. The second group of somatic pathologies (chronic obstructive pulmonary disease, obesity, chronic kidney disease and atrial fibrillation) leading to the development of hypoxia in organs and tissues, prevailed in patients of the second group, p<0.001. In the meantime, the patients with the second group of somatic pathology show a meaningful (p<0.001), almost 2-fold increase in the number of those having chronic obstructive pulmonary disease: 10.28±0.55% vs. 5.20±0.43% respectively. The proportion of patients with chronic kidney disease in the second study group was higher than in the first group of operated patients (t=1.91): 5.32±0.41 and 4.24±0.39% respectively, p>0.05. Other risk factors for the development of complications due to concomitant pathology in both groups of patients were not significant, with obesity constituting 24.57±0.79 and 25.00±0.83% respectively, and atrial fibrillation - 8.53±0.51 and 8.26±0.53% respectively.

However, using a direct standardization method it was found that differences in the incidence of somatic pathology in the compared groups did not affect the rate of postoperative complications, the standardized rate of complications being 4.7% and 2.4% in the first and the second group of patients respectively.

The change in the structure of somatic pathology among patients with postoperative infectious complications admitted to Clinical Hospital №1 arouses a certain concern. The incidence of diabetes mellitus in 2019-2021 as compared to 2016-2018 did not change significantly - 38.3% and 45.0% respectively (p>0.05). Postoperative complications were more common in patients with chronic kidney disease and obesity (p<0.05) in the last three years – from 2019 to 2021 - as compared with the 2016-2018 period. Chronic obstructive pulmonary disease, cardiogenic pathology in the form of atrial fibrillation in both groups of patients admitted to Clinical Hospital №1 with postoperative infectious complications occurred equally often and remained at almost the same level of 17.02% and 20.00% respectively.

The incidence of inflammatory complications after cardiac surgery performed by sternotomy approach in the second group of patients under study decreased by 80% to 2.41±0.36% (p<0.001) in contrast to the corresponding indicator in the first group of patients - 4.54±0.52%. This trend which is especially typical for patients with the second group of somatic pathology (p<0.001) did not change in patients with diabetes mellitus.

The authors believe that the introduction of a method of systemic prevention during cardiac surgery turned out to be a significant factor in reducing the incidence of postoperative complications during surgical treatment of the category of patients under consideration which does not depend on the nature of the noted somatic pathology with Fisher's criterion equaling 37.65, that is higher than the significant value according to the critical values of $\chi 2$ at p<0.001 (10.83).

As a result of the introduction of systemic prevention of cardiac surgery complications at the Federal Center of Cardiovascular Surgery in Khabarovsk, the number of infectious complications of median sternotomy after cardiac surgery decreased significantly by 2.6-fold from 1.73±0.25 to 0.67±0.15% (p<0.001). The number of superficial complications, such as wound dehiscence, skin necrosis, and sternal osteomyelitis, decreased by 2.7-fold from 1.18±0.21 to 0.43±0.12% (t=3.11, p<0.001). There was a trend towards a decrease in deep infectious complications (t=1.92; p>0.05), namely sternomediastinitis - from 0.55±0.14 to 0.23±0.09% (Table 3).

It should be noted that the isolation of the internal thoracic artery without surrounding retrochondral tissues (costal pleura, intercostal muscle and endothoracic fascia), preserves the collateral blood supply to the sternum in contrast to the traditional technique, which is more important in bilateral transplantation and has been recognized as the leading principle of coronary artery bypass grafting [12] in order to reduce infectious complications [15]. As has been observed, this technique for bimammary bypass surgery made it possible to reduce to a certain extent the incidence of infectious complications from 8.77±3.75 to 1.72±0.54% (t=1.86, p>0.05), which was obviously achieved by maintaining the collateral blood supply to the sternum. Setting aside bimammary bypass surgery, the incidence of postoperative infectious complications has significantly decreased by 3.8-fold in the last three years (from 2019 to 2021) to 0,42±0,13% vs. 1,58±0,24 % in 2016-2018, p<0,001.

One of the factors contributing to the growing number of postoperative infectious complications is the use of wax for hemostasis caused by mechanical blockage of bone marrow lacunae. At that, the introduction of wax into bone tissue inhibits the activity of osteoblasts and bone regeneration [13]. At the same time, bone wax behaves like a foreign body and prevents the formation of callus [11]. In the first group of patients with complications, wax was used in 91.52±4.07% of cases. In the second group, wax was not used; in case hemostasis was necessary, vancomycin paste (3 g of the drug mixed with 3 ml of saline solution to obtain a homogeneous waxy mass) was used.

Conclusion. The introduction into clinical practice of the Khabarovsk Federal Center of Cardiovascular Surgery of systemic complications prevention after median sternotomy during cardiac surgery made it possible to achieve a 2.7-fold reduction in the incidence of superficial complications from 1.18 ± 0.21 to 0.43 ± 0.12%, p<0.001, as well as to reduce the rate of postoperative sternomediastinitis from 0.55±0.14 to 0.23±0.09% (t=1.90, p>0.05), which indicates that a wider use of the above-mentioned systemic preventive measures in the clinical practice is appropriate.

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DETERMINATION OF ANTINUCLEAR ANTIBODIES BY IMMUNOBLOTING TO CLARIFY THE IMMUNOLOGICAL CHARACTERISTICS OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND SJOGREN'S SYNDROME

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Objective: to study the immunological characteristics of patients with systemic lupus erythematosus and Sjogren's syndrome by determining antinuclear antibodies using immunoblotting.

Materials and methods. We observed 69 patients whose average age was 38.9 years [23.2-62.9], of which 63 (91.30%) were women and 6 (8.69%) men. BMI was 27.3 kg/m2 [21.8-49.2]. Inclusion criteria: age from 18 to 70 years, presence of a reliable diagnosis. To study the diagnostic value of determining the ANA profile, patients were divided into 3 groups: 1st group – 15 patients with systemic lupus erythematosus (SLE), 2nd – 21 patients with the disease and Sjögren's syndrome (SS), 3rd (control) group – 33 patients with osteoarthritis. The control group was comparable to the study groups by gender and age.

Results. The determination of anti-SS-A in SLE has good quality (area under the ROC curve - 0.66). A cut-off value was determined with 79.6% specificity and 53.3% sensitivity. Anti-RNP/SM, anti-Sm, anti-dsDNA and anti-HI were somewhat less sensitive (30%), with a specificity level of 91% for anti-dsDNA and anti-Sm and 100% for anti-RNP/Sm and anti -HI. The most informative diagnostic tests for the disease and Sjogren's syndrome are anti-Ro-52 recombinant (sensitivity 57.1%, specificity 96%), anti-SS-Anative (sensitivity 52.4%, specificity 86%). The determination of anti-Ro-52 in SS is of good quality, which confirms the value of the area under the ROC curve (>0.7). The optimal cut-off value corresponded to 99.6% specificity and 57.1% sensitivity. Somewhat less sensitive (28.6%) were anti-Sm (specificity - 92%), anti-dsDNA (specificity - 92%) and anti-RIB (specificity 100.0%).

Findings. The laboratory tests studied, as a rule, had high specificity, but rather low sensitivity. The most specific tests for diagnosing SLE are antibodies to the antigens RNP/Sm, SS-Anative, antibodies to histones, for SS - anti-SS-Anative, anti-Ro-52 recombinant, anti-RIB.

Keywords: systemic lupus erythematosus, Sjögren's syndrome, immunoblotting, antinuclear antibodies.

Introduction. Rheumatic diseases are a huge economic and social burden and, according to WHO recommendations, the study of their prevalence, morbidity, mortality and prevention should be an integral part of national programs for maintaining public health and the basis for planning medical care [1]. The pathogenesis of rheumatic diseases is based on the interaction of environmental and genetic factors. The most studied genetic factors are human leukocyte antigens (HLA), specific haplotypes of which are reliably associated with a specific diagnosis. Thus, haplotypes HLA-DRB1*03:01 and *15:01 are genetic risk factors for systemic lupus erythematosus in the European population, and PTPN22 occurs not only in systemic lupus erythematosus, but also in other rheumatic diseases, in particular rheumatoid arthritis (RA) [8]. Systemic rheumatic diseases have a heterogeneous clinical phenotype, which complicates their clinical diagnosis and requires the active use of laboratory and instrumental research methods. Experts emphasize the need for early diagnosis of SLE, but recent studies confirm that patients with SLE still face late diagnosis of the disease (on average 2 years from the onset of symptoms) [4].

The advantages of laboratory research methods are the objectivity of the data obtained on the nature of the immunopathological process and autoimmune diseases, the possibility of using them for diagnosis, assessing disease activity, determining prognosis, identifying damage to individual organs, choosing a treatment method and monitoring the effectiveness of therapy [2, 9].

The basis for the nosological diagnosis of systemic rheumatological diseases are immunological studies [3]. Immunofluorescent determination of antinuclear antibodies (ANA) is the standard laboratory examination of patients with systemic rheumatological diseases [6]. ANAs are a class of antibodies that bind to cellular components in the nucleus, DNA, RNA, and nucleic acid-protein complexes [9].

Traditional methods for studying ANA are screening methods that assess the presence of ANA in blood serum, without specifying the specifics (indirect immunofluorescence method on tissue sections of rats or mice). In recent years, new methods have emerged to determine the type of ANA a patient has. These include the ELISA method, used to determine a large number of autoantibodies, requiring the simultaneous use of several test systems (up to 20) [1, 5].

One of the most common methods is to determine the entire ANA profile simultaneously using immunoblotting. This method allows you to detect antibodies to autoantigens: Sm, RNP/Sm, SS-A(60 kDa), SS-A(52 kDa), SS-B, Scl-70, PM-Scl, PCNA, CENT-B, dsDNA/ Histone/ Nucleosome, RibP, AMA-M2 and Jo-1. It is believed that the method can be used for ANA screening [10], but the value of this method has not been sufficiently studied and requires clarification.

Objective: to study the immunological characteristics of patients with systemic lupus erythematosus and Sjogren's syndrome by determining antinuclear antibodies using immunoblotting.

Materials and methods. The study was conducted on the basis of the Federal State Budgetary Institution “Research Institute of Clinical and Experimental Rheumatology named after. A.B. Zborovsky", Volgograd. We observed 69 patients whose average age was 38.9 years [23.2-62.9], of which 63 (91.30%) were women and 6 (8.69%) men. BMI was 27.3 kg/m2 [21.8-49.2]. Inclusion criteria: age from 18 to 70 years, presence of a reliable diagnosis.

Diagnoses were made based on generally accepted clinical guidelines [8].

To study the diagnostic value of determining the ANA profile, patients were divided into 3 groups: 1st group – 15 patients (14 (93.3%) women, 1 (6.7%) man) with systemic lupus erythematosus (SLE), 2- y – 21 patients (19 (90%) women and 2 (10%) men) with Sjögren’s disease and syndrome (SS), 3rd (control) group – 33 patients (30 (91%) women and 3 (9%) men) with osteoarthritis. All groups were comparable to each other by gender and age.

Diagnoses were made based on generally accepted clinical guidelines [3, 6, 7].

When performing the work, a set of reagents was used to determine IgG antibodies to nuclear antigens by immunoblotting (EUROLINEANAProfile 3 (IgG), cat. no. DL 1590-1601-3), with which the following types of antibodies were determined:

RNP - antibodies to the protein components of the small nuclear nucleotide U-1-RNA;

Sm - antibodies to U1-, U2-, U4-ribonucleoproteins;

SS-A native - antibodies to proteins associated with RNA Y1-Y5 in spliceosomes;

Ro-52 recombinant – antibodies to recombinant antigen (52 kDa protein);

SS-B - antibodies to RNA polymerase-3 associated protein

Scl-70 - antibodies to DNA topoisomerase 1;

PM-Scl100 – antibodies to the recombinant antigen PM-Scl;

Jo-1 - antibodies to histidine-tRNAsynthetase,

CENPB-anticentromere B antibodies;

PCNA - antibodies to proliferating cell nuclear antigen,

Table 1

Frequency of detection of antinuclear antibodies in rheumatic diseases

Antibodies	Groups of patients according to the main diagnosis			Reliability, $\chi 2$; p
	SLE (n=15)	SS (n=21)	Control group (n=33)	
RNP/Sm	5(30)	0(0)	0(0)	13.2; p<0.0001
Sm	5(30)	6(28.6)	0(0)	14.0; p=0.001
SS-A native	8(53.3)	11(52.4)	0(0)	28.19; p<0.0001
Ro-52 recombinant	2(13.33)	12(57.1)	0(0)	25.81; p<0.0001
SS-B	2(13.33)	4(19.0)	0(0)	6.88; p=0.017
Scl-70	0(0)	0(0)	0(0)	-
PM-Scl100	0(0)	2(9.52)	0(0)	3.28; p=0.134
Jo-1	0(0)	3(14.3)	0(0)	5.02; p=0.034
Centromere B	0(0)	0(0)	0(0)	-
PCNA	0(0)	0(0)	0(0)	-
dsDNA	5(30)	6(28.6)	0	13.97; p=0.001
Nucleosomes(NUC)	3(20)	2(9.52)	0(0)	6.24; p=0.025
HI	5(30)	0(0)	0(0)	13.16; p<0.0001
Ribosomal-P-protein (RIB)	0(0)	6(28.6)	0(0)	11.78; p<0.0001
AMA-M2	0(0)	0(0)	0(0)	-

dsDNA - antibodies to double-stranded DNA,

NUC – antibodies to nucleosomes,

HI – antibodies to histones,

RIB – antibodies to ribosomal protein P,

AMA-M2 - antimitochondrial antibodies.

Statistical calculations were performed using the STATISTICA 10.0 program. The threshold value at the cut-off point for detecting SLE and SS was determined by determining the point of the highest value of the intersection of sensitivity and specificity.

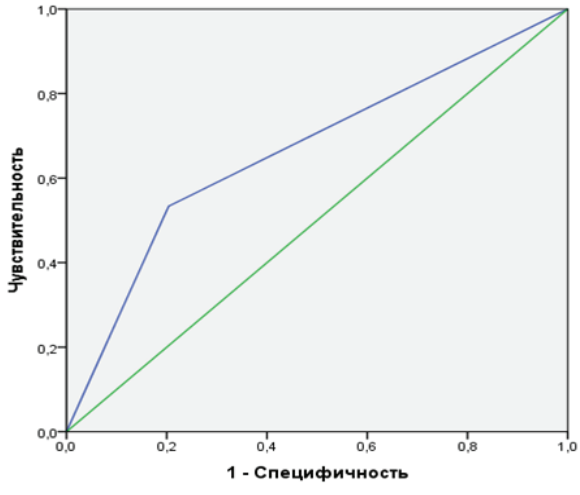
Results. We investigated the frequency of detection of ANA in rheumatic diseases, the results are presented in Table 1.

Table 1 shows that autoantibodies to the extractable nuclear antigens RNP/Sm, which are considered the traditional criterion for diagnosing SLE, were detected in 30% of patients with SLE. Sm antibodies to U1-, U2-, U4-ribonucleoproteins were determined in patients with SLE and SS. In groups 1 and 2, anti-SS-A native was detected significantly more often (53.3 and 57.1%, respectively). Recombinant anti-Ro-52 was detected in half of the patients with SS. Anti-SS-B was detected statistically more often in patients with SS compared to group 3. In 3 patients with SLE and 2 with Sjögren's disease, anti-NUC was detected. Anti-HI was detected significantly more often (30%) in the group of patients with SLE.

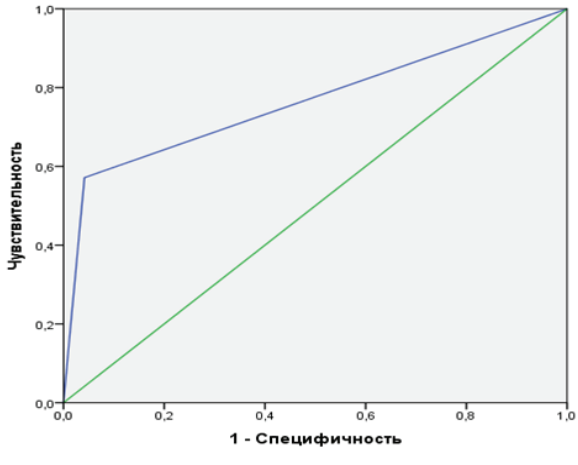
Next, we determined the sensitivity and specificity of laboratory tests for SLE and SS, which made it possible to identify the most optimal method that is most suitable for diagnosing a specific nosology. The sensitivity of the test is determined by a formula that shows the proportion of reliable diagnostic indicators in patients with a given disease. Specificity is determined by the percentage of significantly negative indicators among obviously healthy individuals. The results are presented in Table 2.

Table 1 shows that autoantibodies to the extractable nuclear antigens RNP/Sm, which are considered the traditional criterion for diagnosing SLE, were detected in 30% of patients with SLE. Sm antibodies to U1-, U2-, U4-ribonucleoproteins were determined in patients with SLE and SS. In groups 1 and 2, anti-SS-A native was detected significantly more often (53.3 and 57.1%, respectively). Recombinant anti-Ro-52 was detected in half of the patients with SS. Anti-SS-B was detected statistically more often in patients with SS compared to group 3. In 3 patients with SLE and 2 with Sjögren's

a



b



Roc curve characterizing the diagnostic value of anti-SS-A in SLE (a) and anti-Ro-52 in SS (b)

Table 2

Sensitivity and specificity of antibody tests

Antibodies	SLE		SS	
	Sensitivity	Specificity	Sensitivity	Specificity
RNP/Sm	30	100	0	94
Sm	30	91	28.6	92
SS-A native	53.3	82	52.4	86
Ro-52 recombinant	13.3	82	57.1	96
SS-B	13.3	94	19.0	97
Scl-70	-	100	-	100
PM-Scl100	-	97	9.52	100
Jo-1	0.0	96	14.3	100
CENP B	-	100	-	100
PCNA	-	100	-	100
dsDNA	30	91	28.6	92
NUC	20	97	9.52	95
HI	30	100	28.6	93
RIB	-	91	28.6	100
AMA-M2	-	100	-	100

Table 3

Main descriptive characteristics of the ROC curve characterizing the diagnostic value of anti-SS-A in SLE and anti-Ro-52 in SS

	Анти-SS-A for SLE	Анти- Ro-52 for SS
Area under the ROC curve	0.665	0.765
Standard error	0.084	0.071
Confidence interval	0.499-0.830	0.65-0.905

disease, anti-NUC was detected. Anti-HI was detected significantly more often (30%) in the group of patients with SLE.

Next, we determined the sensitivity and specificity of laboratory tests for SLE and SS, which made it possible to identify the most optimal method that is most suitable for diagnosing a specific nosology. The sensitivity of the test is determined by a formula that shows the proportion of reliable diagnostic indicators in patients with a given disease. Specificity is determined by the percentage of significantly negative indicators among obviously healthy individuals. The results are presented in Table 2.

According to Table 3, the anti-SS-A laboratory test for SLE is of good quality (area under the ROC curve - 0.66). We determined the cut-off threshold value with 79.6% specificity and 53.3% sensitivity. The laboratory test for anti-Ro-52 in SS is of good quality, which is confirmed by the value of the area under the ROC curve (>0.7). The optimal cut-off value corresponded to 99.6% specificity and 57.1% sensitivity.

Thus, using additional methods of statistical analysis, we were able to confirm the previously calculated sensitivity and specificity of anti-SS-Anative for the diagnosis of SLE and anti-Ro-52 for SS.

Conclusions. In our study, the main markers of autoimmune connective tissue diseases were studied using immunoblotting.

In the groups of patients with SLE and SS, anti-SS-A native was observed significantly more often (53.3 and 52.4%, respectively). Antibodies to histones were detected significantly more often with a frequency of 30% in the group of patients with SLE. It can be assumed that extractable nuclear antigens have the greatest diagnostic value in SLE, antibodies to the SS-A and Ro-52 antigens - in SLE and Sjögren's disease (syndrome), and antinuclear antibodies to histones are more characteristic of patients with SLE.

The laboratory tests studied, as a rule, had high specificity, but rather low sensitivity. The most specific tests for diagnosing SLE are antibodies to the antigens RNP/Sm, SS-Anative, antibodies to histones, for SS - anti-SS-Anative, anti-Ro-52 recombinant, anti-RIB. Thus, these tests are optimally used to confirm a specific nosological diagnosis in a patient with an already identified rheumatological disease, however, for screening studies in order to identify rheumatological pathology in the population, these tests are not rational to use.

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CLINICAL EXPERIENCE IN DIAGNOSIS AND TREATMENT OF MALLORY-WEISS SYNDROME IN A MULTIDISCIPLINARY SURGICAL HOSPITAL

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The **aim** of this study was retrospective assessment of the effectiveness of surgical treatment tactics in the treatment of Mallory-Weiss syndrome in a specific surgical hospital. **Material and methods.** The material is based on a clinical analysis of the results of observations of 73 patients with MWS who were treated in surgical hospitals of the of the Republican Hospital №2 – Center for Emergency Medical Care (CEMC) of the Republic of Sakha (Yakutia) in the period from in the period from 2019 to 2023. **Results.** In the course of the study, it was established that the widespread use of endoscopic methods of stopping bleeding in MWS in clinical practice of multidisciplinary surgical hospitals can improve the immediate results of treatment, reduce the number of complications and reduce mortality. **Conclusion.** The results of the study we presented allow us to recommend the use of endoscopic methods of hemostasis for MWS as the method of choice.

Keywords. Mallory-Weiss syndrome, endoscopic hemostasis, surgical treatment tactics.

Introduction. One of the most common pathologies encountered in urgent surgery is “rupture hemorrhagic syndrome”, or Mallory-Weiss syndrome (MWS). The detection rate among all types of bleeding from the upper gastrointestinal tract is, as a rule, at least 15-20% [3] and is characterized by a fairly high percentage of the risk of re-bleeding (at least 20-25%), as well as the likely development of severe complications (at least 1-3%) [4]. Mortality in this case can reach values of 5-10%, especially with the development of tension pneumothorax, purulent mediastinitis, and severe forms of widespread purulent peritonitis [6]. The above indicators clearly reflect the real problem of diagnosing and treating MWS along with other pathologies of the gastrointestinal tract that are accompanied by bleeding: gastroduodenal ulcers, portal hypertension syndrome, esophagitis, vascular abnormalities of the gastrointestinal tract, etc.

It is known that in the vast majority of cases (at least 75-80%), the onset of this disease is associated with repeated or uncontrollable vomiting after a heavy meal, or after drinking alcohol and its surrogates [3]. Also, the development of MWS can be facilitated by physical exercise after a heavy meal, persistent hiccups, abdominal trauma, as well as the procedure of esophagogastroduodenoscopy in patients unprepared for this [1]. Cases of the occurrence of MWS due to vomiting occurring against the background of a number of diseases and pathological conditions, such as mechanical and dynamic intestinal obstruction, damage to the peripheral and central nervous system, and vestibular disorders are not uncommon [2].

Direct surgical treatment tactics for patients with MWS today include the use of minimally invasive endoscopic technologies of combined effects on the bleeding site (chemical, physical and mechanical methods of hemostasis). In cases of unsuccessful use of endoscopic techniques, an informed decision is made to carry out traditional laparotomy, gastrotomy and suturing of the resulting injuries. At the same time, a wide range of conservative measures is carried out, including correction of hemostasis, water and electrolyte disturbances, suppression of gastric secretory function, and, if necessary, blood transfusions and blood substitutes [1, 4, 5]. There is no doubt that the success of the entire strategy for treating the disease depends entirely on the competent use of the algorithm of actions for applying the most effective methods of endoscopic hemostasis, taking into account the prognosis of recurrent bleeding, the presence or absence of comorbid pathology, dynamic control over the general condition and much more.

The **aim** of this study. To retrospectively evaluate the effectiveness of surgical treatment tactics in the treatment of Mallory-Weiss syndrome in a specific surgical hospital.

Material and methods. The presented material is based on a clinical analysis of the results of treatment of 73 patients with Mallory-Weiss syndrome who were treated in surgical hospitals of the Republican Hospital № 2 – Center for Emergency Medical Care (CEMC) of the Republic of Sakha (Yakutia) in the period from 2019 to 2023. The diagnosis of MWS was made on the basis of a standard clinical examination. The average age of the patients was 36,7±2,1 years, there were 51 (69,9%) men and 22 (30,1%) women. To assess the depth of damage to the walls of the esophagus and stomach, we used the clinical and anatomical classification of Sh.V. Timerbulatov (2010) [6]. To predict the risk of bleeding from the upper gastrointestinal tract, was used the classification of J.A. Forrest (1974) [7]. The therapeutic and diagnostic procedure of esophagogastroduodenoscopy (EGD) was carried out by us according to standard methods and in accordance with developed generally accepted technical techniques using a GIF-2T160 video gastroscope from «Olympus» (Japan). All patients with suspected bleeding from the upper gastrointestinal tract were immediately placed in the anti-shock therapy ward, located directly in the emergency room of RH №

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2 – CEMC. All endoscopic examinations were performed during the first 2 hours of the patients stay in the clinic after the necessary preparation (stabilization of the general condition, gastric lavage, consultation with specialists of related specialties) under the supervision of an anesthesiologist-resuscitator. In cases of massive bleeding, EGD performed in a fully operational operating room and in the presence of a team of surgeons.

Results and discussion. According to our observations, the average time from the onset of bleeding to admission to the clinic was: from 1 to 3 hours – in 37 (50,7%) patients, from 3 to 6 hours – in 25 (34,2%) patients, from 6 to 12 hours – in 7 (9,6%) and more than 12 hours – in 4 (5,5%) patients. As a result of primary esophagogastroduodenoscopy, it was possible to detect the source of bleeding in 86,7% of patients. In other cases, additional time was required to prepare the upper gastrointestinal tract for examination. This was due to the urgency of the incoming patients, and whose stomach could be filled with food masses.

According to our observations, the immediate cause of MWS was: consumption of alcohol and its surrogates – in 59 (80,8%) patients, heavy food intake – in 10 (13,7%) patients, intestinal obstruction – in 4 (5,5%) sick. The presence of ongoing bleeding was recorded in 45 (61,7%) patients with MWS, its absence – in 28 (38,3%). When assessing signs of bleeding according to the classification of J.A. Forrest (1974) we obtained the following data (table № 1):

The depth of the detected defects was variable. So, according to the classification of Sh.V. Timerbulatov (2010) on the stages of MWS, obtained the following data (table № 2):

In our observations, stage IV MWS – esophageal rupture with complications in the form of pneumomediastinum, pneumothorax, pneumoperitoneum was not observed. The predominant localization of the rupture was the cardioesophageal junction – in 61 (83,6%) patients, less often, isolated gastric and esophageal localization of the defect – in 9 (12,3%) and 3 (4,1%) patients.

According to our observations, in all cases, with ongoing bleeding from damaged areas caused by MWS, it was possible to achieve bleeding stop using endoscopic hemostasis methods. Analysis of observations showed that the most effective method of stopping bleeding when it was jet-like in nature was mechanical – the application of endoscopic clips. This type of hemostasis was used in 10 (22,2%) patients; not a single case of recurrent bleeding was observed. The combined method of endoscopic hemostasis, usually the use of chemical and physical methods (injections of adrenaline solution and diathermocoagulation or argon plasma coagulation) was used in 35 (77,8%) patients. Recurrent bleeding was observed in only 3 (8,5%) patients. Most often, relapse was associated with coagulation disorders due to severe endogenous intoxication and the development of hepatic-renal failure syndrome. In the same clinical cases, when active bleeding was not observed, preventive measures were performed in the form of injections of vasoconstrictor drugs, diathermocoagulation, and irrigation with ε-aminocapronic acid. In the absence of signs of bleeding, control endoscopic examinations were performed on the 3rd and 5th days of the patient's stay in the surgical hospital. Subsequently, most of the patients (at least 75,5%) were transferred to therapeutic hospitals, mainly gastroenterological departments. The average length of stay of patients with Mallory-Weiss syndrome in a surgical hospital, as a rule, did not exceed 5,5±2.0 days.

In conclusion, it should be noted that the problem of the effectiveness of using various types of endoscopic methods of hemostasis, including for MWS, has been actively developed over the past 25-30 years. For hemostasis and prevention of recurrent bleeding, methods that differ in their range of effects, effectiveness and safety are currently used. An important point in successfully stopping bleeding are preparatory measures and, above all, preparation of the surface of the gastrointestinal tract and the source of bleeding [4]. Thus, in addition to washing the stomach and esophagus, prescribing prokinetics and premedication, irrigation of the area of the source of bleeding with chlorethyl or ethers turned out to be quite effective. The use of ethyls and ethers promotes cooling and drying of tissue, which creates the prerequisites for temporary hemostasis and more effective use in the future of physical and other methods of influencing the source of bleeding [3]. Regarding the frequency and effectiveness of using certain methods of hemostasis, we can say with confidence that everything depends on the specific clinical situation (source and intensity of bleeding, patients condition, availability of the necessary endoscopic equipment and personnel training). Undoubtedly, a medical institution that has a full range of advanced technologies in its arsenal will be able to more effective-

Table 1

Structure and characteristics of bleeding according to J.A. Forrest (1974)

Type	abs.	%
Type F-I-active bleeding (n=45)		
I a (pulsating jet)	14	19.2
I b (blood leakage)	31	42.5
Type F-II-signs of recent bleeding (n=28)		
II a (visible non-bleeding vessel)	7	9.6
II b (fixed thrombus-clot)	15	20.5
II c (flat black spot, black bottom of the defect)	6	8.2
Total:	73	100

Table 2

Structure and characteristics of the stages of MWS according to Sh.V. Timerbulatov (2010)

Stage	abs.	%
Stage I (the rupture involves only the mucous membrane)	21	28.7
Stage II (the rupture involves the submucosal layer)	38	52.1
Stage III (the muscle layer is involved in the rupture zone)	14	19.2
Total:	73	100

ly cope with its tasks. According to world literature [1, 4, 7], the effectiveness of endoscopic methods of hemostasis should be at least 85%, and the risk of complications should not exceed 0,7-1,0%. All this creates the prerequisites for searching for more effective and safe methods of endoscopic hemostasis, as well as improving organizational measures to improve the quality of medical care.

Thus, we can draw the following **conclusions** that the use of endoscopic technologies remains a priority and quite effective direction in surgical treatment tactics for MWS. The wider introduction of endoscopic technologies for MWS helps to reduce the number of complications and mortality rates, as well as the use of traditional invasive methods of treatment. In cases of recurrent bleeding after endoscopic hemostasis, the method of choice remains the use of traditional laparotomy, gastrotomy and bleeding control by suturing the ruptured areas. At the same time, endoscopic technologies help to achieve temporary controlled hemostasis for the purpose of subsequent adequate preoperative preparation in patients with MWS.

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HEALTHY LIFESTYLE. PREVENTION

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REGIONAL FEATURES OF NUTRITION OF CHILDREN OF MIDDLE SCHOOL AGE

The aim of the study was to study the nutritional habits of secondary school students living in the territory of the Republic of Bashkortostan. Analysis of the actual nutrition of the child population is an urgent task, since the preservation of the health and development of the child determines the health of the nation in the future. The paper examined the actual nutrition of children on school and weekend days. The survey involved students of grades 5-9, from 16 educational institutions of the city of Salavat (Republic of Bashkortostan), aged 11-16 years. By the method of daily reproduction of the diet, the intake of macro- and micronutrients with food was studied. To assess the chemical composition of the diets, the results were compared with the norms of physiological needs (NPN) for children and adolescents.

It was revealed that the nutrition of the respondents meets the standards for energy value, protein and fat intake. The amount of carbohydrates ingested with food is reduced relative to NPN by 28%, but the proportion of intake of mono- and disaccharides exceeds the norm. An increased consumption of added salt by 1.8 times was found. The daily diet of schoolchildren is adequately provided with vitamins. The content of calcium is deficient (68% of the norm), the intake of sodium is almost 5 times excessive. The analysis of the diet revealed a reduced share of the calorie content of breakfast and lunch both on school days and on weekends.

The main violations in the nutrition of middle school children are expressed in the increased consumption of SFA, simple carbohydrates and added salt. Combined with a calcium deficiency and an excess of sodium, this imbalance, in the future, can cause the risk of developing nutritional diseases.

Keywords: food; assessment of actual nutrition; macro - and micronutrients; middle school age.

Introduction. The organization of a balanced and rational nutrition of children and adolescents is an important social factor that allows maintaining health, harmonious growth, psychomotor development and high performance of schoolchildren in the learning process [3,4,10].

At the age of 12-17 years there is an intensive anatomical and physiological development; change in height (pubertal jump) and weight; secondary sexual characteristics appear; there are difficulties in the functioning of the body. All this leads to a rapid change in the physical health of a teenager, his moods and emotions [1,2,6]. Intensive growth and a high metabolic rate require a constant supply of the required amount of macro- and micronutrients with food. Studies conducted in recent years indicate a deficiency in the intake of calcium, iron, polyunsaturated fatty acids, fiber, vitamins A, C, B2 with food [5,11]. An imbalance of nutrients in the future may become a trigger for the development of chronic non-communicable diseases [14].

An important role in maintaining and strengthening the health of schoolchildren is played by the regimen and hygiene of food. Deterioration in the structure of nutrition of schoolchildren in educational institutions, combined with irrational and malnutrition at home, in the future may lead to the risk of developing alimentary-dependent diseases [12, 18].

The purpose of the work: to study the actual nutrition of schoolchildren, students in grades 5-9, living in the Republic of Bashkortostan, to assess and identify risk factors for the development of health disorders.

Materials and methods. The work studied the actual nutrition of children on a school day and a day off. Students in grades 5-9 were surveyed from 16 educational institutions in the city of Salavat (which is the largest industrial center of the Republic of Bashkortostan) aged 11-16 years. After the survey and the sampling, the questionnaires were divided into groups according to the days of filling: a day off and a school day. 159 questionnaires for the weekend and 166 questionnaires for the school day were available for analysis.

To determine the amount of actually consumed products and dishes, the method of 24-hour nutrition reproduction was used [15].The intake of macro- and micronutrients with food was compared with the norms that are presented in sanitary rules and regulations 2.3 / 2.4.3590-20 [13] and guidelines 2.3.1.0253-21 [8], and the added salt - with the value recommended by WHO [19].

The questionnaires were processed using the Nutri-prof computer program (developers: Federal Research Center for Nutrition and Biotechnology together with Samara State Medical University). The basis of the program is a reference book on the chemical composition of Russian food products and dishes prepared from them [17].

Statistical data processing was carried out in Microsoft Excel 2016 and SPSS Statistics 21 programs. Descriptive statistics methods were used to analyze the obtained data. For each indicator, mean values (M), standard deviation SD (M±SD), median (Me) were calculated.

Results and discussion. The use of the Nutri-prof software package allows, based on the questionnaire data entered into the database, to obtain a detailed picture of the respondent's daily diet and establish the types of foods consumed, their energy value, and the nutrient content in the diet in quantitative (in grams) and in percentage terms. In addition, the

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program allows you to analyze the energy distribution of meals during the day.

Table 1 presents the average values and medians of the energy value and chemical composition of the diet.

The disadvantage of the 24-hour playback method is that the actual supply of energy, food and biologically active substances in it is underestimated by 20%. Therefore, the optimal level of nutrient intake is when their content is more than 80% of the physiological requirement [6].

Based on the data obtained, it can be seen that the median values of the daily intake of calories, proteins and fats on a school day and a day off for the majority of respondents did not significantly deviate from the NPN. Violation of the principles of rational nutrition was revealed in the increased consumption of saturated fatty acids (13% of the caloric content of the daily diet, with a consumption rate of not more than 10%). Excessive intake of SFA leads to an increase in cholesterol levels, the likelihood of developing type 2 diabetes, obesity, diseases of the cardiovascular and digestive systems [7, 16].

A decrease in the intake of carbohydrates with food was also revealed, by 28% relative to the recommended value, while the intake of simple carbohydrates (mono- and disaccharides) with food exceeds the norm by 2 times. The analysis of the structure of food packages of respondents showed that sugar consumption on a school day is 55.1±28.1 g/day, on a day off - 51.1±29.3 g/day (with the recommended amount of 35 g/day) [9].

An assessment of the intake of dietary fibers involved in the processes of digestion, assimilation, microbiocinosis and excretion of food residues from the body showed their sufficient intake with the diet (24 g/day on a school day and 22 g/day on a day off). Thus, fruit consumption is 161.1±118.7 g/day on a school day and 101.6±70.8 g/day on a day off, which is 87% and 54.9%, respectively, of the recommended value. Bread consumption is 55.0% of the recommended amount.

Added salt intake is 1.8 times higher than recommended by the World Health Organization (9 g at a rate of 5 g/day).

Table 1

Daily consumption of energy and nutrients by school-age children in the city of Salavat in comparison with the norms of physiological needs

Indicators (per day)	NPN in energy and nutrients	The actual diet of the studied group of children aged 11-16 years					
		School day			Day off		
		M±SD	Me	% NPN	M±SD	Me	% NPN
Energy and macronutrients							
Energy value (kcal)**	2720	2383±703	2287	84	2354±734	2312	85
Proteins. g**	90	92±39	83	92	85±30	81	88
Proteins. % of kcal*	12-15	15±4	14	104	15±3	14	93
Fats. g**	92	96±35	93	101	101±41	93	101
Fats. % of kcal*	25-35	36±6	36	120	38±7	38	109
Percentage of saturated fatty acids % of kcal*	< 10	13±3	13	-	14±3	13	-
Cholesterol. mg*	< 300	273±140	255	-	305±179	258	-
Carbohydrates. g**	383	286±91	274	72	276±91	275	72
Carbohydrates % of kcal*	55-60	48±8	49	85	47±8	48	80
The proportion of simple carbohydrates. % of kcal	< 10	21±6	21	-	21±6	20	-
Added sugar. % of kcal*	< 10	10.3±5.2	9.9	-	9.8±5.4	9.9	-
Dietary fiber. g*	20	31±18	24	120	24±12	22	110
Added salt. g***	5	10±4	9	180	9±3	9	180
Vitamins							
Vitamin A. mcg ret. eq**	900	866±541	734	82	800±350	768	85
Vitamin B_1. mg**	1.4	1.3±0.5	1.2	86	1.2±0.5	1.1	79
Vitamin B_2. mg**	1.6	2.1±1.5	1.6	100	1.8±0.9	1.6	100
Vitamin C. mg**	70	106±77	84	120	99±55	87	124
Vitamin PP. mg**	18-20	22±15	17	85	19±11	17	85
Minerals							
Calcium. mg**	1200	1117±742	888	74	920±407	829	69
Magnesium. mg**	300	377±146	362	121	446±297	352	117
Phosphorus. mg**	1200	1847±1187	1461	122	1591±728	1429	119
Kalium. mg**	1200	3699±1973	3182	265	3793±1833	3381	282
Natrium. mg*	1000	4820±1583	4656	466	4627±1385	4634	463
Ferrum. mg*	18	16±7	15	83	16±6	15	83

Note: * - NPN according to guidelines 2.3.1.0253-21; ** - NPN according to sanitary rules and regulations 2.3/2.4.3590-20; *** - NPN according to WHO recommendations

Table 2

Daily diet of children from the city of Salavat

Product group	school day			day off		
	M	SD	Me	M	SD	Me
Dairy products, g	376.8	253.2	350.0	379.2	276.3	330.0
Fruits, berries, fruit and berry drinks, g	261.2	192.6	230.0	299.7	208.8	280.0
Porridge, cereals, pasta, g	196.0	160.0	180.0	147.9	141.2	150.0
Bread, bakery products, pastries, g	185.2	121.3	155.0	187.5	137.4	155.0
Meat, meat products, ready meat dishes, g	184.6	134.9	170.0	192.5	134.2	180.0
Vegetables, vegetable dishes, g	94.5	95.4	100.0	100.4	94.1	100.0
Potatoes, potato dishes, g	70.5	95.5	0.0	74.5	97.7	0.0
Egg products, g	19.7	50.1	0.0	29.9	57.3	0.0
Fish, seafood, ready-to-eat fish dishes, g	15.3	41.6	0.0	25.6	54.6	0.0
Candies, chocolate, jams, g	10.9	27.5	0.0	10.6	21.8	0.0
Fats and oils, g	2.8	4.6	0.0	2.4	6.1	0.0
Nuts, legumes, g	1.5	11.1	0.0	3.2	15.0	0.0
Tea, coffee, soft drinks, g	519.4	337.1	500.0	484.9	292.8	450.0

This leads to excessive consumption of processed meat products and snacks.

Analysis of the average daily intake of vitamins (A, C, B1, B2 and PP) with food corresponds to the optimal level for children aged 11-16 years. According to the results of the survey, it was found that 52.5% of the respondents take additional vitamins and microelements.

An analysis of the intake of minerals in the body revealed a calcium deficiency (68% of the norm) and an excess intake of sodium (4.7 times). The ratio of Ca:Mg and Ca:P is broken. The level of phosphorus exceeds the content of calcium by more than 1.6 times. Taken together, such an imbalance of macronutrients can lead to pathological changes in the functioning of the cardiovascular system and the risk of developing arterial hypertension.

Table 2 reflects the results of the quantitative consumption of various food products by school-age children (presented by reduction in consumption).

Most of all, in quantitative terms, dairy products are in the diet of the respondents. Despite the fact that dairy products are consumed the most, this amount is 1.5 times lower than the norm (the norm is 562 g/day). This explains the existing calcium deficiency (see Table 1).

he consumption of vegetable dishes and potato dishes does not exceed 100 grams per day. The consumption of fish, seafood, eggs and nuts is sporadic, as indicated by the median value (0 g).

Qualitatively important in rational nutrition is not only the quality and quantity of food taken, but also its distribution throughout the day. Table 3 shows the contribution of individual meals to the daily caloric intake of children in the city of Salavat.

When evaluating the average values for schoolchildren in grades 5-9, it was noted that the share of breakfast calories in the diet was reduced both on the school day and on the day off (19.3% and 19.7% instead of 25%). The contribution of the second breakfast is 8.0% on the school day and 9.1% on the day off (the norm is 10-15%). At lunchtime, only 27.6% of food comes on a school day and 24.8% on a day off, with the recommendation for energy consumption of 35-40% of daily calories. The contribution of afternoon tea and dinner are optimally distributed and amount to 13% and 25%, respectively.

Conclusion. Today, the study and analysis of the actual nutrition of adolescents is an important task, as it reflects the current socio-economic situation in a particular region, taking into account all its features (traditions, climate).

Analysis of the nutrition of middle school children on weekdays and weekends in terms of caloric content, nutrient and food composition does not have significant differences.

The main violations of the principles of rational nutrition are expressed in the deficiency of carbohydrate intake with excessive consumption of simple carbohydrates, in the increased intake of saturated fatty acids and added salt. In combination with calcium deficiency and excess sodium, such disorders in the future can become risk factors for the development of alimentary-dependent diseases.

Violations in the structure of nutrition of schoolchildren are expressed in insufficient consumption of vegetables, potatoes, eggs and fish, with an excess in the diet of foods with a high sugar content.

An important strategy in reducing the prevalence of alimentary-dependent diseases and their prevention is the creation of a permanent information and propaganda system to explain to schoolchil-

Table 3

Contribution of individual meals to the daily caloric intake of urban children, % (Salavat)

meal	Contribution of meals to daily calorie intake, %	
	School day	Day off
Breakfast	19.3±9.3	19.7±8.3
Lunch	8.0±10.3	9.1±7.6
Dinner	27.6±10.0	24.8±10.4
Afternoon tea	12.8±11.0	13.4±9.2
Dinner	25.5±10.1	25.3±9.9
Late dinner	6.7±6.8	7.6±6.1

dren the basic principles of healthy nutrition, as well as improving the hygiene education of the younger generation, and promoting a healthy lifestyle in educational institutions.

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ORGANIZATION OF HEALTHCARE, MEDICAL SCIENCE AND EDUCATION

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QUALITY OF LIFE AND FEATURES OF MEDICAL AND DEMOGRAPHIC DEVELOPMENT OF THE FAR EASTERN FEDERAL DISTRICT TERRITORIES

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The aim of the study was to analyse the indicators characterising the quality of life and health of the population in the subjects of the Far Eastern Federal District (FEFD). Official data of the Federal State Statistics Service and the Analytical Centre under the Government of the Russian Federation were used as sources of information. It was found that despite the fact that most of the Far Eastern territories have a high level of human development, they are significantly inferior to the Russian Federation in terms of some indicators characterising the social well-being of the FEFD residents (life expectancy, mortality from certain causes, crime and suicide rates, etc.). In some constituent entities of the FEFD there is still a high level of mortality from "injuries with uncertain intentions", which may include a part of socially caused and socially significant incidents; the quality of official statistics on mortality from external causes in these territories is highly questionable. In order to achieve sustainable growth in the well-being of the residents of the Far Eastern Federal District, it is necessary to implement a comprehensive regional policy aimed at realizing the development potential of each region, overcoming infrastructural and institutional limitations, creating equal opportunities and promoting human development.

Keywords: quality of life, human development index, social well-being of the population, mortality, Far Eastern Federal District.

Introduction. The development of the Far Eastern Federal District (FEFD), which is under the close attention of the President of Russia, is one of the state's priority tasks.

From his first public speech as President V.V. Putin has identified demography as one of the most pressing topics. V.V. Putin has identified demography as one of the most pressing issues. The topic of demographic development of the Far East has been repeatedly raised in the President's annual messages to the Federal Assembly, and V.V. Putin did not ignore it at the WEF-2023 held recently in Vladivostok. Putin did not ignore it at the WEF-2023 recently held in Vladivostok. One of the strategically important tasks for the socio-economic development of Russia as a whole and the Far East in particular is to strengthen human potential, which is inextricably linked to health and a competent demographic policy. That is why, in order to realize the objectives set by the Government and the President of the Russian Federation for the development of the Russian Far East, the solution of the issue of formation and preservation of the labor potential of the population acquires special significance. A number of government programs aimed at attracting and retaining human capital in the region have been developed and are currently being implemented. The Russian Government Order No. 1298-r dated 20.07.2017 approved the Concept of demographic policy of the Far East for the period until 2025, and the national project "Demography" is being implemented. However, despite the measures taken, the Far Eastern region, which is the richest in terms of natural resources, remains unattractive for human resources.

Materials and Methods. The analysis of statistical data characterising the quality and standard of living of the population of the Far Eastern Federal District, individual mortality rates in the context of the territories of the district and in comparison with Russian indicators was carried out.

Official data of the Federal State Statistics Service and the Analytical Centre under the Government of the Russian Federation were used as sources of information [1, 2]. The study was carried out using statistical, mathematical methods, as well as methods of comparative analysis. The dynamics of individual mortality indicators in the Far Eastern Federal District was analysed.

Results and discussion. Two aspects of the demographic situation in the Far Eastern region seem to be the most important: the economic aspect, which is reflected in the reduction in the growth of labor resources, and the demographic aspect itself.

Over the period from 1990 to 2018, the population of the Far Eastern Federal District decreased by 1,892.2 people: from 8,054.2 to 6,165.3 thousand people, or by 23.5%, which corresponds to the number of residents of Khabarovsk Krai and Sakhalin Oblast, while the working-age population of the Far Eastern Federal District decreased by a quarter. The largest losses were registered in the Chukotka Autonomous District (by 3 times), Magadan Oblast (by 2 times), and Sakhalin Oblast (by 32%). As of January 1, 2023, the population of the Okrug amounted to 7903.9 thousand people after the addition of the Republic of Buryatia and Zabaikalsky Krai, or 5.4% of the population of the Russian Federation.

The main reasons for the decline in the population of the Far Eastern Federal District since the early 1990s are natural (up to 40%) and mechanical population loss (up to 60%), significantly outpacing the Russian Federation.

In the last 10 years, this trend has continued in the majority of the FEFD subjects. In 2022, population reduction due to natural decline and migration outflow was noted in the Republic of Buryatia, Transbaikal, Kamchatka, Khabarovsk and Primorsky Krai, Amur, Magadan, Sakhalin and Jewish Autonomous Oblasts. In the Republic of Sakha (Yakutia), Chukotka Autonomous Okrug there was a decrease in population due to the excess of migration outflow over natural population growth.

The main reason for the unfavorable

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demographic trends is that the real standard of living of the population lags behind the national average. In this case, the quality and standard of living simultaneously act both as a condition and as a result of the development of labor potential [3].

The quality of life of the population is a generalizing socio-economic category, through which the level of consumption of goods and services by the population, the ability to meet intellectual and moral needs, as well as public health, life expectancy, environmental conditions surrounding a person, moral and psychological climate, mental comfort, etc. are assessed.

The share of the population with incomes below the poverty line (subsistence minimum) in the FEFD territories is still very high. While in the Russian Federation as a whole this indicator amounted to 9.8% in 2022, in the Jewish Autonomous Region - 20.3%, the Republic of Buryatia - 19.0%, Transbaikal Territory - 18.0%, the Republic of Sakha (Yakutia) - 15.6%, Kamchatka Territory - 12.8%, Amur Region - 13.3%, Primorsky Territory - 11.5%, Khabarovsk Territory - 10.5%. Only in 3 territories of the Far East (Magadan, Sakhalin Oblasts and Chukotka Autonomous Okrug) the number of residents with incomes below the subsistence minimum was lower than the Russian average (7.4%, 7.0% and 6.7%, respectively).

In 7 out of 11 territories of the Far Eastern Federal District the unemployment rate in 2022 was higher than the Russian average (3.9%). The highest unemployment rate is observed in the Transbaikal Territory (8.7%), the Republic of Buryatia (7.4%), the Republic of Sakha (Yakutia) (6.5%), the Jewish Autonomous Region (5.2%).

Various indices and indicators are regularly calculated to measure the situation of the population in the world, to assess the level and quality of life. One of the most universal indicators is the Human Development Index (hereinafter - HDI), which is an integral indicator characterizing the ability to lead a long and healthy life, the ability to acquire knowledge and the ability to achieve a decent standard of living. In calculating the HDI, such indicators as life expectancy, per capita income and education are taken into account. The HDI can take values from 0 to 1. Regions with an index below 0.5 are considered to have a low level of human development, 0.5-0.8 - an average level, 0.8 and more - a high level of development.

The leading country in terms of human development today remains Norway with an index of 0.957 (2019 data), Russia was 52nd in the rating out of 189 countries (HDI - 0.824), again falling into the group of countries with a "very high level of human development".

In 2019, in the regional breakdown of individual subjects of the Russian Federation, the leaders in terms of the Human Development Index are traditionally Moscow (0.940), St. Petersburg (0.918) and the Khanty-Mansi Autonomous Okrug (0.914). These regions lead with a large gap from the Yamalo-Nenets Autonomous Okrug (0.902) [2]. In the Far Eastern Federal District in 2019, the HDI amounted to 0.846 against 0.870 in the Russian Federation as a whole, which corresponded to the penultimate, 8th place among the federal districts.

Most of the territories of the Far Eastern Federal District had a high or average level of the Human Development Index according to the assessment criteria in 2019. Three territories of the Far East had HDI indicators above or at the level of the national average (Sakhalin Oblast - 0.889, Republic of Sakha (Yakutia) - 0.886 and Magadan Oblast - 0.871). The Jewish Autonomous Region (HDI - 0.788) was again among the outsider regions in terms of human development, ranking 84th out of 85.

If we consider the place of the Far Eastern territories in the Russian HDI ranking, we can note positive dynamics for most of the territories: the Republic of Sakha (Yakutia) moved from 14th in 2000 to 9th place in 2019, the Sakhalin Oblast - from 37th to 8th, the Magadan Oblast - from 48th to 14th. Chukotka Autonomous Okrug - from 75th to 43rd.

At the same time, interregional differentiation in the Far East has significantly increased over the past decade, as evidenced by the analysis of the dynamics of the human development index of the regions. According to the results of 2019, only the Sakhalin Region and the Republic of Sakha (Yakutia) were among the leaders of the human development rating. The explanation is simple, as the regional economy in these territories is built around the extraction of minerals with high added value and high demand in global markets. The development of mining contributes to higher growth rates of the gross product, thanks to which the regions' positions in the rating are consistently high.

Despite the fact that GRP per capita in Sakhalin, Magadan Oblasts and Chukotka AO exceeds GRP in Moscow and St. Petersburg, the HDI in these territories is nevertheless much lower (Fig. 1).

It is no coincidence that the concept of human development emerged precisely in the years of dramatic progress in the fight against mortality, because health and longevity are not only components and consequences, but also the most important prerequisite for the development of human potential. Thus, the reduction of mortality opens up the possibility of accumulating knowledge both on the basis of personal longer life experience and in the course of intergenerational interaction. The intergenerational transmission of cultural values is becoming much more reliable, and the development of science is accelerating. In addition, health is an important prerequisite for education in youth and its further improvement.

