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ORIGINAL RESEARCH

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УДК 796.81.577.161.577.164

L.I. Konstantinova, R.V. Tambovtseva

THIAMINE SUPPLY TO THE FREESTYLE WRESTLERS OF YAKUTIA

The study is devoted to a comparative analysis of the results of thiamine supply to the body of freestyle wrestlers training in the conditions of the North at the age of 18 to 29 years. Vitamins play an important role in ensuring high physical performance of athletes during training and competitions. Insufficient intake of vitamins into the body against the background of intense muscle activity can lead to a relative vitamin imbalance with a subsequent decrease in performance, and excessive uncontrolled intake of vitamins can cause toxic effects.

The assessment of thiamine content in blood serum was carried out by photometric method in all seasons of the year. The analysis of the data obtained showed the dependence of the vitamin B1 level on the season of the year: adequate provision of the body with thiamine was noted in the autumn period of the year in all the athletes studied, the most suboptimal provision of the body with vitamin B1 was observed in the spring season of the year in 55% of wrestlers. When analyzing the actual nutrition, it was revealed that the reason for the optimal provision of the athletes' body with vitamin is its insufficient intake with food. An increase in the vitamin content in the body of athletes should be provided not only by foods rich in thiamine, but also by taking proven vitamin complexes, as well as biologically active additives in which the ratio of vitamins is optimal. Correction in order to prevent hypovitaminosis B1 in the spring in the body of wrestlers by taking a vitamin drink in winter increased its level to 20%.

Keywords: freestyle wrestlers, vitamin availability, hypovitaminosis, thiamine, vitamin B1.

Introduction. The need for vitamins in athletes training in the conditions of the Far North is doubly increased. With excessive physical exertion in extreme climatogeographic conditions, metabolism increases, oxygen consumption increases, which accelerates oxidative processes. In this regard, in addition to a balanced diet and special diets, a constant saturation of the body with vitamins, including thiamine, is required.

Freestyle wrestling is a sport in which there is a high physical and psycho-emotional tension. The athlete is required to tolerate large training and competitive loads, rapid recovery after them. The value of thiamine is that it has a beneficial effect on the nervous system. Vitamin B1 stimulates metabolism, promotes accelerated energy production and rapid growth of muscle tissue [14]. Therefore, maintaining the necessary concentration of this compound in blood and tissues is a prerequisite for the effectiveness of martial arts and the expansion of adaptive potential to extremely high physical and mental loads [3].

Materials and methods of research. The study participants were 38 freestyle wrestlers UOR and SHVSM of Yakutsk, yakut nationality, aged 18 to 29 years. All athletes had high sports qualifications: CMS, MS, MSMC, ZMS. The studies were conducted in all seasons of the year: summer (June), autumn (October), winter (December), spring (March).

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The level of thiamine (vitamin B1) in whole blood taken from the ulnar vein in the morning on an empty stomach, in a state of relative muscle rest, was determined by photometric method on the Fluorat-02-ABLF bio-liquid analyzer of Lumex (St. Petersburg).

To assess the content of vitamin B1 in the diet of the athletes examined by us, the vitamin composition of the daily diet was determined using the questionnaire method of 24-hour nutrition reproduction [5] using the "Table of chemical composition and caloric content of Russian food" [11].

In order to eliminate hypovitaminosis, in the winter period of the year, a study was conducted in which 21 highly qualified freestyle wrestlers of the UOR and SHVSM of Yakutsk took a dietary supplement "Dry mixture with vitamins and minerals" in the form of a drink, 1 time a day after evening training, for 20 days. To prepare the drink, 10 g of a dry mixture containing 0.95 mg of vitamin B1 was diluted in 250 ml of bottled water at room temperature.

Statistical processing of the study results was performed using the SPSS 17.0 software package. The method of descriptive analysis was used to calculate arithmetic averages (M) and mean errors (m). The significance of the differences was assessed using the Student's t-test for independent samples in the case of a normal distribution and Mann-Whitney in the case of deviations from the normal distribution. To identify the relationship between the studied indicators, the method of correlation analysis of data with the calculation of the coefficient and rank correlation of Spearman and Pearson was used. The significance of multiple group differences was revealed using single-factor analysis of variance. The threshold level of significance was taken to be $p<0.05$.