Health is clearly linked to the ability to work more efficiently and productively and to increase personal and social well-being. Poor health, on the other hand, hinders economic development by reducing productivity, increasing disability, and leading to higher living costs.

For a long time, the Far East has registered lower overall mortality rates compared to the Russian Federation. In 2022, the total mortality rate in the Far Eastern Federal District exceeded the Russian average (13.3 and 12.9 per 1,000 population, respectively), although for many years it did not rise above the Russian average (Fig. 2).

The most pronounced natural population decline (above the Russian average) was observed in the Primorsky and Khabarovsk Territories, the Amur and Jewish Autonomous Regions.

Standardized mortality rates for men in the Far Eastern Federal District exceed the national average by 19%, and for women by 15%. For individual classes of causes of death, this excess is as follows: 44% and 45% respectively for respiratory diseases, 29% and 47% for digestive diseases, 20% and 19% for diseases of the circulatory system, 19% and 54% for external causes of death.

In 2020, working-age mortality rates from all causes in the Far Eastern Federal District exceeded the Russian average by 18%, from external causes of mortality by 51% (46% for men and 60% for women), from diseases of the digestive system by 27% (18% for men and 46% for women), from diseases of the respiratory system by 35% (35% for men and 30% for women), and from diseases of the circulatory system by 18% (12% for men and 36% for women), from respiratory diseases - by 35% (35% for men and 30% for women), from diseases of the circulatory system - by 18% (12% for men and 36% for women), from neoplasms - by 8% (2% for men and 19% for women).

The average age of death from all causes in 2020 was 66.4 years for men in the Russian Federation and 64.0 years for the Far Eastern Federal District (2.4 years less), and 76.3 years and 74.4 years for women, respectively (1.9 years less). In some territories, the average age of death for men was 9 years less than the Russian average (Amur Oblast, Jewish Autonomous Okrug), for women - almost 20 years less (Chukotka Autonomous Okrug) (Table 1).

Today, the Russian Far East lags significantly behind the Russian average in such an important indicator as life expectancy at birth. The dynamics of this indicator repeats the Russian average, but there has been a lag of about 3 years for many years. While the average indicator of life expectancy in 2022 is 69.58 years in the Far Eastern Federal District, in the Chukotka Autonomous District it amounted to 66.27 years, in the Jewish Autonomous District - 67.74 years, with the maximum level in the Republic of Sakha (Yakutia) - 72.7 years. The average for the Russian Federation in 2022 was 72.76 years. The difference between women's and men's life expectancy is more than 10 years, both in the Russian Federation and in the Far Eastern Federal District. This gender disparity has been persisting for many years, is indicative of the hypermortality of men of working age, and is one of the largest in the world. This trend should be expected to persist with further growth in life expectancy as a result of measures taken to improve the social sphere.

Since the calculation of life expectancy is based on age-specific mortality indicators, a significant reserve for its increase is the reduction of infant mortality, which, despite positive dynamics, remains higher in the Far Eastern Federal District than the Russian average. In 2022, it amounted to 5.2 per 1,000 live births (RF - 4.4), from 3.4 in Magadan Oblast to 15.8 in Chukotka AO.

When analyzing the structure of infant mortality in recent years, we can note an increase in the proportion of children who died from external causes. This class of diseases in a number of territories of the Far Eastern Federal District is persistently moving from the fourth place to the second or third place, ahead of respiratory diseases (Republic of Buryatia, Jewish Autonomous Okrug, Chukotka Autonomous Okrug).

Such dynamics cannot but be alarming. Most studies devoted to the analysis of infant mortality allow us to conclude that more than half of the factors determining the health of children of the first year of life and infant mortality relate to manageable, avoidable exogenous factors - socio-hygienic and medical-organizational. These include housing and material conditions, family composition, child care, family climate and, most importantly, family lifestyle. All these factors can be successfully managed, and they constitute an operational reserve for reducing infant mortality and increasing life expectancy.

The high prevalence of socially significant diseases such as alcoholism and drug addiction, which have a significant

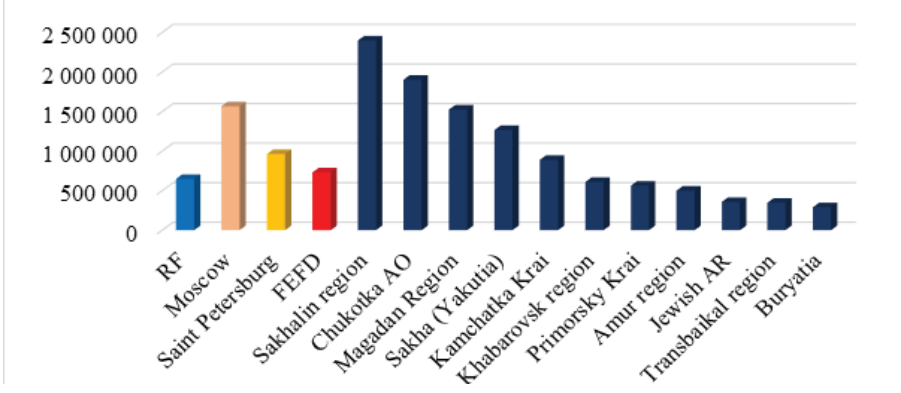

Fig. 1. Gross regional product per capita in the Russian Federation and the subjects of Far Eastern Federal District in 2019 (rubles) [1]

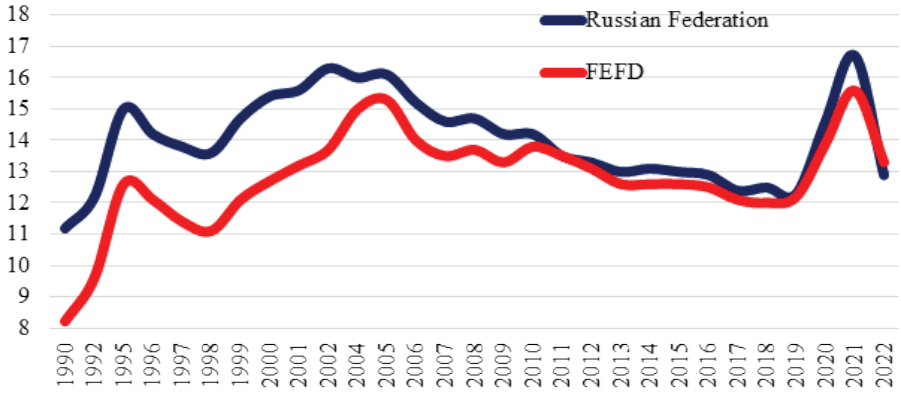

Fig. 2. Dynamics of mortality rate in the Russian Federation and FEFD in 1990-2022 (per 1000 population) [1]

Table 1

Average age of death from all causes in 2020 (years) [1]

	man	Δ	woman	Δ
RF	66.4		76.3	
Far Eastern Federal District	64.0	- 2.4	74.4	- 1.9
The Republic of Buryatia	65.3	- 1.1	75.0	- 1.3
The Republic of Sakha (Yakutia)	66.0	- 0.4	75.9	- 0.4
Transbaikal region	62.9	- 3.5	73.9	- 2.4
Kamchatka Krai	64.0	- 2.4	75.0	- 1.3
Primorsky Krai	64.5	- 1.8	74.7	- 1.6
Khabarovsk region	63.2	- 3.2	74.2	- 2.1
Amur region	57.2	- 9.2	72.8	- 3.5
Magadan Region	63.5	- 2.9	74.9	- 1.4
Sakhalin region	64.6	- 1.8	75.0	- 1.3
Jewish AR	57.5	- 8.9	72.6	- 3.7
Chukotka AO	62.5	- 3.9	56.5	- 19.8

impact on mortality rates, should also be considered a serious sign of social disadvantage in the Far Eastern territories. The incidence of alcoholism in the Far East is 1.96 times higher than the national average, and in some territories (Sakhalin Oblast and the Republic of Sakha (Yakutia)) it is 2.8-3.1 times higher than the national average. - 2.8-3.1 times. In Chukotka, the alcoholism incidence rate in 2021 was 8.4 times higher than the national average (Fig. 3). The number of alcoholism patients registered per 100,000 population in the FEFD exceeds the Russian figures by 40%, in some territories from 2 (Kamchatka Krai, Magadan and Sakhalin Oblasts) to 5 times (Chukotka Autonomous Okrug) (Fig. 4).

In the case of drug addiction, the situation is similar, but here the "leader" is the Jewish Autonomous Region and the Amur Region, with the Primorsky and Khabarovsk Territories and the Sakhalin Region lagging slightly behind (Fig. 5). Thus, the task of preventing and treating addiction to psychoactive substances remains highly relevant for the Far East.

The incidence rate of malignant neoplasms in the Far Eastern Federal District as a whole does not differ much from the national average. In a number of territories (Khabarovsk, Kamchatka Krai, Amur, Sakhalin, and Jewish Autonomous Oblasts), morbidity rates exceed the national average by 3.6-12.1%. At the same time, the mortality rate for causes of death from neoplasms in the Far Eastern Federal District has increased in recent years, approaching the Russian average, which may indicate a decline in the quality and availability of medical care. The mortality rate from neoplasms in the working age group exceeds the national average. The growth of mortality from neoplasms is observed in most Far Eastern territories. Especially high values of the indicator are in Primorsky Krai, Amur and Sakhalin Oblasts, Jewish Autonomous Okrug.

Tuberculosis as a cause of death was registered 2.2 times more often in the FEFD compared to the RF in 2022, 4.6 times more often in the Jewish Autonomous Region, 3.3 times more often in the Amur Region and Primorsky Krai.

The mortality rate from external causes in the Far East regions for many years remains noticeably higher than the Russian average (in 2022 - 147.6 and 99.5 per 100 thousand population, respectively) (Fig. 6). Among the Far Eastern territories, the values of this indicator are particularly high in the Chukotka Autonomous Okrug (225.6 per 100,000 population), the Amur Region (184.8

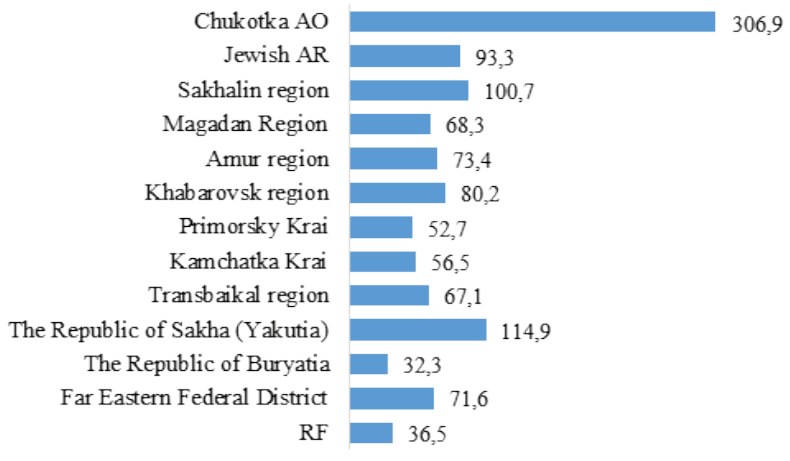

Fig. 3. Number of first-time detections of persons with alcohol dependence syndrome in 2021 (per 100 thousand population) [1]

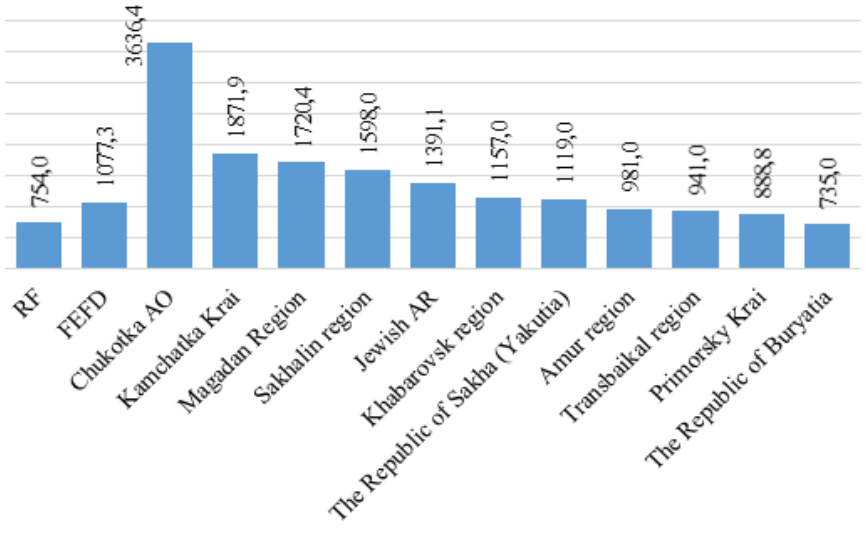

Fig. 4. Population with alcoholism and alcoholic psychosis in 2021. (per 100 thousand population) [1]

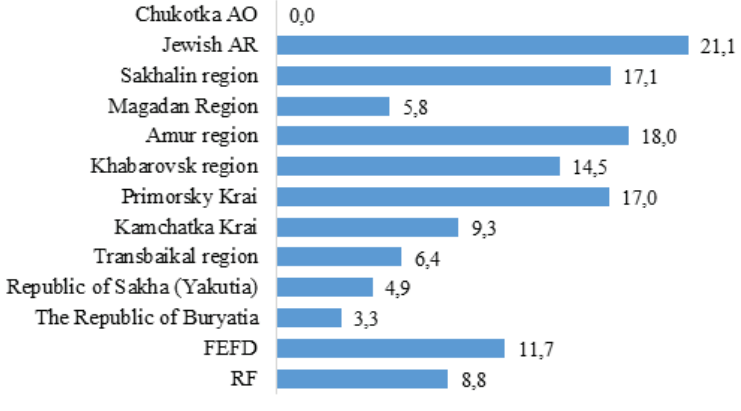

Fig. 5. Number of first-time detected persons with substance dependence syndrome in 2021 (per 100,000 population) [1]

per 100,000 population), the Republic of Buryatia and the Transbaikal Territory (182.7 per 100,000 population) (Fig. 7).

In the context of a difficult socio-economic situation in the country and the world, the analysis of suicide mortality deserves special attention. Despite a significant decrease in the frequency of suicides in recent years, the Far Eastern Federal District still consistently ranks first among the territories with an unfavorable suicide situation. It is believed that the suicide mortality rate worldwide is one of the most reliable indicators of the level of social and economic well-being of society, as well as the state of mental health of the population.

In the District as a whole, the indicator was 1.9 times higher than the Russian one, and only three territories of the FEFD in 2022 (as in previous years) had suicide mortality rates significantly lower than the average for the Russian Federation and the FEFD (Khabarovsk and Kamchatka Krai, Sakhalin Oblast) (Fig. 8). At the same time, in these territories in recent years there has been a significant increase in the causes of death referred to as "injuries with undetermined intent" (IUI), i.e. such cases when the actual cause of death remained unclear. The excess of IUI cases over suicides in these territories can be tens and hundreds of times, with the average value for the Russian Federation being 3.3, and for the Far Eastern Federal District - 2.8 (Table 2).

This situation speaks about the quality of medical statistics, the degree of responsibility for the health of the population and may be due to conscious or unconscious deformation of the structure of causes of mortality, both due to undercounting of mortality from individual causes, and due to masking some deaths from homicides, suicides and alcohol poisoning under the rubric of "damage with uncertain intentions" in an effort to achieve the monitored indicators of social well-being of the territories. But this does not bring real well-being, and the picture of mortality formed in this case calls into question the real scale of losses from external causes, trends in mortality from external causes as a whole and from individual causes, including homicides and suicides, and does not allow to objectively assess the situation and make the right decisions on its correction.

When assessing the homicide mortality rate in the Far Eastern Federal District, it should be remembered that the crime rate in the Far East remains one of the highest in Russia. In 2022, 21 regions of the Russian Federation were categorized as disadvantaged (with high and very high severity of the problem) in terms of crime. Half of them belong to the Far Eastern Federal District. 10 out of 11 territories of the Far East fell into the disadvantaged group, except for the Republic of Sakha (Yakutia). The most unfavorable situation in 2022 is in the Amur Region, the Jewish Autonomous Region and the Transbaikal Territory. All these regions are among the least safe, they are united by low urbanization, low living standards and significant migration outflow.

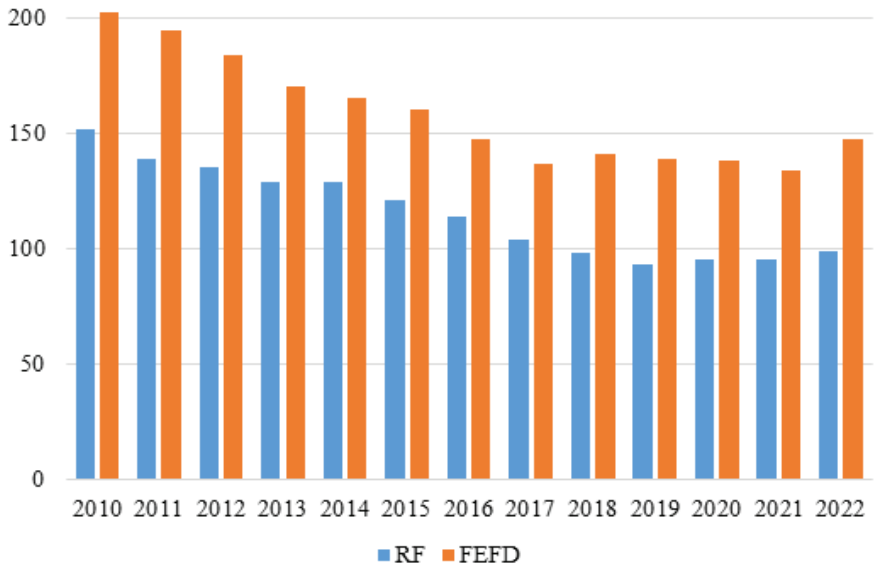

Fig. 6. Dynamics of mortality rate from external causes in the Russian Federation and FEFD in 2010-2022 (per 100 thousand population) [1]

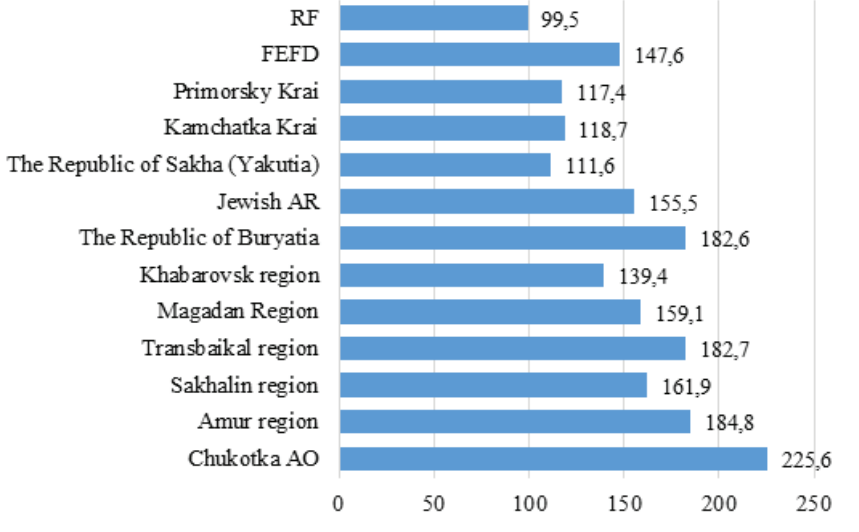

Fig. 7. Mortality rate from external causes in the Russian Federation and FEFD subjects in 2022 (per 100,000 population) [1]

This is confirmed by mortality data: in 2022, as in previous years, the Far Eastern Federal District ranked 1st in the homicide mortality rate among all federal districts (8.6 cases per 100,000 population, 2.3 times higher than in the Russian Federation). In some territories of the FEFD, the homicide mortality rate exceeded the Russian rate from 2 (Khabarovsk Krai) to 5 (Chukotka Autonomous Okrug) times (Fig. 9).

It should be remembered that this indicator, along with many others, is an indicator of the social climate in society and the attitude to human life in general, largely reflecting the state of the level of physical security in a particular territory.

Conclusion. The above data reflect only some social indicators characterizing the level and quality of life and health of the population. But even this analysis shows that, despite the fact that most of the Far Eastern territories are now categorized as territories with a high level

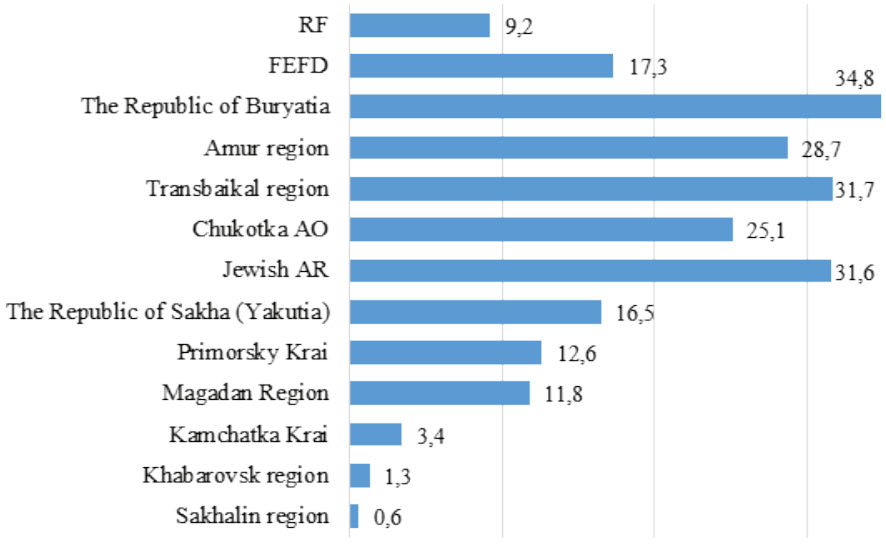

Fig. 8. Level of suicide mortality rate in the Russian Federation and FEFD subjects in 2022 (per 100 thousand population) [1]

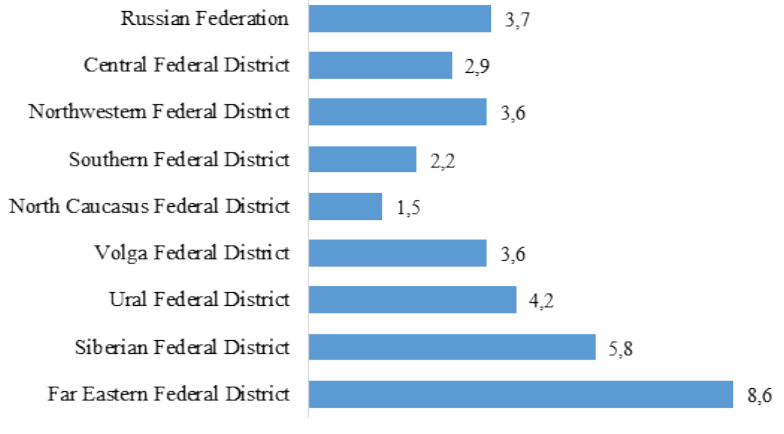

Fig. 9. Suicide Mortality Rate by Federal Districts of the Russian Federation in 2022 (per 100,000 population) [1]

of human development, they are significantly inferior to Russia in some positions. This is a factor that largely determines the stable outflow of population to the western regions of the country, to the near and far abroad.

In the near future, significant efforts will be required by both the authorities and citizens themselves to create better development opportunities in most of the Far Eastern territories. Longevity remains the most problematic component of human development. First and foremost, it is necessary to expand the opportunities for residents of the Far East to live long and healthy lives. According to the forecast, even in 2030 the longevity index in most regions of the country will not reach the critical value of 0.800, while in the countries of the Organization for Economic Cooperation and Development (OECD) it was already 0.880 in 2004. It is impossible to achieve the goals of reducing poverty, reducing mortality, and increasing life expectancy, especially for men, without technological restructuring, without a transition to a knowledge economy, when labor efficiency will increase significantly and skilled labor will be adequately paid.

The issue of improving the quality of life of Far East residents and overcoming territorial differentiation remains the top priority today. This follows from the statements of the President of the Russian Federation V.V. Putin at the plenary session of the 8th Eastern Economic Forum. Putin's statements at the plenary session of the 8th Eastern Economic Forum - the Far East is becoming a strategic priority for Russia for the entire 21st century and should become an attractive place not only for work, but also for life.

In order to achieve sustainable growth in the well-being of FEFD residents, it is necessary to pursue a comprehensive regional policy aimed at realizing the development potential of each region, overcoming infrastructural and institutional constraints, creating equal opportunities and promoting human development.

As a result of the forum, a number of instructions were given to the Government of the

Russian Federation, federal and regional authorities, which will be implemented in the near future.

Table 2

Ratio of cases of "injuries with uncertain intentions" and suicides in the territories of the Far Eastern Federal District, 2022 [1]

	IUI/suicide
RF	3.3
Far Eastern Federal District	2.8
The Republic of Buryatia	0.5
The Republic of Sakha (Yakutia)	1.3
Transbaikal region	1.4
Kamchatka Krai	16.7
Primorsky Krai	2.9
Khabarovsk region	71.5
Amur region	1.1
Magadan Region	6.8
Sakhalin region	197.2
Jewish AR	0.4
Chukotka AO	2.9

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ORGANIZATION OF MEDICAL EVACUATION OF PATIENTS WITH SEVERE COVID-19 AND THE RESULTS OF THEIR TREATMENT IN THE INTENSIVE CARE RESUSCITATION UNIT

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In order to study the timeliness of medical evacuation of the patients with severe novel coronavirus from the districts of the Sakha Republic (Yakutia), a retrospective analysis of data from the Republic's Center for Disaster Medicine (RCDM) for 2019-2022 was carried out. To compare the treatment results of patients living in the city of Yakutsk and patients evacuated from the districts of the republic ("city", "district"), we conducted a prospective observational case-control study of 600 patients with severe COVID-19 in the specialized anesthesiology, resuscitation and intensive care unit (ARICU) of the Sakha Republic Clinical Hospital in 2020-2022. Lethal outcome (n=397) was chosen as the studied criterion. It was found that the study groups had statistically significant differences in age (p=0.002), body mass index (BMI) (p=0.001), saturation (SaO2) of mixed blood upon admission to the ARICU (p=0.003), oxygenation index (p=0.011), and the severity of the condition according to the SOFA (Sequential Organ Failure Assessment) score. The patients evacuated from the districts were characterized by younger age, higher body mass index, and greater damage to lung tissue. City residents were more prone to experience brain failure, acute kidney injury, and the development of multiple organ dysfunction. The mortality rate for the district patients with severe COVID-associated community-acquired pneumonia was 65.8%; for urban patients it made 66.3%, with no statistically significant differences established (p=0.906). Thus, the arrangement of medical evacuation for COVID-19 patients to a specialized institution during the pandemic ensured the availability and timeliness of specialized care provided to them.

Keywords. Novel coronavirus, community-acquired pneumonia, city, district, lethal outcome.

Introduction. The timeliness of specialized and high-tech medical care plays a decisive role in the outcome of a disease. Medical evacuation makes a major contribution to the availability of medical care in high-level medical institutions in emergency situations. Emergency medical evacuation requires quick and correct solving of organizational and clinical issues. It is necessary to justify the evacuation of a patient, determine indications and contraindications for transportation, select the optimal type of ambulance transport, as well as to form and equip an evacuation medical team, taking into account characteristics of the pathology and severity of the patient's condition.

Medical evacuation has become particularly relevant in the context of the spread of the novel coronavirus (nCoV) COVID-19, characterized by the massive scale of the disease, the need to comply with infection safety measures and provide respiratory support during the transportation of patients. In regions with large territories and underdeveloped transport infrastructure, including the Sakha Republic (Yakutia), the main burden of transporting COVID-19 patients to specialized departments fell on the air ambulance service.

With the beginning of the spread of nCoV COVID-19 in the Sakha Republic (Yakutia), a comprehensive action plan was adopted to provide medical care to patients with a severe course of the disease [1].

To provide inpatient care to COVID-19 patients, a three-level system of medical care was deployed in the republic: Level 1 medical care was provided in central district hospitals on beds allocated for patients with mild forms of COVID-19; Level 2 medical care was provided by medical organizations equipped with a PCR laboratory and equipment for radiation diagnostics (X-ray computed tomography (CT); Level 3 was carried out at the Sakha Republic Clinical Hospital, where specialized departments for patients with COVID-19 were formed, including the Anesthesiology, Resuscitation and Intensive Care Unit (ARICU) with 36 beds [4].

To provide qualified medical care to residents of the entire republic, sanitary flights of the Republic's Center for Disaster Medicine (RCDM) carried out both inter-district transfer and transportation to medical institutions in Yakutsk.

When arranging the evacuation of COVID-19 patients, the RCDM introduced a set of measures to increase the epidemiological safety: additional briefings for flight and technical personnel; purchase of personal protective equipment and isolation boxes for transporting patients; increased supply of medical oxygen; and additional contracts with organizations providing post-flight disinfection of the aircraft. A significantly increased burden of evacuating patients from the districts of the republic required additional resources. Thus, to perform sanitary flights to COVID-19 patients, 100

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million rubles were allocated by order of the Head of the Sakha Republic (Yakutia) of November 13, 2020, No. 433-RG from the reserve fund of the Russian Federation within the framework of the subprogram "Equalization of financial capabilities of the budgets of constituent entities of the Russian Federation and local budgets" under the state program of the Russian Federation "Development of federal relations and creating conditions for effective and responsible management of regional and municipal finances". In addition, the Republic's Medical Center "Reserve" provided medical protective suits, respirators, protective screens, pump sprayers, isolation boxes, and anti-epidemic kits. Additional medical and paramedic teams were formed to evacuate COVID-19 patients. The airlines providing medical flights added aircraft (a MI-8 helicopter and an An-26 aircraft) equipped with isolation boxes. The routing of COVID-19 patients from certain districts was promptly revised to optimize the workload of the central air ambulance station, taking into account the availability of beds in infectious diseases hospitals in Yakutsk.

Obviously, the outcome of the patient's treatment is one of the main criteria for the proper arrangement and adequacy of medical and evacuation measures. Therefore, along with studying the features of arranging medical evacuation for COVID-19, it is necessary to analyze the final treatment results of the patients evacuated to a specialized department to assess the continuity and effectiveness of the measures taken. This established the aim of the study.

Aim of the study: to analyze the features of arranging medical evacuation of patients with severe COVID-19 and the results of their teratment at the specialized unit of anesthesiology, resuscitation and intensive care in the Sakha Republic (Yakutia)

Materials and methods. To achieve this aim, a retrospective analysis of the main performance indicators of the Republic's Center for Disaster Medicine (RCDM) of the Ministry of Health of the Sakha Republic (Yakutia) was carried out. The volume and structure of completed air ambulance missions during the spread of the nCoV COVID-19 were studied by air ambulance mission logs and patient evacuation records for 2019-2022.

To compare the treatment results of the patients evacuated by air ambulance, a prospective observational case-control study was performed on 600 patients with COVID-19 complicated by community-acquired pneumonia (281 men (46.8%) and 319 women (53.2%)), treated at the ARICU, Sakha Republic Clinical Hospital, in the period 2020-2022. The patients were divided into groups: those admitted by referral from clinics or transferred by ambulance medical teams in Yakutsk (city patients, n=451) and those transported by the RCDM from the central district hospitals (CDH) of the republic (district patients, n=149).

Lethal outcome (n=397) was chosen as the studied criterion.

The inpatient study was carried out in accordance with the ethical standards of the Declaration of Helsinki of the World Medical Association "Ethical principles for medical research involving human subjects" as amended in 2008, and the "The rules of clinical practice in the Russian Federation", approved by order of the Ministry of Health of the Russian Federation of June 19, 2003, No. 266, and approved by the local Committee on Biomedical Ethics, Institute of Medicine, Ammosov North-Eastern Federal University. Before participating in the study, the patients were informed about the aims and methods of the study and gave their consent.

Inclusion criteria for the study: age over 18 years, inpatient treatment in the ARICU, diagnoses U07.1 "COVID-19, virus identified" and U07.2 "presumed COVID-19, virus not identified"; patients with severe community-acquired COVID-19-associated pneumonia with pulmonary lesions according to CT results at 50-75% (CT-3) and 75-100% (CT-4), patient's informed consent to participate in the study.

Exclusion criteria: age under 18 years, patient's refusal to participate in the study.

When statistically processing the RCDM data, the analytical, expert assessment and mathematical analysis methods were used. A statistical analysis of the ARICU data was performed using IBM SPSS Statistics version 26.0. The indicators were checked for normal distribution using the Kolmogorov-Smirnov test with Lilliefors correction (for n>50) and the Shapiro-Wilk test (for n<50), with p-value>0.05 as normal distribution. All measured quantitative indicators had a distribution different from normal, and

Table 1

The distribution of evacuated patients by some disease entities in 2019-2022 (abs. number)

Disease	2019	2020	2021	2022
Acute coronary syndrome	378	443	462	532
Acute cerebrovascular accident	355	385	389	502
Injuries	416	396	497	606
Pregnancy, childbirth and postnatal period	362	356	338	364
COVID-19		503	1511	398

Table 2

Number of air ambulance missions and evacuated COVID-19 patients by groups of districts

Groups of districts	2020		2021		2022	
	Missions	Patients	Missions	Patients	Missions	Patients
Arctic	81	141	230	459	97	134
Northern	22	25	51	117	38	65
South-Western	63	98	144	232	30	35
Zarechnaya	82	121	165	246	65	87
Vilyui	73	91	198	437	52	75
Central	15	27	16	20	2	2
TOTAL	336	503	804	1511	284	398

Table 3

A comparative characteristic of the COVID-19 patients in the study groups

Indicator	City patients, n=451		District patients, n=149		p-value
	Me [IRQ]	Min;Max	Me [IRQ]	Min;Max	p
Age, years	68 [60; 76]	18-94	63 [57; 70]	20-100	0.002
BMI, kg/m^2	29.3 [25.8;33.0]	14.69-52.1	31.2 [27.9;36.2]	20.0-57.46	0.001
SaO_2 of mixed blood upon admission to ARICU, %	84 [78;89]	40-99	80 [76;88]	52-94	0.003
Oxygenation index, mm Hg	267 [169;333]	58-450	218 [140;333]	70-430	0.011
APACHE II, score	16 [14;18]	5-44	17 [14;18]	8-49	0.972
SOFA, score	6 [5;8]	1-23	6 [4;8]	2-18	0.05
Duration of treatment at ARICU, bed-day	6 [3;10.5]	0-56	7 [4;11]	1-40	0.112

then nonparametric statistical methods were used. For descriptive statistics of quantitative data, medians (Me) and interquartile range (IQR) were calculated; for categorical data, absolute numbers with percentages were calculated. A comparative nonparametric analysis of quantitative data was carried out using the Mann-Whitney U test. A comparative analysis of nominal binary data was performed by constructing a four-field table with calculation of Fisher's exact test or Pearson's χ2 test depending on the expected minimum number, with calculation of the odds ratio at 95% confidence interval.

Results and discussion. An analysis of completed air ambulance missions showed that in the period 2019-2022 the main reasons for the medical evacuation of patients were acute coronary syndrome (ACS), acute cerebrovascular accident (ACVA), severe injuries, pregnancy and childbirth, with the growing trend. Since March 2020, patients with nCoV COVID-19 contributed to the changes in the structure of air ambulance mission; their maximum number was observed in 2021 at 1,511 patients, which exceeded the number of patients with the above diagnoses more than 3-fold (Table 1).

Table 2 presents the distribution of air ambulance missions by groups of regions of the republic.

The largest number of patients were evacuated from the Arctic group of regions: 141 patients in 2020, 459 in 2021, 134 in 2022; it was followed by the Zarechnaya (across the Lena River from Yakutsk) group of districts: 121 patients in 2020, 246 in 2021, 87 in 2022; and the Vilyui group: 91 patients in 2020, 437 in 2021, 75 in 2022 (Table 2).

While being in central district hospitals before evacuation, all patients with severe COVID-19 were consulted by

Table 4

Comorbidities in the COVID-19 patients in the study groups (abs. number; specific weight)

Indicator	City patients, n=451	District patients, n=149	p-value
Chronic cardiovascular diseases, including AH	422 (93.6) 407 (90.2)	140 (94.0) 139 (93.3)	0.865 0.260
Chronic kidney disease	218 (48.3)	64 (43.0)	0.254
Chronic lung diseases, including bronchial asthma	194 (43.0) 29 (6.4)	149 (35.6) 5 (3.7)	0.109 1.159
Diabetes mellitus, type 2	169 (37.5)	57 (38.3)	0.864
CNS chronic diseases	166 (36.9)	30 (20.1)	<0.001
Chronic liver diseases	28 (8.3)	11 (9.6)	0.666
Oncological diseases	35 (7.8)	9 (6.0)	0.485
Rheumatic diseases	6 (1.3)	6 (4.0)	0.082

Table 5

Clinical and laboratory characteristic of the patients (abs. number; specific weight)

Indicator	City patients, n=451	District patients, n=149	p-value
Total lung damage (CT 4)	253 (56.1)	101 (67.8)	0.012
Vasopressor support	77 (17.1)	18 (12.1)	0.145
Acute brain failure	144 (31.9)	33 (22.1)	0.023
Acute coronary syndrome	17 (5.1)	2 (1.8)	0.129
Noninvasive ALV on day 1	308 (68.4)	106 (71.1)	0.537
Invasive ALV on day 1	8.9% (40)	7.4% (11)	0.586
Acute kidney injury	210 (46.6)	36 (24.2)	<0.001
Acute liver failure	100 (22.2)	37 (24.8)	0.511
Multiple organ dysfunction syndrome (MODS)	316 (70.1)	85 (57.0)	0.003
Deaths	299 (66.3)	98 (65.8)	0.906

doctors of the Regional Center for Telemedicine Consultations, established on the basis of the Sakha Republic Clinical Hospital under orders of the Ministry of Health of the Sakha Republic (Yakutia) No. 01-07/437 of 09 April 2020 "On remote advisory centers of anesthesiology and resuscitation for the diagnosis and treatment of infectious diseases caused by coronavirus strain COVID-19 and pneumonia" [2] and No. 213 of 18 April 2020 "On the organization of telemedicine consultations on COVID-19 "[3].

Along with studying the features of arranging medical evacuation for COVID-19, in accordance with the aim of the research and in order to study the effectiveness of the air ambulance missions completed, we performed a comparative analysis of the treatment results of the most severe category of the patients evacuated by air ambulance, whose course of illness was complicated by community-acquired pneumonia.

The data analysis showed that the study groups demonstrated statistically significant differences in age (p=0.002), body mass index (BMI) (p=0.001), saturation (SaO2) of mixed blood upon admission to the ARICU (p=0.003), oxygenation index (p=0.011) and severity of the condition according to the SOFA (Sequential Organ Failure Assessment) scale. There were no significant differences in the APACHE II (Acute Physiology Age Chronic Health Evaluation) severity scale and duration of treatment in the ARICU (Table 3).

Generally, the groups did not differ in comorbidities, among which arterial hypertension/hypertensive disease (AH/HD), chronic kidney disease and chronic lung diseases prevailed (Table 4).

The exceptions were diseases of the central nervous system (CNS) like post-stroke encephalopathy, dementia, Alzheimer's disease, Parkinson's disease, epilepsy, post-traumatic encephalopathy, which were more common in the city patients. This factor is also responsible for the more frequent presence of acute brain failure in this group of the patients (p=0.023). In addition, acute kidney injury (p=0.001) and multiple organ dysfunction syndrome were more often observed in the city patients. At the same time, the patients evacuated from the central district hospitals more often demonstrated total lung damage (more than 75% of the lung tissue) according to computed tomography of the chest organs, which indicated the severity of their condition, the presence of severe respiratory failure and the justification for their admission to the specialized intensive care unit (Table 5).

All patients in the study groups received basic therapy in the ARICU in accordance with the Temporary Guidelines for the Prevention, Diagnosis and Treatment of the novel coronavirus (COVID-19) that were current during the period of their treatment. There were no deaths observed during transportation of the patients from the central district hospitals. The mortality rate of patients with severe COVID-associated community-acquired pneumonia evacuated from central district hospitals to the ARICU of the Sakha Republic Clinical Hospital was 65.8%; for city patients - 66.3%, with no statistically significant differences established (p=0.906).

Conclusion. Air ambulance service in the Sakha Republic (Yakutia) is critical for ensuring the availability, timeliness and completeness of emergency medical care. The results of our study indicate that during the COVID-19 pandemic, the total number of air ambulance calls increased by an average of 32.3% compared to 2019; in 2021, medical evacuation of patients with severe COVID-19 to a specialized department in the city of Yakutsk ranked first in the structure of air ambulance missions. The analysis of the treatment results of patients transported by air ambulance to the specialized department in Yakutsk showed the validity and timeliness of their evacuation. During the transportation of the patients from the districts of the republic, no deaths were recorded; the results of their treatment in a specialized ARICU for patients with nCoV COVID-19 did not differ from the treatment outcomes of the patients from Yakutsk, who had access to comprehensive medical care.

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HYGIENE, SANITATION, EPIDEMIOLOGY PAND MEDICAL ECOLOGY

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EPIDEMIOLOGICAL MANIFESTATIONS OF HEPATITIS C IN THE REPUBLIC OF SAKHA (YAKUTIA) DURING THE GLOBAL INFECTION ELIMINATION PROGRAM IN THE RUSSIAN FEDERATION

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The Republic of Sakha (Yakutia) is the largest administrative-territorial unit in the world, more than 40% of its territory is located beyond the Arctic Circle. At the same time, the population of the republic is the lowest among all subjects of the Russian Federation (0.32 people/km2). All this together significantly distinguishes this region from other territories of Russia. The purpose of this study: to assess the main manifestations of the epidemic process of chronic hepatitis C on the territory of the Republic of Sakha (Yakutia) at the stage of implementation of the national program for the elimination of viral hepatitis. Materials and methods. An epidemiological analysis of chronic hepatitis C and liver cancer was carried out for the period from 2000 to 2019. The incidence of liver cancer was assessed according to ICD-10, in which malignant neoplasms of the liver and intrahepatic bile ducts are summarized under code C22. Statistical analysis was carried out in the application package R. The study of differences in the distribution of incidence rates of chronic hepatitis C and malignant liver diseases between the Russian Federation and the Republic of Sakha (Yakutia) was carried out using the method of nonparametric assessment of the weighted average median of the Mann-Whitney test. Results and discussion. The decrease in the intensity of the incidence of acute and chronic hepatitis C in Russia was unidirectional in nature with a fairly close manifestation of their long-term movement. In contrast, in the Republic of Sakha (Yakutia) there was a significantly less pronounced decrease in the incidence of acute hepatitis C (4.9 times, rate of increase -6.2%), and the incidence of chronic hepatitis C in general for the entire analyzed period was cyclical and had a pronounced upward trend (2.4 times growth, rate of increase +2.6%). It was shown that there are statistically significant differences ($p<0.01$) between the median incidence rates of chronic hepatitis C and malignant liver diseases between the Russian Federation and the Republic of Sakha (Yakutia). Conclusion. To achieve the appropriate targets for hepatitis C elimination in the country, it is necessary to take into account the specific natural, climatic, social and ethnic characteristics of the Republic of Sakha (Yakutia).

Keywords: epidemiology, morbidity; hepatitis C; liver cancer; The Republic of Sakha (Yakutia).

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Introduction. Parenteral viral hepatitis B and C are a global medical and social problem, and therefore in May 2016, at the 69th World Health Assembly, the first global strategy to combat these diseases was adopted, and in September 2016, a similar long-term the action plan was approved by the WHO Regional Office for Europe [8]. In the Russian Federation, work on organizing and implementing regional programs to reduce the burden of hepatitis B and C in the format of WHO documents has only recently intensified. The systematic measures taken in recent years in the Russian Federation to combat parenteral viral hepatitis have contributed to a decrease in the intensity of epidemic processes for both nosological forms, which was especially clearly manifested in hepatitis B. In the Russian Federation for 2000-2020. the incidence of acute hepatitis B decreased by 121 times, and chronic hepatitis B by 3.3 times. In hepatitis C, the decrease in these indicators was much less pronounced and amounted to 32 and 1.3 times, respectively [2].

The President of the Russian Federation, in his message to the Federal Assembly dated April 21, 2021, clearly identified long-term tasks in this direction. “Hepatitis C also claims many young lives. Solutions are needed here that will allow us to minimize this danger to the health of the nation within a decade,” the President said. The subsequent decree of the Government of the Russian Federation dated November 2, 2022 No. 3306 determined a phased plan for the implementation of measures aimed at combating hepatitis C until 2030.

Obtaining adequate responses to ongoing activities (epidemiological control) is achieved mainly under homogeneous conditions, under which the development of epidemic processes of infectious diseases manifests itself in different territories. In this regard, it should be noted that the Russian Federation is the largest state entity on our planet, which determines a variety of natural, climatic and

social conditions in its individual territorial units. This, in turn, can contribute to various manifestations of epidemic processes of diseases that are similar in their pathogenetic properties and/or even with a single etiological agent causing them [5]. It is clear that these conditions must be taken into account when organizing regional programs.

A convincing example of the stated thesis is the position that the Russian Federation is essentially a northern country, since more than half of its territory consists of the regions of the so-called Far North. This definition (Far North) is a collective historical concept to designate the most distant northern territories of the Russian Federation, which are harsh in nature and climate, usually located beyond the Arctic Circle [7]. The main representative of this territory is the Republic of Sakha (Yakutia), the area of which is almost comparable to the entire European part of the country. The Republic of Sakha (Yakutia) is part of the Far Eastern Federal District and is not only the largest subject of the Russian Federation, but also the largest administrative-territorial unit in the world, more than 40% of its territory is located beyond the Arctic Circle. At the same time, the population of the republic, according to Federal state statistics service of Russia (2023), is 996,243 people, which determines one of the lowest population densities among all subjects of the Russian Federation (0.32 people/km^2). The Yakuts in the national structure of the population of the Republic make up half of the population with the number of urban residents as of 2022 being 67.1%. All this, together with the natural, climatic and social living conditions of the population, significantly distinguishes this region from other territories of the Russian Federation.

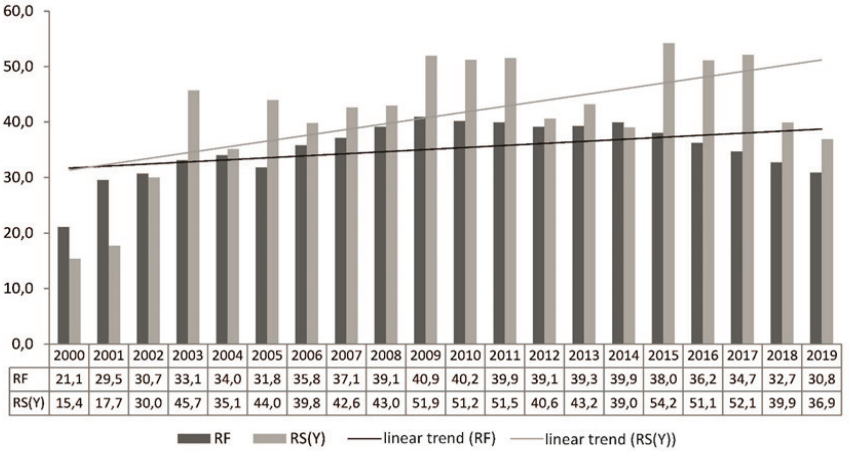
The purpose of this study is to assess the main manifestations of the epidemic process of chronic viral hepatitis C on the territory of the Republic of Sakha (Yakutia) at the stage of implementation of the national program for the elimination of viral hepatitis.

Materials and methods. The epidemiological analysis was carried out mainly for the period from 2000 to 2019. The choice of the final point of the study was determined by subsequent violations of anti-epidemic measures in 2019 associated with the COVID-19 pandemic, which, according to V. Isakov, D. Nikityuk, (2022), leads to a distortion of statistical indicators when assessing the manifestations of the epidemic process of chronic hepatitis C (CHC) [11]. One of the unfavorable outcomes of CHC is hepatocellular carcinoma (HCC). Considering that there are no specific statistics on HCC, the incidence of this nosological form was assessed using ICD-10, in which malignant neoplasms of the liver and intrahepatic bile ducts are summarized under code C22. The acceptability of this approach is due to the fact that 95% of all liver cancer cases are represented by HCC, which allows the use of official statistical reporting with a small degree of error.

Statistical analysis was carried out in the application package R. The study of differences in the distribution of morbidity rates between the Russian Federation and the Republic of Sakha (Yakutia) was carried out using the method of nonparametric assessment of the weighted average median of the Mann-Whitney test.

Results and discussion. An analysis of the incidence of infectious diseases in the Russian Federation over the first two decades of the 21st century revealed a unidirectional downward trend in this indicator for the vast majority of all major infectious diseases. An increase in long-term morbidity was detected only for infections caused by the human immunodeficiency virus and a group of acute respiratory viral infections [2]. At the same time, for acute respiratory viral infections, this increase was due mainly to their joint recording in 2020 with a new coronavirus infection, which began to be separately recorded in the relevant forms only in 2021.

As noted above, from the group of parenteral viral hepatitis, its most unfavorable component is CHC due to the signifi-



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
RF	21,1	29,5	30,7	33,1	34,0	31,8	35,8	37,1	39,1	40,9	40,2	39,9	39,1	39,3	39,9	38,0	36,2	34,7	32,7	30,8
RS(Y)	15,4	17,7	30,0	45,7	35,1	44,0	39,8	42,6	43,0	51,9	51,2	51,5	40,6	43,2	39,0	54,2	51,1	52,1	39,9	36,9

Fig. 1. CHC incidence rates in the Russian Federation (RF) and the Republic of Sakha (Yakutia) (RS (Y)) in 2000-2019, according to official registration (per 100,000 population)

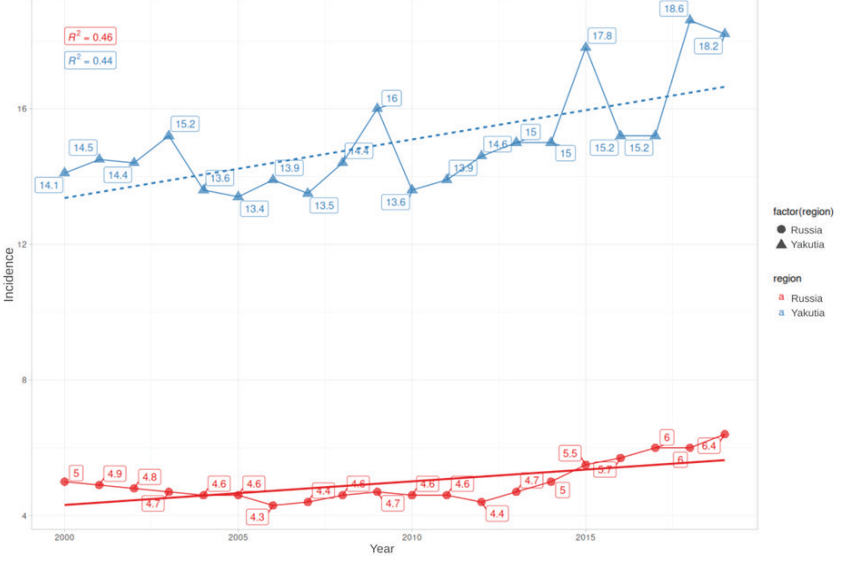


Fig. 2. Long-term dynamics of the incidence of malignant neoplasms of the liver and intrahepatic bile ducts in the Republic of Sakha (Yakutia) and the Russian Federation

cantly lower efficiency of epidemiological control in this disease. Consequently, despite significant advances in the creation of effective methods of treating hepatitis C, it still continues to be one of the leading causes of HCC, which is causally related to mortality from CHC [1].

It should also be noted that current studies indicate that the clinical manifestations of both CHC and HCC associated with HCV infection have not revealed any differences in the ethnic groups of Caucasians, Mongoloids and the Turkic-speaking population of Northeast Asia [3]. As for the epidemiological manifestations of the epidemic process of CHC in the territory of the Russian Federation and the Republic of Sakha (Yakutia), there are significant differences when comparing territorial indicators of the movement of the incidence of this infection [9].