The results of the study. Anthropometric indicators of the athletes studied by us showed that 61% of freestyle wrestlers were short athletes (< 1.67 m), 26% had a height from 1.67 m to 1.79 m and the proportion of tall (> 1.80 m) was 13%. The athletes' body weight ranged from 58.0 to 72.0 kg and averaged 62.5 kg . The average body mass index was 23.7 kg/m2 and ranged from 22.7 to 26.0 kg/m2. The analysis of the obtained data showed that among the wrestlers 13 (34.2%) were overweight.

Analyzing the data we obtained on the vitamin availability of the body of the athletes we examined, it can be noted that the level of vitamin B1 in the blood of freestyle wrestlers depends on the season of the year (Fig. 1).

So, in the summer, the level of thiamine in the blood of most athletes was within the normal range. On average, its blood level was 6.83±0.30 ng/dl with a norm of 5-20 ng/dl [12]. Not optimal security was found only in 5% of the surveyed athletes.

In autumn, all athletes have an adequate supply of thiamine. The content of vitamin B1 in the blood plasma of freestyle wrestlers ranged from 5.00 to 9.04 ng/dl and averaged 7.24±0.39 ng/dl.

In the winter season of the year, there is a decrease in the level of vitamin B1 in the body of athletes compared to the data obtained in the summer and autumn periods. At the same time, this indicator varied from 4.03 to 8.11 ng/dl, the average value was 5.75 ± 0.26 ng/dl. Suboptimal provision of this vitamin was detected in 28% of wrestlers.

In spring, the lowest amount of vitamin

B1 is observed in the blood of athletes. Thus, the average level of thiamine in the blood plasma of athletes ranged from 3.50 to 10.02 ng/dl and amounted to 4.99 ± 0.22 ng/dl. Normal levels of vitamin B1 in the body were observed in 45% of athletes. Hypovitaminosis was detected in 55% of wrestlers, which was 2 times higher compared to the winter period.

Thus, a comparative analysis showed that the content of vitamin B1 in the blood of athletes was optimal only in the autumn period of the year; in summer, winter and spring, hypovitaminosis states were detected in some of the surveyed wrestlers.

The analysis of the daily diet of the studied freestyle wrestlers showed that adequate intake of vitamin B1 with food was noted only in the summer, in other seasons of the year its content in the diet was below normal [7]. The greatest deficit was noted in the winter period of the year, which is 1.9 times less than in the summer season ($p<0.01$) and in the autumn season – 1.7 times less than in the summer season ($p<0.05$) (Fig. 2).

The assessment of the vitamin level in food was carried out by us during the training process, when the athletes were on an organized meal in the SHVSM canteen. However, the competitive training activity of a martial artist has its own specifics. So, during the competitive season, athletes participate in 8-9 competitions and change up to 5 bases per year, where training camps take place with the need for a certain adaptation to the conditions of these bases, in particular to radically different nutrition. For example, the bases may have a restaurant type of food, a buffet, meals in public canteens or self-catering. At the same time, in most cases, the nutrition of highly qualified athletes is controlled not by a nutritionist (there was no full-time position at the time of collecting the material), but only by a coach and a team doctor.

The method of assessing actual nutrition is questionnaire-based, the respondents describe the consumed products for the previous day, which does not guarantee that the respondents fully described all the consumed products. In addition, there were few products containing thiamine in the diet according to the survey over the past 24 hours. In this regard, the data obtained may have an error.

The data obtained by us show that the level of thiamine in the blood of athletes in summer and autumn was within the normal range, since firstly vitamins tend to accumulate in the body, and secondly athletes begin taking multivitamins in autumn with the beginning of the training

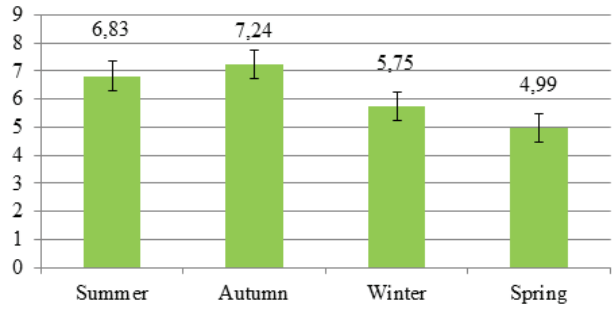

Fig. 1. Vitamin B1 availability of the body of freestyle wrestlers in different seasons of the year (ng/dl)