The decrease in the intensity of the incidence of acute and chronic hepatitis C in Russia was unidirectional and the manifestation of their long-term movement was quite close. In contrast, in the Republic of Sakha (Yakutia) there was a significantly less pronounced decrease in the incidence of acute hepatitis C (4.9 times, growth rate -6.2%), and the incidence of CHC in general for the entire analyzed period was cyclical in nature and had a pronounced upward trend (2.4 times growth, growth rate +2.6%). The minimum value occurred in 2000 (15.4 per 100,000 population), and the maximum was noted in 2015 (54.2 per 100,000 population), with a long-term average of 41.2$^{0}/_{0000}$ (Fig. 1).

Currently, HCC is in second place among cancer causes of death [10]. The main etiological causes of HCC are hepatitis B and C viruses, and due to effective vaccine prevention of hepatitis B, the emphasis in etiological significance in recent years has shifted towards hepatitis C. In this regard, as a rule, the incidence of HCC is more correlated with the prevalence of CHC than with other risk factors.

To determine the incidence rates between CHC and malignant neoplasms of the liver and intrahepatic bile ducts in the Russian Federation and the Republic of Sakha (Yakutia), the Mann-Whitney criteria were used. The long-term dynamics of incidence in these territories followed a general trend, but with more factorial trends in the territory of the Republic of Sakha (Yakutia) (Fig. 2). It was found that there are additional statistically significant differences between the median incidence rates of CHC (p=0.0043) and liver cancer (p<0.00001) in comparable regions (Fig. 3). At the same time, if the incidence rate of CHC according to the

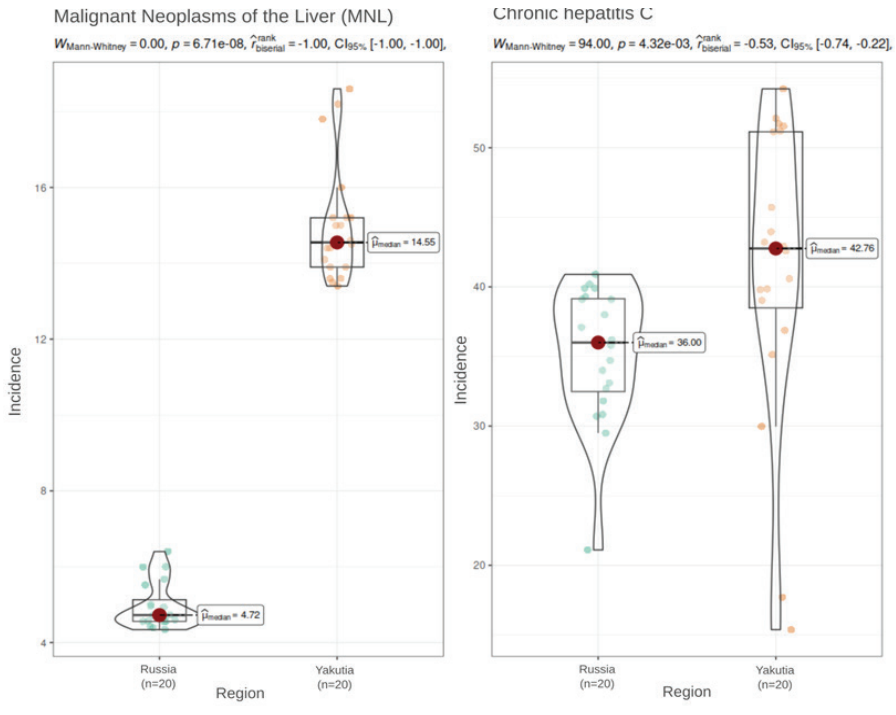


Fig. 3. Comparative level of long-term incidence of malignant neoplasms of the liver and intrahepatic bile ducts and CHC according to the weighted median of the Mann-Whitney test in the Republic of Sakha (Yakutia) and the Russian Federation

median in the Republic of Sakha (Yakutia) is 1.2 times higher according to observations with signs in the Russian Federation, then for malignant neoplasms of the liver and intrahepatic bile ducts in the Republic of Sakha (Yakutia) there is a 3-fold excess of the average long-term indicators federal estimates. Significant differences in the incidence of malignant neoplasms of the liver and intrahepatic bile ducts may be significant with the presence of additional risk factors in the Republic of Sakha (Yakutia). These include the widespread prevalence of hepatitis D virus in the republic, co-infection with hepatotropic viruses, diabetes mellitus, and metabolic syndrome [6].

Thus, at present, the manifestations of the epidemic process of CHC and malignant neoplasms of the liver and intrahepatic bile ducts in the Republic of Sakha (Yakutia) have pronounced unfavorable epidemiological differences compared to similar long-term indicators in the Russian Federation. These data indicate the need to apply proactive anti-epidemic measures to combat hepatitis C in the territory of the Republic of Sakha (Yakutia). These measures should include active efforts to identify new cases of HCC and prevent infection, improve the health care delivery system, and increase the coverage of patients in need of antiviral therapy and early diagnosis of HCC. Only in this case can we achieve target indicators and fit into the general trend of hepatitis C elimination in the country.

Conclusion. To assess the effectiveness of state programs for the elimination of hepatitis C in the Russian Federation, a comparative analytical assessment of the development of the epidemic process in certain territories of the country is necessary with mandatory consideration of natural, climatic, social and ethnic factors characteristic of a particular region. This approach is a necessary condition for obtaining reliable conclusions about the successful implementation and effectiveness of anti-epidemic measures in various territorial entities of the Russian Federation. Reducing the incidence of CHC in the Republic of Sakha (Yakutia) is a necessary, but not sufficient condition for reducing the incidence of malignant liver tumors. In this regard, attention to other risk factors of an infectious and constitutional nature should become an important element in a comprehensive strategy to combat diseases associated with viral hepatitis [4, 6].

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ANALYSIS OF THE MEDICAL AND DEMOGRAPHIC SITUATION IN THE REPUBLIC OF SAKHA (YAKUTIA) IN THE CONTEXT OF HEALTH THREATS DUE TO THE COVID-19 PANDEMIC

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UDC 614.2

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The analysis of fertility, morbidity (primary and general) and mortality in the Republic of Sakha (Yakutia), in dynamics, over a 10-year period (2013-2022). Differences in the structure of morbidity in the Republic of Sakha (Yakutia) and in the Russian Federation as a whole were revealed. The peak of mortality rates of the urban and rural population of the Republic of Sakha (Yakutia), caused by the COVID-19 pandemic, has been determined. Problematic aspects of rural health care have been identified, as well as diseases complicated by the pandemic that require rehabilitation. The results of the study should be taken into account by health authorities and institutions for management decisions on countering challenges and threats to the health of the population of the Republic of Sakha (Yakutia) caused by a new coronavirus infection.

Keywords: Republic of Sakha (Yakutia), health threats, morbidity of the population, rural health, COVID-19.

Introduction. The geopolitical and demographic situation in Russia and its territories necessitates the development of a promising model of medical and demographic policy [8, 9, 11, 13].

Inequality in the provision of medical care to the population of Russia is associated with geographic, climatic and national characteristics, as well as the territorial accessibility of medical care to rural residents [5]. The Republic of Sakha (Yakutia) (RS(Y)) is part of the Far Eastern Federal District (FEFD), which is the largest in the Asia-Pacific region [6, 12]. The COVID-19 pandemic has worsened the medical and demographic situation in the Russian Federation and its regions, including the Far Eastern Federal District and the Republic of Sakha (Yakutia) [1, 2, 4, 7].

The purpose of the study: to provide an analysis of the medical and demographic situation and newly identified morbidity among the population, including rural ones, in the Republic of Sakha (Yakutia) during the COVID-19 pandemic and to develop proposals for management decisions in healthcare at the regional and municipal levels.

Materials and methods of research: statistical and analytical. Materials from Rosstat, data from official state statistics of the Ministry of Health of Russia and the Republic of Sakha (Yakutia) were used.

Results and discussion. The Republic of Sakha (Yakutia) belongs to the Arctic territories of the Russian Federation, including the Arkhangelsk region, Krasnoyarsk region, Murmansk region, Chukotka, Nenets, Yamalo-Nenets autonomous districts, the Republic of Karelia, Komi. The Arctic zone of the Republic of Sakha (Yakutia) includes Anabarsky, Abyysky, Allaikhovsky, Bulunsky, Vernoyansky, Verkhnekolymsky, Srednekolymsky, Eveno-Bytantaysky and Ust-Yansky national uluses, Zhigansky, Momsky, Nizhnekolymsky, Oleneksky national districts. About 68 thousand people live here. (6.9% of the total population of the republic).

The Republic of Sakha (Yakutia) is a large administrative territory and ranks 8th in the world in terms of area (more than 3 million km2). The permanent population as of January 1, 2023 amounted to more than 997.6 thousand people, while the population density in the republic is tens of times lower than in the central part of Russia. The share of the urban population is 67.2%, the rural population is 32.8%, in the Russian Federation the share of the rural population is 36.9%.

Over 10 years of study in the Republic of Sakha (Yakutia), the mortality rate by 2021 increased from 8.7 to 10.7‰0 due to COVID-19; in 2022, the rate dropped sharply and amounted to (8.3‰). The birth rate in the Republic of Sakha (Yakutia) over the 10 years of analysis decreased from 17.5 to 11.8‰. In the Russian Federation, the mortality rate was (in 2022): mortality 12.9‰, birth rate 8.8‰.

The mortality rates of the rural population in the Republic of Sakha (Yakutia) for all years of analysis are significantly higher than those of the urban population; in 2022 the indicator was 9.5, urban -7.7 per 1000 of the corresponding population (Fig. 1). In the Russian Federation, these figures are 13.8 and 12.6‰, respectively.

A comparative analysis of the main causes of death in the RS(Y) and in the Russian Federation in 2022 showed that in the RS(Y) the indicators for all main causes of death were lower than in the RF. Mortality in the Republic of Sakha (Yakutia) is lower than in the Russian Federation: due to diseases of the digestive system (46%), some infectious and parasitic diseases (39), diseases of the circulatory system (36), neoplasms (36), diseases of the respiratory system (25%). Mortality from injuries, poisoning and some other consequences of external causes in the Republic of Sakha (Yakutia) is 12% higher than in the Russian Federation.

The average life expectancy at birth (number of years) in the Republic of Sakha (Yakutia) in 2022 was 72.7 years for the entire population (men 67.7, women 77.6). In rural areas for men this figure is low – 66.7 years.

During the study, an analysis was carried out of the newly identified morbidity in the Republic of Sakha (Yakutia) in pre-Covid 2019 and subsequent, so-called Covid years (2020-2022). In the covid year of 2020, compared to the pre-covid year of 2019, in the Republic of Sakha (Yakutia), the primary incidence decreased by 12.5%, from 103291.2‰$_{00}$ to 90425.5‰$_{00}$, which was the result of a decrease in preventive and dispensary work in the republic, as well as quarantine restrictions, which reduced the number of patients.

In the next 2021-2022. indicators began to increase and in 2022 the primary incidence rate was 123709.1‰$_{00}$, which is 19.8% higher than in pre-Covid 2019 (103291.2‰$_{00}$). This indicates the strengthening of preventive and clinical work with the population in the Republic of Sakha (Yakutia) at the regional and municipal levels.

During covid years 2020-2022. In the Republic of Sakha (Yakutia), there has been an increase in morbidity complicated by the COVID-19 pandemic. In 2022, compared to the pre-Covid year (2019), the incidence of diseases detected for the first time in the class of musculoskeletal and connective tissue diseases increased by 21.1% (from 2625.6 to 3178.8‰$_{00}$), this is mainly arthropathy, determining dorsopathies, rheumatoid arthritis, etc.

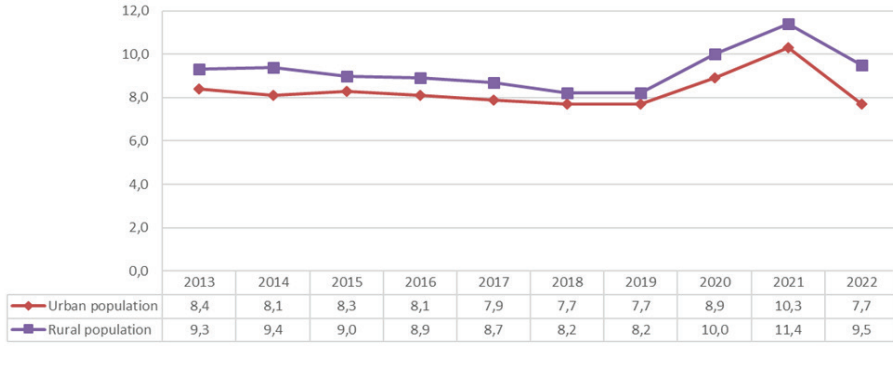
The COVID-19 pandemic has further aggravated the unfavorable situation with respiratory diseases in the republic, which is an Arctic region with a low population density. In the class of “respiratory diseases” in 2022, newly diagnosed morbidity increased by 13.7% compared to 2019 - from 57978.5 to 65916.2‰$_{00}$, this was mainly due to an increase in lesions of the upper respiratory tract. At the same time, the coronavirus determined the increase in clinical manifestations of pneumonia caused by the high tropism of the SARS-COV-2 virus to lung tissue with subsequent severe complications.

The noted increase in morbidity (primary) over the years of our analysis in the class “diseases of the blood, hematopoietic organs and individual disorders involving the immune mechanism” (by 4.3%) was associated mainly with anemia (which accounted for 88% in this class of diseases) and bleeding disorders, purpura, other hemorrhagic conditions (2.7%), etc.

The analysis indicates the need for an in-depth study of morbidities complicated by the pandemic at the municipal and regional levels, as well as the introduction of patient rehabilitation programs and the development of management decisions to enhance treatment and recreational activities for the population of the Republic of Sakha (Yakutia).

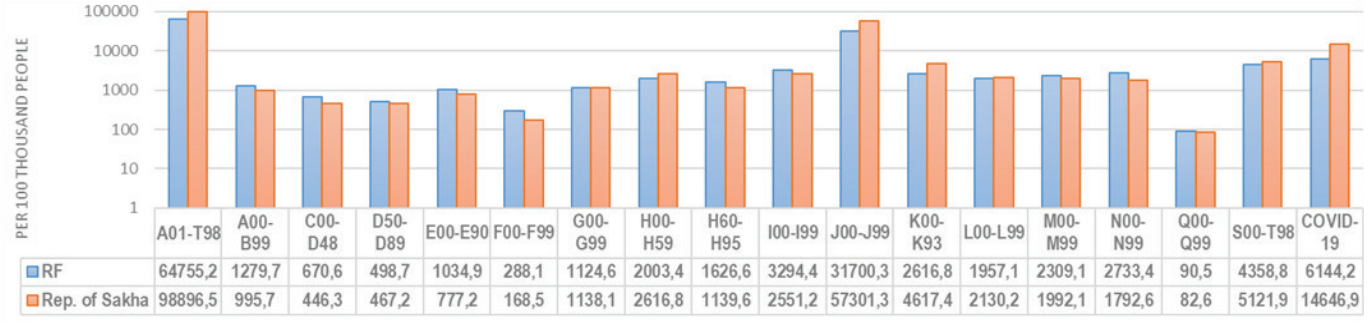
It should be noted that the incidence of COVID-19 in the Republic of Sakha (Yakutia) in 2020 was 4806.7‰00, in 2021 it increased to 9323.1‰$_{00}$, in 2022 the figure increased further to 17196.6‰$_{00}$, which is 3.6 times higher than in 2020. In the Russian Federation, this figure was respectively 3391.1; 8063.4 and 8538.0‰$_{00}$.

Fluctuations in the incidence of COVID-19 in the constituent entities of the Russian Federation amounted to 15.8 times, from 1089.3‰$_{00}$ in the Chechen Republic to 17195.6 in the Republic of Karelia. This is to a certain extent the result of the ambiguity in the coding of this pathology. It should be noted that the mortality rate from COVID-19 in the Republic of Sakha (Yakutia) was significantly lower (47.1‰$_{00}$) than in the Russian Federation as a whole (94.9‰$_{00}$), which indicates the effectiveness of the response of bodies and institutions to the pandemic situation healthcare in the republic.



	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Urban population	8,4	8,1	8,3	8,1	7,9	7,7	7,7	8,9	10,3	7,7
Rural population	9,3	9,4	9,0	8,9	8,7	8,2	8,2	10,0	11,4	9,5

Fig. 1. Mortality rates for the urban and rural population of the Republic of Sakha (Yakutia) in 2013-2022. (per 1000 of the corresponding population). Source: Sakha (Yakutia) stat



	A01-T98	A00-B99	C00-D48	D50-D89	E00-E90	F00-F99	G00-G99	H00-H59	H60-H95	I00-I99	J00-J99	K00-K93	L00-L99	M00-M99	N00-N99	Q00-Q99	S00-T98	COVID-19
RF	64755,2	1279,7	670,6	498,7	1034,9	288,1	1124,6	2003,4	1626,6	3294,4	31700,3	2616,8	1957,1	2309,1	2733,4	90,5	4358,8	6144,2
Rep. of Sakha	98896,5	995,7	446,3	467,2	777,2	168,5	1138,1	2616,8	1139,6	2551,2	57301,3	4617,4	2130,2	1992,1	1792,6	82,6	5121,9	14646,9

Name and code of disease classes according to ICD-10:
A01 - T98. Total diseases, including: A00-B99 Some infectious and parasitic diseases;
C00-D48 Neoplasms; D50-D89 Diseases of the blood, hematopoietic organs and certain disorders involving the immune mechanism; E00-E90 Diseases of the endocrine system, nutritional disorders and metabolic disorders; F00-F99 Mental and behavioral disorders; G00-G99 Diseases of the nervous system; H00-H59 Diseases of the eye and its adnexa; H60-H95 Diseases of the ear and mastoid I00-I99 Diseases of the circulatory system; J00-J99 Respiratory diseases; K00-K93 Diseases of the digestive system; L00-L99 Diseases of the skin and subcutaneous tissue; M00-M99 Diseases of the musculoskeletal system and connective tissue; N00-N99 Diseases of the genitourinary system; Q00-Q99 Congenital anomalies [malformations], deformations and chromosomal disorders; S00-T98 Injuries, poisoning and certain other consequences of external causes

Fig. 2. Morbidity rates (primary) for the rural population in the Russian Federation and in the Republic of Sakha (Yakutia) (2022) depending on the class of diseases (ICD-10) (per 100,000 of the corresponding population) [10]

Taking into account the climatic and geographical features of the Arctic zone of the Republic of Sakha (Yakutia), we analyzed the indicators of newly identified morbidity among the rural population in the Republic of Sakha (Yakutia) in comparison with the Russian Federation (2022), which made it possible to identify problematic aspects of providing medical care to rural residents.

The analysis established that, in general, the primary morbidity rate of rural residents in the RS(Y) is almost 1.5 times higher than in the Russian Federation (the indicator is 98896.5 and 64755.2‰$_{00}$, respectively). In the Republic of Sakha (Yakutia), higher rates were noted in the following classes: "diseases of the respiratory system" (80.8% higher), "diseases of the digestive system" (76.5), "diseases of the eye and its appendages" (up 30.6), "injuries, poisoning and some other consequences of external causes" (by 17.5%), etc. (Fig. 2).

At the same time, rural residents in the Republic of Sakha (Yakutia) showed lower rates of primary morbidity in the following classes than in the Russian Federation: "mental disorders and behavioral disorders" (by 41.5%), "diseases of the genitourinary system" (by 34.4), "neoplasms" (by 33.4), "diseases of the ear and mastoid process" (by 29.9), "diseases of the circulatory system" (by 22.6%), etc.

The reasons for the lower newly diagnosed incidence among the rural population in the Republic of Sakha (Yakutia) is the poor territorial accessibility of medical care for residents of rural settlements, which determines the importance of strengthening preventive and dispensary work with this contingent of patients.

The results of the analysis determine the importance of rehabilitation of rural residents with this pathology, the implementation of dispensary observation and preventive work in rural areas.

Conclusion. Over the 10 years of our study (from 2011 to 2022), in the Republic of Sakha (Yakutia) there was an increase in mortality from 8.7 to 10.7‰$_{0}$ due to COVID-19; in 2022, the figure decreased and amounted to (8 .3%). The birth rate in the Republic of Sakha (Yakutia) over the 10 years of analysis decreased from 17.5 to 11.8‰. In the Russian Federation, the mortality rate was 12.9‰, the birth rate – 8.8‰. The mortality rate of the rural population in the Republic of Sakha (Yakutia) is significantly higher than in the city; the figures were respectively: village - 9.5‰ and city - 7.7‰. The incidence of COVID-19 in the Republic of Sakha (Yakutia) is growing and in 2020 it was 4806.7‰$_{00}$, in 2021 - 9323.1, in 2022 - 17196.6, which is higher than in 2020, 3.6 times. In the Russian Federation, the figures were 3391.1, 8063.4 and 8538.0‰$_{00}$, respectively. In the constituent entities of the Russian Federation, fluctuations in the incidence of COVID-19 amounted to 15.8 times.

In 2020, the Covid year, compared to the pre-Covid 2019 in the Republic of Sakha (Yakutia), the primary incidence decreased by 12.5%, from 103291.7 to 90425.6‰$_{00}$. In the subsequent covid years in the Republic of Sakha (Yakutia), there was an increase in morbidity, complicated by the COVID-19 pandemic and requiring rehabilitation, in the following classes: "respiratory diseases", "blood diseases, hematopoietic organs and certain disorders involving the immune mechanism", "diseases musculoskeletal system and connective tissue", etc.

A comparative study of the newly identified morbidity of the rural population in the Russian Federation and in the Republic of Sakha (Yakutia) (2022) was carried out. The analysis revealed problematic aspects of rural health care. The incidence of disease detected for the first time among residents of rural settlements in the Republic of Sakha (Yakutia) is almost 1.5 times higher than in the Russian Federation. In the Republic of Sakha (Yakutia), higher and lower rates of newly diagnosed morbidity among rural residents than in the Russian Federation have been determined, which determines the need for their rehabilitation, clinical examination and preventive work in rural settlements.

Conclusions. The results of the study are important and should be used to develop management decisions to counter threats to public health in the Republic of Sakha (Yakutia) caused by coronavirus infection.

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TOPICAL ISSUE

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INCIDENCE OF HIV INFECTION AND AWARENESS OF HIV INFECTION AMONG THE POPULATION OF THE IRKUTSK REGION

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The article presents certain aspects of the epidemiological situation regarding HIV infection in the Irkutsk region: morbidity in adults, children and adolescents, dynamics of transmission routes and age groups at risk. According to the results of the sociological study, a satisfactory level of awareness of the region's residents on HIV infection issues has been shown, with significant differences by gender and age groups. The results obtained are necessary to increase the effectiveness of information and educational work among the population, with an individual approach to each gender and age group.

Keywords: HIV infection, morbidity, awareness, age groups at risk, prevention.

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Introduction. The epidemic spread of HIV infection continues on the territory of the Russian Federation (RF). In 2022, 34 constituent entities of the Russian Federation had rates of newly diagnosed morbidity that exceeded the Russian average [8]. The Irkutsk region is one of the five most disadvantaged regions: in 2022, the incidence rate was 1.8 times higher than the all-Russian one (79.3 versus 43.3 per 100 thousand), the incidence rate was 2.5 times higher (1977.9 versus 794 .7 per 100 thousand, respectively) [8].

The economic damage caused by HIV infection in the Russian Federation in 2022 is estimated at 262.5 billion rubles. [8]. The high epidemiological, social and economic significance of the consequences of the spread of the human immunodeficiency virus (HIV) determines the main directions of prevention [9]. The leading preventive measure remains awareness-raising activities. Taking into account the peculiarities of the epidemiological situation in the region, the priority is to study the awareness of different age groups of the population on current issues of HIV infection.

Purpose of the study: to study the incidence of HIV infection and awareness in different age groups of the population of the Irkutsk region on the epidemiology

and prevention measures of this infection.

Materials and methods of research. A descriptive retrospective epidemiological study was conducted using continuous samples from statistical forms of the Irkutsk region (No. 2 «Information on infectious and parasitic diseases», No. 61 «Information on HIV infection»). The dynamics of HIV transmission routes are presented from the beginning of the epidemic rise in incidence (1999–2022); the incidence of three main population groups and the newly diagnosed incidence of HIV infection among 7 age groups, calculated based on long-term average values for 2016–2022, were studied.

The population's awareness of HIV infection issues was studied during a sociological study (questionnaire) on the Google platform from October 2022 to July 2023. The questionnaire included closed-ended questions about the epidemiology and basic measures to prevent HIV infection. 2063 people took part in the survey – 457 men and 1606 women (77.8 and 22.2 %, respectively) with the following distribution by age groups: 16-17 years old – 234 people (11.3 %); 18-25 years old – 885 people (43.0 %), 26-45 people (37.6 %) and over 46 years old – 168 people (8.1 %). To assess the statistical significance of differences in relative indicators, confidence intervals were calculated with a significance level of 95 % (95 % CI). To assess the awareness of groups on certain grounds (by gender and age groups), the ratio of the proportion of respondents who marked all the correct answers to the proportion of people who selected partially correct answers was determined. Based on the obtained ratios, the ranking positions of the four age groups of respondents were determined, separately for two questions. After summing these ranking positions, the final ranks were obtained. Graphical processing of data was performed using Excel (Windows 2010).

Results and discussion. For a number of years, the Irkutsk region has been among the regions with high levels of incidence and prevalence of HIV infection [8]. In the long-term dynamics of morbidity among adults, adolescents and children under 14 years of age, during the observation period there was a downward trend, the rate of decline was 4.5; 9.5 and 8.3 % respectively. Moreover, the period 2020–2022 was characterized by low incidence rates (Fig. 1) [1, 10, 12, 13].

Over the entire period of the epidemic spread of HIV, significant changes in the leading transmission routes have been observed (Fig. 2). If at the beginning of the epidemic, from 1999 to 2007, the parenteral route predominated (specific gravity more than 90.0 %), then since 2008 the HIV epidemic in the region has entered a generalized phase – with a predominance of sexual transmission (more than 55.0 %), as in other regions of Russia [1, 4, 10, 11].

The age groups involved in the epidemic process have also undergone significant changes [1, 3]. Thus, if in the first years of the HIV epidemic the main contribution was made by persons under the age of 24 years, currently HIV infection is registered mainly among persons 25-49 years old with the highest rates in the age group 35-44 years (Fig. 3).

Based on the results of the survey, to the question "Do you consider yourself in-

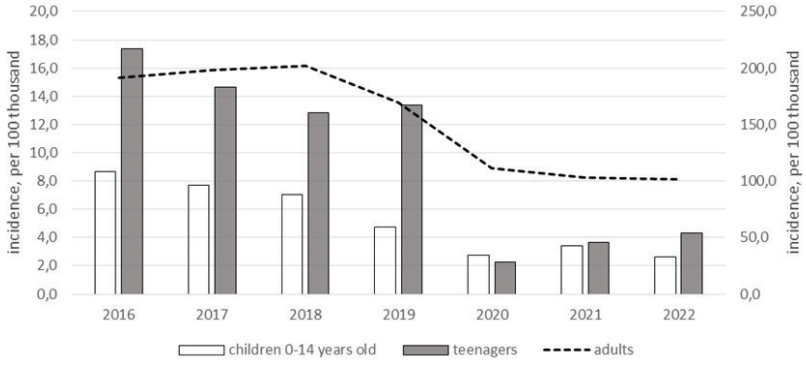

Fig. 1. Dynamics of newly diagnosed incidence of HIV infection among different population groups for 2013-2022 (per 100 thousand)

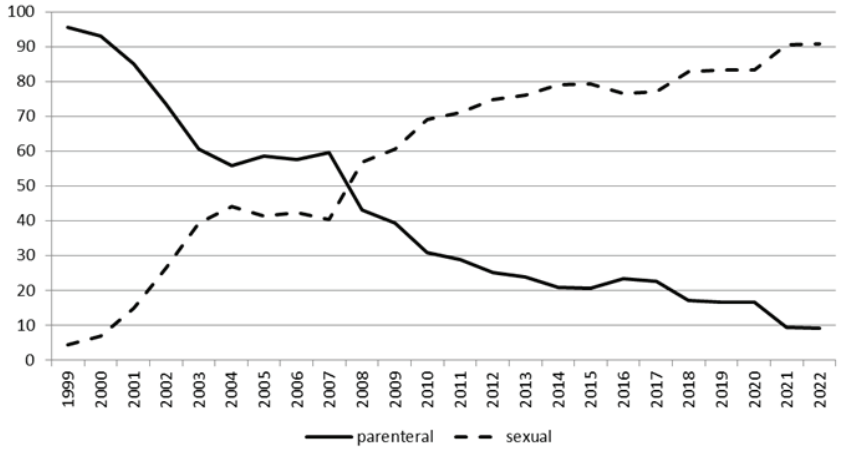

Fig. 2. Dynamics of the share of HIV transmission routes for 1999-2022. (percentage)

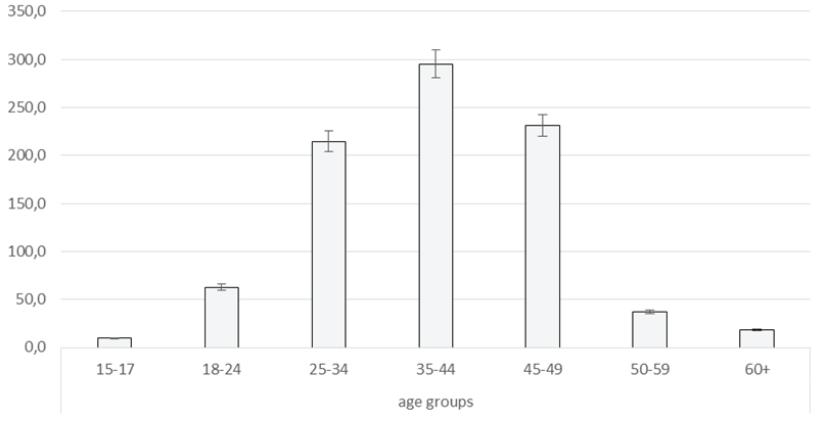

Fig. 3. Newly detected incidence of HIV infection in individual age groups based on long-term average values for 2016-2022. (per 100 thousand)

formed on issues of HIV infection/AIDS?" 85.0 % of respondents answered affirmatively, 5.0 % responded negatively, and 10.0 % found it difficult to answer. As in a similar survey [5], women consider themselves to be more informed on HIV issues than men surveyed (87.1 versus 77.5 %), and the proportion of men who do not consider themselves informed is 2.6 times higher. than women (9.6 versus 3.7 %). Among the respondents who found it difficult to answer this question, 9.2 % were women and 12.9 % were men. In terms of age groups, people aged 18-25 years (88.6 %) and 26-45 years (87.8 %) consider themselves more knowledgeable about HIV issues. Teenagers aged 16-17 years consider themselves least informed (64.1 %), every fifth of them found it difficult to answer this question (21.4 %), while among all respondents – only every tenth.

When asked whether the problem of HIV infection could affect you personally, 47.4 % of respondents answered «yes»; 42.0 % – «no»; 10.6 % found it difficult to answer. There was no statistically significant difference in the answers of men and women.

One third of the respondents, when asked how one can become infected with HIV, noted all the correct answers about the routes of infection – 31.3 %; two-thirds of respondents chose partially correct answers – 68.7% (Table 1). Thus, the ratio of shares was 1: 2.2. There is a statistically significant gender difference, both in the proportion of people who chose all the correct answers – 25.4 % of men and 32.9 % of women, and in the group of people who chose partially correct answers – 74.6 and 67.1 %, respectively . This is clearly demonstrated by the ratios of shares (Table 1).

The choice of partially correct answers to the question about possible routes of transmission of HIV infection by individual age groups ranged from 66.4 to 78.0% (Table 2). Those surveyed aged 16-17 and 26-45 years were more knowledgeable about transmission routes. Moreover, the proportion of respondents in the middle age group from 26 to 45 years old who correctly noted all routes of HIV infection (33.6 %) was statistically significantly different from the proportion of persons aged 18-25 (25.4 %) and over 46 years (22.0 %).

To prevent HIV infection, respondents believe that the following measures can be used: a condom with every sexual intercourse (96.3 %); disposable syringes for intravenous infusions (90.4 %), sexual relations with only one partner (60.2 %). All correct answers to the question of how to prevent HIV infection were given by 32.3 % of respondents. At the same time, the proportion of respondents who knew all the answers to this question was statistically significantly higher among women than among men – 35.8 versus 19.9% (Table 1). Age groups with the choice of all correct answers about preventive measures were distributed as follows (in descending order of share): 18-25 years (35.3 %), 26-45 years (32.0 %), over 46 years (28.0 %) and 16-17 years old (25.6 %) with a statistically significant difference between the age groups 16-17 and 18-25 years old (Table 2).

Based on the results of the final ranking, we can conclude that the most informed age groups in the Irkutsk region on HIV issues are people 26-45 years old, and the least informed are people over 46 years old [14]. The youngest respondents, persons from 16 to 25 years old, have an average level of awareness, occupying the 2nd and 3rd ranking positions. Moreover, if 16-17-year-old adolescents know better the ways of transmitting HIV infection and less well – prevention measures, then young people from 18 to 25 years old do the opposite, which indirectly indicates a high risk of the spread of HIV infection among young people [5, 13].

Conclusion. Against the background of the current situation regarding HIV infection in the region, the results of a sociological study showed a sufficient level

Table 1

Distribution of answers to questions about routes of HIV infection and measures to prevent it among men and women (percentages, 95% CI)

choosing the correct answers	question about ways of contracting HIV infection			question about HIV prevention measures		
	men	women	total	men	women	total
all selected	25.4 [21.5÷29.3]	32.9 [30.6÷35.2]	31.3 [29.4÷33.2]	19.9 [16.4÷23.4]	35.8 [33.5÷38.1]	32.3 [30.4÷34.2]
partially selected	74.6 [70.7÷78.5]	67.1 [64.8÷69.4]	68.7 [66.8÷70.6]	80.1 [76.6÷83.6]	64.2 [61.9÷66.5]	67.7 [65.8÷69.6]
share ratio	1:2.9	1:2.0	1:2.2	1:4.0	1:1.8	1:2.1

Table 2

Distribution of answers to questions about routes of infection and prevention measures among different age groups (percentages, 95% CI)

choosing the correct answers	age groups			
	16-17 years old	18-25 years old	26-45 years old	over 46 years old
question about ways of contracting HIV infection				
all selected	32.9 [27.1÷38.7]	25.4 [22.5÷28.3]	33.6 [30.5÷36.7]	22.0 [16.0÷28.0]
partially selected	67.1 [61.3÷72.9]	74.6 [71.7÷77.5]	66.4 [63.3÷69.5]	78.0 [71.8÷84.2]
share ratio	1:2.0	1:2.9	1:2.0	1:3.5
ranking position*	1.5**	3	1.5	4
question about HIV prevention measures				
all selected	25.6 [23.9÷27.3]	35.3 [32.2÷38.4]	32.0 [28.9÷35.1]	28.0 [21.4÷34.6]
partially selected	74.4 [68.5÷80.2]	64.7 [61.6÷67.8]	68.0 [64.9÷71.1]	72.0 [65.4÷78.6]
share ratio	1:2.9	1:1.8	1:2.1	1:2.6
ranking position	4	1	2	3
final rank for two questions	3	2	1	4

* by share ratio
** two age groups share 1st and 2nd place

of awareness on HIV infection issues: 85% of respondents consider themselves informed; to prevent HIV infection, 90.4 % indicated the mandatory use of disposable syringes for intravenous injections and 96.3 % – condoms. At the same time, there is a statistically significant difference in the level of awareness on epidemiological issues and preventive measures by gender and by age group – men and people aged 16-25 and over 45 years are less informed. The results obtained to assess the level of knowledge about HIV infection are necessary to increase the effectiveness of outreach work among the population [1, 2, 5, 6, 10, 12-14], with a focus on risk groups and an individual approach to each sex and age group according to the State Strategy to Combat the Spread of HIV Infection in Russia for the Period until 2030 [7].

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DIAGNOSIS AND TREATMENT OF BILIARY TRACT DISEASES IN PATIENTS WITH COVID-19

The features of diagnosis and treatment of biliary tract diseases in patients with COVID-19 were studied. An increase in the number of non-calculous cholecystitis and gallbladder gangrene in severe cases of COVID-19 was revealed. The immunosuppressive effect of SARS-CoV-2, anti-inflammatory and antibacterial therapy, and multiple organ failure led to a decrease or complete absence of local symptoms and leukopenia in acute cholecystitis. In severe cases of COVID-19, the basis for diagnosing acute cholecystitis was dynamic ultrasound examination of the abdominal cavity, diagnostic laparoscopy and laparotomy in patients with the highest levels of leukocytosis, CRP and PCT. The greatest number of postoperative complications and deaths were observed in patients with severe COVID-19. In patients with malignant neoplasms of the biliary tract, the main symptom was "painless" jaundice. The diagnosis was confirmed by abdominal CT scan. All patients underwent minimally invasive ultrasound and endoscopic drainage operations.

Keywords: Acute cholecystitis, new coronavirus infection, COVID-19.

Introduction: The pandemic of the new coronavirus infection () COVID-19 showed that, affecting the respiratory organs, the SARS-CoV2 virus was found in almost all organs and tissues of the body, causing multiorgan lesions [9, 11].

The pathogenesis of COVID-19 is complex, with the formation of immunopathological reactions and multiple organ failure (MOF), and its manifestations are heterogeneous due to the varying severity of the disease [10].

Treatment of COVID-19 is accompanied by antibacterial (ATB), anti-inflammatory, antiviral, and detoxification therapy, which affects the manifestation of concomitant pathology, causes reactions and complications of drug therapy [11].

All this eliminates the symptoms of combined surgical diseases or causes their false symptoms.

There are numerous reports in the available literature on the treatment of combined surgical pathology of the abdominal cavity organs (ACO) in patients with COVID-19 , however, almost all of them are devoted to compliance with the epidemiological safety regime and the organization of emergency surgical care [3,7,8].

At the same time, the effect on the diagnosis and treatment of combined surgical diseases of abdominal cavity organs in pathological changes in the immune system, homeostasis and multiple organ lesions due to COVID-19 , as well as combined ATB and anti-inflammatory therapy has not yet been studied.

Materials and methods. The analysis of 109 cases of diagnosis and treatment of acute diseases of the biliary tract in patients with COVID-19 , who were in the infectious diseases hospital (IH) on the basis of the City Clinical Hospital named after Prof. A.M. Voino-Yasenetsky of the Ministry of Health of the Khabarovsk Krai in the period from January 2020 to January 2021.

Of these, 104 cases revealed acute cholecystitis FC and 4 cases – tumor lesions of the biliary tract (TLBT).

According to the clinical situation during the pandemic, all patients were divided into 3 groups by us.

The first group consisted of patients who had acute pathology of the biliary tract in the absence of clinical manifestations of the COVID-19 ("virus carriers"). The reason for their referral to the IH admission department in the detection of acute surgical pathology was the positive result of the mandatory PCR test for SARS-CoV2.

The 2nd and 3rd groups included patients with clinical manifestations of COVID-19 . At the same time, in the 2nd group, some patients with a milder course of COVID-19 were treated on an outpatient basis and against this background, they revealed the presence of acute pathology of the biliary tract. The other part was made up of patients from surgical departments of multidisciplinary medical institutions, who, during the treatment of acute pathology of the biliary tract, were diagnosed with the presence of COVID-19 S with their referral to IH.

The 3rd group included patients with a more severe course of COVID - 19 , who are in IH, in whom a combined acute surgical pathology of the biliary tract was detected later during the treatment of the underlying disease.

There were 29 (27.9%) men and 75 (72.1%) women among patients with acute cholecystitis

Patients with acute cholecystitis in group 1 had 30 (28.8%) patients, in group 2 - 45 (43.3%) patients and in group 3 - 29 (27.9%) patients.

The average age of patients in group 1 was 56.5±9.2 years, group 2 - 71.2±8.1 years and group 3 – 73.8±8.9 years.

The risk of concomitant pathology was assessed using the Charlson index [4].

The severity of the course of the COVID-19 was assessed on the News scale [14]. The assessment of postoperative complications was based on the Clavien-Dindo scale [2]. The assessment of the degree of lung damage was carried out according to CT of chest [1]. The degree of impaired consciousness was assessed on the Glasgow Coma Scale (GCS) [6]. The severity of acute cholecystitis was assessed on a scale, TG 13 [12].

The diagnosis and treatment of COVID-19 s was carried out according to the interim clinical guidelines for the diagnosis and treatment of COVID-19 s [16].

Quantitative indicators were evaluated for compliance with the normal distribution using the Shapiro-Wilk criterion (with fewer than 50 subjects) or the Kolmogorov-Smirnov criterion (with more than 50 subjects). In the absence of a normal distribution, quantitative data were described using the median (Me) and the lower and upper quartiles (Q1 – Q3).

Table 1

Values of the CT criterion, respiratory failure (RF), and GCS in patients with acute cholecystitis and COVID-19

Parameter	Value	Patient groups					
		1st		2nd		3rd	
		n	%	n	%	n	%
CT criterion (st.)	0-1	30 (9)	100.0	34 (27)	75.6 (60.0)	-	-
	2	-	-	11 (6)	24.4 (13.3)	6 (5)	20.7 (17.2)
	3	-	-	-	-	11 (9)	37.9 (31.0)
	4	-	-	-	-	12 (7)	41.4 (24.1)
RF (st.)	0-1	30 (9)	100.0	43 (32)	95.6 (71.1)	10 (9)	34.5 (31.0)
	2	-		2 (1)	4.4 (2.2)	12 (8)	41.4 (27.6)
	3	-		-	-	7 (4)	24.1 (13.8)
GCS (points)	15	30 (9)	100.0	42 (30)	93.3 (66.7)	16 (10)	55.2 (34.5)
	13-14	-	-	3 (3)	6.7 (6.7)	11 (9)	37.9 (31.0)
		-	-	-	-	2 (2)	6.9 (6.9)
Total:		30 (9)	100.0 (30.0)	45 (33)	100.0 (73.3)	29 (21)	100.0 (72.4)

The number of operated patients out of their total number is indicated in parentheses.

Table 2

The severity of the course of COVID-19 in patients with acute cholecystitis on the News scale

Value of the News scale points	Patient group			P
	1st	2nd	3rd	
1-4	30 (100.0)	36 (80.0)	0 (0.0)	< 0.001*
5-6	0 (0.0)	6 (13.3)	10 (34.5)	$p_{1\text{ группа}-2\text{ группа}} = 0.033$
Over 7	0 (0.0)	3 (6.7)	19 (65.5)	$p_{1\text{ группа}-3\text{ группа}} < 0.001$
				$p_{2\text{ группа}-3\text{ группа}} < 0.001$

* – differences in indicators are statistically significant ($p < 0.05$).

Categorical data were described with absolute values and percentages.

The comparison of percentages in the analysis of multipole conjugacy tables was performed using Pearson's chi-squared criterion.

The analysis of the obtained data was performed in the statistical package StatTech v. 1.2.0 (developed by Stattech LLC, Russia).

Results and discussion. In patients with AC, the Charlson index value was 3.46±1.2 in group 1, 4.48±2.5 in group 2 and 5.65±3.1 in group 3.

From the data presented (Tables No. 1 and No. 2), it can be seen that in patients with acute cholecystitis, the age of patients, the severity of the course of COVID-19, the degree of respiratory failure and impaired consciousness significantly increased from group 1 to group 3.

Patients of the 1st group in 96.7% of cases during their stay in the IH did not have clinical manifestations of COVID-19 s, remaining "virus carriers". The most severe course of COVID-19 s was observed in patients of the 3rd group.

The main clinical manifestation of acute cholecystitis in group 1 patients was acute pain in the right hypochondrium.

Leukocytes count in the clinical blood test (CBT) in 83.3% of cases remained within the normative indicators (Table 3).

In accordance with the presented table, when comparing the "Leukocyte count" value relative to the "Group" value, statistically significant differences were found ($p < 0.001$) *(method used: Kraskel–Wallis criterion)*.

Ultrasound of the abdominal cavity revealed calculous acute cholecystitis in all cases.

In group 2 patients, acute pain in the right hypochondrium was noted in 43 (95.4%) cases. In 2 (4.4%) cases, abdominal pain was non-localized and unexpressed, which was associated with the therapy with antibacterial and anti-inflammatory drugs.

In the laboratory, leukopenia up to $3.0x10^9$/l was observed in the clinical blood test, as well as a significant increase in the level of PCT and CRP ($p<0.05$) (Table 3, 4).

In the 1st case (2.0%), there was an increase in bilirubin levels to 54.2 μmol/l.

When analyzing the "CRP" parameter relative to the "Group" parameter, statistically significant differences were revealed ($p < 0.001$) *(method used: Kraskel–Wallis criterion)*.

Ultrasound of the abdominal cavity revealed calculous acute cholecystitis in 41 (90.0%) cases and non–calculous AC in 4 (10.0%) cases. In the 1st case, the presence of choledocholithiasis was revealed.

In patients of the 3rd group with a level of consciousness of 14-15 GCS points in 24 (82.7%) cases, abdominal pain of varying severity was detected. In 3 (10.4%) cases with depression of consciousness up to 9-12 GCS points, palpation of the abdomen showed a patient's reaction in the form of the patient pulling back the doctor's hand and "grimacing pain" on the face.

In 2 (6.9%) patients with depression of consciousness up to 9 GCS points, general clinical diagnosis was not available. Clinical diagnosis was especially difficult in patients on a ventilator.

The basis for a targeted diagnostic search for acute surgical pathology of an inflammatory nature in these patients was a progressive increase in cardiovascular inflammatory response phenomena in the form of high leukocytosis in the clinical blood test, refractory to antibacterial and anti-inflammatory therapy, as well as high values of CRP and PCT levels exceeding their average values in the group of patients with COVID-19 (Figure).

Ultrasound of the abdominal cavity revealed calculous acute cholecystitis in 24 (82.8%) cases and non–calculous AC in 5 (17.2%) cases.

With repeated ultrasound of the abdominal caviyu organs for 10-12 hours,

Table 3

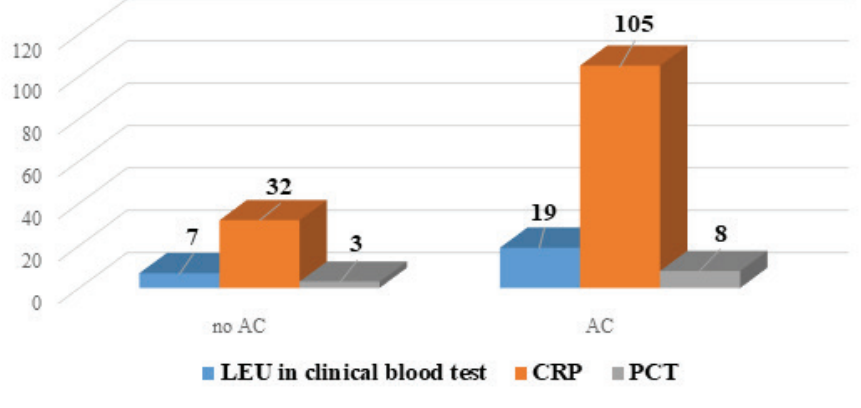
Leukocytes count in the clinical blood test in patients with acute cholecystitis and COVID-19

Patient group	Leukocytes count			P
	Me	$Q_1 – Q_3$	n	
Group 1	6	5 – 8	30	< 0.001*
Group 2	3	2 – 4	45	$p_{2\ группа\ –\ 1\ группа} < 0.001$
Group 3	19	16 – 26	29	$p_{3\ группа\ –\ 1\ группа} < 0.001$ $p_{3\ группа\ –\ 2\ группа} < 0.001$

Table 4

PCT and CRP values in patients with acute cholecystitis and COVID-19

Parameter	Group	Me	$Q_1 – Q_3$	n	p
Procalcitonin test	1	0	0 – 0	30	< 0.001*
	2	3	2 – 5	45	$p_{2\ group\ –\ 1\ group} < 0.001$
	3	8	5 – 9	29	$p_{3\ group\ –\ 1\ group} < 0.001$ $p_{3\ group\ –\ 2\ group} = 0.001$
C-reactive protein	1	0	0 – 0	30	< 0.001*
	2	69	25 – 88	45	$p_{2\ group\ –\ 1\ group} < 0.001$
	3	105	79 – 167	29	$p_{3\ group\ –\ 1\ group} < 0.001$ $p_{3\ group\ –\ 2\ group} = 0.008$



Average values of leukocyte, CRP and PCT levels in patients with COVID-19

an increase in destruction in the wall of the gallbladder was noted in 71 (68.7%) patients, which we used for timely diagnosis of acute cholecystitis in patients with impaired consciousness up to 9 GCS points.

Ultrasound of the abdominal cavity revealed calculous acute cholecystitis in 24 (82.8%) cases and non–calculous acute cholecystitis in 5 (17.2%) cases, which indicates an increase in the number of cases of non-calculous cholecystitis with an increase in the severity of the course of COVID-19 .

Assessment of the severity of the course of acute cholecystitis in patients with patients with COVID-19 on the TG 13 scale in groups (Table 5) showed the presence of a direct correlation (r =0.981) between the severity of the course of acute cholecystitis and COVID-19 , which is objective, since the combined nature of these diseases reflects inflammatory processes on the TG 13 scale changes and multiple organ disorders caused by the COVID-19 s.

Conservative treatment of acute cholecystitis included antispasmodic, antibacterial and infusion therapy before relief of acute inflammation or early cholecystectomy.

In all patients of group 1, the operation was performed on the first day of admission to the IH. Open cholecystectomy was performed in 5 (55.6%) cases and laparoscopic in 4 (44.4%) cases.

After surgery, the 1st “virus carrier” patient recorded the development of the COVID-19 clinical symptoms with lung damage up to CT grade 2. Respiratory failure grade 0. The remaining patients were discharged after a negative result of a PCR test for SARS–COV2. There were no postoperative complications or deaths (Table 6).

In the 2nd group of patients, 33 (73.3%) people were operated on. 25 (75.8%) open cholecystectomies and 8 (24.2%) laparoscopic ones were performed. In 2 (6.0%) cases with open cholecystectomies, choledocholithiasis was detected, choledocholithotomy was performed, and external drainage of the choledochus was performed. In 4 (18.2%) of them, acute cholecystitis was stone-free.

In group 3 patients, open cholecystectomy was performed in 14 (68.2%) cases and laparoscopic in 7 (31.8%) cases. In 5 (23.8%) cases, acute cholecystitis was stone-free.

According to the pathohistological study, gangrenous acute cholecystitis was detected in 5 (55.6%) cases in the 1st group of patients, in 12 (36.4%) cases in the 2nd group and in 14 (67.7%) cases in the 3rd group.

Thus, in the 1st group of patients with acute cholecystitis , gangrenous cholecystitis occurred in 16.7% of cases, in the 2nd group - in 26.7% of cases and in the 3rd group - in 46.7% of cases. According to literature data, gangrene, empyema and perforation of the gallbladder occur in 10-30% of patients with AC without COVID-19 [13].

The largest number (48.2%) of postoperative complications were found in the most severe COVID-19 patients of group 3.

There were 6 postoperative deaths. Of these, 2 (1.9%) patients in group 2 and 4 (2.4%) patients in group 3 died. The cause of deaths is the progression of COVID–19 s with the development of CT grade 4.

Among patients with tumor lesions of biliary tract, 2 (50.0%) patients were “virus carriers” in group 1 and 2 (50.0%) patients in group 2.

The Charlson index value was 3.5±1.4 points in group 1 and 5.1±2.3 points in Group 2

The leading clinical symptom of tumor lesions of biliary tract in these patients was the presence of “pain-free” jaundice.

The level of consciousness in all patients was 15 GCS points. Patients of the 2nd group had CT grade 0-1, respiratory failure grade 0.

In a biochemical blood test, the bilirubin level was 214±23 μmol/l, ALT and AST up to 150 units/l.

Ultrasound and SCT scan of the abdominal cavity were performed. In 2 cases, a tumor of the pancreatic head was detected and in the remaining 2 cases, a Klatskin tumor.

All patients underwent minimally invasive intervention: in 3 cases, percutaneous transhepatic cholangiostomy and in 1 case, endoscopic papillosphincterotomy with stenting of the common bile duct with a plastic stent.

The peculiarity of minimally invasive interventions in tumor lesions of biliary tract was the need to correct hemostasis in patients of the 2nd group.

There were no postoperative complications. Patients were discharged after a negative result of a PCR test for SARS-CoV2.

Conclusions: Immunopathological reactions, impaired consciousness, and the ongoing antibacterial and anti-inflammatory therapy of COVID-19 s make it difficult to diagnose acute cholecystitis,

Table 5

Severity of the course of acute cholecystitis in patients with COVID-19 on the TG 13 scale

Severity of cholecystitis	Patient groups					
	Group 1		Group 2		Group 3	
	n	%	n	%	n	%
Grade 1	22	73.3	9	20.0	-	-
Grade 2	8	26.7	19	42.2	9	31.0
Grade 3	-	-	17	37.8	20	69.0
Total:	30	100.0	45	100.0	29	100.0

Table 6

Postoperative complications in patients with acute cholecystitis and COVID-19 according to Clavien-Dindo

Group of complications	Nature of the complications	Patient groups						Degree of severity
		1-я		2-я		3-я		
		абс	%	абс.	%	абс	%	
From other organs	Weighting of the CT criterion, degree of respiratory failure	-	-	1	2.2	-		II
		-	-	2	4.4	4	13.8	V
From surgical wound	Suppuration, seromas, eventration	2	6.7	4	8.9	5	17.2	III a, III b
Related to intestinal motility disorders	Postoperative intestinal paresis	-	-	3	6.7	5	17.2	I, II
Total:		2	6.7	10	22.2	14	48.2	

leading to smoothness or complete absence of local pain symptoms, and cause the presence of leukopenia.

With an increase in the severity of the course of COVID-19 , the severity of the course of acute cholecystitis according to TG 13 increases, and the frequency of detection of non-calculous and gangrenous acute cholecystitis increases.

In patients with impaired consciousness according to the GCS of 9-13 points, CT grade 4, respiratory failure grade 3 the basis for a targeted diagnostic search for acute surgical pathology of an inflammatory nature was a progressive increase in cardiovascular inflammatory responce phenomena in the form of high leukocytosis in the clinical blood test, refractory to antibacterial and anti-inflammatory therapy, high values of CRP and PCT levels exceeding their average values in the group of patients with COVID-19

In severe cases of COVID-19 , the main method of diagnosing acute cholecystitis is ultrasound of the abdominal cavity in a dynamic mode after 10-12 hours.

The number of postoperative complications and mortality in acute cholecystitis is directly dependent on the severity of the course of COVID-19 .

In case of tumor lesions of biliary tract in patients with COVID-19 s, the most rational is to perform minimally invasive ultrasound interventions.

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ARCTIC MEDICINE

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POLYMORPHISM OF CANDIDATE GENES FOR THE FORMATION OF "POLAR STRESS SYNDROME" IN CHILDREN LIVING IN THE CIRCUMPOLAR TERRITORY (BY THE EXAMPLE OF *ANKK1/DRD2* (RS18004976) AND *TNF* (RS1800629))

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"Polar stress syndrome" is the result of a negative extreme climatic and geographical conditions impact in the circumpolar territories with the subsequent formation of maladaptation disorders of immune and nervous regulation. There is no doubt the relevance of studying the SNP features of candidate *ANKK1*/*DRD2* (rs18004976) and *TNF* (rs1800629) genes in the aspect of identifying probable predisposition markers to the "polar stress syndrome" development in the circumpolar territory population. **The aim** is to study the features of polymorphism of immune and nervous systems regulatory genes as possible markers of predisposition to the "polar stress syndrome" formation in the children population of circumpolar territory by the example of the dopamine receptor *ANKK1*/*DRD2* (rs18004976) and the tumor necrosis factor *TNF* (rs1800629) genes**. Materials and methods**. 717 children aged 7-13 years were examined. 136 people live in conditions conducive to the formation of "polar stress syndrome" (circumpolar territory); 581 people live in the middle latitude territories. The identification of apoptosis receptors $CD3^+CD95^+$ and TNFR was carried out by flow cytofluorometry, dopamine production was analyzed by ELISA. The SNP of *ANKK1*/*DRD2* (rs18004976) and *TNF* (rs1800629) genes were identified by real-time PCR. **Results.** The results of children genotyping established the reliable association of the T-allele and TT-genotype of the *ANKK1*/*DRD2* gene (rs18004976) with dopamine hyperproduction and the similar relation of the G-allele and GG-genotype of the *TNF* (rs1800629) gene with an excessive content of TNFR and $CD3^+CD95^+$ lymphocytes ($p<0.05$). Overexpression of TNFR, $CD3^+CD95^+$ and dopamine in children was significantly associated with T-allele and TT-genotype of the *ANKK1*/*DRD2* gene (rs18004976) and G-allele and GG-genotype of the *TNF* gene (rs1800629) relative to the CC-genotype of the *ANKK1*/*DRD2* (rs1800497) gene and AA-genotype of *TNF* (rs1800629) gene independently of the analyzed sample ($p<0.05$) and reached the maximum values in carriers of the TT-genotype of the *ANKK1*/*DRD2* (rs18004976) gene and GG-genotypes of *TNF* (rs1800629) gene in the observation group. Moreover, the difference in the allele and genotype frequency distribution of candidate genes between analyzed groups was significant (TT-genotype of the *ANKK1*/*DRD2* gene (rs18004976) (OR=2.43; 95% CI=1.43-4.15; p=0.04); GG-genotype of the *TNF* gene (rs1800629) (OR=1.66; 95% CI=1.02-2.70; p=0.03)), which verified the contribution of genetic predisposition to the development of "polar stress syndrome" in children in extreme climatic and geographic conditions of the circumpolar territory.

Keywords: "polar stress syndrome", children, dopamine, apoptosis, genetic polymorphism, candidate genes.

Introduction. "Polar stress syndrome" or "northern stress" is a complex of specific changes in regulatory and metabolic processes in the body by the reason of adaptive reserves depletion in extreme climatic and geographic conditions of a circumpolar territory. The phenomenon of "polar stress syndrome" and its consequences are considered as a polysyndrome characterized by metabolic disorders; detoxification inhibition; oxidative stress, cellular and tissue hypoxia; increased blood clotting, regenerative-plastic insufficiency, immunosuppression, endocrine disorders, biological rhythm desynchronization, meteopathy, functional asymmetry of hemispheric interactions and the formation of chronic psycho-emotional stress [3, 4]. School-age children are more vulnerable to the stressful action of external factors because of active morphofunctional internal organs and systems restructuring in a growing and developing organism and as a consequence of intensive educational process. The nature of "polar stress syndrome" manifestations and their severity is largely determined by the hereditary adaptive potential of an individual organism, including by the polymorphic variants of immune and nervous regulation genes [1, 2]. Therefore, the study of the polymorphism of dopamine receptor *ANKK1/DRD2* (rs18004976) and tumor necrosis factor *TNF* (rs1800629) genes as possible neuroimmune predisposition markers to the development of "polar stress syndrome" in school-age children (7-13 years) living in a circumpolar territory is particularly relevant in the terms of prompt diagnostics and effective prevention on the early stages of its formation.

The aim is to study the features of *ANKK1*/*DRD2* (rs18004976) and *TNF* (rs1800629) polymorphism as candidate predisposition genes to the formation of "polar stress syndrome" in children living in a circumpolar territory.

Material and methods. 717 children aged 7-13 years were examined. The observation group consisted of 136 children living in the circumpolar territory (69° n.l.). The comparison group consisted of children (581 people) living in the middle latitude (56° n.l.). According to the results of the neuropsychological testing (STROOP test) the observation group significantly differed from the comparison group with a decrease in the indicators of figurative and numerical memory, atten-

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tion level, signs of emotional instability, frequent headaches and sleep disorders, as possible manifestations of the "polar stress syndrome".

The study was carried out in accordance with the Helsinki Declaration of the WMA "Ethical principles of conducting medical research involving people as subjects" and the National Standard of the Russian Federation GOST-R 52379-2005 "Good Clinical Practice" (ICH E6 GCP). Parents or other legal representatives of the children have signed a voluntary informed consent to conduct a medical examination.

The content of TNFR and CD3+CD95+ lymphocytes was determined by flow cytofluorimetry on the FACSCalibur device ("Becton Dickinson", USA) using the universal program "CellQuestPrO". The dopamine production level was determined by the ELISA method on the Infinite F50 analyzer ("Tecan Austria GmbH", Austria).

Statistical processing of the results is implemented in the Statistica 10 application software package (StatSoft, USA). The Shapiro-Wilk criterion was used to determine the data distribution nature in the surveyed samples. The Student's parametric criterion was used to assess the level of reliability of the obtained data, taking into account the normal distribution of variables in the compared groups. The nonparametric Mann-Whitney U-test was used to compare the data in the case of deviation from the normal distribution. The study results are presented in the form of the arithmetic mean (X) and its standard error (SE) of the studied indicators. The differences between the groups were considered statistically significant at $p<0.05$.

The SNP of dopamine receptor *ANKK1*/*DRD2* (rs1800497) and tumor necrosis factor *TNF* (rs1800629) genes were analyzed using real-time PCR on the CFX96 Real Time System C1000 Thermal Cycler ("BioRad", Singapour). The genetic material was extracted from buccal scraping using a set of reagents for DNA extraction "AmpliPrime DNA-sorbB Form 2 Variant 100" ("NextBio" LLC, Russia) by the sorbent method. The test systems - reagent kits for SNP (C2137T *ANKK1*/*DRD2* (rs1800497) and G308A *TNF* (rs1800629) ("Syntol", Russia)) identification were used to determine the genetic polymorphism of the studied genes. The allelic discrimination method was used to establish the human genotype in the TaqMan program. The calculation of allele and genotype frequency distribution according to the Hardy-Weinberg equilibrium, the odds ratio (OR) and its 95% confidence interval (CI) was carried out using the online "SNPStat" and "Gen-Expert" programs.

Results and discussion. The results of genotyping of the examined children revealed polymorphic variants of the dopamine receptor *ANKK1*/*DRD2* (rs1800497) and tumor necrosis factor *TNF* (rs1800629) genes that characterize signs of a possible genetic predisposition to the development of "polar stress syndrome" in the circumpolar territory children population associated with the maladaptation disorders of immune and neurohumoral regulation. The frequency allele and genotype distribution of these genes corresponds to the Hardy-Weinberg equilibrium ($p<0.05$) and is described by multiplicative (test $\chi 2$, df = 1) and additive (Cochrane-Armitage test for linear trends, xi = [0,1,2], df = 1) inheritance models (Table 1).

The polymorphism of the dopamine receptor *ANKK1*/*DRD2* (rs1800497) gene in children with the signs of "polar stress syndrome" living in the circumpolar territory is characterized by the significant increase in the T-allele and the corresponding homozygous TT-genotype frequency relative to the comparison group ($p<0.05$). It is associated with reduced expression of this gene and, as a consequence, a decrease in the D2-dopamine receptors density. In turn, a significant increase in the production of their dopamine ligand in the observation group relative to the comparison group and the reference level ($p<0.05$) is a response to acute stress conditions, where genome–mediated inhibition of reception enhances the effects associated with the unrelated ligand persistence. It has been shown that it is the acute impact of unpredictable and uncontrolled stress factors such as sharp and sudden fluctuations in the climatic and geographical parameters of the circumpolar territories leads to an increase in the extracellular dopamine content in the mesocortical system and striatum due to the pulsed phasic dopaminergic neurons activation, whereas chronic moderate stress inhibits the production of this neurotransmitter, causing a depression development in the future [5, 6].

At the same time, an increased G-allele and GG-genotype frequencies of the *TNF* gene (rs1800629) were found in the observation group ($p<0.05$). It is related with the overexpression $CD3^+CD95^+$-lymphocytes as marker of cell death - in relation to the comparison group and excess

Table 1

The allele and genotype frequency distribution of *ANKK1/DRD2* (rs1800497) and *TNF* (rs1800629) genes in children with the manifestations of "polar stress syndrome"

SNP	Genotype / Allele	Observation group (n=136)	Comparison group (n=581)	OR	
					95% CI
ANKK1/DRD2 (rs1800497)	CC	0.611	0.644	0.87	0.59 – 1.27
	CT	0.213	0.275	0.71	0.46 – 1.12
	TT	0.176	0.081	2.43	1.43 – 4.15
	C	0.717	0.781	0.71	0.53 – 0.95
	T	0.283	0.219	1.41	1.05 – 1.90
TNF (rs1800629)	GG	0.831	0.747	1.66	1.02 – 2.70
	GA	0.162	0.225	0.66	0.40 – 1.09
	AA	0.007	0.028	0.26	0.03 – 1.99
	G	0.912	0.860	1.68	1.07 – 2.64
	A	0.088	0.140	0.59	0.38 – 0.93

Note. $\chi[T(ANKK1/DRD2)]^2 = 5{,}10$, $p = 0{,}02$; $\chi[TT(ANKK1/DRD2)]^2 = 4{,}03$, $p=0{,}04$; $\chi[G(TNF)]^2 = 5{,}22$, $p = 0{,}02$; $\chi[GG(TNF]^2 = 4{,}93$, $p = 0{,}03$.

Table 2

The content of TNFR, CD3+CD95+ and dopamine in children with the manifestations of "polar stress syndrome"

Indicator	Reference interval	Observation group (n=136)	Comparison group	p
TNFR, %	1 – 3	5.703±0.683*	3.842±0.586	0.001
CD3+CD95+-lymphocytes, %	15 - 25	25.755±0.967	22.900±0.916	0.032
Dopamine, pg/cm^3	5.6 - 44	59.358±2.133*	36.945±5.899	0.001

Note: * - differences with the reference level are significantly significant ($p<0.05$).

of tumor necrosis factor receptor TNFR in relation to the comparison group and the reference interval ($p<0.05$). The physiological meaning of the lymphocyte apoptosis excess in extreme climato-geographic conditions in the circumpolar territory is associated with cell life cycle acceleration and cellular phenotypes changes, reflecting the need to compensate for energy losses and maintain the cytokine profiles stability, which is accompanied by immunoregulatory stress in the form of immunosuppression [9, 10].

The results of a comparative analysis of the TNFR, $CD3^+CD95^+$ and dopamine production levels in children with different polymorphic variants of the *ANKK1*/*DRD2* (rs1800497) and *TNF* (rs1800629) genes demonstrate similar trends in these indicators for the identified polymorphic markers both in the general sample (n=717) and in isolation in the observation group (n=136) and in the comparison group (n=581) (Fig. 1, 2). In children with TT-genotype of the *ANKK1*/*DRD2* (rs1800497) gene and GG-genotype of the *TNF* (rs1800629) gene in the general sample and in the compared groups, a significant increase in the content of dopamine, TNFR and $CD3^+CD95^+$-lymphocytes was found in relation to the carriers of CC-genotype of *ANKK1*/*DRD2* (rs1800497) gene and AA-genotype of TNF (rs1800629) gene in the same groups ($p<0.05$). It shows signs of a possible genetic predisposition to the neuroimmune profile changes characterizing the northern stress development, including in the population of 56 ° n.l., but to a lesser extent. It was found that TNFR, $CD3^+CD95^+$ and dopamine production levels in children with TT-genotype of the *ANKK1*/*DRD2* (rs1800497) gene and the GG-genotype of the *TNF* (rs1800629) gene in the observation group significantly exceeds similar values shown in children with the same genotypes in the comparison group and in the general sample ($p<0.05$). The revealed maximum values of TNFR, $CD3^+CD95^+$ and dopamine content in the carriers of TT-genotype of *ANKK1*/*DRD2* (rs18004976) gene and GG-genotype of *TNF* (rs1800629) gene in the observation group confirm that the living conditions extremity implements a genetically determined neuroimmune mechanism for the "polar stress syndrome" formation in children.

The immune and nervous systems work in constant interaction, providing a body homeostasis in changing environmental conditions. Thus, dopamine specifically bound to receptors acts as an immune coregulator, ensuring the relationship not only between neurons, but

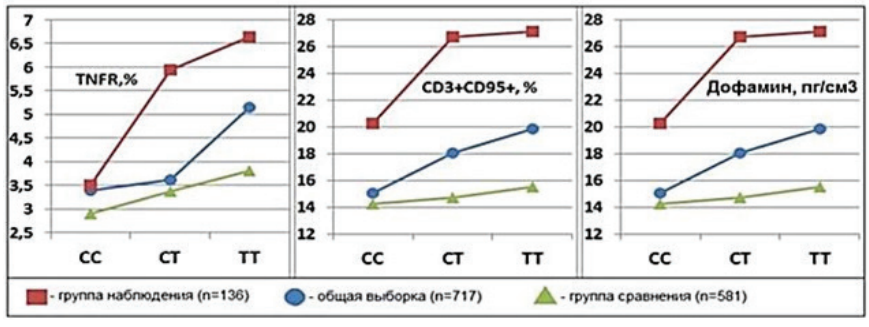

Fig. 1. Changes in the production of TNFR, CD3+CD95+ and dopamine in children with different genotypes of the *ANKK1/DRD2* gene (rs1800497)

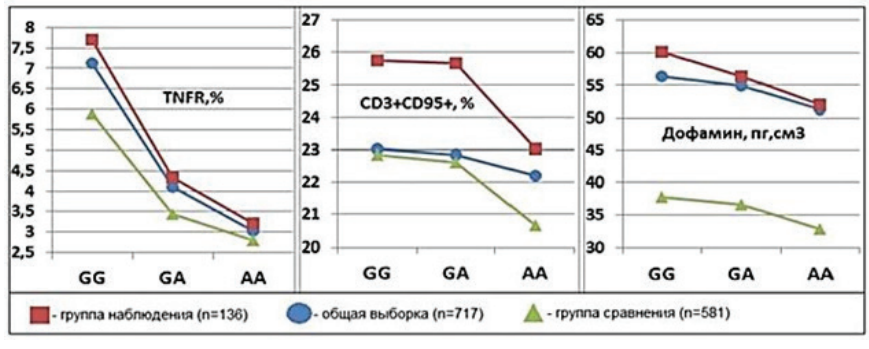

Fig. 2. Changes in the production of TNFR, CD3+CD95+ and dopamine in children with different genotypes of the *TNF* gene (rs1800629)

also between immunocytes. Human peripheral blood lymphocytes express dopamine receptors and transport proteins, synthesize endogenous dopamine and related catecholamines – epinephrine and norepinephrine. When dopamine binds to specific D2 and D3-receptors, it leads to an integrin-dependent chemotaxis activation, selective adhesion to the intercellular matrix and increased cytotoxic $CD8^+$-lymphocytes migration, as well as signs of proinflammatory cytokines (TNFα and IFNγ) hyperproduction [8, 11]. It is believed that dopamine-induced cytotoxicity is not associated with receptor activation and it manifests itself through spontaneous oxidation, leading to programmed lymphocyte death caused by oxidative stress, which signs are observed in examined children with "polar stress syndrome" [7].

Conclusion. The genetic profile of children with the "polar stress syndrome" living in the circumpolar territory is characterized by an increased frequencies of the T-allele and TT-genotype of the *ANKK1*/DRD2 (rs18004976) gene, as well as the G-allele and GG-genotype of the *TNF* (rs1800629) gene associated with an increase in TNFR, $CD3^+CD95^+$-lymphocytes and dopamine relative to the reference level and the comparison group ($p<0.05$). It indicates the signs of excessive cell death and chronic inflammation as manifestations of the immune mechanism for the formation of acute stress reactions associated with dopamine-induced hypersympathicotonia. TNFR, $CD3^+CD95^+$ and dopamine expression variability in the general sample, in the observation group and in the comparison group is characterized by a significant increase in the level of their production in the TT-genotype carriers of *ANKK1*/*DRD2* gene (rs18004976) and in the GG-genotype carriers of the *TNF* (rs1800629) gene relative to the CC-genotypes of the *ANKK1*/*DRD2* (rs1800497) gene and AA-genotypes of *TNF* (rs1800629) gene in all analyzed samples ($p<0.05$). It demonstrates the contribution of genetic polymorphism to the formation of "polar stress syndrome". The revealed maximum values of TNFR, CD3+CD95+ and dopamine in the TT-genotype carriers of *ANKK1*/*DRD2* (rs18004976) gene and GG-genotype carriers of TNF (rs1800629) gene in the observation group confirm the combined contribution of genetic predisposition and living conditions in the circumpolar territory to the formation of "polar stress syndrome" in children.

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THE PROBLEM OF SUICIDAL BEHAVIOR AND ALCOHOL DEPENDENCE SYNDROME IN THE ARCTIC ZONE OF THE REPUBLIC OF SAKHA (YAKUTIA)

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UDC 614.2(571.56)

An analysis of data on suicides in the Arctic zone of the Republic of Sakha (Yakutia) from 2000 to 2021 is presented, as well as their relationship with the prevalence of alcoholism and mental disorders. Official data show that during this period, 8,160 people, mostly men of working age, committed suicide in Yakutia. The overall suicide rate in the region has decreased, but is still significantly higher than the Russian average. Alcohol abuse is considered a leading cause of suicide, especially among indigenous people. There is a direct correlation between the prevalence of alcohol dependence and suicide, as well as the incidence of alcoholism and mental disorders. However, the connection between these indicators and mortality from suicide in the Arctic zone has not been established. The problem is caused, among other things, by insufficient diagnosis of mental and addictive disorders due to a shortage of qualified doctors in the region. The authors of the article come to the conclusion that it is necessary to strengthen the prevention of alcoholism and suicidal behavior, as well as improve the quality and availability of psychiatric care in the Arctic zone.

Keywords: suicide, alcohol addiction, alcohol, Arctic zone, Yakutia.

Introduction. Over the past two decades, both in the world and in Russia, there has been a significant decrease in the number of suicides. Thus, from 2000 to 2022, the average Russian mortality rate from this cause decreased by 3.5 times, i.e. with 38.8 people up to 11 people per 100 thousand of us. However, it must be taken into account that the Russian Federation is the only country in which regional suicide mortality rates for various reasons can differ dozens of times. Thus, according to Rosstat data from 2019, the top five most prosperous regions in this regard (Ingushetia, Chechnya, Sakhalin and Astrakhan regions, Khabarovsk Territory) have an indicator per 100 thousand of us. was 0.2-1.1 people, then in the last five this value varied from 28.8 to 35.6 people. In addition, it is known that men are 5-6 times more likely to commit suicide, and the frequency of suicides in rural areas is 2 times higher than in cities [1]. Thus, the national averages do not entirely objectively reflect the real situation with suicides.

In Yakutia, the mortality rate from suicide has long been significantly higher than the Russian average. Back in the late 1920s. this fact was noted in his study by D.T. Shepilov [7], later Corresponding Member of the Russian Academy of Sciences and Minister of Foreign Affairs of the USSR. In addition, according to a number of modern scientists, clustering of suicides is observed in places where small peoples live [5, 8, 10]. It is important to point out that even within a region, the frequency of suicides is quite variable. A particularly acute situation was noted in some Arctic uluses [2].

Purpose: to analyze data on suicides in the Arctic zone of Yakutia (AZ RS(Ya)) and determine current trends in suicidal behavior in dynamics, taking into account the general incidence of alcohol dependence syndrome (ADS) and alcoholic psychoses (AP) (2000-2021).

Materials and methods: We analyzed the materials of the organizational and methodological departments of the State Budgetary Institution of the Republic of Sakha (Yakutia) of the Yakut psychoneurological dispensary and the Yakut narcological dispensary, as well

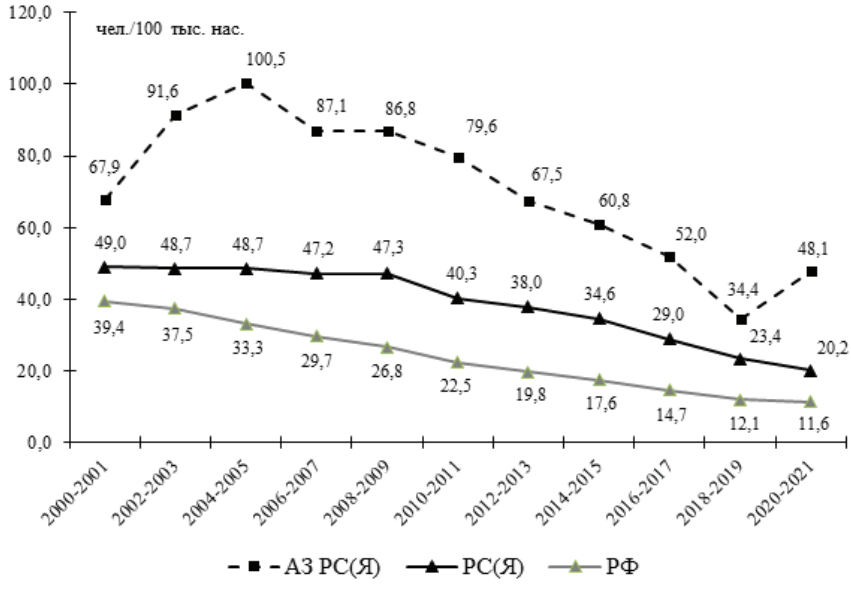

Fig. 1. Suicide mortality in Yakutia and Russia

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Table 1

Absolute number of suicide victims in the territory of the AZ RS(Y), 2019-2021

Улусы	Годы									in just 3 years, people
	2019			2020			2021			
	absolute quantity		per 100 thousand of us.	absolute quantity		per 100 thousand of us.	absolute quantity		per 100 thousand of us.	
	men	women		men	women		men	women		
Abyisky.	0	0	-	0	0	-	1	1	51,5	2
Allaikhovsky	0	1	37,0	1	1	73,8	1	0	37,2	4
Anabar	1	1	55,2	4	0	109,2	3	0	82,2	9
Bulunsky	0	0	-	4	1	58,8	2	1	35,2	8
Verkhnekolymsky	0	0	-	0	0	-	0	0	-	0
Verkhoyansky	5	0	45,1	4	3	63,5	3	0	27,4	15
Zhigansky	3	0	72,4	2	0	48,2	0	1	24,0	6
Momsky	0	0	-	1	0	24,9	1	0	24,9	2
Nizhnekolymsky	0	0	-	3	0	70,7	3	0	71,6	6
Oleneksky	0	0	-	2	0	46,7	2	0	46,2	4
Srednekolymsky	5	3	108,4	5	1	81,9	4	1	69,1	19
Ust-Yansky	2	0	42,7	1	1	28,5	0	0	-	4
Ev.-Bytantaysky	2	1	105,8	1	1	69,9	1	2	103,8	8
Total for the Arctic	**18**	**6**	**35,5**	**28**	**8**	**53,2**	**21**	**6**	**42,2**	**87**
Total by RS(Ya)	**185**	**37**	**22,9**	**165**	**35**	**20,5**	**171**	**24**	**19,8**	**617**
As a % of the total number of deaths in Yakutia	9,7	16,2	-	17,0	22,9	-	12,3	25,0	-	14,1

as data from the territorial body of the Federal State Statistics Service for the Republic of Sakha (Yakutia) on the morbidity and mortality of the population in the 13 uluses that are part of AZ RS(Y) - Abyisky, Allaikhovsky, Anabarsky, Bulunsky, Verkhnekolymsky, Verkhoyansky, Zhigansky, Momsky, Nizhnekolymsky, Oleneksky, Srednekolymsky, Ust-Yansky, Eveno-Bytantaysky from 2000 to 2021. The level of suicides is indicated according to the WHO gradation: low (up to 10 people/100 thousand people), medium (10-20 people), high (≥ 20) levels. Accumulation, adjustment, systematization of initial information and visualization of the results obtained were carried out in Microsoft Office Excel spreadsheets. Statistical analysis was carried out using IBM SPSS Statistics v.26.

Research results. According to official data, from 2000 to 2021. in Yakutia, 8160 people committed suicide, of which the vast majority (>85%) were people of working age, predominantly men (ratio 6:1).

But, as in the Russian Federation as a whole, a gradual decrease in the frequency of its indicator is observed in the region. If in 2000-2010 There were an average of 453.4 suicides per year, then in 2011-2021. this figure decreased by 1.6 times (288.5 cases). However, Fig. 1 clearly illustrates that in the AZ RS (Y) the frequency of suicides has always significantly exceeded the data for the Russian

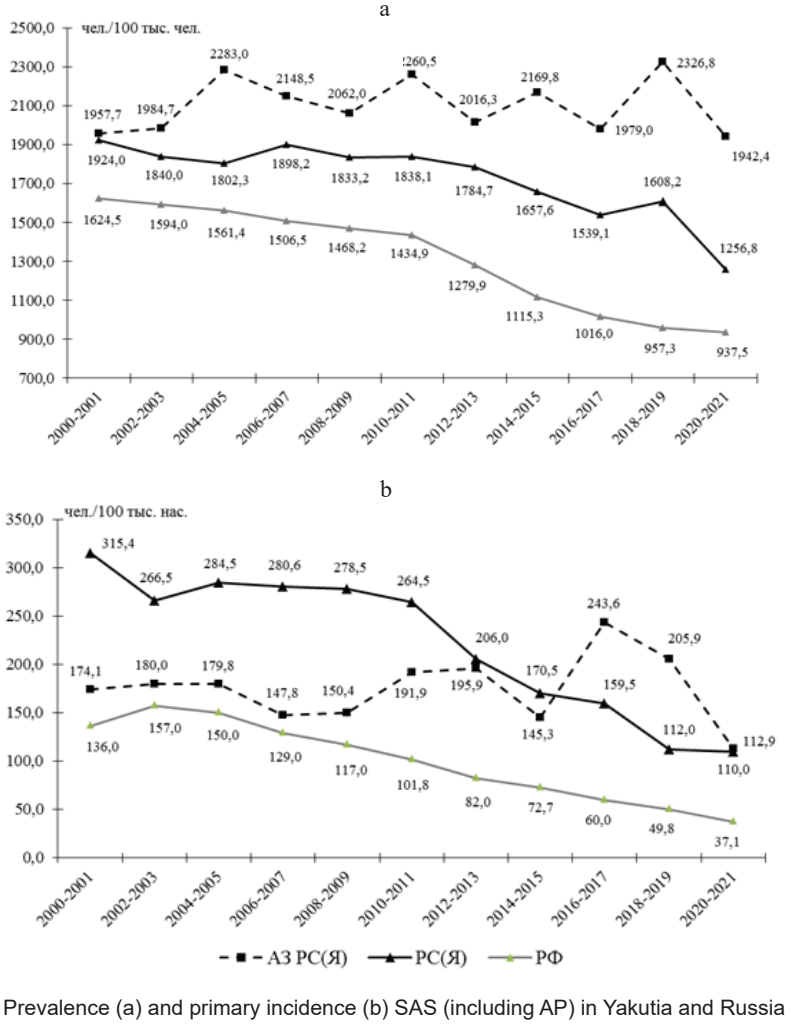

Fig. 2. Prevalence (a) and primary incidence (b) SAS (including AP) in Yakutia and Russia

Federation (in 2000-2010 - by 2.8 times, 2011-2021 - by 3.5 times) and Yakutia (by 1 .8 times over the entire period of research). At the same time, it is necessary to take into account the fact that due to the sparse population of the Arctic regions, even isolated cases of suicide can lead to sharp fluctuations in the indicators under consideration.

In absolute terms, over the last 3 accounting years (2019-2021), 87 suicides were recorded in the AZ RS (Yakutia) (Table 1). Their maximum number was noted in the Srednekolymsky (19 people), Verkhoyansk (15 people), Anabarsky (9 people) uluses. The absence of suicide cases in the Verkhnekolymsky ulus is most likely explained by the insignificant number of representatives of the local population - according to VPN-2010, 1950 Sakha, Yukaghirs, Evens, Evenks and Dolgans lived in the area.

The number of male suicides in the AZ RS(Y) exceeded the number of female suicides by 5.4 times. Of the total number of suicides committed in Yakutia, AZ RS(Y) accounts for 14.1%. For comparison, in the overall structure of regional mortality, the share of Arctic regions averages 8.8%.

According to the literature, most suicides in the Russian Federation are associated with alcohol consumption [6, 9]. For example, every fourth suicide in the Trans-Baikal Territory suffered from alcohol dependence syndrome [4]. By the way, the Trans-Baikal Territory is one of the subjects of the Russian Federation with high rates of suicide mortality. It is evident that alcohol abuse also significantly increases mortality from other external causes such as homicide, accidental alcohol poisoning, etc., especially in indigenous populations [3].

Unfortunately, the prevalence of SAZ and AP in Yakutia still remains extremely high - in 2000-2010 it exceeded Russian indicators by 20.6%, and in 2011-2021. this difference increased by 46.5%, that is, 1589 versus 1092 cases per 100 thousand of us. The situation in AD RS(Y) is even more acute: over two decades, there was no obvious decrease in overall morbidity, and in different years this figure varied from 1942.4 to 2326,8 cases/100 thousand population (fig. 2).

We have established a pronounced direct correlation between the prevalence of alcohol dependence and suicides (for the RF p<0.001, rxy=0.976, strong correlation; for RS(Ya) p= p<0.001, rxy=0.958, strong correlation), as well as the incidence of alcoholism and suicides (for the RF p<0.001, rxy=0.969, strong correlation; for RS(Ya) p= p<0.001, rxy=0.814, strong correlation). However, we did not find any visible correlation between the above indicators and suicide mortality in AZ RS(Ya) (p=0.58 and 0.74, respectively).

Table 2

Results of correlation analysis of suicides in AZ of RS(Ya) with prevalence and incidence rates of mental disorders and alcoholism in RS(Ya) and RF

Indicator	Psychiatric disorders					
	Prevalence			Primary morbidity		
	AZ RS(YA)	RS(YA)	RF	AZ RS(YA)	RS(YA)	RF
Correlation coefficient	0.251	**0.783****	**0.610****	0.150	**0.609****	**0.781****
The value of p	0.260	**0.000**	**0.003**	0.506	**0.003**	**0.000**
	Alcohol dependence syndrome, including alcoholic psychosis					
	Prevalence			Primary morbidity		
	AZ RS(YA)	RS(YA)	RF	AZ RS(YA)	RS(YA)	RF
Correlation coefficient	0.125	**0.663****	**0.770****	-0.075	**0.741****	**0.850****
The value of p	0.580	**0.001**	**0.000**	0.740	**0.000**	**0.000**

Note: statistically significant results (p<0.01) are highlighted in bold.

A similar pattern has been established between suicide rates and primary morbidity of mental disorders: for the RF p<0.001, rxy=0.918, strong correlation; for the RS(Ya) p= p<0.001, rxy=0.771, strong correlation; for the Arctic zone no such correlation was also revealed (p=0.506).

Interestingly, there was a clear direct quantitative correlation between suicides in the Arctic zone and the prevalence and incidence of alcoholism and mental illness in the RF and RS(Ya), which is not observed when comparing with similar indicators in the AZ of RS(Ya) (Table 2).

The most likely reason for the above is the shortage of staff in the Arctic zone of narcologists. This explains the relatively low data on the primary morbidity of ASP (including AS) in the northern regions compared to regional indicators. For the same reason, in remote areas of Yakutia there is no proper diagnosis of mental illnesses, which led to the fact that the official data on the primary morbidity of mental disorders in the AS of RS(Ya) are 3.7 times lower than the average Russian figures. It should be noted that as of October 2023, vacant positions of district psychiatrists are not occupied in 9 uluses of RS(Ya), including two Arctic uluses - Anabar and Moma. Out of 137 staff units of psychiatrists in the Yakutsk Republican Psychoneurological Dispensary providing mental health care in the Republic of Sakha (Yakutia) as of October 2023, only 77 units are filled.

Conclusions. The data analysis showed that the suicide rate in the Arctic zone of RS(Ya) was characterized as high, and exceeded the average Russian indicators in 2.8-3.3 times, regional - 1.8 times. One of the most significant reasons for this is not only the wide spread of depressive and anxiety disorders in the population of the North, but also the high incidence of alcohol dependence syndrome.

Prevention of alcoholism as a direct trigger of suicidal behavior in Arctic indigenous populations is an important area of suicide prevention.

In addition, it is necessary to improve the quality and accessibility of psychiatric, psychotherapeutic and narcological assistance to the population of the Arctic uluses, to strengthen the prevention of suicidal behavior and alcoholism among the inhabitants of the North.

The work was carried out within the framework of the state contract No. 7161 for the research work «Efficiency of the health care system of the Arctic zone of the Republic of Sakha (Yakutia) in the context of innovative development: analysis and forecast. Stage 1».

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SCIENTIFIC REVIEWS AND LECTURES

A.P. Vorobyeva, Y.V. Bykov, V.A. Baturin, A.A. Muravyeva, V.V. Massorov

GLYCOCALYX DISORDERS IN CRITICAL CONDITIONS: PATHOPHYSIOLOGICAL AND CLINICAL ASPECTS

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Aim: to evaluate the results of clinical studies devoted to the study of the role of endothelial glycocalyx (GC) in the pathogenesis of critical conditions.

Materials and Methods. Scientific information was searched in domestic (E-Library) and foreign databases (PubMed, Scopus, Oxford University Press, Springer, Web of Science Core Collection). 120 publications were analysed, 42 of them were selected to meet the requirements of the review.

Results. GC is a gel-like polysaccharide-protein layer covering the surface of vascular endothelial cells. GC maintains homeostasis of the vascular network, including controlling vascular permeability and microvascular tone, preventing microvascular thrombosis, and regulating leukocyte adhesion. Endothelial GC damage is a universal link of pathogenesis in various pathological processes. The proposed review considers the structure and functions of GC, its participation in the pathogenesis of such diseases as diabetes mellitus, sepsis, covid-19, polytrauma, pre-eclampsia, epilepsy and others. A decrease in GC thickness in patients with diabetes mellitus has been described. The effect of hyperglycaemia on GC structure has also been noted. In sepsis, GC is damaged by free oxygen radicals, which are released by circulating leukocytes, which in turn triggers a cascade of reactions that lead to systemic oedema, hypovolaemia with further development of organ and tissue damage. In severe trauma, damage to GC is noted, which is accompanied by the release of syndecan, heparan sulfate, hyaluronic acid into the bloodstream. Preeclampsia is also associated with GC damage, which can be detected by elevation of specific markers. Epilepsy and many other neurological diseases are associated with disruption of the blood-brain barrier, whose dysfunction is associated with GC dysfunction.

Conclusion. Timely diagnosis of GC degradation can improve life prognosis and therapeutic outcomes in critically ill patients.

Keywords: glycocalyx, sepsis, pre-eclampsia, polytrauma, status epilepticus, coronavirus infection, syndecan, hyaluronic acid.

Introduction. At the present stage of medicine, the earliest possible diagnosis of glycocalyx (GC) dysfunction in critical conditions is extremely important, since its structure disorder is a predictor in the development of many pathological processes and their complications [1]. This issue is especially acute in the practice of intensive care physicians, since timely diagnosis of GC disorders can improve the prognosis of the course of the disease and increase the chances of survival [2]. GC damage and development of endothelial dysfunction are a component in the pathogenesis of many diseases, such as diabetes mellitus (DM), cardiovascular diseases, strokes, epilepsy, which are widespread in the clinic of critical conditions [31]. Modern methods of GC dysfunction assessment, which are the most

applicable for use in practice, include dark-field microscopy of the superficial microcirculatory bed and enzyme immunoassay, which is used to detect the main components of endothelial GC, such as syndecan, glypican, heparan sulfate, hyaluronic acid, etc. [1]. It has been shown that earlier determination of GC destruction markers in the blood is able to predict the development of severe complications and allows to judge about the unfavourable course of the disease, which can be useful in the practice of intensive care physician in order to carry out the correction of modern methods of treatment [31] .

The aim of this review was to analyse modern literature sources describing GC damage in various critical condition.

Structure and functions of the glycocalyx GC is a general term for polysaccharide protein complexes that coat the surface of vascular endothelial cells (ECs) [1]. GC is a complex, negatively charged gel-like layer on the lumenal side of ECs, composed of glycosaminoglycans (GAGs), which are bound to membrane spanning proteins and glycoproteins characterised by short branched carbohydrate side chains [2]. The GAGs that make up GC are primarily heparan sulfate, chondroitin sulfate and hyaluronic acid (also called hyaluronan or hyaluronan) [2].

Notably, the dynamic balance between biosynthesis and excretion makes it rather difficult to correctly describe the geometric location and distribution of GC [11]. GC has a total negative charge that helps to determine interactions with proteins [22]. In particular, it can adsorb positively charged regions of some plasma proteins and complements the barrier function of the endothelium by acting as a first barrier to leakage of plasma proteins (which are mostly negatively charged, such as albumin) into the interstitium [2]. In addition, by preventing protein leakage from the vascular network, GC helps to maintain osmotic pressure towards the blood vessel lumen, thereby preventing water from entering the tissues [22]. Finally, GC has antithrombotic/profibrinolytic effects and also inhibits neutrophil/leukocyte attachment [22]. Several components of GC including syndecans, heparan sulfate and hyaluronic acid are altered in cases of ischaemia, hypoxia, sepsis, atherosclerosis, renal disease, DM and some viral infections [19]. This alteration has a negative impact on the endothelium, leading to microcirculatory dysfunction with subsequent organ ischaemia and subsequent organ damage [22].

Modern methods of GC dysfunction assessment, which are the most applicable for use in practice, include dark-field microscopy of the superficial microcirculatory bed and enzyme immunoassay, which is used to detect the main components of endothelial GC, such as syndecan, glypican, heparan sulfate, hyaluronic acid, etc. [1]. It has been shown that earlier determination of GC destruction markers in the blood is able to predict the development of severe complications and allows to judge about the unfavourable course of the disease, which can be useful in the practice of intensive care physician in order to carry out the correction of modern methods of treatment [31]

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Diagnosis of glycocalyx disorders in some critical conditions.

Sepsis. Sepsis is defined as life-threatening organ dysfunction caused by dysregulation of the host organism's response to infection [38]. Sepsis and septic shock are accompanied by severe endothelial damage and degradation of GC, leading to dysregulation of homeostasis and vascular wall permeability, causing damage to the microcirculatory channel [40]. GC plays a key role in the physiology of the microcirculatory system and endothelium and is involved in the regulation of microcirculatory channel tone and vascular permeability, maintenance of oncotic gradient across the endothelial barrier, as well as leukocyte adhesion/migration and prevention of thrombosis [3]. Conformational changes in GC structure lead to the release of nitric oxide, which contributes to the regulation of vasomotor tone and tissue perfusion [14]. Local and systemic inflammation leads to changes in the structure and physiology of GC and, as a result, to endothelial dysfunction [4]. GC degradation during inflammation is associated with increased capillary permeability and release of albumin and fluid into the intercellular space [4]. Degradation of heparan sulfate leads to a procoagulant state with subsequent microthrombosis and loss of antioxidant properties with progressive oxidative damage to the endothelium [4].

Insufficiency of the endothelial system and GC against the background of sepsis triggers the mechanism of multi-organ failure (MOF). The main triggers of MOF are proinflammatory mediators, including interleukin-1 (IL-1), IL-2, IL-6, tumour necrosis factor (TNF) and other molecules released during inflammation (bradykinin, thrombin, histamine, vascular endothelial growth factor), which cause damage and activation of GC components during septic shock, as well as stimulate the release of intercellular and vascular cell adhesion molecules [23]. These mediators lead to accumulation, adhesion and migration of leukocytes, which triggers inflammatory processes in endothelium and tissues and leads to further GC damage with progression of capillary leakage into the interstitial space [23].

Some clinical studies have reported that on the day of admission to the intensive care unit (ICU), patients with sepsis had significantly higher median plasma concentrations of GC and heparan sulfate compared to controls, with those who died within the next 90 days having significantly higher GC concentrations in the sepsis patient population [29].

More recently, the plasma concentration of syndecan-1 (SDN-1) in patients with septic shock was found to be more than twice as high as in healthy volunteers on day 1 of admission to the ORIT and was significantly associated with the SOFA total score (a scale to assess the likelihood of sepsis in patients in the ORIT) and the SOFA coagulation subscale [33]. In cases of sepsis, the blood coagulation system may become pathologically activated, leading to disseminated intravascular coagulation syndrome and thrombosis. Measurement of whole blood coagulation in patients with sepsis may reveal hypo-, normal or hypercoagulable state, while conventional laboratory tests may show that plasma is not hypercoagulable per se, leading to the hypothesis that endothelial dysfunction may be a major contributor to DIC syndrome [30].

According to another paper, hyaluronic acid and SDH-1 concentrations were higher during the first five days in the ORIT of patients with severe sepsis (sepsis with acute organ dysfunction) and septic shock (sepsis with refractory hypotension despite adequate fluid load) compared to patients with sepsis [6]. In addition, levels of GC and SDH-1 were elevated for at least the first 3 days in patients with septic shock compared to

patients with severe sepsis. More importantly, in surviving patients, GC and SDH-1 concentrations tended to decrease during the ORIT stay, whereas in non-surviving patients they tended to be slightly elevated or remained unchanged [6]. Thus, monitoring the progression of markers of GC damage (e.g. hyaluronic acid or SDN-1) may be useful for assessing sepsis progression and predicting survival.

Severe trauma/polytrauma. Despite modern advances in the prevention and treatment of severe trauma, traumatic injuries continue to be the leading cause of morbidity and mortality in children and adults worldwide [16]. It has been found that after initial direct injury to the vascular surface and subsequent inflammatory response, persistent disruption of GC integrity leads to the development of vascular dysfunction in adults with traumatic injuries, culminating in organ dysfunction [27]. Trauma-induced coagulopathy may begin with a state of hypercoagulability that progresses to hypocoagulability, or vice versa, and may depend on several factors, including the degree of injury, the amount and rate of intravascular fluid administered, and the presence of excessive fibrinolysis [26]. Blood concentration of SDN-1 was elevated in trauma patients after admission to the ORIT, and patients with higher than average SDN-1 concentration showed more signs of microcirculatory dysfunction [28].

While microcirculatory dysfunction improved over time and SDN-1 concentration decreased, SDN-1 remained elevated for 30-50 h compared to healthy controls [27]. According to a study [21], intensive care for adults with traumatic haemorrhagic shock usually includes balanced transfusion of blood product components (administration of equal volumes of fresh frozen plasma and platelets with transfused red blood cells). On the other hand, haemorrhagic shock after severe trauma does not usually occur in children, which is probably due to the epidemiology of the injury and the nature of the injury (i.e. more isolated head trauma). In addition, those children who present with trauma-related haemorrhagic shock that does not require massive transfusion are more likely to be resuscitated with crystalloid fluid and packed red blood cells without a balanced transfusion approach [34]. However, this strategy may lead to worse clinical outcomes and has been questioned [34]. Although trauma itself leads to GC degradation, the choice of intravenous resuscitation solution also contributes. When healthy subjects were administered 0.9% saline, Hartmann's solution, 4% and 20% albumin in a double-blind crossover study, only 0.9% saline showed GC degradation due to an increase in plasma SDH-1 content [7]. In resuscitation of patients with haemorrhagic trauma, an approach with limited use of saline solution is recommended and emphasis is placed on balanced transfusions including fresh frozen plasma [31].

Pre-eclampsia. Pre-eclampsia (PE) is one of the most serious complications of pregnancy, ranking third in the list of causes of maternal mortality and is a major cause of neonatal morbidity and mortality [9]. Currently, pulmonary embolism is considered as a multisystem pathological condition with clinical manifestations beginning after the 20th week of pregnancy [9]. It is characterised by arterial hypertension combined with proteinuria and often oedema and signs of multi-organ/polysystemic failure[9].

The pathophysiology of PE is not fully elucidated, but most agree that varying degrees of impaired placental perfusion result in the release of soluble factors into the maternal bloodstream, leading to maternal endothelial dysfunction [39]. The development of placental ischaemia is characterised by increased apoptosis in placental structures and the entry of necrotic debris and microparticles of trophoblastic origin into maternal blood [32]. These changes initiate the triggering of a systemic inflammatory response: activation of immune cells and complement system, synthesis of proinflammatory cytokines and, consequently, the development of endothelial dysfunction [32]. GC release causes capillary leakage leading to oedema and proteinuria, dysregulation of vascular tone leading to hypertension and impaired microcirculation, activation of the blood coagulation system causing platelet consumption, and inflammatory changes [20].

Maternal plasma concentrations of SDH-1 increase during pregnancy and reach concentrations comparable to those in sepsis at term [24]. Circulating concentrations of hylauronic acid are elevated in PE compared to normotensive pregnancies [41].

Circulating concentrations of GC degradation products are elevated in PE compared to normotensive pregnancies. Thrombomodulin as a marker of endothelial damage in PE has been associated with disease severity and may be useful in at-risk women with PE [8]. Evidence that endothelial GC is an important pathophysiological link in PE requires further investigation [8].

Status epilepticus. Status epilepticus (SE) is a frequent life-threatening emergency in which patients suffer from continuous or rapidly recurring seizures [5]. These incessant seizures lead to death, accelerate the progression of epilepsy and reduce the quality of life [5]. Normal neuronal function and brain homeostasis require blood-brain barrier (BBB) interaction [42]. The HEB is a dynamic and complex neurovascular unit that protects the brain parenchyma from circulatory factors and regulates and maintains the stability of the internal environment of the central nervous system [42]. Recently, the GC has been identified as a component of the extended neurovascular system, an important physiological structure that maintains proper neuronal homeostasis [10]. GEC disruption has been described in several neurological diseases [18]. Recently, it has been reported that seizure frequency in epilepsy increases with an increase in the permeability of the GEB [18]. Cerebral herniation syndrome, intracranial hypertension, and cerebral oedema during epilepsy have been shown to be key causes of early death [17]. A vicious circle is formed between cerebral oedema and prolonged seizures, exacerbating cerebral oedema, accelerating the progression of epilepsy and worsening the outcome of patients with epilepsy [17].

Lee et al. described a decrease in GC levels compared to controls, following status epilepticus (SE), which was ameliorated by heparin. GC impairment was associated with higher GEC permeability and increased brain oedema 72 h after ES, as well as decreased survival and worse neurological outcome. Conversely, preservation of GC by heparin could reduce ES-induced glia cell activation, GEC leakage, brain oedema, reduce the expression of inflammatory factors and improve neurological outcome. The study highlights the importance of GC degradation in brain oedema and ES outcome, and indicates that heparin treatment may be a novel strategy for brain protection in ES [25].

Coronavirus infection (Covid-19). Although coronavirus 2019 (COVID-19) is a recently emerged SARS-CoV-2-related disease, numerous studies have rapidly identified microvascular injury and GC degradation as the main pathophysiological mechanisms of the disease [36]. Similar to bacterial sepsis, GC damage in COVID-19 follows a familiar pattern, and the GC degradation and endothelial damage observed in COVID-19 results in a prothrombotic state that leads to multi-organ thrombosis in severe cases [36].

Fraser et al. obtained data indicating that GC degradation was greater in patients with COVID-19, in contrast to age- and sex-matched ORIT patients without COVID-19, possibly explaining the greater risk of thrombosis in COVID-19. Compared with COVID-19-negative sepsis patients, COVID-19-positive patients had consistently higher levels of soluble P-selectin, hyaluronic acid, and SDN-1, especially on day 3 of the ICU and thereafter. In fact, SDN-1 levels continued to increase during the 7 days that COVID-19 patients were tested [13].

Fraser DD et al. published a case report of a 15-year-old female admitted to the hospital with COVID-19-related multisystem inflammatory syndrome (MIS-C) and demonstrated that plasma GC levels were elevated almost 7-fold compared to age- and sex-matched controls [13]. Measurement of the perfused border region of the hyoid blood vessels has become a useful bedside indicator of GC damage. It has been shown that ventilated COVID-19 patients have thinner GCs compared to non-ventilated COVID-19 patients or healthy controls [Rovas A, 2021]. The same study showed that plasma GC concentrations were significantly higher in both ventilated and non-ventilated patients with COVID-19 compared to controls, while SDN-1 was higher in ventilated patients with COVID-19 compared to both non-ventilated and control groups [37]. Studies using cultured endothelial cells treated with COVID-19 patient plasma in vitro have found similar changes in GC as well as hyaluronidase and cathepsin activity [35]. Several studies show that markers of GC degradation in blood correlate with disease severity in COVID-19 patients. The serum concentration of SDN-1 during the first day of admission to the ORIT was significantly higher in non-surviving COVID-19 patients compared to survivors [43].

Taken together, the published studies strongly suggest that GC clearly undergoes significant degradation as a result of COVID-19, which likely contributes to platelet adhesion and the increased risk of thrombosis seen in many COVID-19 cases. Thus, therapies aimed at inhibiting platelet adhesion (e.g. administration of nitric oxide via inhalation or by donor) and protecting/restoring GC (e.g. sulodexide and/or sphingosine-1-phosphate) may be indicated therapeutically [31].

Conclusion. The examples of the described nosologies demonstrate the undoubted clinical value of GC assessment, which serves as an impetus for further research in this field. Methods for assessing GC degradation, given its involvement in the development and progression of many disease groups, are of great importance in the work of clinicians. The possibility of drug correction of GC disorders is of great scientific interest. Despite the abundance of basic and preclinical studies of strategies to preserve and restore GC, human clinical trials are still lacking. In the paediatric population, there are still few studies on GC, which should also prompt future research.