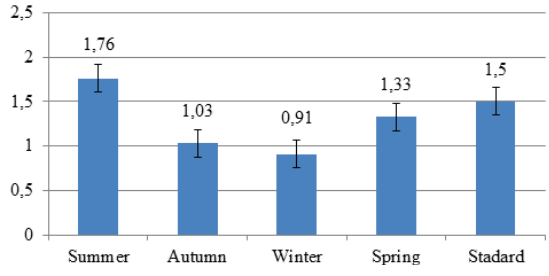

Fig. 2. Vitamin B1 content in the daily diet of freestyle wrestlers (mg)

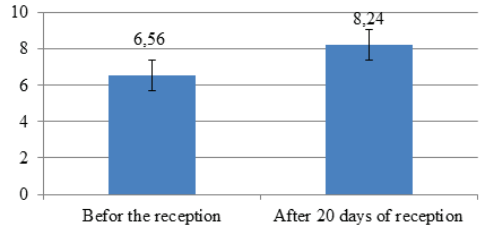

Fig. 3. Vitamin B1 content in the body of freestyle wrestlers before and after taking a vitamin drink (ng /ml)

period. The low content of thiamine in the daily diet of freestyle wrestlers affects the content in the body in winter.

Probably, the reason for thiamine deficiency in freestyle wrestlers training in Yakutia is its accelerated excretion from the body during intense physical exertion and high psychoemotional loads at low temperatures, as well as insufficient intake of this vitamin from food and prevention of the occurrence of hypovitaminosis.

The population of the Far North has an inadequate intake of vitamins. The conditions of hypovitaminosis are especially pronounced in the winter season of the year, which are caused by a lack of vitamin intake from food and an increase in metabolism in a harsh climate [1, 2, 6, 8, 9, 13].

There is information in the literature sources that insufficient provision of vitamin B1 was detected in athletes-rowers in the autumn and winter seasons of the year [10]. Insufficient intake of this vitamin was found in Turkish gymnasts [16] and in young athletes of both sexes [15, 18, 21]. Sufficient intake of vitamin B1 was observed in gymnasts of France and the USA [17, 19] and women engaged in judo [20].

Based on the data obtained, in order to prevent the development of hypovitaminosis B1 in the spring, we carried out a correction in winter [4]. The average level of vitamin B1 in the blood of athletes before taking the vitamin drink was within the normal range (5-20 ng/ml) and amounted to 6.56 ng/ml, and by the end of the 20-day course, the concentration of vitamin B1 in the blood of athletes increased by 20% compared with the value before taking the drink and amounted to 8.24 ng/ml ($p<0.05$) (Fig. 3).

Thus, a 20-day intake of a vitamin drink significantly ($p<0.05$) increases the level of thiamine in the blood of athletes, cases of hypovitaminosis B1 were not noted.

Conclusion. Thus, the assessment of the thiamine supply of the body of freestyle wrestlers of Yakutia showed that the vitamin level depends not only on the season of the year, but also on the vitamin content in the daily diet. Seasonal suboptimal provision of vitamin B1 in the body of freestyle wrestlers was noted:

the most suboptimal provision of vitamin B1 in the body of wrestlers was observed in the spring season of the year in 55%. A positive correlation was revealed between the concentration of vitamin B1 ($r=0.457$, $p<0.000$) in the blood of athletes with the intake of vitamin B1 with nutrition ($r=0.310$, $p<0.018$). When analyzing the actual nutrition, it was revealed that inadequate intake of vitamins from food was the cause of hypovitaminosis in the body of the freestyle wrestlers examined by us. Vitamin deficiency in the body of wrestlers is also caused by accelerated excretion during intense physical exertion and high psychoemotional loads and high psychoemotional loads in the conditions of the North and the lack of measures to prevent the occurrence of hypovitaminosis B1. To prevent vitamin B1 hypovitaminosis in athletes in the spring, it is necessary to begin correction in winter, since the decrease in its level begins in winter.