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THE ROLE OF MICRORNAS IN THE PATHOGENESIS OF OVARIAN CANCER

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This review collects and summarizes the literature data accumulated over the past few years on the participation of microRNAs in the pathogenesis, progression and metastasis of ovarian cancer, as well as their role in the emergence of multidrug resistance, and considers their possibility of use as prognostic and diagnostic biomarkers.

Keywords: ovarian cancer, microRNA, oncogenetics, drug resistance and sensitivity, methylation.

Introduction. Ovarian cancer (OC) is the most aggressive tumor among malignant neoplasms of the female reproductive system and occupies a leading place in mortality among gynecological oncological diseases. According to the latest global statistics, the number of new cases of the disease in 2020 exceeded more than 300 thousand and more than 207 thousand women died from this pathology [20]. The high mortality rate of ovarian cancer is primarily due to its nonspecific symptoms, which usually appear as the disease progresses, as well as the lack of effective screening methods to detect it in the early stages.

Currently, clinical treatment of OC is based on cytoreductive surgery to reduce tumor volume and subsequent combination chemotherapy using cisplatin and paclitaxel. However, despite an initial good response to therapy, most patients progress to disease relapse and eventually develop chemotherapy-resistant pathology. In addition, ovarian cancer has a high metastatic and invasive potential, and metastasis increases multidrug resistance and sharply reduces patient survival [22].

One of the most outstanding discoveries in biology of the last decade should be considered the discovery of a systemic level of regulation of gene activity using small non-coding molecules - microRNAs [1].

This review collects and summarizes the literature data accumulated over the past few years on the participation of microRNAs in the pathogenesis, progression and metastasis of ovarian cancer, as well as their role in the emergence of multidrug resistance, and considers their possibility of use as prognostic and diagnostic biomarkers.

MicroRNA – formation, signaling pathways and target genes. MicroRNAs (miRNAs) are a type of small non-coding RNAs, approximately 19–25 nucleotides in length, that are involved in the regulation of gene expression, typically by inhibiting translation and attenuating the stability of messenger RNAs (mRNAs). The first works describing microRNAs were published in 1993 by a group of researchers led by V. Ambros and G. Ruvkun, who studied the mechanisms of regulation of development of the nematode Caenorhabditis elegans [28]. To date, about 1917 precursors and 2654 mature human microRNAs have been identified, their description is provided in the microRNA database (miRbase.org). MicroRNA genes are evolutionarily conserved and distributed throughout the human genome. A small part of microRNAs (about 10%) is located in the introns of coding genes. About half of all microRNAs are found within or adjacent to sites of chromosome fragility, in areas of loss of heterozygosity, or in regions of genome amplification in tumors. This type of non-coding RNA regulates the expression of more than 60% of human genes at the transcriptional and post-transcriptional levels [51].

Transcription of microRNA genes is carried out by RNA polymerase II with the formation of a primary transcript - pri-microRNA, about 1000 nucleotides in length. Primary transcripts form several double-stranded regions - hairpins, which are then cut into individual molecules of 60 to 75 nucleotides in length (pre-microRNA) using a nuclear complex formed by Drosha RNase III and the Pasha protein (from partner of Drosha, DGCR8), which recognizes double-stranded RNA . Pre-microRNA molecules are transported by the exportin 5/Ran GTPase complex into the cytoplasm, where further microRNA maturation occurs. In the cytoplasm, pre-microRNA is cut by RNase III Dicer into duplex RNA 18–25 nucleotides long (mature microRNA). Mature microRNA binds to the Ago2 protein from the Argonaute family and forms the so-called RISC complex (miRNA-induced silencing complex), which provides the main function of microRNA - suppression of gene expression. The choice of target gene is

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determined by the complementarity of the key sequence (seed sequence) of the microRNA and the mRNA sequence (binding sites for microRNA), which are most often located in the 3' untranslated region (Figure) [1,38].

It has been established that microRNAs are actively involved in the regulation of a wide variety of biological processes, including cell proliferation and differentiation, apoptosis, angiogenesis, inflammation, etc. The effects of microRNAs cover such key processes for tumor growth as migration, invasion and metastasis, epithelial-mesenchymal transition (EMT)) [3].

The first data on the involvement of microRNAs in the development of malignant neoplasms were obtained in 2002 by G.A. Calin et al. [11]. Over the next 13 years, various scientific groups have carried out many studies on the role of microRNAs in carcinogenesis. An association of specific microRNA expression profiles with the TNM stage of the disease, histological type of tumor, molecular genetic events in tumor cells, and response to therapy has been shown [2, 37, 57,58].

The first study of changes in the level of microRNA expression in OC was performed in 2007 in the laboratory of S.M. Croce on 69 tissue samples from patients with ovarian cancer and 15 normal tissue samples. A significant increase in the expression levels of miR-200a, miR-141, miR-200c and miR-200b and a decrease in the levels of miR-199A, miR-140, miR-145 and miR-125b1 were found. In addition, the authors of the work were able not only to differentiate ovarian cancer samples from normal ovarian tissues, but also to identify some of its histological subtypes. For example, miR-21, miR-203 and miR-205 were overexpressed only in tumor samples of the endometrioid histotype OC [23,40]. A number of other studies have also shown that different OC histotypes demonstrate differential expression of specific microRNAs. Thus, miR-509-3-5p, miR-509-5p, 509-3p and miR-510 were significantly overexpressed in clear cell ovarian carcinoma samples compared to high-grade serous OC, while increased expression of miR-200c- 3p has been associated with poor survival prognosis in patients with high-grade serous ovarian cancer [45,46]. In the work of Agostini et al. It was found that the expression of miR-192, miR-194 and miR-215 was significantly increased in ovarian carcinomas of the mucinous subtype, but was suppressed in other histotypes and sex cord stromal tumors [6].

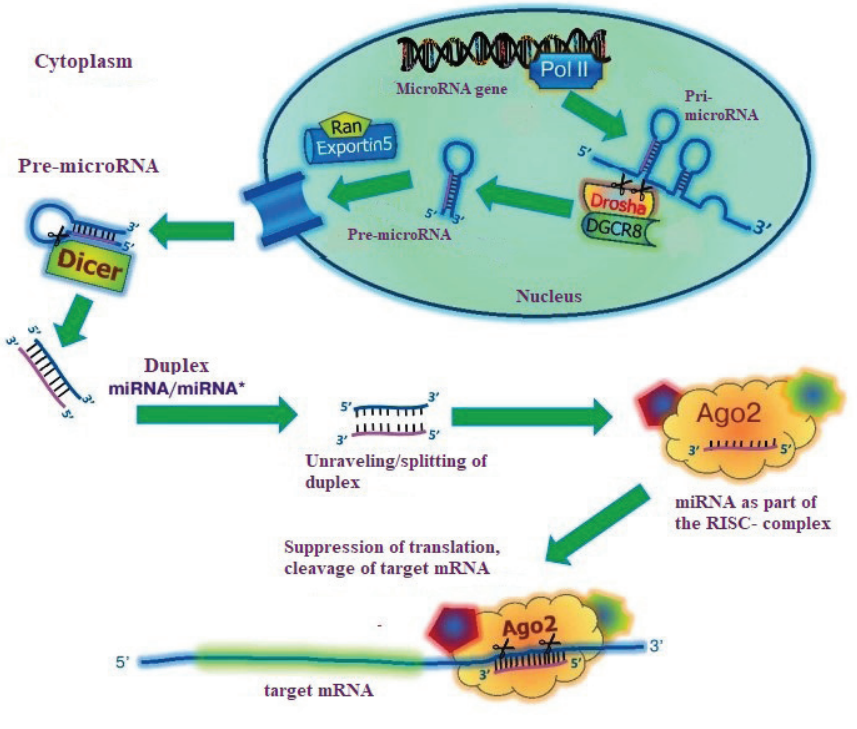
Depending on which gene expression is suppressed by microRNAs, they can function as tumor suppressors or oncogenes. The expression of oncogenic miRNAs is typically upregulated in most tumor types, promoting malignant transformation and cancer progression. For example, in the work of Wang Z. et al. Using a comprehensive meta-analysis approach, it was demonstrated that miR-27a may promote the progression of ovarian cancer through the regulation of one of the transcription factors, the FOXO1 protein [49]. In an experiment on human ovarian cancer cell lines HO8910 and OVCAR-3, Hu Y. et al. showed that miR-934 promoted tumor cell proliferation through inhibition of the metastasis suppressor BRMS1L [21].

Tumor suppressor microRNAs can suppress cancer development by inhibiting oncogenes. The main effects of suppressor microRNAs are inhibition of proliferation, migration and invasion, stimulation of apoptosis, suppression or reversal of EMT, as well as overcoming or reducing multidrug resistance, in particular resistance to taxanes and platinum drugs [3]. Similar to protein-coding tumor suppressor genes, such microRNAs are often deleted, mutated, or methylated in various human tumors.

Thus, Li et al. showed that the expression of miR-542-3p was significantly reduced in tissues and cell lines of epithelial ovarian cancer. Further functional assays showed that overexpression of miR-542-3p suppressed tumor cell proliferation, migration and invasion in vitro, whereas knockdown of miR-542-3p promoted tumor cell proliferation and invasion. In vivo analysis also showed that overexpression of miR-542-3p significantly attenuated tumor growth [29]. In a similar study, Jia et al. reported that upregulation of miR-34 induces autophagy and apoptosis of tumor cells, regulates tumor proliferation, and inhibits cell invasion by suppressing Notch1 protein expression [24].

Other representatives of suppressor microRNAs include the let-7 family. MicroRNAs of this family inhibit the growth and invasion of tumor cells by suppressing the expression of proto-oncogene-encoded proteins KRAS, HRAS, c-MYC and HMGA-2, as well as cell cycle regulators such as CDC25, CDK6 and cyclins A, D1, D2 and D3. A decrease in the expression of let-7e, let-7f, let-7d, let-7c, let-7i, let-7a, let-7b in the tumor and let-7f, let-7d in ovarian cancer cell lines was detected [54].

Depending on the cellular and tissue environment, some microRNAs can suppress or promote malignant cell transformation [7]. The most striking example is the miR-200 family of microRNAs. MicroRNAs of this family are responsible for regulating the EMT process by suppressing the expression of E-cadherin transcription inhibitors ZEB1 and ZEB2 [8]. In turn, ZEB may reduce transcription of the miR-200 family. Presumably, in the



MicroRNA biogenesis [1]

early stages of ovarian cancer development, a mesenchymal-epithelial transition occurs, increasing the expression of microRNAs of this family, and with the spread of metastases, EMT occurs, reducing it [2,19]. The miR-200 family has also been reported to inhibit blood vessel formation by directly or indirectly affecting interleukin-8 secreted by tumor epithelial cells and the chemokine CXCL-1. Transfection of microRNAs of the miR-200 family into the epithelium showed a significant reduction in tumor cell metastasis and angiogenesis, as well as normalization of blood vessels [7].

Recent work by Choi et al., examining plasma and serum samples from 118 patients with epithelial ovarian cancer (EOC) and 96 healthy controls, found increased levels of miR-200a, miR-200b and miR-200c in patients compared to controls. . Researchers also found differences in miR-200 expression levels associated with subtypes, with serous and mucinous tumors showing increased levels of miR-200b and miR-200c, and clear cell and endometrioid tumors having increased expression of miR-429 [17].

The expression level of miR-200 family microRNAs may be a prognostic factor for survival. In particular, increased expression of miR-200a and miR-200b in serum and tissue correlates with lower overall and disease-free survival [10,55].

For the microRNA cluster miR-214-199-a2, both overexpression in ovarian cancer and a decrease in the level of synthesis compared to normal have been described. Thus, in a study by Liu et al., it was shown that SKOV3 cells transfected with a miR-214 mimic showed significantly increased viability and proliferation, as well as a noticeable decrease in the rate of apoptosis. In addition, PTEN protein expression was decreased and PIP3, p-Akt, and p-GSK-3β protein expression was significantly increased. The authors of the study concluded that miR-214 can activate the PI3K/Akt signaling pathway by suppressing PTEN, which can promote proliferation and inhibit apoptosis of OC cells [34]. Another study reported that overexpression of miR-214 suppresses cell proliferation and induces apoptosis by negatively controlling the semaphorin-4D gene in tumor cells [35]. However, miR-214 belongs to microRNAs that are found in exosomes and circulate in the blood, and therefore it can be used for non-invasive diagnostics.

Thus, to date, extensive information has been accumulated on the effect of microRNAs on the progression of ovarian cancer. It is known that microRNA expression profiles are specific for both different types of histologically normal and tumor tissues. However, the results of research to date are quite contradictory, which undoubtedly requires a more detailed study of microRNA expression for each specific tumor type, which will ultimately contribute to the understanding of the pathogenesis of malignant neoplasms, as well as the development of sets of molecular markers for the prognosis and diagnosis of cancer. diseases based on microRNA analysis.

2. Drug resistance and sensitivity in the treatment of malignant neoplasms: disruption of microRNA genes. Chemoresistance remains a major barrier to effective treatment of patients with ovarian cancer, and recently, increasing evidence suggests that microRNAs are involved in the development of drug resistance [18, 25, 50]. Studies of the role of microRNAs in the formation of chemoresistance in ovarian cancer are based on comparing the levels of microRNAs in cells of insensitive and sensitive tumors or cell lines, identifying differentially expressed microRNAs and their targets. Due to the wide heterogeneity of the molecular genetic characteristics of tumor cells within one histological type and the dual role of individual microRNAs in carcinogenesis, researchers are obtaining a large number of potentially significant microRNAs, including conflicting results.

Members of the ABC transporter family play an important role in the development of multidrug resistance (MDR). Yang et al. It has been shown that suppression of miR-130a can inhibit MDR1 gene mRNA expression and overcome treatment resistance in the cisplatin-insensitive ovarian cancer cell line SKOV3/CIS [53]. Similar results were obtained in the work of Li et al., who found that miR-130a and miR-374a mimetics reduce the sensitivity of A2780 cells to cisplatin, and vice versa; their inhibitors can resensitize cells of the cisplatin-resistant A2780/DDP line. In addition, the authors of the study noted that overexpression of miR-130a can increase the levels of MDR1 gene mRNA in A2780 and A2780/DDP cells, while knockdown of miR-130a can inhibit the expression of the MDR1 gene and activate the PTEN protein [30].

Another study showed that miR-199a significantly increased the chemosensitivity of CD44+/CD117+ ovarian cancer stem cells to cisplatin, pacitaxel, and adriamycin, and decreased mRNA expression of the multidrug resistance gene ABCG2 compared to cells transfected or untransfected with miR-199a mutants [16]. In a study by Zong et al., transfection of miR-130b into the OC cell line A2780 and paclitaxel-resistant A2780/Taxol cells resulted in suppression of MDR1 protein and increased sensitivity to paclitaxel and cisplatin in both cells [59]. The same results were obtained for miR-490-3P, miR-133b, miR-873 and miR-186 in the same ovarian cancer cell lines [12, 13, 51, 41,42].

In addition to drug transporters, a number of genes involved in the regulation of apoptosis may be potential targets of microRNAs in the regulation of chemosensitivity in human cancer. For example, it was found that microRNAs miR-130a, miR-137 and miR-142-5p are able to regulate the sensitivity of OC cells to cisplatin by influencing the expression of XIAP (X-linked inhibitor of apoptosis) [14, 31, 32,56]. A study by Kong et al found that miR-125b promotes cisplatin resistance by suppressing Bcl-2 expression in the resistant C13* cell line [26]. Decreased serum miR-125b levels were also significantly associated with increased chemoresistance in patients in a study by Chen et al [15]. Additionally, a study by Parayath et al showed that miR-125b encapsulated in hyaluronic acid-based nanoparticles (HA-PEI-miR-125b) in combination with intraperitoneal paclitaxel could enhance the antitumor efficacy of paclitaxel in patients with ovarian cancer [39].

The most frequently studied miRNAs that are associated with chemotherapy sensitivity are the let-7 and miR-200 families. Lu et al. observed that let-7a expression was significantly lower in ovarian cancer patients who were sensitive to platinum and paclitaxel compared with those who were resistant to these drugs. In addition, overexpression of this miRNA may enhance the effect of platinum alone, but may negatively affect the prognosis of combination treatment (for example, carboplatin + paclitaxel first line) [37]. In the work of Wang et al., a novel targeted hyaluronic acid-modified nanosystem using gold nanorods coated with functionalized mesoporous silica nanoparticles was developed for the combined delivery of paclitaxel and let-7a microRNA to overcome MDR in ovarian cancer. The authors of the study showed that this nanosistema can stably combine and transport paclitaxel and microRNA, and also specifically bind to the CD44 receptor, which is highly expressed in SKOV3 cells and chemotherapy-resistant SKOV3 TR cells, ensuring effective uptake by cells and increasing the permeability of the tumor site by 150 %. Analysis of SKOV3 TR cells and the SKOV3 TR xenograft model in BALB/c-nude mice showed a significant decrease in P-glycoprotein levels

in heterogeneous tumor sites, release of paclitaxel, and subsequent induction of apoptosis [48]. A decrease in expression in tumor tissues compared to normal was also noted for let-7g, which may be associated with acquired chemoresistance in late-stage patients. Thus, let-7g acts as a tumor suppressor and can be used to inhibit EOC progression and resistance to cisplatin-based chemotherapy. Similar results were obtained for let-7i. In particular, low levels of let-7i expression in tissues and in vitro cause low sensitivity to cisplatin [54].

Research on the miR-200 family in relation to drug resistance in OC is inconsistent. In vitro experiments have shown that miR-200c expression falls 4- to 5-fold compared to normal levels in tissues with observed paclitaxel resistance. At the same time, miR-200c reduces the sensitivity of cells to carboplatin by increasing sensitivity to taxanes [22]. A number of studies have demonstrated that activation of miR-200c, miR-200a and miR-141 increases the sensitivity of OC cell lines to carboplatin and paclitaxel [40, 43]. The work carried out by Liu et al. revealed that increased expression levels of miR-200b and miR-200c contributed to the death of epithelial OC cells in the presence of cisplatin. In addition, it was found that these microRNAs can increase the sensitivity of tumor cells to cisplatin by suppressing DNA methyltransferases (DNMTs) [33].

Table shows the results of studies by different groups of researchers on the expression of microRNAs on cell lines and in ovarian tumor samples, which showed an association with the formation of chemoresistance.

3.Methylation of microRNA genes in ovarian cancer and development of treatment resistance. An important mechanism for inactivation of microRNA genes in malignant neoplasms is methylation of promoter CpG islands. It was revealed that among microRNA genes, hypermethylation of regulatory CpG islands occurs several times more often than among genes encoding proteins, which makes them promising biomarkers. Aberrant methylation of the promoter regions of both suppressor and oncogenic miR-

MicroRNAs involved in the formation of chemoresistance in ovarian cancer

MicroRNA	Chemotherapy	Function	Target/Signal Path	Reference
miR-130a	Cisplatin	Inhibition of proliferation	MDR1/P-gp, PI3K/Akt/PTEN/mTOR XIAP	[30, 53, 56]
miR-374	Cisplatin	Inhibition of proliferation	Akt, VEGF, PTEN, Wnt	[30]
miR -130b	Cisplatin, Paclitaxel	Inhibition of proliferation, increased sensitivity to chemotherapy	MDR1/P-gp, GST-π	[60]
miR-199a	Cisplatin, Paclitaxel, Adriamycin	Inhibition of proliferation, increased sensitivity to chemotherapy	ABCG2	[16]
miR-490-3P	Cisplatin, Paclitaxel	Inhibition of proliferation	ABCC2	[12,42]
miR-133b	Cisplatin, Paclitaxel	Inhibition of proliferation	GST-π, MDR1	[13]
miR-873	Cisplatin, Paclitaxel	Inhibition of proliferation	MDR1	[51]
miR-186	Cisplatin, Paclitaxel	Inhibition of proliferation	MDR1, GST-π, ABCB1	[41]
miR-137	Cisplatin	G1/S cell cycle arrest, proliferation inhibition, chromatin remodeling, sensitization of ovarian cancer cells to cisplatin-induced apoptosis	XIAP, MCL1	[14,31]
miR-142-5p	Cisplatin	Inhibition of drug resistance	*XIAP, BIRC3, BCL2, BCL2L2, MCL1*	[31]
miR-125b	Cisplatin, Paclitaxel	Cell cycle arrest in G2/M, suppression of proliferation and metastasis, increased resistance to therapy	*BCL2, VEGF, VEGFR, IGFR1*	[15,26,39]
семейство miR-let-7	Cisplatin, Paclitaxel	Inhibition of proliferation and stimulation of apoptosis, increasing sensitivity to chemotherapy	Сигнальный путь PI3K/Akt/mTOR, TGFR-2,Ras, циклин D, цитохром С, *EZH2*	[8, 27, 34, 37,52, 54]
семейство miR-200	Cisplatin, Paclitaxel, Carboplatin	Overexpression of microRNAs of the miR-200 family suppresses the tumorigenicity of OC stem cells by inhibiting EMT; suppresses proliferation and induces apoptosis in tumor cells; reduces migration and invasive activity; suppresses resistance to chemotherapy	*ZEB1, ZEB2, VIM, CREB1*	[10, 33, 44]
miR-34a	Cisplatin	Suppression of proliferation, motility, EMT, invasion, metastasis	*HDAC1, MET, AXL, IL6R, YY1*	[47]
miR-34a-5p	Cisplatin	Inhibition of proliferation and G1-phase cell cycle	PD-L1	[60]

NA genes is involved in all the main processes associated with carcinogenesis: uncontrolled proliferation, bypass of the apoptosis program, neoangiogenesis, the ability to invade and metastasize, etc. [5]. Thus, suppression of apoptosis in tumors is associated with hypermethylation and inactivation of a number of miRNA genes, for example, miR-34b/c, miR-137 and miR-129-2. Methylation of the miR-34b/c and miR-34a loci was observed in tumors of various locations, including ovarian cancer [47,60].

The genes of the miR-200 family have also been shown to be inactivated in tumor cells, associated with hypermethylation. Methylation and decreased expression of these genes is a marker of poor prognosis in ovarian cancer [46].

In a study by Vera et al, the following conclusions were made when examining the effect of miR-7 methylation on platinum resistance. Patients with platinum-sensitive tumors containing unmethylated miR-7 had better progression-free survival rates than patients with methylated miR-7. In addition, patients carrying the unmethylated marker had less aggressive tumors, and overall survival after platinum treatment was three times higher than that of patients with methylated DNA. In addition, the percentage of methylation increased in grade III/IV tumors and in the analysis of highly serous ovarian cancer and platinum-resistant tumors. Thus, miR-7 methylation may play a role as a clinical tool predicting aggressive behavior of this malignancy and poorer response to platinum-based treatment [44].

Recent work by Pernar Kovač et al., through microRNA and cDNA profiling and subsequent integrative analysis, identified the epigenetically regulated and prognostic miR-103a, which plays a role in the migration and invasion of carboplatin-resistant ovarian cancer cells that have acquired a mesenchymal-like phenotype [27].

Russian scientists found that miR-9-1, miR-9-3, miR-107, miR-1258, and miR-130b were methylated in the majority of tumor samples compared to paired normal tissue samples. Moreover, methylation of miR-9-1, miR-9-3 and miR-130b correlated with disease progression [9]. Another work by this team assessed the clinical significance of methylation of 13 microRNA genes (miR -124a-2, miR -124a-3, miR -125-B1, miR -127, miR -129-2, miR -132, miR-137, miR -203a, miR -34b/c, miR -375, miR-9-1, miR-9-3, miR-339) in 26 patients with ovarian cancer. For all 13 genes, an increase in the level of methylation was detected during the transition from unchanged tissue to primary tumors and further from primary tumors to peritoneal metastases, and in the genes miR-203a, miR-375 and miR-339 the level of methylation in metastases increased most significantly (2 or more times). Analysis of microRNA gene methylation in clinical samples of ovarian cancer showed the connection of the observed molecular changes with both the initial stages of tumorigenesis and the progression and dissemination of ovarian cancer, with the presence of metastases in the greater omentum and with the appearance of ascites [36].

Conclusion. Ovarian cancer remains one of the most common causes of death from gynecological cancer in women worldwide. Due to its insidious onset, most patients in the early stages of the disease do not have specific manifestations or symptoms. The lack of a sensitive and effective clinical screening technique results in most cases being diagnosed at late stages. Standard treatment includes platinum-based chemotherapy, and most tumors develop resistance to therapeutic drugs [52].

MicroRNAs (miRNAs) are a group of small non-coding RNA molecules of 19–25 nucleotides that have demonstrated important regulatory functions in cancer over the past decade. Because they are involved in various biological processes as well as post-transcriptional gene regulation, it has been shown that their dysregulation through genetic or epigenetic modifications may contribute to the development of cancer and they may be involved in the development of chemoresistance. Available evidence suggests that they can be considered either oncogenes or tumor suppressor genes, depending on their specific role and level of expression [4].

Numerous miRNAs have been investigated for their potential involvement in ovarian cancer chemoresistance, including miRNA -21, miRNA -29, miRNA -30-5p, miRNA -34a, miRNA -98-5p, miRNA -125b, miRNA -130a, miRNA - 130b, miRNA -133b, miRNA-136, miRNA 137, miRNA -142-5p, miR-146a-5p, miRNA -186, miRNA -199a, miRNA -374a, miRNA -383-5p, miRNA -490-3p, miRNA -503-5p, miRNA -708, miRNA -873, miRNA -1246, miRNA -200 and miRNA-7 families and many others.

A new approach to determining the role of microRNA is to analyze its epigenetic regulation, for example, the methylation status of promoter CpG islands. MicroRNA gene hypermethylation profiles have been proposed as potential markers for the diagnosis and prognosis of cancer of various localizations [47]. At the same time, the analysis of hypermethylation of microRNA genes in ovarian cancer is limited to single studies and requires further research [9, 36].

However, it can be concluded that the current findings on the role of microRNAs in the pathogenesis of ovarian cancer may be useful in assessing the prognosis of metastasis and drug resistance of the tumor, as well as for the selection of new targets for targeted therapy.

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HUMORAL ASPECTS OF BROWN ADIPOSE TISSUE THERMOGENESIS AS A PHYSIOLOGICAL STRATEGY OF ADAPTATION TO COLD

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The review is devoted to the study of humoral factors that directly affect the processes of non-contractile thermogenesis and the activity of brown adipose tissue. The review is based on research conducted in various research laboratories.

Keywords: thermogenesis, brown adipose tissue, adaptation, cold, insulin, glucagon.

Exposure to cold stimulates heat production through muscle tremors caused by contraction of skeletal muscles, as well as the influence of non-contractile thermogenesis. The concept of non-contractile thermogenesis was first proposed in Voight's research in 1878, the occurrence of non-contractile thermogenesis in the human body was accurately described by W. Cannon et al. [5] in 1927, who argued that the medulla oblongata of the adrenal glands plays a significant role in non-contractile thermogenesis. Currently, a number of studies have established that metabolic acclimatization to cold is characterized by an increase in non-contractile thermogenesis in the human body as a more effective way of obtaining heat than muscle contractions, and the main source of non-contractile thermogenesis is a unique brown adipose tissue (BAT), which is exclusively differentiated for thermogenesis and is the only known tissue whose main function is to produce heat. Enough works have been devoted to the biochemical and physiological mechanisms of the functioning of non-contractile thermogenesis and the role of BAT [3, 15, 40, 46].

Cold acclimatization enhances not only the metabolic activity of BAT, but also significantly proliferates this tissue. The degree of hyperplasia in the BAT is greater than in any other tissues or organs under various physiological stimuli. It is assumed that such features of BAT are under the control of numerous neuroendocrine factors. However, the mechanisms involved in this process have not been fully clarified. This review is devoted to the study of humoral factors that directly affect BAT, mainly on the basis of studies conducted in various research laboratories.

Humoral regulation of brown adipose tissue. Norepinephrine is the main regulator of the BAT function during acclimatization to cold. It is known that some hormones, such as adrenaline, glucocorticoids and thyroid hormones, are involved in the regulation of this tissue, enhancing its thermogenesis directly [40, 41]. Pancreatic hormone glucagon plays the role of an energy-supplying hormone, satisfying the increased need for energy and fuel during physical activity, fasting [17], pain syndrome, the influence of noise and fever [2]. What is of interest in studying the role of glucagon in the functioning of BAT during cold acclimatization.

Exposure to cold increases the level of glucagon in the blood plasma of rats at an early stage for 2 weeks at a temperature of 5 °C [21, 22], when the animals develop an almost maximum phase of non-shivering thermogenesis [15]. There is also a significant positive correlation between the concentration of glucagon and the level of free fatty acids in blood. It has been shown that the main substrate for non-shivering thermogenesis is fatty acids [28]. It was also found that the level of glucagon in blood plasma in men has significant seasonal fluctuations, so the level of glucagon is significantly higher in winter than in summer, and there is a positive correlation between the level of glucagon and the concentration of free fatty acids in blood plasma in general during the year [18]. These data suggest that glucagon may play a role in the development of cold acclimatization due to its lipolytic effect. However, the level of glucagon in blood plasma does not differ from the control value after prolonged cold acclimatization for 4 weeks, while it was noted that the glucagon-induced increase in oxygen consumption by the whole body, as well as intraperitoneal temperature and BAT temperature is greater in cold-acclimatized rats than in heat-acclimatized [20], and an increase in consumption oxygen and BAT temperature are positively correlated with BAT mass. A similar phenomenon is observed in the reaction to norepinephrine, as previously reported [15, 41]. Such an altered reaction of the body to biogenic factors such as norepinephrine and glucagon can provide a kind of adaptation effectiveness. This concept can be described as a "mechanism for saving on adaptation." Moreover, chronic administration of glucagon causes an increase in tolerance to cold and to non-shivering thermogenesis, possibly due to an increase in weight and an increase in the thermogenic ability of BAT [49]. Cold acclimatization increases the level of glucagon in BAT when the level of glucagon in plasma is the same as in rats in heat [12]. These data suggest that BAT is a target tissue for glucagon, and glucagon serves as one of the members of the humoral team, which is responsible for enhancing the processes of non-shivering thermogenesis in BAT during cold acclimatization. It is well known that an enhanced thermogenic reaction to norepinephrine, in addition to increased secretion of this sympathetic factor, is caused by cold acclimatization [15], and BAT is the dominant anatomical site of enhanced norepinephrine-induced non-contractile thermogenesis during cold acclimatization [10]. It is believed that such a contribution of BAT is mediated by an increase in mass (hyperplasia) [21], blood flow [10] and metabolic activity, estimated by the mitochondrial thermogenic ability of this tissue (an increase in the thermogenin protein UCP1) [45]. Thus, it can be concluded that in combination with norepinephrine and other hormonal factors, glucagon functions as

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a thermogenic hormone and participates in the regulation of non-contractile thermogenesis through the activation of BAT.

In vivo research. BAT in cold-adapted rats exhibits a greater thermogenic response to cold [9], norepinephrine [8, 24] and glucagon [8]. Increased non-contractile thermogenesis is associated with increased metabolism of free fatty acids and a decrease in respiratory metabolism [28]. The level of triglycerides decreases in the cells of the BAT of rats during acute exposure to cold and adaptation to cold [34]. It is assumed that the oxidation of fatty acids accounts for a large part of the thermogenesis of BAT during norepinephrine infusion [32]. It has been shown that the rate of fatty acid synthesis is more than ten times higher in rats with cold acclimatization compared with controls that were not exposed to cold [46]. These results indicate that fatty acids are the main energy substrates for BAT thermogenesis. In this context, it is interesting to note a lower venous drainage of free fatty acids from the BAT of cold-acclimated rats compared with the control group after infusion of norepinephrine [36] or glucagon [18, 21]. This may be due either to a decrease in lipolysis or to an increase in the utilization of free fatty acids in the BAT. When norepinephrine was administered to cold-acclimated rats and the control group, the concentration of glycerin did not have significant differences. Glycerol release is an indicator of the intensity of the lipolysis process, since glycerol is less utilized in adipocytes of white adipose tissue and BAT compared with free fatty acids [36]. Therefore, a low concentration of free fatty acids from the BAT adipocytes of rats acclimated to cold may be the result of increased utilization of free fatty acids under the influence of norepinephrine or glucagon. Since glucagon is known to stimulate the secretion of catecholamines, it is possible that an increase in the level of fatty acids in the blood and BAT is secondary to an increase in circulating norepinephrine levels. However, this is unlikely, since the response to glucagon does not change under the action of the propranolol Q blocker, which suppresses the lipolytic and calorigenic effects of catecholamines [19].

It is also suggested that the activation of BAT contributes to increased glucose consumption for thermogenesis, since this tissue has a high concentration of key glycolytic enzymes, hexokinase and 6-phosphofructokinase, and the activity of these enzymes doubles when adapting to cold [6]. In addition, it is believed that BAT can play an important role in glucose excretion after a carbohydrate load by controlling the concentration of glucose in the blood. It was found that the glycogen level in the BAT of cold-acclimated rats is lower [20], and glucagon infusion does not increase the glucose level in the venous drainage from the BAT, despite the increased glucose level in the systemic venous blood [24]. The data obtained show that glucose may be one of the exogenous substrates used by BAT, although its contribution to BAT thermogenesis may be relatively small [14, 32]. At the same time, glucose may be an important substrate for lipogenesis in BAT. It is known that the main fuel for thermogenesis in BAT are lipids synthesized de novo and stored in multilocular fat droplets in the cytoplasm of BAT adipocytes [14]. It has also been established that BCT has a high activity in lipogenesis, especially in animals acclimatized to cold. Thus, in the study Trayhurn P, 2018, it was shown that the total synthesis of fatty acids is three times higher than the total hepatic synthesis in rats with acclimatization to cold [46]. Another pancreatic hormone, insulin, is a powerful anabolic hormone, as well as an anti-lipolytic factor and stimulates lipid synthesis. Therefore, the action of insulin would be a necessary condition for maintaining a high thermogenic capacity of BAT. It has also been proven that glucose is the predominant substrate for the synthesis of fatty acids in BAT, and this process is stimulated by insulin [39]. In addition, it has been shown that tolerance to cold and to non-oxidative thermogenesis are markedly reduced in rats with streptozotocin diabetes mellitus [11], which may be due to some disorders in BAT caused by insulin deficiency, such as tissue atrophy, decreased ability to Q-oxidation of fatty acids and a decrease in the amount of mitochondrial uncoupling protein (UCP 1). A recent study [35] showed that insulin is involved in the regulation of the function of BAT in cold weather, directly demonstrating changes in the binding sites of insulin, as well as its content in BAT. The concentration of insulin in the BAT was increased both in rats exposed to acute exposure to cold, as well as in the group of rats exposed to prolonged exposure to cold, but it should be noted that insulin receptors were elevated in the first group of animals and were significantly lower in the second group. The exact mechanism of increasing the insulin content in adipose tissue remains unknown. However, there is an assumption that an increase in insulin in the tissue is associated with increased lipogenesis to meet the increased need for energy fuel in the cold. It has been shown that the internalized insulin receptor complex releases insulin and places it in cellular organelles such as lysosomes, Golgi apparatus [37] and nuclei [41, 42]. Moreover, several proofs indicate that intracellular insulin is associated with the proliferation and differentiation of BAT during adaptation to cold. Taken together, these data indicate that insulin may be closely related to the regulation of BAT function in many aspects.

The authors of the study showed that the systemic caloric effect of glucagon decreases with a deficiency of adrenocorticoids [7]. In thyroidectomized or adrenalectomized rats, glucagon infusion does not lead to an increase in the level of free fatty acids in the venous drainage from the BAT [19]. It is possible that the lipolytic and thermogenic effect of glucagon in BAT depends on the presence of thyroid and adrenocortical hormones.

Thus, in L. Jansky study, when norepinephrine is infused at a dose of 40 g intravenously / 100 g of body weight, it causes non-contractile thermogenesis in the body of rats [15]. Studies have shown that the administration of norepinephrine also increases the level of glucagon in both plasma and BAT adipocytes. The degree of increase of glucagon in plasma is higher, and the initial level of glucagon in BAT, as well as the level of glucagon induced by noradrenaline, is higher in cold-acclimatized rats than in the control group [25]. The results show that norepinephrine stimulates glucagon secretion, and cold acclimatization enhances this effect of norepinephrine, suggesting that the glucagon released by norepinephrine will interact with norepinephrine to enhance the process of non-contractile thermogenesis in BAT in the cold. However, exposure to cold stimulates glucagon secretion in adrenodemidulated and chemically sympathectomized rats to the same extent as in rats in control groups, which indicates that cold-induced glucagon release is at least partially independent of the sympathoadrenal system [13].

In vitro research. In vitro studies have been conducted in order to directly learn the regulatory mechanisms of the function of BAT. Isolated BAT cells, thin tissue sections or finely ground tissue blocks were used for in vitro studies. Norepinephrine and glucagon provide a comparable maximum response in the in vitro oxygen consumption by cells and tissue blocks of the BAT of rats [25, 26]. Thus, in vitro experiments revealed that the concentrations of glucagon and norepinephrine necessary for the effect were increased compared to concentrations in blood plasma. The thermogenic re-

sponse to glucagon in vitro is suppressed by thyroidectomy or adrenalectomy, as well as the lipolytic effect of animals acclimated to cold has increased metabolic activity, which is estimated by biochemical parameters associated with the mitochondrial thermogenic mechanism, such as the UCP1 protein [47].Therefore, it is expected that the BAT of cold-climatized animals will demonstrate an enhanced thermogenic response to norepinephrine or glucagon at the tissue or cellular level. Thus, in BCT adipocytes [33], BAT fragments [27] and BAT blocks [26] exposed to cold, a low reaction was detected, estimated by oxygen consumption and lipolysis processes stimulated by norepinephrine and glucagon, compared with the control. These in vitro results contradict the aforementioned in vivo data and biochemical results. An increase in the thermogenic response of BAT in cold-climatized animals may be caused by BAT hyperplasia [3], accompanied by an increase in the supply of energy substrates and oxygen due to increased blood flow through this tissue [10, 51]. Indeed, a positive correlation was noted between the mass of BAT and in vivo norepinephrine and glucagon-induced thermogenesis in BAT [8]. Another possible factor in the differences between in vivo and in vitro results is that the preparation of BAT cells or tissues has not yet been optimized. However, under the same in vitro incubation conditions, the tissue blocks of the BAT of guinea pigs acclimated to cold show an enhanced norepinephrine and glucagon-induced respiratory response, while rats acclimated to cold show a weakened one [26]. Oxygen consumption by brown adipocytes during norepinephrine stimulation was higher in guinea pigs acclimated to cold compared with controls [31, 38]. It has been shown that BAT is the main factor in enhancing non-contractile thermogenesis in guinea pigs exposed to cold. Therefore, it can be said that the in vitro BAT reaction well reflects the thermogenic function of tissues in vivo in guinea pigs, but not in rats. Such a discrepancy between the results in vivo and in vitro in rats suggests that in the BAT of cold-climatized rats there is a certain mechanism for protecting tissue with high thermogenic ability from excessive heat release and subsequent self-destruction during cold acclimatization. At the same time, the constant heat production of BAT in the cold is provided by an enhanced biochemical mechanism, such as activation or induction of the uncoupling protein UCP1 in tissue mitochondria [47]. An increase in the virothermogenesis of BAT in rats occurs mainly due to extensive hyperplasia [3, 4] and increased blood flow to the tissue [10, 51]. Prolonged infusion of norepinephrine [39] and glucagon [1, 49] in rats simulates cold acclimatization, increasing tolerance to cold due to stimulation of BAT. However, the BAT of rats with glucagon and norepinephrine infusion does not demonstrate an enhanced thermogenic response in vitro, as does the BAT of rats acclimatized to cold [3].

Conclusion. Activation of the sympathetic nervous system in BAT is mediated by central stimulation by humoral factors that have been proven to act directly on this tissue, such as insulin and glucagon. Therefore, it is appropriate to conclude that the function of BAT is regulated by numerous neuroendocrine factors through their peripheral and central action.

Brown adipose tissue, whose main function is to produce heat by dissipating energy, serves as a specific organ of adaptation to changes in ambient temperature. Numerous studies have proven that this unique tissue has cross-adaptability and is regulated by numerous neutroendocrine factors. But at the same time, there are still some gaps in the understanding of the mechanisms of regulation of this tissue. Therefore, further clarification of the processes and factors involved in the functioning of brown adipose tissue will contribute to our understanding of the adaptability of the body in cold conditions.

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BIOETHICAL PRINCIPLES AND APPLIED BIOETHICS IN THE FIELD OF NEURODEGENERATIVE DISEASE RESEARCH IN YAKUTIA

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Applied bioethics is a field of knowledge, the subject of which is practical moral problems. The ethical principles that form the basis for applied bioethical research related to neurodegenerative disease in Yakutia are discussed. Applying the basic four ethical principles as starting points can lead to different answers regarding specific bioethical problems, in our case the moral problems of providing medical care to patients with neurodegenerative diseases.

Keywords: bioethics, applied ethics, neurodegenerative diseases, Republic of Sakha (Yakutia)

Introduction. Bioethics arose from the need to assess the positive and negative effects of new methods and technologies. Can bioethics prevent the unfair distribution of medical resources, treatments, and medicines among those in need? Bioethics acts as a kind of discussion platform, where scientists themselves, who have created breakthrough technologies, discuss the positive and negative consequences of inventions for both patients and society, and positive and negative criteria depend on knowledge, cultural level and prejudices of the era and society as a whole [8,9,11,46].

Perhaps it is bioethics that is the field of human knowledge where many areas of research have become entrenched and there are many directions for research: the philosophical study of the ethics of medicine, medical law, medical anthropology, medical genetics, medical sociology, health policy, health economics. Philosophers believe that bioethics is one of the branches of practical (or applied) ethics, which, in turn, is one of the branches of philosophy [5,12,45].

On the other hand, there is undoubtedly a problem that the philosopher Benatar (2006) calls the problem of "disciplinary slip", when a person moves from working in his own discipline, in which he is trained, to working in another, in which he is not trained. There are fewer obstacles for health care workers or scientists to engage in moral philosophy than there are for philosophers who would like to practice medicine. This does not prevent lawyers, doctors and scientists of various profiles from cooperating with philosophers on practical ethical issues or working independently to answer questions that are crucial for making ethical decisions [22,24,26,43].

According to Husseinov (2004), ethics is initially a practical science. In his opinion, ethics is a practical science, since it considers human actions and behavior from the point of view of their fundamental principles, and it is the point at which philosophy connects with practice, there-

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fore it is rightly called practical philosophy [6]. Thus, applied bioethics is a field of knowledge and behavior, the subject of which is practical moral problems [6, 23,29,45].

Tom Beauchamp and James Childress in 1977, in the book Principles of Biomedical Ethics, proposed standard approaches to bioethics, which formed the basis for the principles of health ethics, along with the Hippocratic Oath. Gillon R (1994) develops an approach that is easy to comprehend ethical problems - "four principles and the scope of their application." It is based on four common, basic prima facie moral obligations - respect for autonomy, charity, nonviolence and justice, plus concern for the scope of their application, i.e. a common, basic moral and analytical framework and a common language are proposed. Although they do not contain orderly rules, these principles can help doctors and other medical professionals make decisions by reflecting on the moral issues that arise at work. Thus, four ethical principles are proposed: "do no harm" (non-maleficence), "do good" (beneficence); the principle of respect for personal autonomy; justice and four rules: veracity, privacy, confidentiality, fidelity [25,28,31,32,47].

In modern society, with the rapid development of technology, it is quite problematic to find ideal solutions to bioethical problems. "It cannot be said that all decisions have been made. On some issues, an ideal compromise may never be found. But most importantly, the discussion continues," M. Vorontsova emphasized (2024) following the results of the online conference "Bioethics and Genetics: challenges of the XXI century" [4,5].

The purpose of this review is to discuss four ethical principles that are the basis for our applied bioethical research related to the problems of neurodegenerative diseases (NDD) in Yakutia. The provision of medical care to patients with NDDs is associated with many moral issues that require close attention from medical professionals and society. The article outlines bioethical principles and provides examples from practical work, that is, certain results on applied bioethics related to our desire to observe the moral principles of medicine.

Principles of bioethics. *The principle of "do no harm" (non-maleficence).* This principle is fundamental in the ethics of medicine. The moral duty of a Hippocratic physician is to provide the most complete medical care to the patient without causing him any physical or psychological damage. However, a moral conflict arises immediately. As soon as the doctor begins his manipulations, he inevitably risks causing pain and moral suffering to the patient. According to Yudin (1998), the harm coming from a doctor should only be objectively inevitable and minimal harm. In addition, the harm that a doctor's actions can bring to a patient can be intentional or unintentional. Intentional harm occurs in cases of inaction by a doctor in a certain situation, or intentional harm. In cases where the doctor did not have the opportunity to think about the possible consequences of the intervention or uncontrolled external influences arose, we can talk about unintentional harm [21].

Gillon R (1994) emphasizes that a physician should provide a net medical benefit to patients with minimal harm, that is, benefit without harm to health. To achieve these moral goals, health care workers have a wide range of obvious obligations. What are the main obligations of medical professionals? Firstly, effective and continuous training both before and during professional activity; secondly, obtaining valuable empirical information during treatment and as a result of medical research and using it to minimize risks to the patient; thirdly, empowering the patient/client with respect for their autonomy to achieve a common goal [31,32,37].

The principle of "do no harm" is the central ethical issue of our biomedical activities in providing medical care to patients with NDDs and their relatives.

We started bioethical research simultaneously with the introduction of DNA diagnostics of spinocerebellar ataxia type 1 (SCA1) into the clinical practice of medical and genetic consultation at the Republican Hospital No. 1 of the National Center of Medicine. Due to the late-manifesting nature of the hereditary disease, seeking the advice of a patient with the risk of carrying the SCA 1 mutation is accompanied by great moral and psychological stress, under the influence of strong emotions, a person may experience doubts and fear. The task of the doctor is to align ethical principles with the different expectations of his patients and help them adapt to the decision on the need for examination and molecular genetic diagnosis. Following the principle of "do no harm", we adhere to the ethical rule of "non-directivity and voluntariness" in consulting.

The most difficult bioethical problem in our practice is presymtomatic DNA testing. Obtaining a positive result of DNA diagnostics, indicating the detection of an SCA 1 mutation, is a "sentence" for the patient, the psychological consequences of which undoubtedly affect the further life of the individual. Therefore, the ethical rules we have adopted provide for minimizing the damage from negative information, namely, respecting the patient's choice in his desire to conduct a DNA diagnosis, or to abandon it.

The principle of "do good" (beneficence). The principle of charity refers to the moral and psychological component of medical care. A person who has chosen the profession of a doctor undertakes to be spiritual, compassionate, positive, and merciful. According to Gusseynov (2004), medical ethics is aimed at transferring the truth and the mystery of morality, the highest meaning contained in it, to medical practice. Medical activity rises to the level of mission, service; it is not just that a doctor is required to be selfless and other moral qualities, but his very activity is given a moral status, as if it were not just a professional job, but also a kind of sacrament. It is considered morally valuable in itself. Medical ethics proceeds from the presumption that adequate behavior within the framework of medical activity cannot but be moral [6]. Moral norms are not fixed by laws and, for this reason, can be interpreted by each person arbitrarily, at his discretion, according to his morality. Their implementation is controlled not by laws, not by coercion, but by spiritual influence, public opinion [20].

Thus, the central question regarding charity in the patient-doctor relationship is: “What does it mean for a doctor to strive for a greater balance of benefit and harm in patient care?” The charity model answers this question, at least from the point of view that medicine is based on the best interests of the patient, not the doctor. The model clearly explains that the central theme of charity is the duty of the doctor to benefit patients, that is, charity as a principle of medical ethics asserts the obligation (on the part of the doctor) to help others (patients) in the realization of their important and legitimate interests and to refrain from harming them in any way, that is, psychologically, morally or physically. In addition, the achievement of the common goal of well-being is carried out by the joint efforts of the doctor and the patient [25,37,39].

The joint work of charitable organizations and state executive bodies, in particular the healthcare system, can help solve the ethical problems of maintaining life in incurable patients with motor neuron diseases (MND). The issue of using an artificial lung ventilation device (ventilator) at home for most patients with amyotrophic lateral sclerosis (ALS) is a big

problem mainly due to the difficulties of purchasing ventilator equipment for personal use at home. On May 31, 2019, orders of the Ministry of Health of the Russian Federation, the Ministry of Labor and Social Protection of the Russian Federation No. 348n "On approval of the list of medical devices intended to maintain the functions of organs and systems of the human body provided at home" [15] and Order No. 345n/372n on approval of the "Regulations on organizations providing palliative care, including the procedure for interaction between medical organizations, social service organizations and public associations, and other non-profit organizations engaged in their activities in the field of health protection" [16]. Order No. 348n includes general-purpose ventilators provided for use at home.

It is necessary to convince the patient that the use of a ventilator at home is a method of respiratory support, not an intensive care measure, and does not require the patient to stay in the intensive care unit and anesthesiology. At the same time, the patient has the opportunity to stay with his family, can travel and even work remotely. Family members should be warned about the reorganization of their everyday life, adjusted to care for the patient. All patients and their family members need the help of a psychologist and a psychotherapist [2.13].

The principle of "do good" is also implemented by the work of the charity project "Green Cane" within the framework of the activities of the Association of Patients with SCA1 and other NDDs in the Republic of Sakha (Yakutia). The purpose of this project is to provide practical assistance to patients with neurodegenerative and neuromuscular diseases in traveling on public transport, adaptation in an urban environment and public places, as well as identification by society of special people with neurodegenerative and neuromuscular diseases. Our doctors actively make their personal contribution to the activities of the Association, co-financing from the participants of charity projects makes it possible to purchase medical equipment for examinations and basic necessities that facilitate the stay of patients in the clinic. Patients with SCA1 and other NDDs often express gratitude to the medical staff of the YSC CMP Clinic for their professionalism, careful and sensitive attitude towards patients [2,13].

The principle of respect for personal autonomy. According to Kant's deontological ethics, each person is unconditionally invaluable and he himself is able to determine his own fate: "Each person is an end in itself and, in no case, should be considered as a means to accomplish any task, even if they were tasks for the common good" [21].

Autonomy is deliberate self-government. If we have autonomy, we can make our own decisions based on deliberation. Sometimes we may intend to do something as a result of these decisions, and sometimes we may do these things to implement the decisions. Respect for autonomy is a moral obligation to respect the autonomy of others to the extent that such respect is compatible with equal respect for the autonomy of all potentially affected [1,31,32].

In medicine, respect for autonomy must be strictly observed, and it is closely linked to ethical rules:

- *maintaining confidentiality*. Healthcare professionals promise their patients and clients that they will keep confidential the information they have been entrusted with;

- *informed consent*. Medical professionals promise to consult

with patients and get their consent before providing any medical care;

- *a trusting relationship*. Medical professionals promise a type of communication in which it is possible to find out whether patients want more information or less information that they really want to receive about the prognosis and choice of treatment methods, since some patients prefer to leave decisions to doctors, while others leave the decision to themselves [35,38,44].

We investigated the bioethical aspects of medical and genetic counseling for families burdened with SCA1 in the context of the principle of respect for individual autonomy. The main controversial bioethical issues are:

- what is the priority - personal autonomy or the right of family members to information?

- is the genetic information obtained as a result of DNA testing clinically useful for the patient if the disease is incurable?

- can socio-cultural and ethnopsychological features influence the patient's ability to make informed decisions and truly voluntary decision-making.

Here, a lot depends on the skills of the consulting geneticist, when consulting families with SCA1, the doctor must assess the psychological well-being of the family. Hodgson (2005) argues that genetic counselors are ethically obligated to consider the family as a meaningful unit. This forces them to reconcile the interests of their patients' autonomy with more subtle concerns about the benefits and harm to families [27,34,40]. Moreover, in practice, patients rarely insist on non-disclosure of the results of genetic tests to relatives [30,36]. Rather than using confidentiality towards an individual patient as a default priority, they suggest that genetic information should be conceptualized as family information. According to this so-called "joint accounting" model, disclosure of medically useful genetic information to relatives is the default practice, unless there are compelling reasons to maintain the confidentiality of individual patients [36,41].

Indeed, when consulting patients with SCA1, compliance with the rule of confidentiality within the family seems almost impossible, since family priorities often prevail over personal ones. In addition, the population in small villages is usually aware of SCA1 patients in burdened families, so information about the disease cannot be withheld. As a result, there is some self-isolation of families with an SCA1 positive family member, or a forced change of residence.

We have identified some ethnopsychological aspects that affect the medical and genetic counseling of families with NDDs. To do this, we turned to the characteristics of the Yakuts described earlier by researchers of the mentality of the people.

Bravina R (2008) notes: "... among the Yakuts, "Destiny" fell by lot to each person in accordance with his innate and genealogical parameters. Destiny, as a burden, provided for the whole set of everyday events assigned to a person, successes and failures, personal values. The "top of happiness" is first of all health and longevity, then offspring (especially sons - heirs and successors of the family) ..."[3].

Yakuts and the peoples of the north have developed a special attitude towards diseases, namely the ability not to dramatize certain manifestations of any disease. Yakuts have a sharply negative attitude towards emphasizing or ridiculing physical disabilities or diseases in people. Mercy is a national trait of character [19]. As many researchers have noted, Yakuts showed special, extraordinary pity and care for their sickly or physically handicapped children and nursed them as best they could. They have always been compassionate towards the disabled and the elderly [3, 10, 18,19]. V.L. Seroshevsky wrote: "The crippled, the frail, the sick could count on a certain guardianship. Taking care of them has always been considered the duty of the family. Iitimni (orphan), kumalaan (disabled adults and the elderly) – this is how the Yakuts call those who are dependent on the family – an ancient family institution… According

to Yakut concepts, it is a sin to despise iitimni, ... anyone can become one" [18].

Ethnopsychological features, in our opinion, can have a positive impact on the psychological aspects of medical and genetic counseling of hereditary neurodegenerative diseases, including informed consent and making difficult decisions.

The principle of justice. The principle of justice in bioethics seems to be the most controversial and relative. In the field of health ethics, equity obligations are divided into three categories: - equitable allocation of limited resources (distributive justice);

- Respect for human rights (justice based on rights);

- respect for morally acceptable laws (legal justice).

For example, in the context of the allocation of medical resources, there are possible contradictions between several common moral considerations:

- Is it possible to provide sufficient medical care to meet the needs of all who need it, if it is impossible to allocate health resources in proportion to the degree of people's needs for medical care;

- Can health care workers prioritize the needs of so-called "own" patients if they must ensure equal access to health care;

- Should medical professionals provide people with as much choice as possible

to maximize the benefits derived from available resources, to respect the autonomy of the people to whom these resources are provided. All these criteria for the fair distribution of health resources can be morally justified, but not all of them can be fully met simultaneously [31,32].

Let's consider the "principle of justice" on the example of the most common neurodegenerative disease in the Yakut population - spinocerebellar ataxia type 1, which belongs to rare (orphan) hereditary diseases, its prevalence in world populations is 1-4 per 100,000 population. At the same time, Yakutia is a focus of accumulation of SCA1, according to the latest data, 376 patients were registered, the prevalence was 77.6 per 100,000 population [17,33,42].

This hereditary disease is one of the most studied: a dynamic mutation responsible for the manifestation of clinical signs was discovered by molecular genetic methods, the spectrum of phenogenotypic characteristics, population-genetic features were studied in detail, epidemiology and prevalence in Yakutia were studied. It was found that the disease is late-manifesting and is characterized by the phenomenon of anticipation [14,33,42]. The high prevalence of SCA1 in the population undoubtedly causes concern to the health service of Yakutia, measures such as the medical examination of patients, the maintenance of registers for SCA1, the organization of prenatal diagnostics, the creation of an association of patients and SCA1 and other NDDs have been taken. The translation of scientific research into practical medicine, as it turned out, is a very long process, for example, for SCA1 it took more than 20 years [7]. During this time, we investigated the bioethical problems of using gene methods (DNA testing) in practical medicine. When direct DNA diagnosis became a routine clinical analysis, geneticists initially had a paternalistic desire to advise patients prescriptively for mandatory DNA testing of the carrier of the SCA1 mutation. Discussions of bioethical problems of new gene technologies led us to the adoption of ethical rules of medical and genetic counseling, where non-directive, voluntary, informed consent, and alternative informed choice were fixed when making a decision about DNA testing. For the prenatal diagnosis of SCA1, the ethical principle was adopted that prenatal diagnosis is not a method of getting rid of the fetus carrying the SCA1 mutation, but provides a burdened family with a way to choose termination or prolongation of pregnancy through an informed decision. Thus, we strive to comply with the "principle of fairness" of medical care for patients with SCA1.

Conclusion. Applying basic ethical principles as starting points can lead to different answers regarding specific bioethical problems, in our case the moral problems of neurodegenerative diseases. The underlying principles can help doctors and other healthcare professionals make decisions by reflecting on the moral issues that arise at work. As a result of empirical and ethical research, normative solutions are proposed that have far-reaching consequences for society and the future of individuals. Applied bioethical research identifies morally relevant issues, provides facts, describes the actual behavior of stakeholders, and discusses the possibility of intervention to improve the moral quality of clinical practice.

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THE ROLE OF ANDROGENS IN THE PATHOGENESIS OF ENDOMETRIAL CANCER

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Over the past decades, endometrial cancer has become the most common gynecological cancer worldwide. Its increasing incidence cannot be attributed only to the increasing age of women in socially secure countries. The leading risk factor for the endometrial cancer development is obesity, and its epidemic is gradually covering the female population of North Africa, Europe and Asia. Endometrial cancer is pathogenetically associated with hyperestrogenism, and this was the basis for the dualistic theory of clinical and pathological variants proposed by Ya.V. Bohman. The foundations of this theory about the hormonal dependence of endometrial cancer are now being actively supplemented by molecular genetic parameters of the TCGA classification. Recent studies show steroid dependence of endometrial cancer both on estrogens and, to a large extent, on androgens which are directly involved in the complex processes of transformation into estrogens. Published research data, rather contradictory and ambiguous, confirm the antiproliferative role of androgens in the pathogenesis of endometrial cancer. This review analyzes papers on the role of androgens in pathogenesis and their potential clinical antitumor application.

Keywords: endometrial cancer, androgens, androgen receptor, classification of endometrial cancer.

Endometrial cancer (EC) is a prevalent cancer globally [27]. It is the most frequent gynecologic cancer in developed nations, accounting for almost 5% of cancers in women. The overall incidence of uterine cancer has increased by 132% over the past 30 years, including a doubled number of patients under 40 years of age. The cumulative risk of EC in women under 74 years of age is 1.05% worldwide. However, this risk increases to 3% in countries with a higher sociodemographic index, particularly in North America and Europe [10, 44]. Leading gynecologic oncologists do not predict the incidence and mortality of EC to cease its growth, unlike other cancers [7]. The causes of this phenomenon are not limited to gerontological issues. Other risk factors include bradykinesia, obesity, insulin resistance, and a decrease in the number of prophylactic hysterectomies, as well as the use of hormone replacement therapy during menopause [6, 9]. Since the 1980s, EC has been generally subdivided into two types: type I, which is an estrogen-dependent endometrioid cancer of low malignancy, and type II, which generally includes hormone-independent non-endometrioid cancer of high malignancy [47]. The 2020 World Health Organization (WHO) classification of EC and the ESGO/ESTRO/ESP guidelines are also based on histological confirmation of uterine corpus cancer and surgical staging of the process. Features of EC morphogenesis such as lymphovascular invasion (LVSI) and the presence of tumor emboli in lymphatic and blood vessels are associated with an increased risk of metastasis, not only to lymph nodes but also to other tissues and organs. These features are included in the risk stratification model for adjuvant therapy. TCGA, a new molecular genetic classification system of EC, is intended to significantly change the degree of EC prognosis and optimize adjuvant treatment options [22, 38, 48]. However, clinical decision making is still largely dependent on the previous binary classification of EC into types I and II [9]. Type I EC typically expresses high levels of estrogen receptor α (*ER*). Type II EC is less likely to express *ER* and has a less favorable prognosis [36].

Genetic studies can identify the molecular 'fingerprints' of different EC histotypes. However, only *MSI* status is currently used as a pragmatic criterion for advanced EC, despite the fact that the majority of endometrial tumors contain at least one genomic alteration [1, 43]. Two of the five chemotherapeutic agents approved by the *FDA* for the treatment of EC effectively target programmed death ligand 1 (*PD-1*), which is overexpressed in hypermutated endometrial tumors with *MSI* compared to microsatellite stable tumors [28]. However, with the increased use of prospective clinical sequencing and the growing number of clinical trials, it is expected that EC treatment will move beyond routine variables such as tumor morphology and malignancy grade.

The endometrium is a morphologically and physiologically complex tissue that responds to changes in sex steroid concentrations, both systemic and local (intracrine) in nature. The tissue exhibits hormonal sensitivity in both normal and pathological states. Sex steroids are essential for maintaining the cyclic function or fertility of the endometrium. However, they may also contribute to the development of hormone-dependent endometrial diseases. Androgens and estrogens have similar structures. Additionally, estradiol, which is an aromatization derivative of testosterone, performs various functions in the female body through its specific receptors. These functions include the functioning of not only the reproductive organs but also the brain, bones, heart, vascular system, and liver. Sex hormones are key determinants of an individual's gender identity. Endogenous estrogens in men and androgens in women not only affect the health of each individual, but in certain conditions can also lead to pathologic processes

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with potentially life-threatening effects. It is important to note that androgens generally exceed estrogen levels, except during the preovulatory and follicular phases of the menstrual cycle. Most cases of EC occur during postmenopause. In pathogenetic variant I, EC is associated with excess estrogen and simultaneous suppression of progesterone production. After the onset of menopause, the levels of circulating estrogens sharply decrease while testosterone levels remain unchanged throughout the menopausal period. Menopausal women bodies use increased serum androgen levels to metabolically convert them to estrogens directly in adipose tissue, breast and endometrial cells. This provides an intracrine mechanism for aromatization of androgens into estrogens.

During the female reproductive age, androgen production is contributed to by both the adrenal reticular zone and theca cells of the gonads surrounding the ovarian follicles [13]. As age advances, the adrenal reticular zone undergoes involution and there is a sharp decrease in the number of ovarian follicles, which generally reduces androgen synthesis. However, both glands remain an important source of androgens during menopause. Dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A4), testosterone and dihydrotestosterone (DHT) are the most common androgens found in women. According to Labrie et al, 2017, DHEA and testosterone are considered indicators of androgen secretion by the adrenal glands and ovaries, respectively. During menopause, estrogen production decreases markedly, but the ovaries continue to produce androgens, including DHEA, A4, and testosterone. In postmenopausal women, DHEA is the primary source of androgens and estrogens. About 20% of circulating DHEA is produced by the ovaries, while the remaining 80% is derived from the adrenal glands [19]. The enzyme steroid sulfotransferase type 2A1 (SULT2A1) converts DHEA to DHEAS, while the enzyme 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2) converts it to A4. A4 is converted to testosterone by 17β-hydroxysteroid dehydrogenase type 5 (17β-HSD type 5), also known as aldo-keto reductase family 1 member 3 (AKR1C3) [25]. Testosterone is then converted to DHT by 5α-reductase. DHEAS, DHEA, A4 and testosterone enter the systemic bloodstream by interacting with sex steroid binding globulin (SHBG). In women, 80% of androgens bind to SHBG, 19% bind to serum albumin and only 1% of androgens are free. The active sex steroid is the 1% of free androgens, while the bound androgens enter the circulating resource, awaiting conversion to estrogens.

In addition to classical androgens, the adrenal glands also produce androgen metabolites that share a common oxygen atom at the C11 position, called 11-oxyandrogens. These 11-oxymetabolites are particularly interesting for the physiology of postmenopausal women because their levels, unlike classical androgens, do not decrease with age [2, 26]. Biologically active androgens, such as testosterone (T) and 5α-dihydrotestosterone (DHT), affect target tissues mainly through the androgen receptor (AR). Similarly, some 11-oxyandrogens, such as 11-keto-T (11-KT) and 11-keto-DHT (11-K-DHT), have a comparable affinity for AR binding as classical hormones [14, 35]. AR is a nuclear hormone receptor transcription factor [40] that is mainly localized in the endometrium, mesenchyme, and myometrium of the uterus. It is worth noting that epithelial cells in the functional layer of the endometrium increase AR expression when progestin levels drop during the normal menstrual cycle, resulting in decreased proliferative activity. However, AR expression in basal layer stromal cells remains unchanged during menstruation [12]. Several studies evaluated the expression of AR depending on the degree of malignancy of atypical endometrial hyperplasia and EC histotypes, and compared it with that in benign endometrial hyperplasia and in eutopic endometrium [46]. These studies showed that decreased AR was associated with a higher degree of EC malignancy; the lowest AR expression was found in tumors with non-endometrioid histology. While AR expression in primary endometrioid tumors appeared to correlate with lower malignancy and less aggressive disease, a high AR and estrogen receptor (ER) ratio in EC metastasis tissue correlated with poorer survival [46]. Overall, the data suggest that androgen receptor (AR) signaling in endometrial cells (ECs) is multifaceted and may vary throughout tumor evolution. Convincing evidence of the influence of androgens on EC risk was obtained in studies on patients with ovarian scleropolycystic fibrosis, in whom the risk of type I EC increased in the presence of hyperandrogenism. Tanaka et al. (2015) found that the level of DHT in patients with endometrial adenocarcinoma and ovarian scleropolycystosis was eight times higher than in healthy women [45]. In contrast, Hashmi et al. (2018) did not find such a correlation in their study of 89 patients with EC [15]. In a retrospective study, Shahin et al. (2021) analyzed 40 type I EC tumors and 12 type II EC tumors using AR immunohistochemical expression. Similarly, Mahdi et al. (2017) analyzed 209 cases of type I EC and 52 cases of type II EC. Both studies found a positive effect of AR expression on the prognosis of EC [21, 41]. Furthermore, Mahdi et al. (2017) discovered a significant correlation between AR expression and the absence of LVSI, resulting in a reduction in the number of metastatically altered regional lymph nodes. However, Shahin et al. (2021) did not find such a correlation [21, 41]. In their study of 86 EC samples, Tanaka et al. (2015) demonstrated that AR status did not have any independent prognostic value in patients with this tumor histotype [45]. It is evident that researchers hold polar opinions.

Endometrial tumor tissue contains the necessary enzymes to produce biologically active androgens from their precursors and 11-oxyandrogens. The expression of key enzymes involved in androgen metabolism, such as AKR1C and SRD5A enzymes, was studied in endometrial tumor tissue [16, 17]. Both endometrioid and non-endometrioid types of EC exhibit higher expression of several *SLCO* genes encoding transporters with broad substrate specificity compared to normal endometrial tissues. The upregulation of several transporters may account for the increased influx of steroid precursors, including DHEA-S, in endometrial tumors [30]. AKR1C3 is another important enzyme in androgen metabolism. Its overexpression is believed to contribute to the androgen pool in various pathologies [31]. Additionally, higher expression of AKR1C3 is associated with greater overall survival in EC [16]. It is worth noting that both endometrioid and non-endometrioid tumor tissues do not express CYP11B1, indicating that endometrial tumors are probably incapable of metabolizing classical androgens to 11-oxyandrogens. However, it is possible for 11-oxyandrogens to be produced locally from 11-oxyandrogen precursors, such as 11β-OH-A4, which are present in relatively high systemic concentrations. The presence of genes encoding HSD11B2 and SRD5A enzymes in endometrial tumors indicates this possibility. Furthermore, the expression of SRD5A1 and SRD5A3 isoforms in EC tissue suggests that DHT and 11-K-DHT may be formed locally [42].

Several studies reported an association between elevated serum androgen levels and the risk of developing EC. Postmenopausal EC patients were found to have elevated levels of DHEA,

DHEAS, A4 and testosterone compared to healthy populations. In recent years, two Mendelian randomization studies genetically analyzed hormone levels in over 12,000 EC patients over their lifetime and found that free testosterone was associated with an unfavorable disease course [24, 37]. Mullee et al. (2021) explain that high levels of androgens are actively converted by aromatase to estrogens in carcinoma tissue, promoting tumor cell proliferation [24]. The intracrine mechanism of aromatase expression is found not only in tumor cells but also in endometrial stem cells, which unites their proliferative potential and leads to an unfavorable outcome [4]. Qiu et al. (2014) demonstrated that AR enhances the proliferation of EC cells by binding to forkhead box A1 (FOXA1) and activating the Notch signaling pathway. Androgens and AR were also shown to stimulate the growth of EC stem cells and enhance cancer cell migration, promoting metastasis, by activating the epithelial-mesenchymal transition (EMT) [34]. Furthermore, Chen et al. (2014) found that androgens can stimulate the expression of immunocompetent CD133 cells. These cells are responsible for the formation of resistance of endometrial carcinoma to cisplatin chemotherapy [5].

A comparative study of 313 patients with EC and 354 age-matched healthy women showed that the highest serum concentrations of baseline androgens - DHEA, androstenedione and testosterone [23] are associated with an increased risk of developing EC. Clendenen et al (2016) reached an interesting and somewhat unexpected conclusion in their study. In their analysis of 161 cases of EC compared to data from 303 control patients, the authors found no evidence of androgens influencing the occurrence of EC in women under 55 years of age who were in peri- or early menopause. However, they did observe a significant increase in the incidence of EC in patients over 55 years of age with elevated serum levels of total and free testosterone [8]. The conclusion regarding the increase in systemic levels of total and free testosterone in menopausal patients requires clarification. This is because EC occurs in the vast majority of cases during this age period and is associated with hyperestrogenism due to androgen aromatization. It is believed that total testosterone levels gradually decline from the age of 65 years until the age of 80 years. During deep menopause, the levels of free testosterone and A4 increase, which is associated with an almost threefold risk of EC [8, 18].

The action of aromatase results in a decrease in androgen levels, which in turn suppresses estrogen expression in menopausal women. However, a low concentration of estrogen does not reduce the incidence of EC. Furthermore, there is a correlation between the androgen signaling pathway and the progestin signaling pathway. Aromatase catalyzes the conversion of androgens, such as androstenedione and testosterone, to estrogens, including estrone and estradiol. Drugs that inhibit aromatase are assumed to increase the concentration of androgens, which are its substrates, while simultaneously reducing estrogen synthesis. Tanaka et al. (2015) suggested that synchronized therapy with aromatase inhibitors and androgens may benefit patients with AR-positive EC. Androgens were shown to increase progesterone receptor expression in endometrial cells (ECs). This, in turn, suppresses the stimulatory effects of estrogens on tumor growth. Therefore, therapy with exogenous androgens may be a novel treatment for patients with type I EC who are insensitive to progestin treatment [29]. In mammalian cells expressing exogenous or endogenous AR, medroxyprogesterone acetate (MPA) exerts a marked agonist effect on androgens. After MPA treatment in vitro, a significant increase in AR transcriptional activity was observed in the COS-1 cell line [39].

Elucidating the role of androgens in the development of EC is difficult due to the complex hormonal interaction, cell specificity, androgen type and androgen exposure time, together with other yet undetermined factors [3].

Cancer patients typically experience alterations in their microbiome, which refers to the totality of the genomes of all microorganisms that make up the human body. Research demonstrated that various factors, such as menopausal status and body mass index, can impact the composition of the uterine microbiome in EC. This, in turn, can determine the specificity of premorbid chronic metroendometritis, which may contribute to the development of EC [47]. Pur et al (2020) conducted a study on untreated EC patients included in the TCGA study, examining whole genome and whole transcriptome data. The study found that most major cancer types, including EC, have a unique microbial signature that can distinguish cancer patients from healthy individuals [33].

Altered microbiota could be a possible source of androgens and 11-oxyandrogens in EC patients. The microbiota has a wide range of unique enzymes that can convert steroid molecules into potent androgens after deconjugating them from the glucuronic acid or sulfate group. For instance, a recent study investigated potential sources of androgens in patients with hormone-resistant prostate cancer. The study found that specific species of bacteria in the gut microbiome can convert steroids, such as pregnenolone and 17α-OH-pregnenolone, into classical androgens, such as DHEA and testosterone. In some patients, individual microorganisms were capable of inducing higher levels of testosterone [32]. Furthermore, the microbial community may use C21 glucocorticoids as an atypical source of androgens [11]. Some bacterial species of the gut and urinary tract microbiota were found to contain a bacterial enzyme that converts the glucocorticoid cortisol to 11β-OH-A4 [49].

In conclusion, it is widely debated whether androgens play a significant role in the pathogenesis of EC. While some researchers believe that the role of androgens remains incompletely understood, others consider it controversial. Androgens were shown to have an antiproliferative effect by directly confronting estrogens or activating progesterone receptor, which inhibits the effect of estrogens on the endometrium [29]. On the other hand, A4 and testosterone are precursors for both DHT production and estradiol synthesis as an aromatase substrate. The latter may serve as a negative regulator of DHT production in situ in endometrial carcinoma cells by limiting the availability of testosterone and/or A4 precursors. Aromatase expression in endometrial stromal cells in EC is directly associated with a poor prognosis. The enhancement of proliferative effect of androgens may be related to the activation of epidermal growth factor receptors in the stromal compartment [39].

The role of androgens in carcinogenesis, EC histotype formation, and treatment prognosis remains poorly understood. Fractions of androgens, their precursors, estrogen converters, and androgen receptors may be effective targets for updated endocrine treatment of progestin-resistant EC. The transformation of testosterone to DHT under the action of 5α-reductase is irreversible, leaving less testosterone available for conversion to estradiol. Furthermore, it is necessary to investigate the effect of DHT on endometrial tissue [20]. If aromatase inhibitors not only cause estrogen deprivation but also enhance the antiproliferative action of DHT, combination therapy with DHT and aromatase inhibitors may be a promising new endocrine intervention for the

treatment of endometrial carcinoma, particularly in postmenopausal patients.

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ACUTE CHOLECYSTITIS: PROBLEMS OF CLASSIFICATION AND WAYS OF SOLUTION

Acute cholecystitis undoubtedly remains an urgent problem of urgent abdominal surgery. The incidence of this nosology is 160 thousand cases per year. Postoperative mortality is in the range of 1,2-1,4%. Currently, the classification of acute cholecystitis, which is based on the Tokyo agreements, has received active distribution and use. However, this classification does not allow us to determine the degree of destructive process in the wall of the gallbladder. This often leads to a prolongation of the duration of conservative therapy and an increase in the percentage of intraoperative and postoperative complications. In this publication, we have tried to characterize the available classifications of acute cholecystitis, taking into account the advantages and disadvantages. And also, to propose a more rational classification from the point of view of a practical surgeon.

Keywords: cholelithiasis, acute cholecystitis, classification, destructive forms, gallstone disease, diagnosis.

Acute cholecystitis is one of the most common diseases in emergency abdominal surgery. According to A. Revishvili, the incidence of acute cholecystitis in the last 5 years is about 160 thousand cases per year. At the same time, operational activity in relation to this nosology increases, the frequency of which reaches 60-63%. At the same time, postoperative mortality is in the range of 1,2-1,4%, and in some regions 3-5% [13]. There is a problem of a high percentage of both intraoperative (10-15%) and postoperative complications (15-20%) [1,3,8,9]. Along with this, the frequency of purulent-septic postoperative complications reaches 7-15% [1].

It is known that currently there are a number of classifications of acute cholecystitis. The classification developed by V. Savelyev has found wide application in Russia. Savelyev divides acute cholecystitis into uncomplicated and complicated. The first variant includes the following forms: catarrhal, phlegmonous, gangrenous. Complicated, in turn, occurs in 10-15% of cases and includes complications such as mechanical jaundice, perivesical infiltration, perivesical abscess, gallbladder perforation, peritonitis, cholangitis, external and internal fistulas, empyema or dropsy of the gallbladder. Uncomplicated cholecystitis, according to V. Savelyev's classification, is primary due to thrombosis of the cystic artery, and secondary caused by an infectious agent [2]. It should be noted that, undoubtedly, this classification makes sense in operated patients. At the same time, at the time of admission of the patient to the hospital, we do not have the opportunity to establish a certain form of uncomplicated cholecystitis due to the large range of criteria. Along with the lack of clear criteria for the establishment of one form or another, there are no recommendations for the management of patients with a specific variant of this disease.

According to the pathogenesis, acute cholecystitis is divided into obturation, enzymatic and vascular. From the point of view of a practical surgeon, this division of acute cholecystitis has no value and is of particular interest only for theoretical medicine.

April 1, 2006 becomes a key date in the adoption of a new classification of acute cholecystitis, developed by a group of leading hepatologist surgeons in the Japanese capital. This classification is based on 3 groups of severity of acute cholecystitis [15,20]:

I st (mild stage) is characterized by the absence of multiple organ dysfunction and mild inflammatory changes in the gallbladder in patients with acute cholecystitis.

II st (moderate stage) was based on the following criteria: significant inflammatory changes in the gallbladder (emphysematous cholecystitis, gangrenous cholecystitis, peripusal abscess, biliary peritonitis), duration of the disease over 72 hours, leukocytosis over 18 x10^9/L.

III st (severe stage) is characterized by disorders in vital organs or systems: neurological disorders (decreased level of consciousness); renal insufficiency (oliguria, creatinine > 2 mg/dl (177 mmol/l); hepatic dysfunction (INR > 1.5); respiratory failure (PaO2/FiO2 ratio < 300); cardiovascular insufficiency (hypotension requiring correction with dopamine at a

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dose of ≥ 5 mg / kg per minute or any dose of dobutamine); disorders in the hemostasis system (thrombocytopenia less than 100 x 10^9 / l).

The authors of this classification have established that in the mild stage, surgical treatment (cholecystectomy) is considered a safe intervention. In patients at a moderate stage, performing cholecystectomy can lead to serious adverse consequences. In the severe stage, surgical treatment is dangerous due to the high anesthesiological and operational risk and can be performed with the correction of these disorders.

In 2013, 2018, the Tokyo Agreements (TG13) are being revised and improved [18,19,21,22,23,24]. From this point on, acute cholecystitis should be divided into 3 stages: III st. (severe stage) is accompanied by impaired function of one or more organs or systems (cardiovascular insufficiency: hypotension requiring the administration of dopamine more than 5 mcg / kg per minute or any dose of norepinephrine; neurological insufficiency: decreased level of consciousness; respiratory insufficiency: PaO2/FiO2 less than 300; renal insufficiency: oliguria, creatine level in blood more than 2.0 mg/dl; hepatic insufficiency: liver dysfunction in excess of 1.5; hematological insufficiency: thrombocytopenia <100,000/mm3). For II St. (moderate stage) the patient is characterized by the presence of one of the criteria: leukocytosis > 18,000/mm3; severe pain in the right hypochondrium with muscle tension; duration from the onset of the disease is more than 72 hours and/or signs of local inflammation (gangrenous cholecystitis, peripubular abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis). At the same time, I st. (mild stage) is indicated if the patient does not fall under the criteria of "grade III" or "grade II" acute cholecystitis and is characterized by the presence of acute cholecystitis in the patient without any organ dysfunction and moderate inflammatory changes in the gallbladder. The Tokyo classification was taken as a basis for the development of the domestic NCR "Acute cholecystitis" 2021-2023 [11]. M. Yokoe in his publication shows a direct correlation between the severity of acute cholecystitis and 30-day mortality. He noted that the mortality rate in patients with mild acute cholecystitis is 1.1%, moderate – 0.8%, and severe — 5.4%. If there is a violation of the function of a vital organ or system, then mortality in patients with severe course reaches 3.1%, two organs or systems — 7.8%, three — 18.2% and six — 25.0% [25].

In her scientific study, which includes 10 randomized and 14 non-randomized trials and covers 1,841 patients, Charlotte Lozen (2017) indicates that conservative therapy is effective in 87% of patients with acute calculous cholecystitis and 96% with mild Grad1 [16]. In his study, M. Kossovich (2020) shows the effectiveness of conservative therapy in patients with mild acute cholecystitis and indicates the absence of complications in this group of patients during elective cholecystectomy in the long-term "cold" period after 3 months. The author argues that with a positive effect of conservative treatment, the operation should be performed no earlier than after several months [4]. At the same time, the Tokyo agreements interpret to us information about the safety of cholecystectomy in patients with mild degrees. In fact, as already described above, there is a problem of a high percentage of intraoperative and postoperative complications. Any surgeon will certainly agree on the safety of cholecystectomy in the "cold" period, after the inflammation in the gallbladder has subsided. In her research, L. Koishibaeva (2017) shows that the quality of life of patients who underwent cholecystectomy for acute cholecystitis is 1,1 times lower than in patients with chronic cholecystitis [5]. This author notes that in patients who underwent cholecystectomy during planned hospitalization, the quality of life is 1.1 times higher than in the group where the same surgical intervention was performed during emergency hospitalization. Along with this, surgical treatment should be performed immediately in patients with destructive forms of acute cholecystitis, which directly threaten the patient's life. At the same time, there are no criteria that could accurately identify the destruction of the gallbladder wall in a timely manner, and therefore the time of surgical intervention is delayed. In 2015, Peter Ambe analyzed the charts of 138 patients with varying degrees of severity of acute cholecystitis according to the Tokyo Agreements and found a discrepancy between mild severity (I St.) and intraoperative picture. The conclusions of this scientist were confirmed by histological examination [14].

One of the disadvantages of the Tokyo classification is that a group of patients with acute cholecystitis and simultaneous damage to the bile ducts is not singled out separately. In his publication, I. Natroshvili points out that the methods of treatment of this group of patients may differ significantly [10]. We also believe that in the Tokyo Recommendations and the national clinical guidelines of the Russian Society of Surgeons, it is necessary to identify a group of patients with acute destructive cholecystitis. In a number of studies using criteria for the severity of acute cholecystitis, the treatment outcomes of these patients are taken into account in the general group, but the treatment methods may differ significantly. Special difficulties may arise when solving tactical issues in a group of elderly people with severe concomitant pathology.

It should be noted that new possibilities for the classification of acute cholecystitis are currently being sought.

In particular, in his publications, I. Buriev pointed out the need to change the existing classification. The author noted that such research methods as ultrasound, CT and MRI combined can make it possible to visualize the depth of destruction of the gallbladder wall at the level of the submucosal or musculoserous layer [12]. At the same time, such a view of the structure of things will only allow us to approach the morphological classification of the severity of destruction at the preoperative stage. There are isolated studies by domestic and foreign scientists that are devoted to studying the results of clinical and laboratory studies, ultrasound, CT, and MRI data in patients with acute cholecystitis and make it possible to assess the severity of the disease [6,7,17]. At the same time, it should be taken into account the fact that hospitals are not equipped with computer and magnetic resonance imaging at all levels, which makes it difficult to diagnose destructive cholecystitis in a timely manner.

From our point of view, a rational approach to the classification of acute cholecystitis is to identify two main groups: non-destructive (catarrhal) and destructive. For a practical surgeon, this unit would make it possible to determine the therapeutic tactics.

Acute destructive cholecystitis should be diagnosed based on the following data:

- clinical:

√ positive symptoms: Kera, Murphy, Grekova-Ortner;

√ fever above 38℃;

- laboratory:

√ leukocytosis is more than 11x10^9/l;

√ increase in creatine phosphokinase values of more than 250 units/l, lactate dehydrogenase of more than 290 units/l;

√ reduction of gamma glutamyltransferase concentration of less than 100 U/l and alkaline phosphatase of less than 150 U/l;

√ the concentration of total immunoglobulin is more than 450 IU/ml.

■ instrumental:

● ultrasound data:

√ hyperechogenicity of bile,

√ a symptom of drooping,

√ the layering of the gallbladder wall;

● CT scan data:

√ sandwich symptom,

√ intramural accumulation of gas,

√ accumulation of gas in the lumen of the gallbladder.

To diagnose destructive cholecystitis, there must be a combination of at least 2 signs (marked with √) from each data group. Destructive cholecystitis can be complicated by the development of: perivesical infiltration, perivesical abscess, perforation of the gallbladder, biliary peritonitis, external and internal fistulas, empyema of the gallbladder. The diagnosis of destructive cholecystitis implies performing surgery within 2 hours from the moment of diagnosis. In patients with severe concomitant pathology and in persons with high anesthesiological risk, minimally invasive interventions (drainage of the gallbladder under ultrasound guidance, cholecystostomy, etc.) have shown some effectiveness. In "safe" patients, surgical intervention should begin with laparoscopic cholecystectomy, if it is impossible, an alternative may be cholecystectomy from a mini-access or performing traditional laparotomic cholecystectomy. In the presence of infiltration in the cervical region and the inability to perform cholecystectomy, it is recommended to resect the gallbladder according to Pribraman or Hartmann's pocket in order to avoid traumatization of vital structures and prevent the development of severe intraoperative and postoperative complications.

In the absence of criteria for the destruction of the gallbladder wall, a diagnosis should be made: Acute catarrhal cholecystitis. When establishing this diagnosis, treatment should be conservative with dynamic monitoring, and surgical treatment in such patients is safer to perform as planned. If the development of destruction of the gallbladder wall is suspected, surgical treatment must be performed urgently. It is important that in patients with catarrhal cholecystitis, conservative treatment is successful in 97% of cases.

Similarly, there is a problem of complications of acute cholecystitis, which are also given insufficient attention in national clinical guidelines. We will try to highlight this problem in future publications.

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POINT OF VIEW

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THE EFFECT OF CONSUMPTION OF *CHLORELLA VULGARIS* SUSPENSION ON HEMATOLOGIC AND BIOCHEMICAL INDICES OF HUMAN BLOOD

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Studies of the effect of the use of preparations with microalgae C.vulgaris on the human body are important due to its wide distribution and the presence of a large number of biologically active substances. We investigated biochemical and hematologic indices of a group of persons after a course of microalgae suspension reception. There were immunomodulatory effects, expressed as an increase in LYM% and a decrease in ESR, cellular rejuvenation primarily among healthy men, and trends toward increased ALB and TP at younger ages. After 50 years of age, a tendency for GLU levels to decrease after the course was detected. There was an increase in CREA and UREA, which may be related to both improved availability of protein compounds and the composition of the microalgae growth medium, which requires further investigation.

Keywords: suspension, chlorella vulgaris, hematology, biochemistry, age, sex, health status.

Introduction. Interest in the study of C.vulgaris as a promising source of essential and nutritional substances emerged in the 1950s and was linked to the world food crisis [6]. Recently, interest in studying the effects of consuming this microalgae on the human body has only been increasing. This is due to the fact that products with C.vulgaris have a unique composition, which includes a set of all essential amino acids, mineral compounds, dietary fiber, polyunsaturated fatty acids, vitamins [5], including D2 and B12, which are absent in plant foods [1], and other compounds. Consumption of such a quantity of biologically active substances certainly has an effect on the human body, which requires its more extended and in-depth study through various methods of research.

All manufactured forms of the drug can be divided into those in which the chlorella is preserved in its natural state and those in which it is destroyed mechanically. The most common preparations contain destroyed strains of C.vulgaris. This fact is due to the fact that microalgae cells cannot be digested by humans because of the cellulose cell wall, which reduces the digestibility of proteins [1]. Nevertheless, even in its natural state in suspension, C.vulgaris is capable of producing effects on the human body.

The aim of this work is to investigate the effect of C.vulgaris suspension consumption on human blood parameters to identify patterns to its use.

Material and methods of research. The study was conducted on 34 volunteers volunteers. For 30 days (course) they took C.vulgaris suspension of IFR strain №C-111 200 ml in the morning on an empty stomach. The density of the suspension was 60 million microalgae per 1 ml. Every 10 days, volunteers were given 2 liters (2 bottles) of C.vulgaris suspension for the specified period. The study was conducted under the condition that volunteers signed informed consent, in accordance with all provisions of the Declaration of Helsinki and was approved by the local ethical committee at Penza State University. 28 people were able to complete the course. Among the reasons for discontinuing the course, volunteers cited the following: unpleasant organoleptic properties, increased diuresis. At the beginning of the study, before the reception of C.vulgaris suspension, as well as at the end of the course, whole blood sampling was performed. The following indices of general and biochemical blood analysis were investigated: WBC, RBC, HGB, HCT, MCV, MCH, MCHC, PDW, MPV, P-LCR, PCT, PLT, LYM%, MXD%, NEUT%, LYM#, MXD#, NEUT#, RDW-

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SD, RDW-CV, RET, ESR 30 min, ESR 1 h, ESR 2 h, ALB, ALP, AMYL, SGPT, SGOT, BILT, D-BIL, ID-BIL, CHOL, CREA, GLU, TP, TG, UREA, LDH.

In addition, the volunteers age, sex, and health status were entered into the database. Some volunteers had the following chronic diseases: polycystic kidney disease, anemia, polynosis, allergies, chronic pancreatitis, 12 peptic ulcer, hypertension, type 2 DM, hepatitis. Volunteers were ranked according to the indicated groups (Table 1). The first age group (FAG) included younger volunteers (36.14±6.4 years) and the second (SAG) older volunteers (54.54±7.3).

Statistical analysis was performed using Microsoft Office 2019 software package. Results were provided as a calculation of the median and the 25% and 75% percentiles. A box diagram was used to visualize the results. The data in the sample were not normally distributed, so the non-parametric Mann-Whitney U-test was used to assess the significance of their difference at a threshold value of $p<0.05$. ROC-AUC analysis of some presented blood parameters was also performed according to age periods: 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60 years and older.

Results and discussion. Most of the hematologic and biochemical blood indices we took did not change significantly after the course we took. Nevertheless, certain changes, both expected and not expected, have been identified. When comparing blood parameters before and after the course, without ranking the sample, the following changes were observed: increase in LYM% (p=0.0384), acceleration of ESR 30 min (p=0.0013), increase in CREA (p=0.0000), increase in UREA (p=0.0198) (Figure 1).

When the volunteer group was ranked by health status, it was found that having a chronic disease decreased MCHC (p=0.0455) and increased CREA to a greater extent (p=0.0000) after the course. Healthy volunteers had increased MPV (p=0.0016), accelerated ESR 30 min (p=0.0016), ESR 1 h (p=0.0065), increased CREA (p=0.0104) and UREA (p=0.0182). Both men (p=0.0257) and women (p=0.0257) had accelerated ESR 30 min. CREA was also significantly increased in both men (p=0.0005) and women (p=0.0000).

The FAG had accelerated ESR 30 min (p=0.0257), increased CREA (p=0.0001) and UREA (p=0.0413). In the SAG, ESR 30 min (p=0.0214) and ESR 1 h (p=0.0307) were accelerated and CREA increased (p=0.0024) (Table 1).

In addition to intra-group data analysis, inter-group data analysis was performed.

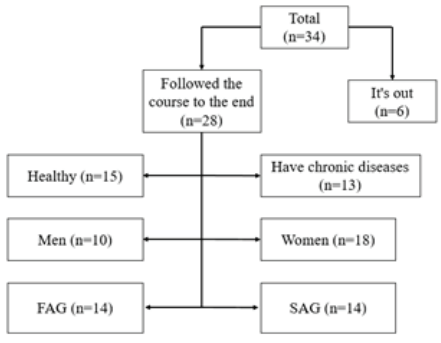

Fig. 1. Design of the study

The disappearance difference (p=0.0477; p=0.8181) between the CREA level of healthy and chronically ill volunteers may indicate its greater elevation in the second group after the course.

The difference in RBC (p=0.0127; p=0.0198), HGB (p=0.0000; p=0.0001), HCT (p=0.0002; p=0.0004) in males and females is explained by the effect of sex hormones.

There was a decrease in MCHC in women, while no change was observed

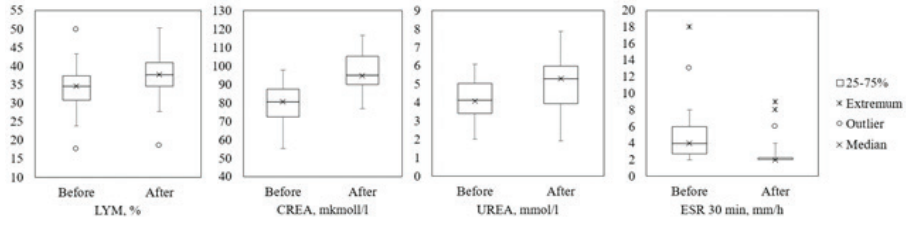

Fig. 2. Significant changes in hematologic and biochemical blood parameters in the total group before and after administration of *C.vulgaris* suspension

Table 1

Intragroup comparison of significant hematologic and biochemical blood parameters before and after administration *of C.vulgaris* suspension

Indicator	Prior to reception	After reception	p	Prior to reception	After reception	p
For health reasons	Healthy (n=15)			Have chronic diseases (n=13)		
MCHC. g/dL	353 [346;356.5]	348 [343;356.5]	0.6965	357 [354.0;363.0]	350 [347.0;358.0]	0.0455
MPV. fL	9.3 [9.2;10.8]	9.9 [9.4;10.9]	0.0016	10.3 [10.1;11.1]	10.4 [10.1;10.8]	0.7948
ESR 30 min. mm/h	5.0 [3.5;7.5]	2.0 [2.0;2.5]	0.0016	4.0 [2.0;5.0]	2.0 [2.0;2.0]	0.1585
ESR 1 h. mm/h	11.0 [6.0;14.0]	5.0 [4.0;8.5]	0.0065	9.0 [4.0;10.0]	5.0 [4.0;8.0]	0.4122
CREA. µmol/l	85.2 [78.1;90.0]	91.1 [89.6;107.2]	0.0104	75.0 [61.5; 85.2]	98.4 [90.1; 102.2]	0.0000
UREA. mmol/l	3.9 [3.5;4.6]	5.3 [4.3;5.7]	0.0182	4.2 [3.4;5.5]	5.37 [3.9;5.9]	0.3575
By sex	Men (n=10)			Women (n=18)		
ESR 30 min. mm/h	4.0 [2.2;6.5]	2.0 [2.0;2.0]	0.0257	4.5 [3.0;5.7]	2.0 [2.0;3.7]	0.0257
CREA. µmol/l	90.0 [85.2;92.3]	105.6 [104.6;110.5]	0.0005	76.1 [63.6; 83.6]	90.1 [89.4; 95.3]	0.0000
По возрасту	ПВГ (n=14)			ВВГ (n=14)		
ESR 30 min. mm/h	3.0 [2.0;4.0]	2.0 [2.0;2.0]	0.0257	5 [4.2;7.7]	2.0 [2.0;4.7]	0.0214
ESR 1 h. mm/h	6.0 [4.2;9.0]	5.0 [4.0;6.7]	0.3472	12.5 [10.0; 14.0]	5.5 [4.2; 12.7]	0.0307
CREA. µmol/l	78.1 [70.8;85.2]	93.3 [90.1;104.5]	0.0001	84.8 [75.5; 87.6]	97.1 [89.4; 107.9]	0.0024
UREA. mmol/l	3.5 [3.2;4.4]	5.0 [3.9;5.5]	0.0413	4.7 [3.8;5.5]	5.3 [4.5;6.1]	0.1556

in men (p=0.0687; p=0.0292). When RET was initially equal after the course, the rate decreased in women and increased in men (p=0.7565; p=0.0110). Also, the initially unobserved difference in ALP after the course increased in men, which was also reflected in the level of significance (p=0.1074; p=0.0018). The difference in CREA levels was present before the course and did not change after the course (p=0.0013; p=0.0004). In the SAG, RDW-SD was higher both before and after the course compared to the FAG, accounting for the difference (p=0.0455; p=0.0348). RDW-SD was higher in the SAG both before and after the course compared to the FAG, accounting for the difference (p=0.0455; p=0.0348). RET levels increased after the course in FAG, while they decreased in SAG (p=0.0366; p=0.5961). ESR 30 min (p=0.0107; p=0.0989), 1 h (p=0.0027; p=0.3125), 2 h (p=0.0038; p=0.3125) before the course was predominant among SAG, while after the course ESR decreased in both groups to equal values.

ALBs increased after the course, more so in FAG (p=0.0703; p=0.0051). ALP levels were relatively increased in SAG both before and after the course (p=0.0307; p=0.0384). CHOL levels were also higher in SAG, however, after the course the difference was worse pronounced due to a non-significant increase in FAG (p=0.0057; p=0.0131). UREA before the course was higher in SAG than FAG, but after the course the difference was worse with a general increase in the two groups (p=0.0292; p=0.3843). LDH both before and after the course was lower in FAG, with an overall decrease (p=0.0146; p=0.0366) (Table 2).

Table 2

Intergroup comparison of significant changes in hematologic and biochemical blood parameters before and after *C.vulgaris* suspension administration

Indicator	Prior to reception		p	After reception		p
For health reasons	Healthy (n=15)	Have chronic diseases (n=13)		Healthy (n=15)	Have chronic diseases (n=13)	
CREA, µmol/l	85.2 [78.1;90.0]	75.0 [61.5;85.2]	0.0477	91.1 [89.6;107.2]	98.0 [90.1;102.2]	0.8181
By sex	Women (n=18)	Men (n=10)		Women (n=18)	Men (n=10)	
RBC, 10^9/l	4.2 [4.3;4.6]	5.1 [4.7;5.4]	0.0127	4.5 [4.2;4.7]	5.0 [4.7;5.3]	0.0198
HGB, g/l	134.0 [130.0;139.0]	156.0 [152.2;165.2]	0.0000	131.0 [126.5;137.7]	152.0 [150.2;157.5]	0.0001
HCT, %	38.0 [36.8;39.1]	43.4 [42.4;45.4]	0.0002	37.7 [36.7;39.0]	42.7 [41.9;45.4]	0.0004
MCHC, g/dL	353.5 [342.7;358.5]	356.5 [353.2;364.5]	0.0687	347.0 [340.0;353.7]	356.5 [351.0;358.0]	0.0292
RET, %	5.0 [3.0;6.0]	5.0 [4.0;8.0]	0.7565	4.5 [4.0;5.0]	7.0 [5.0;10.0]	0.0110
ALP, U/l	50.0 [42.8;55.8]	58.0 [49.6;77.6]	0.1074	50.0 [47.2;62.5]	74.5 [63.2;89.0]	0.0018
CREA, µmol/l	76.1 [63.6;83.6]	90.0 [85.2;92.3]	0.0013	90.1 [89.4;95.3]	105.6 [104.6;110.5]	0.0004
By age	FAG (n=14)	SAG (n=14)		FAG (n=14)	SAG (n=14)	
RDW-SD, %	40.7 [40.1;42.3]	43.2 [40.9;45.2]	0.0455	40.9 [40.1;41.9]	43.8 [41.2;44.6]	0.0348
RET, %	4.0 [3.0;5.0]	6.0 [5.0;8.0]	0.0366	5.0 [4.0;5.7]	5.0 [4.0;9.2]	0.5961
ESR 30 min, mm/h	3.0 [2.0;4.0]	5.0 [4.2;7.7]	0.0107	2.0 [2.0;2.0]	2.0 [2.0;4.7]	0.0989
ESR 1 h, mm/h	6.0 [4.2;9.0]	12.5 [10.0;14.0]	0.0027	5.0 [4.0;6.7]	5.5 [4.2;12.7]	0.3125
ESR 2 h, mm/h	11.0 [8.2;14.5]	20.0 [16.0;25.0]	0.0038	12.5 [9.2;14.7]	13.5 [9.5;25.0]	0.3125
ALB, g/l	45.5 [43.1;48.0]	43.7 [41.2;44.4]	0.0703	46.5 [45.8;47.0]	44.1 [42.0;45.4]	0.0051
ALP, U/l	47.6 [42.1;50.4]	58.0 [53.7;62.2]	0.0307	49.0 [47.2;64.5]	63.5 [58.7;74.5]	0.0384
CHOL, mmol/l	4.5 [4.2;4.9]	5.6 [4.9;6.0]	0.0057	5.0 [4.5;5.3]	5.6 [5.4;6.4]	0.0131
UREA, µmol/l	3.5 [3.2;4.4]	4.7 [3.8;5.5]	0.0292	5.0 [3.9;5.5]	5.3 [4.5;6.1]	0.3843
LDH, U/l	294.0 [266.5;310.7]	320.0 [308.5;339.0]	0.0146	284.0 [258.7;321.7]	316.5 [303.0;360.2]	0.0366

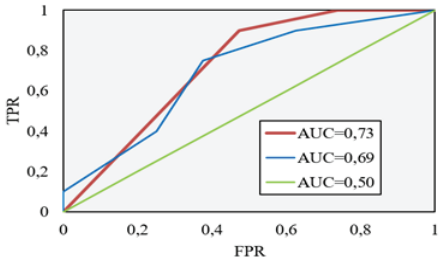

Fig. 3. ROC curves of GLU and TP levels during administration of *C.vulgaris* suspension according to age: red curve – GLU; blue curve – TP; green curve – control

Among the results obtained in the total group as well as in the rest of the groups, an increase in LYM% and ESR at different time intervals of measurement was noticeable, which may indicate the immunomodulatory and anti-inflammatory effects of microalgae suspension on the human body. C.vulgaris is probably characterized by the following mechanism of immunomodulation. The microalgae is rich in arginine, accounting for about 3200 mg per 100 g dry weight, depending on the strain. Arginine promotes the formation of such an important signaling molecule as NO, which in turn is an activator of guanylate cyclase that triggers numerous intracellular chains of reactions, including those leading to immune response in competent cells [1, 7]. In addition, the mechanism of immunomodulation is explained by the presence of a-glucan among the carbohydrates of microalgae, which causes proliferation of splenocytes and restores the level of secretion of cytokines TNF-a and IL-2 [5, 10]. The changes in GLU and TP scores were not significant. However, when considering the trend of these indicators with age, characteristic changes can be found. Thus GLU levels decreased to a greater extent among volunteers over 50 years of age (AUC=0.73). In turn, increased TP was characteristic of volunteers younger than 50 years of age (AUC=0.69) (Figure 2). The antidiabetic effect of C.vulgaris has been described in the literature and may be due to: decreased serum lipid peroxides, [9] increased expression of GLUT4 receptor in skeletal muscle [11], and decreased expression of insulin resistance inducers such as resistrin [3].

The results obtained can be explained by the improved availability of protein compounds, which is also expressed by the tendency to increase ALB and TP, as well as by the joint effect of the composition of the nutrient medium for microalgae cultivation on the human body [1]. It is also worth noting the increase in CREA and UREA, which in itself is not a positive result. Various studies indicate that the preparation property of microalgae depends on the following factors: medium temperature, growth nutrient composition, light availability [8], and the strain itself. Thus, for the synthesis of vitamin B12 and corrinoid compounds [2], Co2+ was added to the growth medium of C.vulgaris, which could also cause an increase in the described parameters. The trend of increased CHOL among young adults is unlikely to indicate the development of a pathologic process, but nevertheless differs from the data presented in the literature. The cell wall of C.vulgaris seems to be supposed to prevent lipid absorption in the intestinal lumen, which accounts for the decrease in CHOL in similar studies [4].

Также непонятно за счет какой фракции липидов (ЛПНП или ЛПВП) происходило повышение показателя. It is also unclear which lipid fraction (LDL or HDL) was responsible for the increase.

Conclusions. Thus, taking C.vulgaris suspension has a pronounced immunomodulatory and anti-inflammatory effect on the human body regardless of sex, age and state of health. Microalgae promotes rejuvenation of erythroid, megakaryocytic and lymphocytic cell lineage, especially in men at a young age. Also at a young age an increase in protein synthesizing function is pronounced. After the age of 50, consumption of microalgae has a hypoglycemic effect. Meanwhile, the detected increase in CREA, UREA, and CHOL warrants further investigation and monitoring of the consumption and production of C. vulgaris.

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STUDY OF THE BIOLOGICAL COMPATIBILITY OF PN-90 POLYTETRAFLUOROETHYLENE ON EXPERIMENTAL ANIMALS

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Polymer products are widely used in the field of medicine in the form of implants, artificial vessels, heart valves, etc. However, the tasks of searching, developing and studying the properties of polymeric materials for medical purposes remain relevant. This paper presents the results of biocompatibility research of PN-90 polytetrafluoroethylene implanted in the subcutaneous fat space of laboratory animals (Wistar rats). The implantation of the polymer was carried out under general anesthesia in the subscapular area. Histological sections of tissues from the control area and adjacent to the implant were studied. Around the implanted polytetrafluoroethylene there was is an intensive growth of new vessels of various calibers combined with severe fibroblasts proliferation. The polymeric material was also investigated by means of an IR spectrometer and a scanning electron before and after implantation. According to the results of IR spectroscopy the chemical composition of the polymer remained unchanged. The surface of polytetrafluoroethylene after implantation was practically identical to the surface of the initial polymer. Based on the data obtained, it can be concluded that polytetrafluoroethylene is biologically compatible and can be used in medicine as a base for implants.

Keywords: biocompatibility, inflammation, wear resistance, implantation, polytetrafluoroethylene, rats.

Introduction. Synthetic polymer materials are widely used in medicine as consumables, drug delivery systems, prostheses and implants, extracorporeal devices, etc. In most cases, the use of polymers is caused by the cheapness and manufacturability in the production process as well as the ability to easily vary their operational properties. Also, a number of requirements are presented to the materials implanted into the human body including: high biocompatibility, chemical inertness, high purity of the product, wear resistance, stability of the main characteristics [1].

A polymer suitable for use in medicine is polytetrafluoroethylene (PTFE) or Teflon. It is a waxy and smooth synthetic polymer material widely used in industries and medicine. It has very high thermal and chemical stability, low coefficient of friction and high hydrophobicity. The list of its properties includes: biocompatibility, corrosion resistance, inertness and relatively low cost. The first medical use of PTFE was in making of artificial heart valves. Subsequently, the scope of application gradually expanded with the development of vascular grafts, supports for bone regeneration and prostheses for hernia repair [2-7].

The degree of biological compatibility of materials is studied on laboratory animals by surgical implantation into physiological spaces. Compatibility is determined by the immunogenicity and the nature of inflammatory processes in the tissues of the body around the study object. During the implantation of materials tissue changes are most pronounced with minimal traumatic effects of a foreign object. Most often, the implantation of the samples is carried out in the hypodermic or subcutaneous layers. Evaluation of the reaction of surrounding tissues to implantation is performed by comparing morphological signs of inflammation, migration of immunocompetent cells and vascularization in the tissues around the implanted material with morphological characteristics of tissues from intact areas of symmetrical zones using microscopy. The absence of a local pathogenic effect is determined indirectly with the use of subcutaneous implantation tests. Taking into account the size of the implanted materials and the short duration of the experiment, small rodents and rabbits are used as test laboratory models [8-9].

The purpose of this study is to test the biocompatibility of PN-90 grade PTFE in vivo on laboratory animals.

Materials and Methods. PN-90 brand PTFE (GaloPolymer, Russia) was used as the implantable material with an average particle size of 90 μm and 2.16 g/cm^3 density. PTFE samples were obtained by cold pressing in a PKMV-100 hydraulic press (Impuls, Russia). The pressing was conducted at room temperature with 50 MPa pressure and further sintering in a SNOL 15/900 (Umega Group, Lithuania) programmable furnace at 375 °C.

The study of wear resistance was evaluated on a UMT-3 tribological machine (CETR, USA) with "finger-disc" friction scheme according to GOST 11629-2017. During the test, the change in volume (ΔV, cm^3), the rate of mass wear (I, mg/h) and the coefficient of friction (f) of the material were determined.

IR spectra of implanted PTFE before and after surgery were obtained on a Varian 7000 FT-IR (Varian, USA) Fourier-transform IR spectrometer. The spectra were obtained using attenuated total reflection (ATR) accessory in the range of 500-4000 cm^{-1}.

Using a scanning electron microscope (SEM) JSM-7800F (Jeol, Japan) in the secondary electrons mode at low accelerating voltage the supramolecular structure of the material was studied before and after implantation.

In vivo study was conducted on the 3 laboratory rats (Wistar line) at the age of 4 months, weighing 450-500 grams. For the operation the laboratory rats were put into general anesthesia by intramuscular injection of 2% xylazine solution at the rate of 0.05 ml per kg of animal body weight and a "Telazol 100 mg" solution containing 50% tiletamine and 50% zolazepam at the rate of 40 ml of the drug per 100 grams of animal body weight. A longitudinal incision was made parallel to the spine line through the entire thickness of the skin with a length of 0.5-0.8 cm then 2 cm long channel with a blind thickening towards the iliac region was formed with a scalpel to contain the implant (Fig. 1) fixed by natural connective tissue formations. Hemostasis was carried out with a sterile cotton swab. The implants measuring 0.5x1.0 cm in width and length were inserted into the formed pocket. Implant fixation was controlled visually and by palpation. The wound was sewn up with a simple continuous interrupted suture.

After 10 days the implant was extracted with a biopsy of all tissue layers in one block directly above the implant. The biopsy area was determined by palpation. Tissue layers were biopsied from the opposite side of the dorsal region for control comparison. The tissues adjacent to the implant were examined visually after removal. All biopsies were placed in a 10% solution of neutral formalin and provided to the histological laboratory for preparation of specimens. Biopsies were enclosed in paraffin wax at an EG 1150 (Leica Microsystems, Germany) histological station. Histological sections with a thickness of 3-5 μm were made on a SM2010R (Leica Microsystems, Germany) semi-automatic sledge microtome. The samples were stained with hematoxylin and eosin on a Autostainer XL (Leica Microsystems, Germany) instrument and sent for examination using an optical microscope.

The study of histological tissues sections after implantation of polymer materials into a laboratory animal was carried out using an BX-41 (Olympus, Japan) optical microscope.

Results and Discussion. The results of tribological studies of the polymer material are presented in Table.

The initial PTFE has average wear resistance values but these characteristics can be varied up to the required properties by adding fillers to the polymer. The nature of the fillers is determined depending on the purpose of the final material [10-11].

The IR spectra of the PTFE implant before and after the clinical trial are shown in Fig. 2.

The peaks showing the most intense absorption bands have 1200 and 1146 cm^{-1} wave numbers and belong to the stretching vibrations of the -CF_2- groups. Oscillations at 640 cm^{-1} are attributed to the wagging vibrations of γω(-CF_2-) and bands at 555 cm^{-1} correspond to deformation vibrations of -CF_2- groups. Also, according to the IR spectra, the material before and after implantation retained its original properties. Thus, it was not subjected to any changes in the body of the laboratory animal [12].

Changes in the morphology of the PTFE surface before and after implantation surgery were investigated by SEM (Fig. 3).

After implantation, the surface of the material did not undergo significant changes (Fig. 3, b) compared to the initial one (Fig. 3, a). Some microprotrusions were formed after implantation which probably appeared after cyclic loads on the polymer occurring in a living organism. To exclude further changes, it is possible to modify the physical and mechanical properties of polymer samples based on PTFE by various methods. It will increase the range of applications of the material in implantology.

Figure 4 shows histological sections of tissues from the control zones and from the area around the implant.

A comparative characterization of histological tissue samples was implemented from unaffected areas as control samples (Fig. 4, a) and around implants (Fig. 4, b). On the 10th day of inflammation, the proliferative stage of inflammation and the final stages of exudation began. The stage was characterized by the active growth of cells involved in the repair processes and the growth of new vessels. The presence of edema and neoangiogenesis indicate the intensity and duration of the exudation stage. The degree of immunoreactivity for the presence of foreign material was assessed by the number of migrated lymphocytes and macrophages. The inflammatory infiltrate in all samples was partially filled with fibroblast-like cells which indicates the activation of reparative processes [13].

Fig. 1. A laboratory rat during PTFE implantation

Results of tribological studies

Characteristics	ΔV, см^3	I, мг/ч	f
PN-90 PTFE	0.07	51.39	0.23

Note: ΔV – volume change, cm3; I – mass wear rate, mg/h; f – coefficient of friction

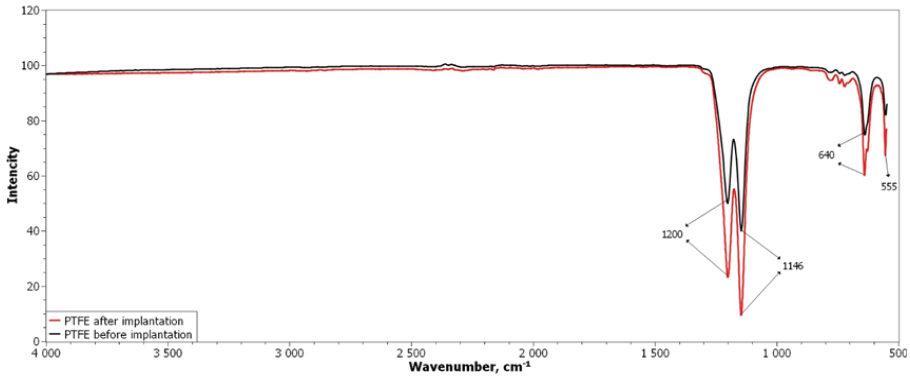

Fig. 2. The IR spectra of the PTFE implant

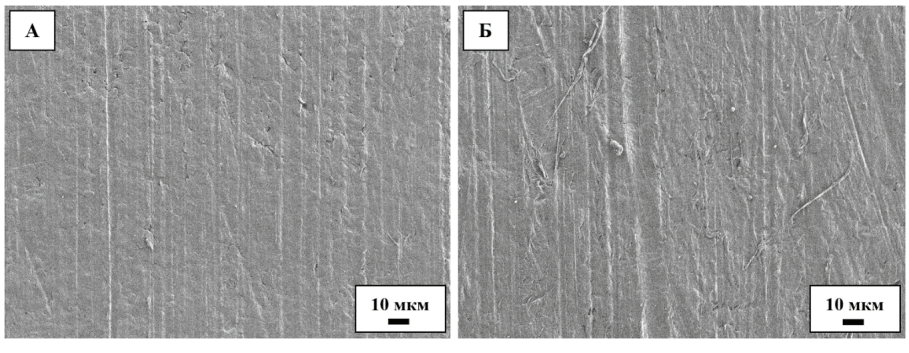

Fig. 3. SEM images of the PTFE surface before implantation (a) and after implantation (b)

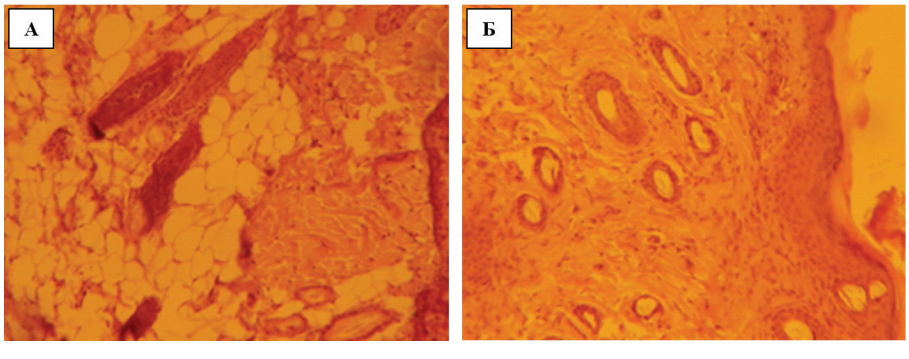

Fig. 4. Histological sections of rat tissues: the control area (a) and the area around the PTFE implant (b)

Intensive growth of new vessels of different calibers is observed around the implanted polymer in combination with a strong proliferation of fibroblasts in all layers of the dermis. This may indicate the onset of a proliferative stage of inflammation and the beginning of reparative processes. The number of fibroblast-like cells in the field of vision varies from 50 to 80 cells. However, there is a low infiltration of immunocompetent cells – the number of mononuclears in the field of vision is on average 20 ± 5 cells. This indicates a low degree of immunoreactivity and destructive processes.

Conclusion. The conclusions based on the results of studies of the biocompatibility of implanted PTFE in the laboratory animal:

- by IR spectroscopy it was found that the PTFE implant did not undergo chemical changes in the body of the laboratory animal;
- SEM results revealed that the polymer surface did not undergo significant changes in the body of the laboratory animal;
- biological PTFE inertness was observed in histological sections, it was manifested by the almost complete absence of an immune response from the body and the polymer easily germinated into the surrounding tissues of the body and was securely fixed by the communicating system of voids.

The results obtained indicate chemical resistance, low toxicity and immunogenicity in vivo. This determines the relevance of the practical application of PN-90 PTFE in medicine as a biologically compatible material. In the future, it is planned to conduct more extensive and long-term preclinical tests for biological compatibility.

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S.I. Sofronova

THE RELATIONSHIP OF HYPERURICEMIA WITH ARTERIAL HYPERTENSION AND RISK FACTORS FOR CARDIOVASCULAR DISEASES IN THE WORKING POPULATION OF SOUTHERN YAKUTIA

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A one-stage population study was conducted in the working population in south Yakutia. The 174 people of non-indigenous nationality were examined. Increased uric acid (UA) levels were found in 27% of the individuals. The association of UA level with BMI, OT, lipid spectrum was revealed mainly in men, systolic blood pressure and blood glucose in women. Abdominal obesity was equally frequently recorded in both men and women, regardless of the presence or absence of hyperuricemia, Logistic regression showed satisfactory information content of the prognostic significance of the level of UA with hypertension only in the female population. Hyperuricemia was not an independent risk factor for the development of cardiovascular pathology.

Keywords: uric acid, hypertension, obesity, lipid spectrum, non-indigenous population, south Yakutia.

Arterial hypertension (AH) remains one of the most common diseases of the cardiovascular system, becoming epidemic in nature. Correction of risk factors, along with decreasing blood pressure, affect the prevention of cardiovascular complications. Over a 20-year period, the prevalence of hypertension in Russia increased from 39.2% to 45.7% [1].

In recent years, there has been a trend towards an increase in hyperuricemia (HU) among the world's population [8]. Multicenter studies by URRAH and NHANES have shown that asymptomatic HU is associated with the development of hypertension, coronary heart disease, obesity, diabetes mellitus, etc. [8,16]. Foreign authors have proven the influence of HU on the prognosis of cardiovascular complications as well [10,12,14]. A retrospective cohort study of 5899 people demonstrated that an increase in UA levels is a powerful factor in the transformation of prehypertension into hypertension [12], and also increases the risk of developing metabolic syndrome, dyslipidemia, diabetes and CKD [14]. Certain data is based on the fact that HU activates the renin-angiotensin system (RAS) and blocking RAS inhibits the action of xanthine oxidase [15]. Nevertheless, a possible direct connection of HU with the development of hypertension is still being discussed.

The aim of the study was to identify the relationship of hyperuricemia with arterial hypertension and its risk factors in the working population of non-indigenous nationality in Southern Yakutia.

Materials and methods of research. A single-stage study of the working population of the Republic of Sakha (Yakutia) of the Aldan district according to the list of industrial businesses was conducted within the framework of research on the State assignment of the YSC CMP "Normal and pathological regional peculiarities of biochemical, immunological and morphological indicators in the indigenous and alien population of the Republic of Sakha (Yakutia)" (FGWU-2022-0014) with a response rate of 75%. 174 people, representatives of non-indigenous nationality (Russians, Ukrainians, etc.) arrived for the examination. The median age was 44 [36; 52] years. 108 women, and 66 men were examined. They were comparable in age for analysis. The main condition for inclusion in the study was the absence of gout, subcutaneous tofuses.

All respondents underwent a questionnaire, an anthropometric study measuring height, body weight, waist circumference (WC) and hips circumference (HC), and blood pressure (BP) measurement. For laboratory tests, venous blood was taken on an empty stomach in the morning 12 hours after the last meal. All par-

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ticipants in the study signed a voluntary consent for the conducted examinations. The study was approved by the Ethics Committee of the YSC CMP.

The body mass index (BMI) or Quetelet II index was calculated using the formula: BMI (kg/m2) = body weight (kg)/ height (m2). Overweight was established at a BMI value of ≥25 and <30 kg/m2, obesity was recorded at a BMI of ≥ 30 kg/ m2 [5].

To detect abdominal obesity, WC was measured from a standing position. The measurement point is the midpoint of the distance between the apex of the iliac crest and the lower lateral edge of the ribs. It doesn't have to be at the navel level. At > 94 cm in men and > 80 cm in women, it can be assumed that the patient has abdominal type of obesity [3].

Laboratory research methods included: determination of the lipid spectrum (total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG)), uric acid concentration (UA) and glucose in blood plasma.

Values of 400 mmol/l in men and 360 mmol/l in women were considered as elevated uric acid levels [1].

Blood pressure levels of ≥ 140/90 mmHg or constant use of antihypertensive drugs were considered as hypertension [7, 18].

Statistical processing of the obtained results was carried out using the SPSS program (version 26.0). Qualitative variables are described by absolute and relative frequencies (%), quantitative variables are described using the mean and standard error of the mean, median (Me) and interquartile range (Q1-Q3). The analysis of variance was carried out using the nonparametric Spearman criterion χ2. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated. Spearman's coefficient was used for correlation analysis. The statistical significance of the differences (p) was assumed to be less than 5%. The significance of the relationship between quantitative indicators was also assessed using logistic regression and ROC analysis.

Results and discussion. Among the participants of the study, hyperuricemia (HU) was detected in 47 respondents, which was 27%. It was slightly more common in men 28.8% than in women 25.9% (χ2=0.17, p=0.680). Our data are consistent with the results of the epidemiological study of ESSE-RF [1]. The following results were obtained in the correlation analysis of UA with anthropometric data (BMI, WC). The UA level was significantly correlated with both BMI (r=0.222, p=0.003) and WC (r=0.271, p=0.000) (Fig.1). Similar results were obtained for sex. Our data confirms the results of a number of foreign authors [11,13,14,17]

Overweight in the general group was detected in 32.2%, obesity by BMI in 44.3%, among whom overweight was significantly more often registered in men (40.9%) compared with women (26.9%) (OR 2.88; 95% CI [1.19-6.99], p=0.017), obesity by BMI, on the contrary, was equally often detected in both men and women (43.9% and 44.4%, respectively) (OR 1.87; 95% CI [0.80-4.37], p=0.144). In individuals with elevated UA, BMI obesity was found in more than half of men (57.9%) and half of women (50%), with no significant difference among the compared groups (χ2=0.633, p=0.426).

Abdominal obesity (AO) was detected in 67.2% of respondents, it was slightly more common in the female population (69.4%) compared with men, who were also frequently diagnosed (63.6%) (χ2=0.694, p=0.405). Next, a variance analysis was performed for the presence of AO in individuals with HU, as a result of which more than two thirds of men with HU (73.7%) and 82.1% of women had AO (OR 0.60; 95% CI [0.14-2.48], p=0.486). In the general population, in the presence and absence of HU, AO was equally common. In particular, AO was registered without HU in 80 cases, which was 63% of all persons with normal UA levels, of which 31 were men (65.9%) and 50 were women (46.2%) (OR 0.86; 95%CI [0.40-1.82], p=0.695). The connection between HU and AO can be traced in our study, but without a significant relationship.

The analysis of the prevalence of hypertension among the study participants revealed a high frequency of its occurrence (56.3%), no statistically significant differences in sex were revealed, it was 62.1% for men and 52.8% for women (χ2=1.45, p=0.227).

HU as a risk factor for the development of cardiovascular complications is described in a number of literary sources. A meta-analysis of 18 prospective cohort studies, including 55,607 participants, showed an association of HU with an increased risk of hypertension (OR 1.41; [95% CI] 1.23-1.58) [10]. A 5-year cohort study of 5,899 individuals in Japan showed an association of asymptomatic hypertension with an increase in the number of patients with hypertension, dyslipidemia, overweight and obesity [14]. In Yakutia, studies were previously conducted among indigenous and non-indigenous populations for the presence of an

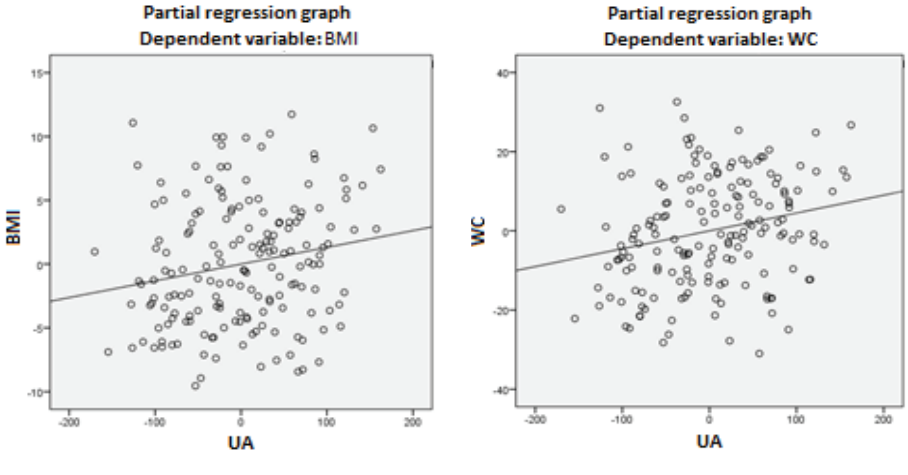

Fig.1. Correlations of uric acid level with BMI and WC (p<0.05)

Correlation analysis of uric acid levels with systolic blood pressure, lipid spectrum and blood glucose by Spearman

parameters		SBP	TC	HDL	LDL	TG	glucose
total	r	0.122	0.387	-0.186	0.330	0.353	0.251
	p	0.107	**0.000**	**0.014**	**0.000**	**0.000**	**0.001**
men	r	-0.086	0.536	-0.404	0.519	0.546	0.158
	p	0.494	**0.000**	**0.001**	**0.000**	**0.000**	0.206
women	r	0.224	0.121	0.118	-0.040	0.232	0.340
	p	**0.020**	0.211	0.224	0.682	**0.016**	**0.000**

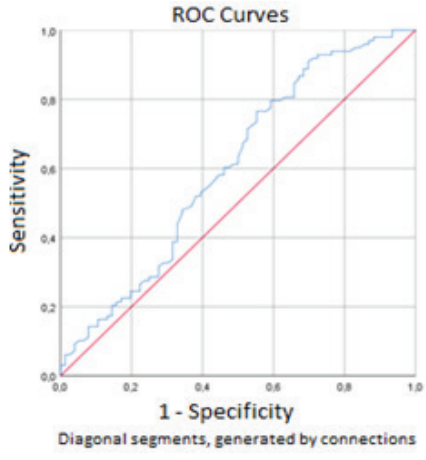

Fig. 2. ROC-curve for predicting UA levels with the development of hypertension

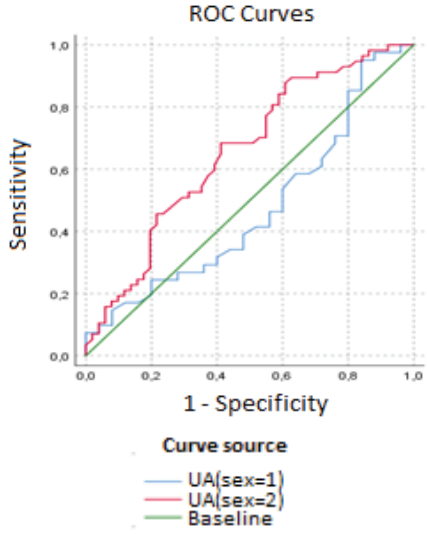

Fig. 3. ROC-curve for predicting UA levels with the development of hypertension depending on sex: 1-male, 2- female

association of UA with coronary atherosclerosis, hypertension, dyslipidemia, described by Romanova A.N., where more associative connections were obtained in non-indigenous residents [6]. For the correlation analysis, we carried out a parallel of the strength and direction of the relationship between the increase in UA level with systolic blood pressure, lipid spectrum in all participants, as well as separately for the male and female population (Table). A correlation with systolic blood pressure was obtained only in women. A direct reliable relationship of the UA level with the parameters of the lipid spectrum, in particular with TC and its atherogenic fractions, and plasma glucose, and a negative significant association with HDL was determined. When analyzing by sex, statistically significant correlations were obtained mainly in men, in women - only with TG levels and blood glucose.

Thus, the relationship between the level of UA with TC and its atherogenic fractions was revealed mainly in the male population, in women - with SBP, TG and blood glucose levels. According to our data, elevated UA levels were an independent risk factor for hyperlipidemia in the male population, hypertriglyceridemia and hyperglycemia in the female. Our data are consistent with the research of foreign and local authors [6,12,14].

The analysis of the presence of HU in hypertensive patients and people without hypertension, as well as sex differences, was carried out. In individuals with hypertension, HU was registered slightly more often (42%) compared with normotonics (31%) ($\chi2=0.757$, $p=0.384$). When comparing by sex among men, regardless of the presence of hypertension or its absence, the incidence of HU had no statistical differences (26.8% and 32%, respectively) ($\chi2=0.202$, $p=0.652$). 31.6% of women with hypertension and 19.6% without it had elevated levels of UA. The incidence of HU in hypertensive women is higher without significant difference ($\chi2=2.008$ $p=0.156$)

In large-scale URRAH studies involving 22,714 people, multivariate Cox regression analysis revealed an independent association of UA concentrations with both total (HR=1.53, 95% CI 1.21-1.93, P<0.001) and cardiovascular mortality (HR=2.08, 95% CI 1.146-2.97; P<0.001) [8]. Taking this into account, in order to identify the prognostic significance of UA values for the risk of hypertension, a significant relationship, we conducted an ROC analysis (Fig.2). The AUC for this model is 0.605±0.044 with satisfactory information value (95% CI: 0.518-0.690), the significance of the model was p=0.019. The cut-off point was 314.5, the sensitivity was 61.2%, and the specificity was 51.2%.

Further, a regression analysis of the association of UA with the risk of hypertension was performed separately for men and women (Fig.3), during which a satisfactory result was obtained only in women (AUC 0.656; [95% CI 0.552-0.760]; p=0.003), with a sensitivity of 68.4% and a specificity of 54.9%.

Thus, the logistic regression showed a less likely prognostic significance of the UA level for the development of hypertension. It can only be considered as a risk factor for hypertension in women. There is a parallel with lipid disorders and hyperglycemia, as well as with both BMI and abdominal obesity.

Conclusion. In conclusion, it should be noted that the frequency of occurrence of HU corresponded to epidemiological studies of ESSE-RF. Our study revealed an association of UA level with BMI, WC, lipid spectrum mainly in men, systolic blood pressure and blood glucose in women. AO was registered equally often in both men and women, regardless of the presence or absence of HU. Logistic regression showed satisfactory information value of the prognostic significance of the level of UA with hypertension only in the female population. Elevated UA levels are an adverse factor affecting the body's metabolism. Determination of its concentration in patients with hypertension by a routine method in primary healthcare is recommended to be introduced according to clinical recommendations for the diagnosis and treatment of hypertension [7, 18]. A recent Consensus on the management of patients with hypertension and high cardiovascular risk indicates a revision of the target levels of UA [4]. However, in our study, the level of UA is not a prognostic risk factor for the development of cardiovascular pathology. Perhaps this is due to the small sample size of the pilot study.

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EVALUATION OF COMPETITIVE ENDURANCE OF AIRBORNE TROOPS PARTICIPATING IN THE ALL-ARMY COMPETITION "AIRBORNE PLATOON" ACCORDING TO THE ANALYSIS OF HEART RATE VARIABILITY

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The article presents the results of a study of the competitive endurance of servicemen of the airborne troops performing at the 3rd stage of the military field training competition "Airborne Platoon". The relevance of the work lies in the fact that a timely assessment of the functional state of military athletes will make it possible to adjust training plans in time and perform more effectively at the competition. The aim of the study was to assess the competitive endurance of military athletes according to heart rate variability data with different military accounting specialties. Based on the data of heart rate variability, the analysis of the state of the regulatory processes of the body was carried out, the assessment of the competitive endurance of the airborne troops before and after performing special tasks in the "Airborne Platoon" military field training competition was carried out. With the help of an orthostatic test, the latent capabilities of the functional systems of the body were evaluated. The body of military personnel serving as driver mechanics is characterized by a pronounced tension of regulatory systems during the orthostatic test, in soldiers of other accounting specialties, the body reacts adequately. It is presented that the physical load during the period of the competition was at the limit of the capabilities of the body of military personnel and almost led to the breakdown of adaptation mechanisms.

Keywords: heart rate variability, military athletes, physical fitness, military field training competition "Airborne Platoon".

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Introduction. For 10 years, complex competitions on military field training of military personnel "Army Games" have been successfully held. One of the most difficult competitions is the "Airborne Platoon".

"Airborne Platoon " is a complex competition of parachute and amphibious assault units, including the performance of physical and combat exercises in a competitive form [4].

The competition consists of 4 stages, which include such disciplines as landing, driving, and using combat vehicles, overcoming obstacles, firing small arms and grenade launchers, terrain orientation, hand-to-hand combat, various marches. These disciplines are held in the form of competitions between teams, which creates, in addition to harmful factors caused by military service (from barometric pressure drop to vibration and motion sickness) [4, 6, 12], psycho-emotional stress affecting the functional state of military athletes [9].

From the above it becomes clear that

the preparation of military personnel for this competition. This is a complex dynamic process that requires the coaching staff to use all possible means to improve the physical capabilities of the body of military athletes [2, 3].

It is also necessary to separately highlight the presence of various harmful factors affecting military personnel. For shooters, the main harmful factors can be considered an increased load on the musculoskeletal system and cardiovascular system, for machine gunners and grenade throwers, this harmful factor is aggravated by the increased weight of equipment from 4 to 10 kg, and for mechanics-drivers and gunners-operators, all this is aggravated by carbon monoxide, fuel and lubricants vapors, repeatedly increased background noise caused by the action of the engine of military equipment and heavy weapons fire, increased vibration, confined space, long stay in one position, limited visibility [6].

The relevance of research. A timely assessment of the functional state of a serviceman using an express method based on HRV should help in the proper planning of the team's preparation for the performance at the "Airborne Platoon " competition, as well as timely identify negative changes in the state of health of soldiers and correct the training process in time [5].

With the development of computer technologies and software, there has recently been a new rise in interest in the study of heart rate variability both in clinical practice and in applied physiology [8, 10, 11, 14]. However, the number of works devoted to the study of heart rate variability in military personnel, despite the relevance of research, is insufficient and requires additional research in this area [14].

The purpose of the study is to evaluate the competitive endurance of military athletes participating in the "Amphibious Platoon" military field training competition using an express test based on heart rate variability, having different military accounting specialties (squad commander, senior shooter, shooter – active with light small arms; machine gunner, grenade launcher - active with heavy weapons; mechanic-driver, gunner-operator – operating in combat vehicles).

Tasks:

1. Assessment of the level of functional state of military athletes in a relative state of physiological rest and distribute them by types of heart rate regulation;
2. To investigate changes in the indicators of the analysis of the variability of the heart rate of military personnel after a competitive load.

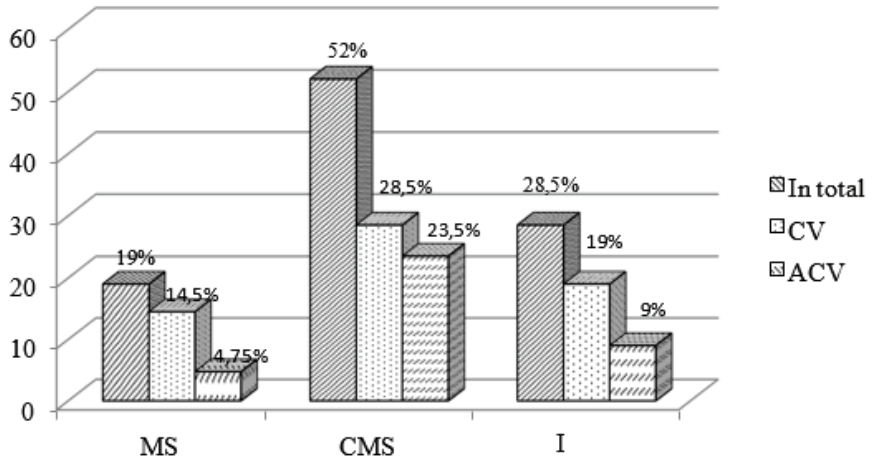

Diagram of the percentage distribution of military personnel by sports in accordance with sports ranks and categories. MS – Master of Sports of Russia; CMS – candidate for Master of Sports of Russia; I – first sports category. CV – cyclic sports; ACV – acyclic sports.

Materials and methods of research. 21 servicemen from the airborne assault unit took part in the study. The average age of the subjects was 24±3.1 years. The servicemen had from 1 sports category to the title of Master of Sports of Russia (Figure 1) in various sports.

Physical fitness of all military personnel participating in the study, it is at a very high level.

The study included 3 stages:

stage 1 – assessment of the functional state of military personnel before performing special tasks in the competition of military field training;

Stage 2 – assessment of the functional state of military personnel after performing special tasks in the "Landing Platoon" competition;

Stage 3 – included mathematical and statistical data processing, analysis of the results of the study, the formation of conclusions of the study/

To determine the level of functional state, an express method of assessing the functional state was used, and heart rate variability (HRV) indicators were analyzed. The analysis of heart rate variability was carried out in the morning. Before the examination, the servicemen were motionless for 15 minutes. The results obtained were recorded in an individual protocol. The cardiorhythmogram was recorded for 300 cardiocycles in a sitting position. The spectral parameters of HRV were evaluated. The frequency parameters of power were calculated in the high frequency range (HF, ms^2/Hz), in the low frequency (LF, ms^2/Hz) range, "very" low frequency (VLF, ms^2/Hz) range and ultra-low (ULF, ms^2/Hz) range, the total power of the spectrum (TP, ms^2/Hz) was analyzed, and also the stress index (SI) was evaluated. The type of regulation of the autonomic system was also determined in military personnel [1, 7].

The following types of heart rate regulation are distinguished in the scientific literature:

- with a moderate predominance of the central circuit of heart rate regulation – the first type of autonomic regulation;
- with a pronounced predominance of the central contour of heart rate regulation – the second type of autonomic regulation;
- with a moderate predominance of the heart rate regulation circuit – the third type of autonomic regulation;

Table 1

Distribution of types of vegetative regulation as a percentage in depending on the combat mission of the military personnel before the start of the performance in the competition of military field training

Military accounting specialties		Types of vegetative regulation			
		I	II	III	IV
with wearable weapons	n=9	4.75	-	33.4	4.75
who are part of the crew	n=6	4.75	14.3	4.75	4.75
with heavy weapons	n=6	14.3	4.75	4.75	4.75

Table 2

Changes in some average heart rate variability indicators before and after the competition

Functional tests	Military personnel with wearable weapons			Military personnel who are part of the crew			Military personnel with wearable weapons			The significance of differences between groups (p)	
	Md [Q_1; Q_2]										
	before	after	p	before	after	p	before	after	p	before	after
HF, ms²/Hz	914 [780.25;1179]	448 [323.5;707.5]	0.003	778.5 [620.5;1032.25]	288.5 [137;478.5]	0.002	1063.5 [1000;1193]	283 [252.75;339.5]	0.02	0.1	0.04
LF, ms²/Hz	1182.5 [967.25;1442.5]	1759.5 [1526.5;2020.5]	0.003	1093.5 [732.5;1436.5]	2169 [1824.25;2328.75]	0.002	657 [592;697.25]	1834 [1599.75;2240.75]	0.02	0.1	0.05
VLF, ms²/Hz	1094 [861.25;1438.25]	2559 [2279.25;2669.75]	0.003	1295 [938.5;1504]	3041 [2751;3268.75]	0.002	950 [646.75;1484.25]	3065 [2685.25;3505.5]	0.02	0.7	0.005
ULF, ms²/Hz	2019 [1635;2155]	1541.5 [1415.75;1824]	0.04	1963.5 [1812.25;2089]	1771.5 [1603.5;2046.25]	0.2	1514 [1404.25;1788]	1918.5 [1819.5;2103.75]	0.1	0.05	0.09
TP, ms²/Hz	5352 [4297;5770]	6322.5 [6142.25;6728]	0.004	5035.5 [4610.75;5325.5]	7242.5 [6998;7741]	0.02	4430 [4254.25;4649.25]	7320 [6730.75;7856]	0.02	0.1	0.04
SI, y.e	52 [44;60.5]	113.5 [90.25;167.5]	0.005	63.5 [37.5;69.5]	288.5 [232;323.5]	0.02	64 [61.75;68.5]	261.5 [216.5;300.5]	0.02	0.7	0.003

- with a pronounced predominance of the autonomous circuit of heart rate regulation – the fourth type of autonomic regulation [10, 11, 14].

The following mathematical and statistical methods were used in the work: Kolmogorov-Smirnov criterion (when checking the quantitative nature of a feature for the normality of the distribution); when comparing the results between groups, the Kruskal-Wallis criterion was used; Student's t-criterion for paired samples (comparison of quantitative features under the condition of their equality) – to compare the results within the team, in the case of comparing the results of qualitative characteristics, the Mcnimar criterion was additionally applied [13]. All mathematical and statistical processing of materials was carried out with the help of the STATISTICA 10 program.

Research results. The first task of the study was to assess the functional state of military athletes in a relative state of physiological rest.

After the end of the training process, the servicemen of the amphibious assault unit team were on vacation for three days. On the first day of the competition, in the morning, a few hours before the start of the first competitive task (landing as part of a platoon and a march for 10 km), an express functional state assessment test was conducted with military personnel using the analysis of heart rate variability (Table 1).

The presented data indicate that before the start of the competition, the military personnel participating in the competition were distributed approximately in a predominant ratio into favorable types (types I and III) - 66.7% (23.8% and 42.9%, respectively) and unfavorable types (types II and IV) of heart rate regulation - 33.3% (19.05% and 14.25%

respectively). The presented results indicate that 66.7% of military personnel are functionally ready to perform special tasks of the competition and a rest of 3 days was sufficient for them. In 33.3% of the platoon members, dysregulatory manifestations of the functioning of the body were revealed. These data indicate insufficient rest for military athletes. Excessive physical exertion, together with the influence of harmful factors of military service, caused an overstrain of the nervous system of military personnel and led to overtraining. The largest number of servicemen with an unfavorable type of heart rate regulation was in the group of paratroopers operating in combat vehicles, 19%, which amounted to 66.6% of the entire group.

The presented data (Table 2) suggest that after completing the competitive tasks of the military field training competition "Landing Platoon", the reaction to orthostasis in the military personnel of the competitive platoon changes, hyporeactivity is recorded when the body position changes according to the TR index, hyperreactivity according to the stress index and a paradoxical reaction according to the spectral indicator "very low frequencies". A change in the presented indicators may indicate a decrease in the performance of paratroopers [1, 4, 7, 10, 11]. Considering the physiological characteristics of type I and IV regulation it occurs in 38% of athletes (19% of each type), type II is registered in 10% of military personnel and type III is registered in 52%.

It should be noted that type III regulation occurs in military personnel of all military accounting specialties; type IV is characteristic of military personnel operating with light weapons; type I manifested in two paratroopers operating in combat vehicles (both mechanics-drivers). After the end of the competition, there is an "alignment" by type, namely, the type of regulation changes to III. Summing up the results of the study, we can say that after the competition, in some military personnel, moderate centralization of heart rate control turns into moderate dominance of the autonomous regulation circuit, and in other military athletes, pronounced dominance of the autonomous mechanism turns into a moderate type of regulation. The transition from type II and IV to type III regulation, that is, the manifestation of the optimal type of vegetative regulation with a moderate predominance of autonomous regulation, confirms the well-known position that it is controlled self-regulation that allows achieving the optimum without overstressing the control system. The inclusion of the central circuit in the control process destabilizes the controlled system (organism), especially when the high activity of the central circuit is expressed, which completely suppresses the processes of self-regulation [5, 7]. It is also necessary to emphasize that, despite the belonging of some military personnel to the III types of regulation of the heart rate, depending on the military accounting specialty during the performance of competitive tasks of the competition, significant changes in individual indicators are possible up to the transition to another type of regulation.

It has been reliably established ($p \geq 0.02$) that in response to the competitive load, the reaction of regulatory systems depends on the type and degree of exposure to harmful factors on military personnel. According to the results of the study, military athletes who are part of the crew and participate in hand-to-hand combat have a significantly increased IN index compared to military personnel operating with small arms.

Conclusions. Assessment of the level of functional condition of military personnel before the start of the competition helped to distribute military athletes by types of regulation and identify soldiers who are in a state of overtraining. The introduction of functional state monitoring by analyzing heart rate variability in the process of preparing military athletes for competitions should help in adjusting training plans for soldiers and officers.

The solution of the second task of the study showed that the study and analysis of heart rate variability in military personnel of the airborne troops before and after participation in the military field training competition "Airborne Platoon" can help in obtaining objective information about the state of the mechanisms of regulation of cardiac activity of military athletes at different levels of neurohumoral regulation. The military personnel belonging to the group "operating with light small arms" have the best competitive endurance. According to the results of the study, it can be assumed that paratroopers competing in the positions of driver mechanics and gunner operators have a lower level of competitive endurance, but this is not due to a lack of physical fitness, but to the impact of more harmful factors of military service (fuel vapors, noise, vibration, confined space, etc. etc.), which leads to increased tension on the part of the regulatory mechanisms of the paratroopers' body, more often turning into maladaptation.

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CLINICAL CASE

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HETEROPLASMIC MUTATION OF M.3243A>G MITOCHONDRIAL DNA IN A YAKUT FAMILY WITH MELAS SYNDROME: ASSOCIATION WITH PHENOTYPIC MANIFESTATIONS

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For the first time, the diagnosis of MELAS syndrome in a Yakut family was genetically verified using mitochondrial genome sequencing. The substitution of adenine for guanine at position 3243 (m.3243A>G) in the *tRNA*$^{Leu(UUR)}$ gene (MT-TL1) was confirmed. The level of the mutant allele (heteroplasmia) in the patient was 38.5%, while in the mother only 9.8%, which is explained by the selection of rapidly dividing blood cells with a low level of mutant alleles during life. It has been shown that the phenomenon of mtDNA heteroplasmy forms a significant clinical heterogeneity in the manifestation of the disease and demonstrates the complexity of diagnosing subclinical forms of MELAS.

Keywords: mitochondrial diseases, MELAS syndrome, m.3243A>G mutation.

Introduction. MELAS syndrome is an orphan disease caused by a mutation in mitochondrial DNA [2, 3, 11]. The mitochondrial genome, inherited through the maternal line, controls the processes of oxidative phosphorylation and ATP production in the cell, playing a key role in the energy balance of the body. Diseases caused by mutations in the mitochondrial genome are characterized by wide clinical heterogeneity and the multisystem nature of damage to organs and tissues [12]. The most characteristic signs of MELAS syndrome are a combination of encephalopathy with seizures and lactic acidosis [2, 3].

An important role in the phenotypic manifestations of mitochondrial diseases is played by the phenomenon of heteroplasmy - the ratio of the levels of normal and mutant variants of mitochondrial DNA (mtDNA). It has been shown that a small increase in the level of heteroplasmy leads to moderate defects in oxidative phosphorylation, changes in nuclear gene expression and cell phenotype [15, 16].

Objects and methods. The family of a 27-year-old female patient with clinical manifestations of MELAS syndrome was studied. Whole genome sequencing of mtDNA was carried out in the Research Institute of Medical Genetics of the Tomsk Scientific Research Center of Siberian Branch of Russian Academy of Science.

Results. Patient N, born in 1995 (27 years old), yakut, a doctor by training, unemployed, not previously registered with a neurologist, without chronic diseases. The onset of the disease occurred at the age of 23 (January 2019) in the form of generalized tonic-clonic status epilepticus during a trip to Japan.

The patient was hospitalized in the intensive care unit. MRI of the brain, lumbar puncture, and general clinical tests were performed. Signs of inflammation and structural changes in the brain were not found. Status epilepticus was treated with fosphenytoin. The patient was discharged the next day after the attacks subsided; it was decided to undergo further examination in Yakutsk due to the lack of medical insurance.

Upon arrival to home in the city of Yakutsk, an epileptologist was consulted; video-EEG monitoring revealed no pathological changes.

In March 2019, the patient began to again experience weakness, headaches, began to forget the names of objects and words, and also began to experience episodes of visual hallucinations (for example, “a huge cockroach ran across her face”). On March 30, 2019, headache, low-grade fever, and right-sided hemianopia appeared, then a series of four generalized tonic-clonic epileptic seizures developed. A CT scan of the brain and a lumbar puncture were performed; the examination did not reveal any evidence of cerebrovascular accident or inflammatory process.

General clinical and biochemical blood tests did not reveal pathological deviations from the norm. The patient was under drug sedation for 3 days.

After the restoration of consciousness, pronounced cognitive impairments were noted in the form of sensorimotor aphasia, apraxia of dressing. Patient did not recognize relatives, and was disoriented in place and time. Right-sided homonymous hemianopsia persisted, hyporeflexia in the hands, and Babinski's sign on the left were detected.

MRI of the brain revealed signs of cerebral hyperperfusion with damage to the left occipital, parietal lobes, and the thalamic cushion on the left (Fig. 1).

Based on the examination, a diagnosis of autoimmune meningoencephalitis with cognitive impairment, elements of sensorimotor aphasia, visual impairment (homonymous hemianopsia), symptomatic simple focal epileptic seizures, with evolution into bilateral synchronous, and a tendency to a serial course, was established.

In order to clarify the diagnosis, the patient was examined at the Federal State Budgetary Institution "Scientific Center of Neurology" in Moscow, where the blood was additionally tested for: L-lactate – 9.40 mmol/l, pyruvate – 0.11 mmol/l, lactate/pyruvate ratio – 84, 0, in dynamics L-lactate – 9.21 mmol/l (normally up to 3.0 mmol/l), pyruvate – 0.11 mmol/l (normally from 0.03 to 0.09 mmol/l), lactate/pyruvate ratio – 82.4.

MR spectroscopy of the brain revealed a lactate peak in both cerebral hemispheres, predominantly on the left in the affected area (Fig. 2).

Based on the identified data, the diagnosis was clarified as mitochondrial encephalopathy.

Patient N. was consulted by a neuropsychologist; acoustic-mnestic aphasia, acalculia, visual-spatial disorders, and changes in dynamic processes were identified.

In 2019-2022, she was annually admitted to the intensive care unit with the development of status epilepticus, which was associated with an increase in lactate levels to 8 mmol/l (normally 0.5-1.6 mmol/l). She underwent video-EEG monitoring several times, the results of which revealed focal in the frontotemporal regions and/or generalized epileptic activity in the form of a peak-slow wave (Fig. 3).

Further brain MRIs from 2019 (Fig. 4A) and 2022 (Fig. 4B) revealed hyperintense FLAIR signals from the left temporal lobe with increasing expansion of the posterior horn of the left lateral ventricle (Fig. 4A, B)

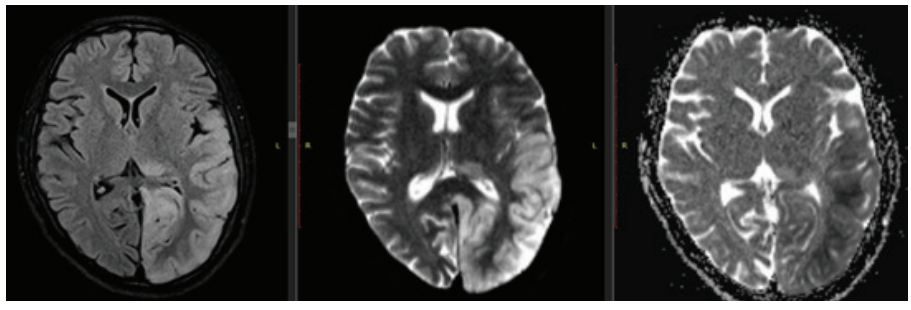

Fig. 1. MRI of the brain of patient N. dated 04/05/2019 with signs of cerebral hyperperfusion with damage to the left occipital, parietal lobe, and thalamic cushion on the left

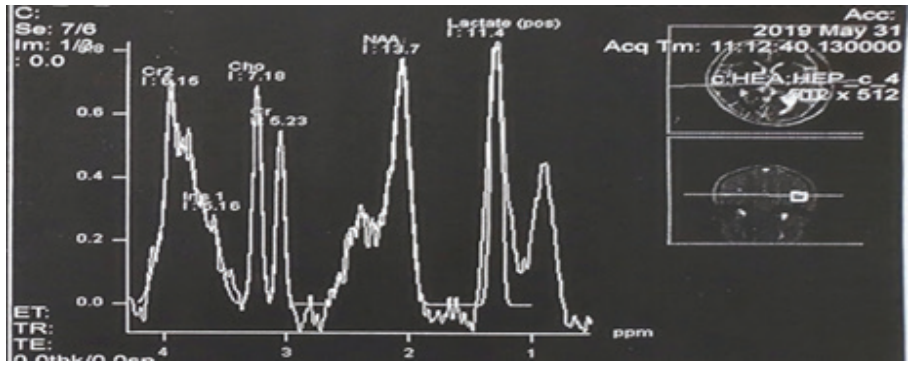

Fig. 2. MR spectroscopy of the brain of patient N. A marked increase in the lactate peak in the area of the altered MR signal in the left temporal lobe and a slight increase in the lactate peak in the unchanged white matter of the right hemisphere of the brain

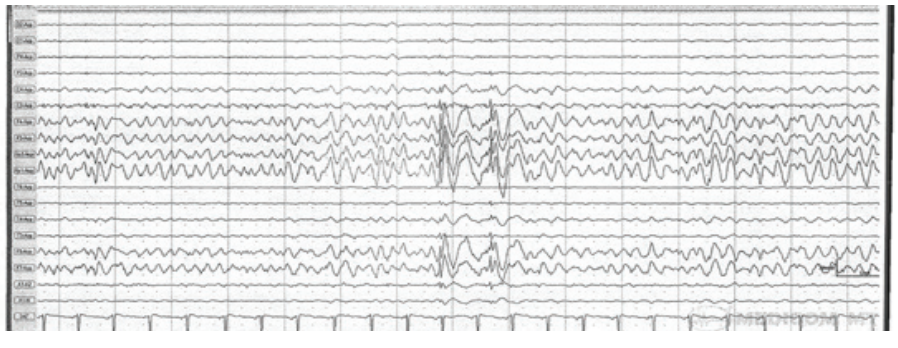

Fig. 2. EEG of patient N. at rest...EEG at rest and activity – focal interictile activity in the form of “peak - slow” waves in the frontotemporal regions, without generation (10/18/2023)

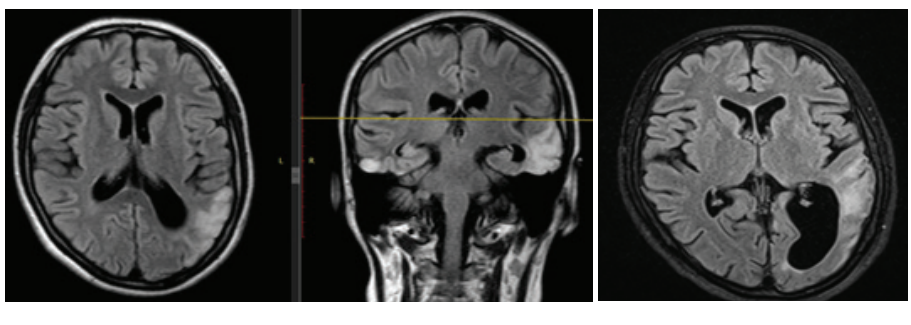

Fig. 4. MRI of the brain: a) from October 2019; b) from October 2022

The patient was examined in May 2023. In neurological status: consciousness is clear, behavior is orderly, makes contact well, sense of smell is normal. Vision is reduced due to myopia, corrected with glasses (–11D), pupils D=S, photoreaction is live. There is no hemianopsia. Sensitivity on the face is preserved, the trigeminal points are painless. Corneal reflexes are alive. The face is symmetrical, the function of facial muscles is preserved. Taste sensitivity in the tongue is preserved. Oral automatism reflexes are not detected. Tongue in the midline, without fibrillations. The strength in the limbs is sufficient, there are no paresis. Diffuse muscle hypotonia. There are no atrophies or hypotrophies in the muscles. Reflexes from the biceps and triceps are low, carporadial are not evoked; knee and Achilles reflexes are not evoked. There are no pathological reflexes. Plantar and abdominal reflexes are not evoked. Performs coordination tests well. There are no sensory disorders. There are no meningeal signs.

Assessment of cognitive functions on the MoCA scale reveals a decrease to 26/30 points: could not repeat two sentences, decreased speech activity (3 words starting with the letter “L” within 1 minute), remembered 4 out of 5 words.

Signs of acoustic-mnestic and optical-mnestic aphasia are determined (for example, the patient cannot remember the names of objects while retaining recognition of their purpose; poorly understands the speech of the interlocutor, especially at a fast pace); phonemic paraphasias are revealed in speech. The patient is unable to read (alexia) and write correctly, both spontaneously and under dictation (agraphia). At the time of examination, no signs of motor, ideational, or constructive apraxia were identified.

During observation, the patient underwent a electrocardiogram (ECG) to exclude non-coronary myocardial infarction type 2. Numerous ECGs revealed sinus tachycardia up to 100 beats/min, early ventricular repolarization, then myocardial changes appeared in the anteroseptal region according to the type of damage (ST elevation V1-V3, negative T wave V4-V6, I-II, (+/-) T IIIAVF0. Consultation with a cardiologist: Dysmetabolic cardiomyopathy associated with the energetic failure of mitochondria (Mitochondrial cardiomyopathy). Chronic heart failure with ejection fraction (EF)=61%, stages I-IIA, functional class (FC) is not differentiated.

Family description and molecular genetic testing. The patient was born from second pregnancy. The mother's first and third pregnancies ended in premature birth. The boys born died due to prematurity after 5-6 hours.

The patient's mother (57 years old) was examined by a rheumatologist, neurologist and geneticist. When examining the mother, a severe deficiency in body weight was revealed (BMI – 15.7 kg/m^2), disorders of phosphorus-calcium metabolism (numerous low-energy bone fractures), osteoporosis, mixed form (surgical menopause in 2000, taking glucocorticosteroids) with multiple clavicle fractures, ribs (2013, 2014), pathological fractures of the distal forearm bones of both upper extremities (2018), proximal left femur (2021). Ischemic heart disease (IHD): Angina pectoris. FC2. Acquired heart disease: aortic valve insufficiency grade 3, mitral valve insufficiency grade 1, tricuspid valve insufficiency grade 1.

Patient’s mother has history of papillary adenocarcinoma of the left lobe of the thyroid gland, condition after the strumectomy operation dated August 25. 2010 and hypothyroidism. Since 2003, she has been suffering from Sjogren's disease, manifested by dry skin, eyes, nephropathy, lymphadenopathy, polyarthralgia, sialadenitis was not excluded, but the diagnosis was not subsequently confirmed by laboratory and instrumental research methods. In addition, the patient’s mother underwent cholecystectomy in 2003, and the lenses of both eyes were replaced with artificial ones in 2014.

No characteristic signs of MELAS syndrome were identified in the patient N.'s mother. The mother and daughter were diagnosed with sensorineural hearing loss.

The mother's brother (patient N.'s uncle, age 60 years) suffers from cerebral palsy, is disabled in group 1, studied in a correctional school, has a neurological deficit in the form of cognitive decline and spastic tetraparesis, in addition, he has structural epilepsy and type 2 diabetes mellitus. Parents of the patient's mother: the mother died in 2023 at the age of 84 from lung cancer. Father, 91 years old, alive. MtDNA sequencing was performed on the patient and her mother. As a result of analysis of the mtDNA sequence in patient N., an adenine to guanine substitution at position 3243 (m.3243A>G) was identified, which, according to the literature, is associated with MELAS syndrome [8]. In the blood sample of patient N., the proportion of the mutant allele G at position 3243, i.e., the level of heteroplasmy, is 38.5% (227 out of 590 reads). In a sample of mitochondrial DNA isolated from the blood of the patient's mother, the mutant allele G was detected with a heteroplasmy level of 9.8% (37 out of 379 reads).

The mtDNA lines of mother and daughter belong to haplogroup D4j5a1a.

Discussion. The m.3243A>G mutation in the *tRNA$^{Leu(UUR)}$* (MT-TL1) mtDNA gene is pathogenic and has significant phenotypic variations. The disease can manifest as multiorgan involvement with a wide variety of clinical manifestations and varying degrees of severity. It is known that the onset of mitochondrial diseases varies from 3 to 40 years [3]. Our patient fell ill at the age of 23, the disease manifested itself in the form of status epilepticus with loss of consciousness and the development of tonic-clonic seizures. During the period from 2019 to 2023, episodes of convulsive seizures with an increase in neurological disorders - cognitive impairment, signs of acoustic-mnestic and optical-mnestic aphasia, motor weakness, decreased hearing and vision - were repeated many times.

Among the characteristic clinical manifestations, the patient has severe cerebral symptoms with epilepsy confirmed by instrumental studies (EEG, MR spectroscopy of the brain), lactic acidosis detected in the blood and by MR spectroscopy of the brain (lactate peaks in both hemispheres of the brain). Other manifestations of MELAS syndrome include cardiomyopathy detected in the patient, which indicates the energetic failure of mitochondria.

According to the literature, cardiac dysfunction occurs in approximately one third of patients with mitochondrial myopathy, encephalopathy, or lactic acidosis, which is a stereotypical example of a mitochondrial disorder leading to cardiomyopathy [6]. Our patient also had visual and hearing impairments in the form of high myopia with astigmatism. Angiopathy of retinal vessels is observed.

Thus, based on typical symptoms characteristic of mitochondrial diseases, as well as genetic (detection of the m.3243A>G mutation), general clinical tests (study of blood lactate levels) and instrumental diagnostic methods (EEG, MRI), the patient was diagnosed with the syndrome MELAS. In the Yakut population, this mutation m.3243A>G of the *tRNA$^{Leu(UUR)}$* mtDNA gene was described for the first time.

The identified mutation is often associated with diabetes mellitus, which is found with a frequency of approximately 1.5% to 5% among diabetic patients from different countries and races [10]. Our patient and her mother were not diagnosed with diabetes mellitus. However, it should be noted that the mother’s brother has

type 2 diabetes mellitus, which does not exclude the presence of heteroplasmy of this mutation.

MELAS syndrome may be accompanied by other disorders – hearing loss, short stature/thin build, myopathy or neurological disorders, disorders of the thyroid and parathyroid glands [1, 5, 10]. The patient's mother was found to have low-level heteroplasmy mutation m.3243A>G (9%). The patient's mother did not show any characteristic symptoms of MELAS, but since childhood she has been short stature, underweight, and during her childbearing years there was miscarriage, fetal failure, bleeding during childbirth with amputation of the uterus and ovaries.

The existing numerous low-energy fractures of long bones, ribs, and clavicle in the patient's mother may have been caused not only by early surgical menopause and removal of the thyroid gland, but perhaps by undetected MELAS syndrome. Damage to the thyroid gland and kidneys may indicate the presence of MELAS syndrome in the mother. From the anamnesis it is known that the mother's chronic kidney disease was interpreted in terms of Sjögren's disease, but the diagnosis was not verified by a sufficient amount of laboratory and instrumental research methods.

Studies of familial cases of detection of the m.3243A>G mutation indicate significant clinical heterogeneity in the manifestations of damage to organs and systems, even within the same family [15]. The low level of mutant mtDNA in the mother at present may be explained by the selection of rapidly dividing blood cells with a low level of mutant alleles during life. The results of long-term studies show that such selection is a common feature of mtDNA carrying the m.3243A>G mutation in blood cells [7]. All these facts, including the m.3243 A>G study, demonstrate that even one point mutation in mtDNA, depending on its level in the cell, can have a profound effect on the state of gene expression, shaping the phenotype of complex hormone-dependent metabolic and degenerative diseases.

A hearing test revealed bilateral sensorineural syndromic hearing loss of 1st degree in the patient and her mother. MtDNA sequencing made it possible to identify another mutation in both subjects: m.7445A>C, previously suspected of being associated with sensorineural hearing loss. L.U. Dzhemileva et al. (2009) considered the possible role of the m.7445A>C mutation in the development of sensorineural hearing loss in Kazakhs, but emphasized that its role in the pathogenesis of auditory dysfunction requires clarification [4]. The literature describes a case of sensorineural deafness in 13 family members with mtDNA variant 7445C [17].

At the same time, it was established that m.7445A>C is a polymorphic variant that defines the D4j5a haplogroup [14], which is widespread in Central Asia and Yakutia [9, 13, 14]. Among the indigenous population of Yakutia, haplogroup D4j5a is found among Yakuts with a frequency of 1.2%, Evenks - 1.6%, Evens - 2.9%, Yukaghirs - 4.5% [5]. Clinical and audiological studies have not been conducted in these individuals; therefore, the role of the m.7445A>C mutation in the molecular pathogenesis of auditory dysfunction requires clarification.

Conclusion. MtDNA sequencing revealed a characteristic mutation m.3243A>G with a heteroplasmy level of 38.8% in a patient with MELAS syndrome in a Yakut family. Family history does not exclude the presence of a mutation in the patient's uncle (mother's brother) and a less pronounced subclinical variant of MELAS syndrome in the mother with a low level of the mutant allele m.3243A>G (9.76%). This mitochondrial DNA mutation was described for the first time among the Yakut population.

In the studied Yakut family, based on a typical syndrome complex and the results of laboratory and instrumental diagnostic methods, the patient was diagnosed with MELAS syndrome. It has been shown that the phenomenon of mtDNA heteroplasmy creates significant clinical heterogeneity in the manifestation of the disease and demonstrates the difficulty of diagnosing subclinical forms of MELAS.

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A CLINICAL CASE OF A COMBINATION OF CROHN'S DISEASE AND JUVENILE RHEUMATOID ARTHRITIS IN A MALE SAKHA ADOLESCENT

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UDC 616.318

The case of the current of two severe autoimmune diseases (Crohn's disease and juvenile rheumatoid arthritis) in a male Sakha adolescent is presented in the article.

Keywords: Crohn's disease, juvenile rheumatoid arthritis, arthralgias, Yakutia.

Introduction. The first description of inflammatory bowel disease was published in 1932 in the USA [6]. Three authors Berrill W. Krohn, Leon Ginsburg, and Gordon D. Oppenheimer described subacute and chronic inflammation of the terminal ileum with chronic narcotic and scarring inflammation in young men. Since then, the history of Crohn's disease research has continued, but the etiology of this disease has not yet been determined and no effective therapy leading to complete recovery has been developed.

Crohn's disease (CD) is a chronic recurrent autoimmune disease of the gastrointestinal tract of unclear etiology characterized by segmental transmural granulomatous inflammation, predominantly with the development of local and systemic complications [1].

Crohn's disease is one of the serious problems in pediatrics. In this disease in children, there are no specific complaints and characteristic changes in general clinical and biochemical tests. The pathological process can involve any part of the digestive organs from the oral cavity to the anus. There may also be extraintestinal manifestations. A multidisciplinary approach is necessary for prompt diagnosis [3].

Progress in the field of determining the mechanisms of autoimmune inflammation and the development of genetically engineered drugs has made it possible to achieve persistent remission [2,5]. In the literature it is described that patients with a combination of several immunoinflammatory diseases are shown the use of genetically engineered biological therapy with good effect [4].

Clinical example. Child L., Sakha, 17 years old.

From the anamnesis: The child from the 2nd pregnancy, 2nd childbirth. Pregnancy proceeded against the background of anemia, threat of interruption. Premature birth occurred at the 25-26th week. Birth weight was 1200 g, body length was 47 cm. Due to prematurity she was nursed in the neonatal pathology department until 2 months of age.

Heredity: aggravated on the father's side - unspecified arthritis.

Past diseases: Acute respiratory viral infections frequently.

Allergologic anamnesis: Since 5 years of age he suffers from bronchial asthma, atopic form, mild course.

Medical history: According to the words of the boy, he has had the disease since the age of 16. At the onset of the disease, the patient was bothered by pain in the lumbar region. Since the beginning of December 2022, he has been concerned about pain in the left foot. He went to the hospital, a plaster cast was applied. On December 18, 2023, pain in the right foot with progressive swelling appeared. The patient repeatedly went to the hospital - recommendations were given, topical ointment Troxevasin was applied. Since December 22, 2022 pain in knee joints, hip joints, fever up to 38°C, which decreased independently without antipyretics. In this connection he was hospitalized in the cardio-rheumatology department of the Pediatric Center of the Republican Hospital No. 1-National Center of Medicine named after M.E. Nikolaev.

Complaints on admission: pain in the joints after physical activity, periodic pain in the epigastrium when eating.

On admission: condition of average severity in the main disease. Height was 171 cm, body weight was 90.4 kg. Respiratory rate was 20 per min. Saturation was 99%. Heart rate was 77 beats per minute. BP was 120/65 mm Hg. Feeling decreased. Appetite not disturbed. Sleep was calm. Consciousness was clear. The physique was normal. Increased nutrition. The pharynx was not hyperemic. Mucous membranes of the mouth and pharynx clean, pale color. Nasal breathing was free. Bone and joint system were without features. Peripheral lymphatic system: lymph nodes were not enlarged. The thorax was regular in shape. Percussion - clear lung sound in all fields. Vesicular breathing, no rales. Heart tones clear, rhythmic. The abdomen was soft, painless. Liver and spleen were not enlarged. Edema of the right foot. Urination was free, painless. No peripheral edema.

Paraclinical: In the general blood test dated 12/22/2022.: hemoglobin - 120 g/L (RI: 120-160 g/L); red blood cells - $4.4x10^{12}$/L (RI: 4.1-5.2x10^{12}/L); platelets - 250 10^9/L (RI: 150 - 450x10^9/L); white blood cells -16.8x10^9/L (RI: 4.5 - 13x10^9/L); lymphocytes - 12% (RI 8-10%); monocytes - 0.4x10^9/L (RI: 0.05 - 0.4x10^9/L); neutrophils - 8% (RI: 1-5%); neutrophils - 81% (RI: 43-60%); eosinophils - 3% (RI: 0-5%); COE - 20 mm/h (RI: 1-15 mm/h). Conclusion: lymphocy-

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tosis, leukocytosis, neutrophilic shift of leukocytic formula, increased ESR.

Biochemical blood test dated 22.12.2022: ALT - 96 units/l (RI: 00-29.00 units/l), AST - 92.5 units/l (RI:00-36 units/l), CRP - 114.9 mg/l (RI:0-5mg/l). Conclusion: Increased levels of alanine aminaminosrasferase, aspartate aminotransferase, C-reactive protein.

Hand radiography dated 21.12.2022 - joint gaps were preserved, articular surfaces with smooth, clear contours, without bone-destructive changes, paraarticular tissues were edematous.

Digital radiograph of knee joints in 2 projections dated 16.10.2023: Bone relationships were not disturbed. Bone dimensions were normal, contours were clear. Intra-articular gaps were irregularly narrowed. The articular surfaces were not deformed, clearly and evenly contoured. The bone structure was preserved. Conclusion: Radiologic signs of arthritis of knee joints.

X-ray of thoracic cavity organs from 22.12.2022 without pathology.

Fibrogastroscopy dated 21.12.2022: The esophageal mucosa was pink, shiny. The dentate line was clear. The cardia was closed. In the stomach cavity there was a large amount of bile, secretory fluid, hematine. The folds of the stomach of the usual shape and height. Gastric mucosa was edematous, hyperemic, vulnerable, with contact bleeding, total with multiple hemorrhagic erosions with hematinous plaque 0.5-1.5 cm in some places with fibrin plaque, expressed contact bleeding. Peristalsis of antral section with medium waves. The preauricle was closed. The bulb was deformed, on the upper wall with formation of pseudodiverticulosis on the lower wall with semicircular scar. The mucous membrane was focal-hyperemic, with slight epithelizing erosions, the mucous membrane of the descending part of the duodenum was pink. Conclusion: Duodenogastric reflux. Erythematous gastropathy.

Ultrasound examination of abdominal cavity organs from 28.12.2022: ECHO-pathology was not revealed.

Computed tomography of abdominal cavity organs dated 28.12.2022: Liver of normal size and shape, contours smooth, structure of parenchyma homogeneous, density indices slightly decreased 47-51ed. Intrahepatic bile ducts were not dilated. Gall bladders 1.5x1 cm, with constriction in the area of the bottom, the walls of the bladder were smooth. Conclusion: Moderate diffuse changes in the liver parenchyma.

Colonoscopy dated 12/22/2022: Bauginia flap was semilunar in shape, its mouth was closed, oriented to the dome of the cecum. The terminal part of the ileum was examined - the mucosa was pink, velvety. The lumen of the examined parts of the colon was not deformed, in the lumen there was a large amount of liquid, yellowish content, asperated. The folding of the intestine was preserved. The folds were well spread when insufflated with air. The tone of the intestine was normal. Visible mucosa of the colon was pale pink. Conclusion: signs of catarrhal proctitis.

Clinical diagnosis: Juvenile arthritis (seronegative), polyarthricular variant, 3rd degree of activity, 2nd radiologic stage. FC 3. Crohn's disease. Chronic gastric ulcer with bleeding. Autoimmune hepatitis.

Prescribed adalimumab (Humira) 40 mg once every 2 weeks (every 2 weeks), mesalazine (salofalc) 1g 3 times a day, with positive effect.

In May 2023, the child was again on a scheduled dispensary examination, in remission.

In October 2023, he was admitted with sharp pains in the epigastric region and stool color change (dark color, viscous consistency). He was examined in the reception-diagnostic department of PCC RB №1-NCM. The child's condition was severe. Self-being was decreased. Appetite was reduced. Anxious. Consciousness was clear. Correct physique. Increased nutrition. The pharynx was not hyperemic. The mucous membranes of the mouth and pharynx were clean, pale in color. Nasal breathing was free. Bone and joint system without features. Peripheral lymphatic system: lymph nodes were not enlarged. The thorax was regular in shape. At percussion of the chest - clear pulmonary sound. On auscultation of the chest there was vesicular breathing, no rales. Heart tones were clear, rhythmic. The abdomen was soft, sharp soreness in the epigastrium. The liver and spleen were not enlarged. Urination was free, painless. There was no peripheral edema. Stool 19.10.2023 1 time, formed.

Paraclinical: General blood test dated 13.10.2023.: hemoglobin - 145 g/L (RI: 120-160 g/L); red blood cells - $5.1x10^{12}$/L (RI: $4.1-5.2x10^{12}$/L); platelets - 221 109/L (RI: 150 - $450x10^{9}$/L); leukocytes - $6.31x10^{9}$/L (RI: 4.5 - $13x10^{9}$/L); lymphocytes - 44% (RI: 8-10%); monocytes - $9.5x10^{9}$/L (RI: 0.05 - $0.4x10^{9}$/L); neutrophils - 1% (RI: 1-5%); basophils - 0.5% (RI: 00-0.7%); eosinophils - 3.2% (RI: 0-5%); ESR -7 mm/h (RI: 1-15 mm/h). Conclusion: lymphocytosis.

Biochemical blood test dated 13.10.2023: C-reactive protein -O (RI:0.00-10.00), ASLO - 265 IU/mL (RI:0.00-200.00), Rheumatoid factor negative, Ig A total >4. 2 mg/mL (RI:0.7-3.00), Ig M total >3.20mg/mL (RI:0.5-2.00), Ig G 10.10 mg/mL (RI:8.00-16.00), Ig E - 139.30 IU/mL, CIC - 48 units. Conclusion: increased ASLO, Ig A, Ig M, Ig E.

Coagulogram dated 10.10.2023: Prothrombin index - 84.00% (RI:20.00-140.00), prothrombin time - 15.00 s (RI:13.5-17.00), INR - 1.09(RI:0.81-1.13), fibrinogen - 2.82(RI: 1.9-4.3), ACTH - 41.1(RI: 30.8-41.4). Conclusion: coagulogram was normal.

Esophagogastroduodenoscopy from 10.10.2023: Conclusion: Duodenogastric reflux. Erosive gastropathy. Non-erosive reflux esophagitis.

Digital radiograph of knee joints in 2 projections dated 16.10.2023: Bone relationships were not disturbed. Bone dimensions were normal, contours were clear. Intra-articular gaps were irregularly narrowed. The articular surfaces were not deformed, clearly and evenly contoured. The bone structure was preserved. Conclusion: Radiologic signs of arthritis of knee joints. Osteochondropathy. Osgood-Schlatter disease.

Ultrasound examination of abdominal cavity organs dated 13.10.2023: Visualization was partial, extremely difficult due to pronounced flatulence and increased subcutaneous fatty tissue. The liver was enlarged, left half was 6.3 mm, right lobe was 129 mm, oblique vertical dimension was 150 mm. The contour was even. The structure was homogeneous, echogenicity was above average. Intrahepatic bile ducts were not dilated. The vascular pattern was smoothed. The hepatic veins were not dilated. The portal vein was 9 mm. The gallbladder was located typically. The shape was oval, with a bend in the area of the bottom. The wall was thin, the lumen was clear. The size was 69 mmx23 mm. The common bile duct was not dilated. The pancreas was not enlarged. The contour was even. The size of the head was 21 mm, body was 13 mm, tail was 24 mm. The structure was homogeneous, echogenicity was average. The kidneys were located typical. The right kidney was 99 mmx40 mm. The contours were even. The parenchyma was 19 mm thick. The calyx-lochanous system was not dilated. The left kidney measures 100 mmx50 mm. Contours were even. The parenchyma was 20 mm thick. The calyx-lochanous system was not dilated. Urinary bladder was empty. Conclusion: Hepatomegaly. Diffuse changes in the liver parenchyma. Deformation of the gallbladder.

Test for Helico bacterium from 18.10.2023: Hp +

Colonoscopy from 12.10.2023: The lumen of the cecum was narrowed by 1/3 due to edema of the bauginia flap, the mucosa of the bauginia flap was sharply edematous and hyperemic, with multiple ulcers of 2.0 cm with fresh undermined edges, the crater was covered with fibrin. The aperture of the flap was spasmodic, impassable for the apparatus. The rest of the examined areas of the colonic mucosa were without peculiarities. For biopsy 2 fragments of the ileum mucosa, 3 fragments of the mucosa of the Bauginia flap were taken. Conclusion: Terminal ileitis. Crohn's disease. Active stage with ulcers and stricturing.

Biopsy of small intestine mucosa fragments from 20.10.2023: biopsy material contains fragments of small intestine mucosa with the picture of chronic active ileitis, with focal cryptitis, with focal hyperplasia of peyer's plaques.

Clinical diagnosis: Inflammatory bowel disease. Crohn's disease with extraintestinal manifestations. Juvenile arthritis (seronegative), polyarthricular variant, grade 3 activity, X-ray grade 2. FC 3. Autoimmune hepatitis. Osgood-Schlatter disease.

Treatment was prescribed: ward regime, table #5, adalimumab (Humira) 40mg p/k, pancreatin 1 capsule 3 times a day with meals, omeprazole 20 mg 2 times a day (8 h-20 h) for 14 days.

On 20.11.2023 the child was discharged with improvement.

Recommendations at discharge: observation of the district pediatrician, table #4, exemption from physical training (exclude physical activity), contraindicated insolation, contraindicated vaccination and administration of gamma globulin, contraindicated hypothermia and bathing in open water, immunomodulators, contact with animals, contraindicated physical and mental trauma. Examination of gastroenterologist and rheumatologist once a month, ophthalmologist once every 3 months, planned hospitalization in Pediatric Endocrinology and Gastroenterology Department every 3 months, cardiac ultrasound once every 3 months, chest Computed Tomography once every 6 months.

Adalimumab (Humira) 40 mg once every 2 weeks. (every 2 weeks) constantly, calcium preparation, vitamin D constantly for 3 months, 1 month break, mesalazine (salofalc) 1g 3 times a day constant intake, Nexium 20 mg once a day for 3 weeks, pancreatin (Creon, Micrazyme) 10 TE 3 times a day with meals for 3 weeks, urodesoxycholic acid 250 mg at lunch, 500 mg in the evening.

Conclusion. This article presents a case of the course of two severe autoimmune diseases (Crohn's disease and juvenile rheumatoid arthritis) in a male Sakha adolescent. Such clinical examples are rare in the publicly available literature. The management of this child requires a multidisciplinary approach and joint therapy by gastroenterologists and rheumatologists to achieve a durable remission.

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COMBINATION OF MILLER FISHER SYNDROME AND UNSPECIFIED PERIPHERAL T-CELL LYMPHOMA

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The article presents a clinical case of combination of Miller Fisher syndrome and unspecified peripheral T-cell lymphoma, which is an aggressive disease with an extremely poor prognosis. The pathogenetic treatment of the identified syndrome did not cause an improvement in the patient's condition and did not affect the expected unfavorable prognosis of the primary malignant disease, for which chemotherapy was not carried out due to the extremely serious condition of the patient. This case emphasizes the importance of an oncological search in patients with Miller Fisher syndrome and the mandatory determination of onconeural antibodies used in the diagnosis of paraneoplastic neurological syndrome, which occurs in malignant tumors of various histogenetic types.

Keywords: unspecified peripheral T-cell lymphoma, paraneoplastic neurological syndrome, Guillain-Barré syndrome, Miller Fisher syndrome.

Paraneoplastic syndrome (PNS) is a clinical and laboratory manifestation of a malignant tumor, caused by nonspecific reactions from various organs and systems or ectopic production of biologically active substances by the tumor. It is

registered in 10-18.5% of cases in colon cancer, small cell lung cancer, breast and ovarian cancer and malignant lymphomas [6]. It is noteworthy that paraneoplastic syndrome can manifest before the tumor is detected or sometimes simultaneously with its clinical manifestations [2]. After radical treatment of a malignant tumor, this syndrome may disappear and reappear with tumor relapses [1].

Domestic and foreign literature describes various manifestations of PNS (hematological, endocrine, neurological, gastroenterological, nephrological, dermatological, etc.).

Recently, clinicians have been particularly interested in Guillain-Barré syndrome (GBS), which has many clinical forms that differ in the characteristics of the pathological process, the primary point of application of autoimmune aggression (nerve sheath or axon core), prognosis of recovery and clinical manifestations. Most often (70-80%) all over the world, including in Russia, acute inflammatory demyelinating polyneuropathy (AIDP) is diagnosed as part of GBS, in which autoantibodies attack the myelin sheath of the nerve. In the second most common place (5-10%) are axonal forms – acute motor and motor-sensory axonal neuropathies (AMAN and AMSAN), characterized by primary damage to the axons of peripheral nerves and differing from each other in involvement (AMSAN) or intactness (AMAN) of sensitive fibers. Other forms of GBS (Miller Fisher syndrome (MFS), pharyngo-cervico-brachial, acute pandysautonomia, paraparetic, sensory) are diagnosed extremely rarely (1-3%). In the Russian Federation, among all forms of GBS, Miller-Fisher syndrome accounts for 2-5% [4,13].

MFS has three defining features: external ophthalmoplegia (ocular weakness resulting in impaired eye movements and consequent diplopia), ataxia (incoordination of the limbs movement), hypo- or areflexia (absence of tendon reflexes). In severe cases, tetraparesis and paralysis of the respiratory muscles may occur [15]. It has been established that the disease can develop after viral and bacterial infections [8]. The occurrence of areflexia in MFS is associated with a decrease in the acetylcholine content in the terminals and peripheral nerves, which is clinically manifested by polyneuropathy [5, 12]. The study of ataxia in this disease using modern neuroimaging methods made it possible to detect changes in the signal from cerebellar structures [9] and suggest a combination of sensitive and cerebellar ataxia due to both central and peripheral demyelination [12]. Damage to the oculomotor nerves is explained by the formation of anti-GQ1b antibodies, which are detected in the blood of the vast majority of patients with MFS [11, 12, 16]. Gangliosides are the components of the myelin sheaths that envelop nerve fibers and ensure the speed of transmission of nerve impulses. According to their chemical structure, gangliosides are lipopolysaccharides containing a sialic acid residue. Many bacteria (the intestinal bacterium *Campylobacter jejuni*, the causative agent of pneumonia – *mycoplasma pneumoniae* and viruses (Epstein-Barr virus, cytomegalovirus)) and others are very similar in composition to gangliosides. When these microorganisms enter the body, the immune system may mistakenly react not only to viruses, but also on gangliosides of nerve cells, which leads to the production of autoantibodies to its own neurons and the development of various clinical forms of Guillain-Barré syndrome.

Many researchers have found that with the development of malignant tumors, specific antitumor antibodies, called onconeural antibodies, begin to be produced. Due to the antigenic identity of some tumor antigens and components of nervous tissue, these antibodies, associated with onconeural antigen-specific T lymphocytes, attack components of normal nervous tissue [7,14].

We present our own clinical observation of Miller Fisher syndrome in a patient with nodal unspecified T-cell lymphoma.

Patient E., 63 years old, was hospitalized to department of medicine of Republic Hospital No.1 – National Center of Medicine (RH No.1- NCM) with complaints of numbness in the lower and upper extremities, inability to move without assistance, severe weakness, fever up to 38^0C, loss of body weight by 10 kg, cough, shortness of breath.

From the anamnesis: ill for about 2 months, when the cervical and supraclavicular inguinal lymph nodes enlarged, there was a daily increase in body temperature to 38^0C. After 1 month from the moment of illness, the patient developed numbness in the extremities, diplopia, unsteadiness when walking, weakness of the right half of the face, cough and shortness of breath during physical activity. In 2 months of illness due to increasing weakness in the legs, the patient stopped walking. The patient was hospitalized in the central district hospital, from where he was sent to RH No. 1-NCM with a diagnosis of lymphadenopathy of unknown origin.

Objectively: at admission the patient's general condition is considered as serious. The skin is clean, of normal color, acrocyanosis is noted. On palpation, the cervical, axillary and inguinal lymph nodes on both sides are enlarged, dense in consistency, painless. Lung auscultation – clear breath sounds on both sides, weakened in the lower sections. Heart sounds are rhythmic and muffled. Blood pressure – 100/60 mmHg. Pulse 96 bpm.

Neurological status: alert and oriented in his own personality, place and time. Emotionally labile. The pupils are equal, and reactive to light. Bilateral converging strabismus is noted, limited upward and outward movements of the eyeballs, ptosis on the right, binocular diplopia. Sensitivity on the face is preserved, the trigeminal points are painless. The face is asymmetrical: the right corner of the mouth is drooping, lagophthalmos on the right, smoothness of the frontal and nasolabial folds on the right. Dysphagia when taking liquid food. Dysarthria. There are no oral automaticity reflexes. The pharyngeal reflex is absent. Tongue in the midline. Flaccid deep tetraparesis (muscle strength reduced to 2 points). Diffuse muscle hypotonia. Deep and periosteal reflexes of the arms and legs are reduced. Hypotrophy of the leg muscles. Hypoesthesia of the "sock" type. It is impossible to check in the Romberg pose. The knee-to-heel, finger-to-nose tests cannot be checked due to paresis. There are no meningeal or pathological signs. Tension symptoms are negative. Controls the functions of the pelvic organs.

Examination data:

Complete blood test

Component Value

Red Blood Cell Count 3.76 x 10^{12}/l
Hemoglobin 10^9 g/l
White Blood Cell Count 11 x 10^{9}/ l
Eosinophilia 3%
Platelet Count 307x10^{9}/l.

Biochemical blood test

ALT 10 units/l
AST 11 units/l
LDH 163 units/l
Total protein 79 g/l
Albumin 30 g/l
Creatinine 68 μmol/l
Urea 2.5 mmol/l
Total bilirubin 10.2 μmol/l
Alkaline phosphatase 92.3 units/l
Ferritin 216 μg/l
Glucose 8.35 mmol/l
Potassium 2.8 mmol/l
Sodium 135 mmol/l
Triglycerides 2.05 mmol/l
Total cholesterol 4.17 mmol/l

Coagulogram
Fibrinogen 3.88
Prothrombin index 03%
Prothrombin time 12
APTT 27.30 sec.
INR 1.10.

Thyroid stimulating hormone (TSH) level is 1.36 mIU/l, the level of free thyroxine (free T4) is 12.80 pmol/l (both hormones are within normal limits).

Serological tests (enzyme immunoassay) for syphilis, human immunodeficiency virus, hepatitis B and C are negative.

Conclusion of nerve conduction study (NCS): signs of damage to the motor and sensory fibers of the median, radial, tibial and peroneal nerves, such as severe axonal demyelinating polyneuropathy, more pronounced in the nerves of the legs (M-waves absent).

Ultrasound of peripheral lymph nodes: submandibular, mental lymph nodes are not enlarged, cervical lymph nodes are enlarged (largest on the right 18x6 mm, on the left 16x7 mm), posterior cervical (right largest 26x15 mm, left 28x16 mm), supraclavicular (right largest 10 mm, left largest 19x11 mm), subclavian (right 10 mm, left 10.2 mm), axillary (right largest 41x16 mm, left 34x19 mm), inguinal (largest on the right 28x9.4 mm, on the left - 28x10 mm) lymph nodes.

Result of ultrasound of the abdominal organs: hepatosplenomegaly, hardening of the kidney sinuses, enlarged lymph nodes in the hilum of the liver and spleen.

Conclusion of computed tomography of thorax: hilar and peripheral lymphadenopathy, right-sided paracostal pleuritis.

Conclusion of CT scan of the brain: signs of dyscirculatory encephalopathy.

For diagnostic purposes, an open biopsy of the enlarged cervical lymph node was performed. Microscopic description of the material: fragments of lymphoid tissue with a disturbed structure, diffuse focal proliferation of atypical medium-sized lymphocytes is noted. Tumor cells with expression of CD4, CD5, bcl-2, CD2, CD43, EBV, in the absence of pax5, CD79a, CD10, CD15, CyclinD1, CD138, CD30, EMA, MUM1, bcl-6, CD1a, CD246, CD56, CD57, TdT. Expression of CD34 in vessels and CD23 in preserved areas of the network of follicular dendritic cells was revealed. ***Conclusion:*** Unspecified T-cell lymphoma.

The patient underwent 5 sessions of discrete plasmapheresis, intravenous immunoglobulin therapy, antibiotic therapy and antiviral treatment without the desired result.

The patient's condition sharply deteriorated due to signs of respiratory failure, and therefore was transferred to mechanical ventilation. Despite the treatment, due to worsening respiratory failure, patient expired on the 22nd day after hospitalization.

Conclusion. Thus, taking into account the data of clinical, laboratory and instrumental research methods, the results of an immunohistochemical study of a cervical lymph node - unspecified peripheral T-cell lymphoma, an indication of a recent history of viral infection, acute development of external ophthalmoplegia, hyporeflexia and ataxia, as well as NCS data, confirming the presence of polyneuropathy, allowed us to establish the diagnosis: Unspecified peripheral T-cell lymphoma combined with Miller Fisher syndrome.

The temporary coincidence of the development of neurological disorders with T-cell lymphoma most likely suggests their paraneoplastic nature. Although MFS is classically associated with infectious diseases, primarily *Campylobacter jejuni* and *Haemophilus influenza* [17], clinical observations of the development of MFS in patients with lung cancer [10] and Burkitt's lymphoma [8] have been described in the literature.

In the case we presented, attention is drawn to the severe course of neurological disorders, namely the development of severe flaccid paresis with the development of respiratory failure, damage to facial muscles. According to the opinion of Professor O.S. Levin, such cases may be the result of the “superposition” of MFS on Guillain-Barré syndrome [3].

A limitation of our observation is undoubtedly the lack of serum testing for antibodies to gangliosides, which are detected in 95% of patients with MFS; examination of cerebrospinal fluid to determine protein-cell dissociation. In this regard, we cannot reliably state the development of neurological disorders within T-cell lymphoma, but only pay attention to their combination. Consequently, the answer to the question whether the Miller Fisher syndrome that developed in the patient can be considered a paraneoplastic syndrome associated with unspecified peripheral T-lymphoma remains controversial and doubtful. It should be noted that many studies have established the trigger role of Epstein-Barr viruses and cytomegalovirus infection in the occurrence of both lymphomas and Miller-Fisher syndrome. In this patient, both viruses were detected in the replication phase, which could serve as a trigger for the simultaneous development of two completely different diseases. In addition, the patient did not have onconeural antibodies, which are used as one of the criteria for identifying definite or probable paraneoplastic neurological syndrome. However, this clinical example demonstrates the possibility of co-occurrence Miller Fisher syndrome with unspecified peripheral T-cell lymphoma, which is an aggressive disease with an extremely poor prognosis. The pathogenetic treatment of the identified syndrome did not cause an improvement in the patient's condition and did not affect the expected unfavorable prognosis of the underlying malignant disease, for which chemotherapy was not carried out due to the extremely serious condition of the patient.

This case emphasizes the importance of an oncological search in patients with Miller Fisher syndrome and the mandatory determination of onconeural antibodies used in the diagnosis of paraneoplastic neurological syndrome, which occurs in malignant tumors of various histogenesis.

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CONGENITAL AUTOSOMAL RECESSIVE CATARACT IN A SAKHA CHILD

The article presents a clinical case of congenital autosomal recessive cataract, first identified in a 3-year-old Sakha child. Congenital cataract is a relatively rare pathology found in children, but it is often the cause of visual impairment and blindness. The restoration of a child's eyesight depends on the early detection and treatment of the disease. Studies show that 30 to 50% of congenital cataracts are caused by genetic mutations.

Keywords: congenital cataracts, child, malformation, genetics.

Introduction. A cataract is a disease that causes clouding of the lens (any light-scattering clouding of the lens). Congenital cataracts, also known as neonatal cataracts, are intrauterine clouding of the lens. According to statistics, congenital cataracts cause blindness in children from 5 to 20% [1,3,4,9]. There are unilateral and bilateral cataracts. They can be classified according to morphology, suspected or definite genetic cause, the presence of specific metabolic disorders or associated ocular abnormalities or systemic features [8,13]. Congenital cataracts are phenotypically and genotypically heterogeneous and can occur alone or in combination with other systemic diseases. Significant progress has been made in identifying the molecular genetic basis of cataracts [6].

The eye begins to develop on day 22 of pregnancy. The lens develops from the superficial ectoderm. Most of fibroblasts growth factors produced in the vitreous are required for differentiation of secondary lens fibers, since lens polarity is determined by fibroblast-regulating growth factor [1,2,6]. PAX6, PITX3, c-Maf and FOXE3 are genes that encode proteins that play the role of a transcription factor in lens development. Mutation of either protein results in defective lens production. The anterior epithelial cells of the lens retain their morphology and proliferative capacity, while the posterior epithelial cells form the primary fiber of the lens [2,9].

In many children with congenital cataracts, the etiology has not been identified, but many authors are inclined to an autosomal dominant type of inheritance. The most common cause of most bilateral congenital cataracts is a genetic mutation. According to epidemiologists, a quarter of all congenital cataracts are hereditary [8]. More than fifteen genes involved in the formation of cataracts have been identified, and inheritance is most often autosomal dominant. Variation in cataract phenotype results from mutations in the *CRYAA, CRYAB, CRYBB1, CRYBB2, CRBB3, CRYGC* and *CRYGD* genes [2,7,8,11]. Congenital autosomal recessive cataract is one of the most common hereditary diseases among the Turkic-speaking population of Yakutia (Eastern Siberia, Russia). Our geneticists under the leadership of Ph.D. Barashkova N.A. have identified the molecular genetic basis of this disease: a mutation in the *FYCO1* gene and carriage of the c.1621C>T mutation [5].

The mutation affects the structure of the eye lens. Studies by some authors indicate that half of genetic mutations are affected by so-called proteins - crystallins; in 20 percent of cases they affect connexins, growth factors and lipid metabolism [11]. The variety of clinical manifestations of congenital cataracts may be due to the fact that a mutation of one gene leads to different phenotypic changes in different families. At the same time, different genetic mutations can manifest themselves in the same way, and this fact suggests that there are other factors involved in morphological changes [1,2,7].

Surgical intervention at an early age and subsequent vision correction can contribute to the timely social adaptation of the child. Late surgery can cause sensory deprivation and cause complications such as strabismus, nystagmus, and the formation of incorrect fixation. To restore a child's vision, the sooner the operation is performed, the better the prognosis [1,4]. Despite early surgical treatment, complications may subsequently develop in children [1,2,14].

Congenital cataracts can be caused by infections that a woman comes into contact with during pregnancy. The main infections that have an increased risk of developing cataracts include rubella virus, cytomegalovirus, herpes simplex virus, and toxoplasmosis.

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For preventive purposes, it is necessary to exclude contact of a pregnant woman with infectious patients, and also to minimize the effects of alcohol, smoking, teratogenic drugs, and radiation. Early detection of chromosomal abnormalities allows a decision to be made to terminate the pregnancy. There is no specific prevention of congenital cataracts [2,10,12].

Thus, congenital cataracts require early recognition and surgical intervention to ensure good clinical outcomes.

Purpose of the study: to describe a clinical case of congenital cataract in a 3-year-old child.

Clinical example. Patient Z., 3 years old, Sakha, a child from the 8th pregnancy, 4 births, the pregnancy proceeded in the first half - toxicosis, in the second half - edema, anemia, gestational diabetes mellitus, suffered from acute respiratory viral infection at 26 weeks. Delivery at term, birth weight – 3350g, body length – 53cm. Apgar score – 8/9 points. He was discharged home on the 6th day in satisfactory condition under the supervision of a local pediatrician at his place of residence. The child grew and developed according to his age. Got preventive vaccinations according to the calendar. There is no hereditary history of eye diseases. Past diseases: frequent acute respiratory viral infections, chalazion.

At the age of 9 months, parents noticed that the child brings small objects and toys closer to his face and examines them, tilting his head to the side. Due to the absence of an ophthalmologist at the district hospital, the child was not examined. At the age of 3 years, he was sent to the Republican Hospital No. 1 - National Center of Medicine (RH No. 1-NCM) with a diagnosis of: Frequently ill child. Visual impairment.

After an examination by an ophthalmologist, the diagnosis was made for the first time: Congenital zonular bilateral cataract. Sent to the ophthalmology department of RB No. 1-NTsM for examination and decision on the issue of surgical treatment. A consultation with a geneticist and an allergist-immunologist is recommended.

Ophthalmological examination: The eyeball is in the correct position, full mobility. Eyelids: on the right side of the upper eyelid there is a trace of a small infiltrate, protruding above the level - 0.1 mm, painless, lacrimal openings are normal. The conjunctiva is calm. The cornea is transparent. The anterior chamber is of medium depth. The moisture in the anterior chamber is transparent. The pupil is round, 3 mm in diameter, reaction to light is friendly. The iris is not changed. The lens is cloudy, more on the left, inhomogeneous, irregularly shaped, in the center. Vitreous body: without features. Fundus: optic disc is pale pink in color, the boundaries are clear. The arteries are slightly narrowed, the course is not changed. The veins are of normal caliber, their course is not changed. The retina is not changed.

Results of instrumental research:

Skiascopy: P30, OD=18.55mm, OS =18.5mm, IOP Icare OD=13 mmHg; OS =13 mmHg

Ultrasound OU: compaction of the lens capsules, the vitreous body is acoustically transparent, the retina is adjacent, the contour is smooth.

Genetic research data:

1. Conclusion of a molecular genetic study in the proband: as a result of a molecular genetic study for a major mutation in the *FYCO1* gene, a homozygous carriage of the c1621C>T mutation was revealed, causing the hereditary disease cataract 18 (autosomal recessive congenital cataract 2).

2. Conclusion of a molecular genetic study of the mother. As a result of a molecular genetic study for a major mutation in the *FYCO1* gene, carriage of the c.1621C>T mutation in a heterozygous state was revealed, causing the hereditary disease cataract 18 (autosomal recessive congenital cataract 2).

3. Conclusion of a molecular genetic study in the father: as a result of a molecular genetic study for a major mutation in the *FYCO1* gene, carriage of the c.1621C>T mutation in a heterozygous state was revealed, causing the hereditary disease cataract 18 (autosomal recessive congenital cataract 2).

Based on complaints, examination data, instrumental and laboratory data, a clinical diagnosis was made: Congenital autosomal recessive incomplete cataract (Q12.0).

The child was sent to the Helmholtz National Medical Research Center for Eye Diseases for surgical treatment.

Conclusion: Based on the presented clinical case, we can conclude that the diagnosis of the pathology and surgical treatment were carried out late (the child is 3 years old). Regardless of the type of cataract, early detection and treatment is necessary, since the restoration of vision in the child depends on this.

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A RARE CASE OF INFLAMMATORY MYOFIBROBLASTIC ABDOMINAL TUMOR IN A CHILD

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The article presents a clinical case of a rare inflammatory myofibroblastic tumor of the abdominal cavity in a 6-year-old boy. The child had a high fever, laboratory tests revealed an increase in acute phase proteins, and according to instrumental studies - a large tumor of the abdominal cavity, without a clear organ affiliation. During laparoscopic revision, the possibility of total tumor removal was established; laparotomy was performed and the tumor was radically removed.

Keywords: rare tumors, children, inflammatory myofibroblastic tumor, ALK gene translocation.

Introduction. Inflammatory myofibroblastic tumor (IMT) is a rare tumor with uncertain biological behavior, characterized by heterogeneity both in its histological pattern and in the molecular genetic changes underlying its development [1]. The etiology and pathogenesis of IMT are not fully understood. Several risk factors have been described, including smoking, trauma, and systemic IgG4-associated sclerosing disease, and there are hypotheses suggesting an inadequate immunological response to tissue damage. Human herpes virus type 8 and Epstein-Barr virus are most often considered as etiological agents [6]. The diagnosis of IMT has long been a diagnosis of exclusion, with a broad differential diagnosis ranging from local inflammatory process and idiopathic retroperitoneal fibrosis to inflammatory fibrosarcoma. The identification of ALK gene rearrangements has made a significant contribution to the understanding of the mechanisms of treatment of this rare mesenchymal tumor.

Most often, this disease is described in childhood and adolescence, and is mainly localized in the lungs, abdominal cavity, retroperitoneal space and soft tissues of the pelvis. IMT has the character of local invasive growth, can recur, but rarely metastasizes [2, 3]. The clinical picture depends on the location of the tumor and is often accompanied by general symptoms of inflammation such as fever or malaise. Laboratory manifestations of IMT include leukocytosis, increased levels of acute phase proteins: C-reactive protein, ESR, fibrinogen. The X-ray appearance of IMT is nonspecific and is often interpreted as malignant neoplasms. Histological examination is decisive in making the correct diagnosis [5].

At the molecular level, approximately half of IMTs contain a clonal cytogenetic aberration, a translocation of the ALK gene, which makes it possible to differentiate IMTs from other spindle cell tumors in children and is a target for inoperable and recurrent cases. Radical surgery is the basis in the treatment of IMT [1].

Overall, retrospective studies have shown that IMT has a favorable prognosis. The 5-year event-free survival (EFS) and overall survival (OS) rates are 82.9% and 98.1%, respectively [7].

Purpose of the study: To describe a rare case of inflammatory myofibroblastic tumor in the abdominal cavity in a child.

Materials and methods. A retrospective analysis of the medical records of a patient who was in the oncohematological and surgical departments of the Pediatric center of the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Hospital No. 1- NCM named after M.E. Nikolaev". A full in-depth examination was carried out in the oncohematology department. Laboratory tests (general blood and urine analysis, biochemical blood test, study of the coagulation system) and instrumental studies (ultrasound of the abdominal organs, ECG, computed tomography of the chest and abdominal organs, MRI of the abdominal organs with contrast enhancement) were performed. A histological examination of the surgical material was carried out at the National Medical Research Center for Pediatric Hematology, Oncology and Immunology named after Dmitry Rogachev.

Clinical case. A 6-year-old boy fell ill acutely with an increase in body temperature of 38.50 C. During examination in the Central district hospital, a clinical blood test revealed leukocytosis up to 11 thousand / ml with a neutrophil shift, normochromic anemia with hemoglobin 82 g/l, thrombocytosis 874 thousand / ml , accelerated ESR 60 mm/h. Antibacterial therapy was prescribed in a combination of 2 drugs: cefotaxime 610 mg x 3 times intravenously, amikacin 135 mg x 2 times intravenously and heparin, but there was no effect from the treatment. Due to high fever, increasing hyperfibrinogenemia and ESR, with suspicion of multisystem inflammatory syndrome, he was hospitalized at the Pediatric Center of the SAI of the Republic of Sakha (Yakutia) "Republican Hospital No. 1 – NCM named after M.E. Nikolaev".

Upon admission, the child's condition was serious, due to a fever of 39 C, pronounced pallor of the skin was noted,

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peripheral lymph nodes, liver, and spleen were not enlarged. A mass was palpated from under the left hypochondrium +4 cm. Breathing, hemodynamics, and urination were not impaired. A clinical blood test revealed severe normochromic anemia (HB 60 g/l), leukocytosis 11 thousand/ml with a neutrophil shift, thrombocytosis up to 1000 thousand/ml, accelerated ESR 78 mm/h, hyperfibrinogenemia (12 g/l), increased level of D dimer (3.69 μg/ml) and CRP (236 mg/l). Biochemical blood test and general urinalysis showed no pathology.

For diagnostic purposes, computed tomography of the chest and abdominal cavity was performed. An abdominal mass measuring 3*4.5*7.5 cm was detected, with accumulation of contrast agent. The formation is adjacent to the tail of the pancreas and intestinal loops (Fig. 1).

In the oncohematology department, studies were carried out to determine the extent of the tumor process; no signs of metastasis were identified.

An MRI examination was also performed (Fig. 2).

According to MRI and CT data, it was not possible to determine the organ affiliation, so a laparoscopic biopsy was planned to determine the histological affiliation and revision of the tumor. During a laparoscopic examination of the abdominal cavity, a tumor-like formation was discovered on the upper floor on the left, intimately adjacent to the body of the stomach along the greater curvature and transverse colon, measuring 12x8.0 cm. A consultation was created intraoperatively, and, taking into account the high vascularization of the tumor and the possibility of complete tumor removal, it was decided to switch to an open approach. After triple treatment, a transverse incision was made on the left - laparotomy. The tumor-like formation is dislocated into the wound (Fig. 3).

During revision, the formation is intimately adjacent to the body of the stomach along the greater curvature and transverse colon. Using Ligash's apparatus, the formation was cut off and removed. A biopsy of the lymph nodes of the gastrocolic ligament No. 1 and mesenteric transverse colic ligament No. 2 was taken. The formation and lymph nodes were sent for histological examination to the National Medical Research Center for Pediatric Hematology, Oncology and Immunology named after Dmitry Rogachev.

On the second day after removal of the formation, normalization of temperature, ESR, and a gradual decrease in the level of fibrinogen and CRP, platelets to normal are noted.

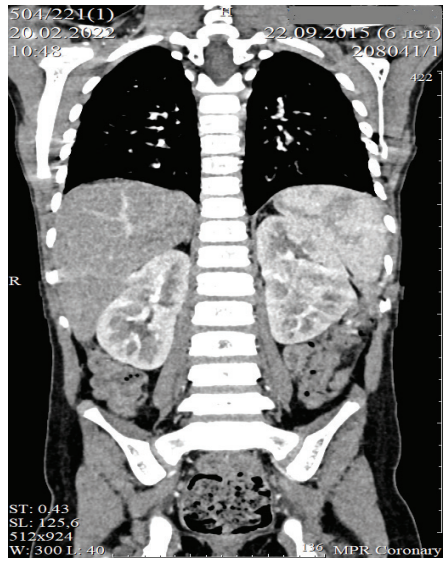

Fig.1. CT scan of the chest and abdomen. Abdominal cavity formation

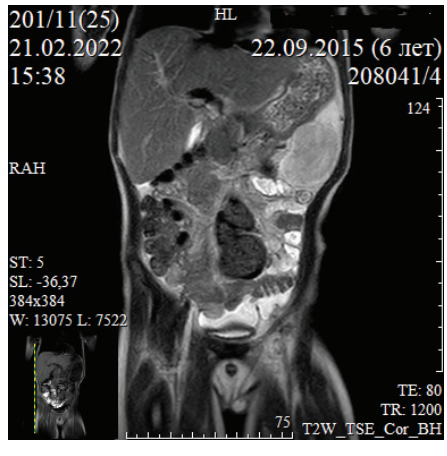

Fig. 2. MRI of the abdominal cavity, formation of the right half of the abdomen

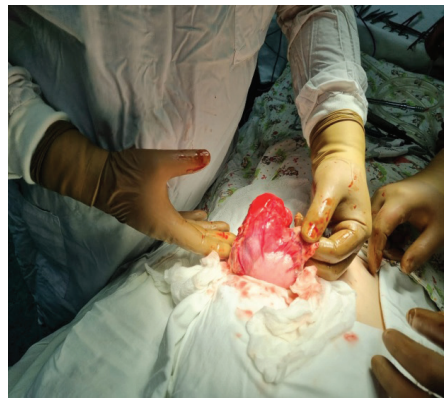

Fig. 3. Photo of the operation: The tumor-like formation is dislocated into the wound

According to histological examination, the tumor is in a thick fibrous capsule, the resection margins are without tumor growth. Neoplastic tissue is represented by long intertwined bundles of medium-sized spindle-shaped cells with a small amount of eosinophilic cytoplasm and ovoid nuclei. The stroma is sclerotic with abundant lymphoplasmacytic infiltration. Expression of SMA, ALKD5F3 was detected. Lymph nodes No. 1, 2 without tumor growth.

The material was further sent for molecular genetic research at the National Medical Research Center of Oncology named after N.N. Petrov". Using reverse transcription PCR and sequencing, unbalanced expression of the ALK gene was revealed, and a chimeric transcript TPM4ex7-ALKex20 was detected. Thus, the child has identified a target for targeted therapy, which can be reserved in case of unresectable relapse of the disease. During the control study, no evidence of tumor recurrence in the child was obtained.

Conclusion. Inflammatory myofibroblastic tumor (IMT) is a rare tumor in children with intermediate biological behavior. The main diagnostic method is histological verification using immunohistochemical methods. The standard of treatment is radical surgical treatment with negative resection margins [4]. If gene expression is present, targeted drugs are used as a second line of therapy or in the case of unresectable tumors.

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