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N.A. Bebyakova, A.A. Kuba, N.A. Fadeeva, A.V. Khromova

INTERACTION OF OESTRADIOL AND VASOACTIVE FACTORS IN WOMEN WITH rs 2070744 POLYMORPHISM OF ENDOTHELIAL NO-SYNTHASE GENE

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The aim of this study is the identification of interaction of oestradiol and vasoactive endothelial factors in women with polymorphism T-786C of endothelial nitric oxide synthase (eNOS) gene during follicular and luteal phase of the menstrual cycle. Sample size was 116 women with average age 19,6 years (95% CI 18,4 – 22,4), being born and living in the circumpolar region. Genotyping of T-786C polymorphism of eNOS gene was performed by pyrosequencing. The peripheral vascular tone was evaluated by tetrapolar reography. Concentration of nitric oxide (NO) was measured by Griss reaction. The level of oestradiol and endothelin-1 (ET-1) was measured by ELISA (enzyme-linked immunosorbent assay). Index ratio vasodilator to vasoconstrictor was calculated (NO/ET-1). «SPSS statistics» (StatSoft, USA) was used for statistical analyses. Our study found that the frequency of T allele was 0,67, C allele – 0,33 and C/C genotype was the rarest. The highest concentration of NO was found in women with C/C genotype during follicular phase. The concentration of NO in luteal phase in women with different genotypes of *eNOS* gene was similar. The level of ET-1 in women with T/T and C/T genotypes was normal during follicular and luteal phase, but in women with C/C genotype the level of ET-1 was above the normal reference range during follicular and luteal phase. The study of peripheral vascular tone found that C/C genotype was correlated with higher level of index of peripheral resistance (IPR) during follicular phase after dosed physical test, higher level of IPR was before and after dosed physical testduring luteal phase. The concentration of oestradiol in women with T/T and C/T genotypes was higher during luteal phase, in women with C/C genotype the level of oestradiol was higher in follicular phase. Correlation analysis between oestradiol and NO determined the moderate correlation (r=0,302; p=0,05) in C/T genotype, the strong positive association in C/C genotype during follicular phase (r=0,755, p=0,03) and luteal phase, and no association in T/T genotype. Thus, it was revealed that the presence of both mutant alleles C was correlated with imbalance of vasoactive factors (higher level of vasoconstrictors), leading to higher vascular peripheral tone. Also it was found that the association between oestradiol and NO manifested only in case of presence of mutant allele C of polymorphism T-786C gene of *eNOS* in genotype, that can approve protective function of oestradiol in relation to NO synthesis and can be confirmed by higher level of NO in women with C/C genotype during follicular phase of cycle.

Keywords: oestradiol, nitric oxide, endotheline-1, polymorphism T-786C gene of *eNOS*.

Introduction. Nowadays genetic predictors of cardiovascular pathologic processes, including endothelial disfunction (ED),are widely studied.ED is accompanied by decrease of nitric oxide (NO) synthesis and active local synthesis of ET-1 [1, 17]. Endothelial nitric oxide synthase (*eNOS*) is the endothelial isoform of NOS, which regulates synthesis of NO in endothelium cellsand is encoded by *eNOS* gene [4]. Some single nucleotide polymorphisms of *eNOS* gene were identified, for example T-786C polymorphism which plays a specific role in the development of ED [5, 7, 8].

Expression of eNOS gene is controlled by different factors, including estrogens. In women estrogens increase the concentration of NO in blood by means of genomic and non-genomic mechanisms of expression [9, 10, 13, 14].

It was established that concentration of estrogens influences on endothelium-related vasodilatation in women [6]. Most studies about mechanisms of ED leading to cardiovascular diseases are performed in menopausal and postmenopausal women with different pathological conditions, chronic endocrine disorders, diseases of reproductive system, in women taking modern medication [2, 3].So the association between women sex hormones and vasoactive endothelial factors in healthy women of reproductive age without confirmed cardiovascular pathology with polymorphism of *eNOS* gene is not studied.

Aim: to determine the association between oestradiol and vasoactive factors (NO and ET-1) in women with T-786C (rs 2070744) polymorphism of *eNOS* during follicular and luteal phase of menstrual period.

Materials and methods: Sample size was 116 women with average age 19,6 years (95% CI 18,4 – 22,4), being born and living in the circumpolar region. Criteria for including: women with constant regular ovulatory cycle(measured by rectal temperature). Criteria for excluding: women with acute and chronic diseases, with hormone therapy [11].Examination was carried out on 5-7 day (follicular phase) and on 19-21 day (luteal phase) of cycle.

The study was approved by ethics committee of Northern State Medical University, Arkhangelsk city. All examined participants were students of this university.

Genotyping of T-786C polymorphism of *eNOS* gene was performed by pyrosequencing (Russia, ApmliSens, *"Тоноскрин"* "Arterial hypertension" kit). Hemodynamic examination was carried out on empty stomachon mornings, dosed physical test (the Martin-Kushelevsky test) was used for estimation of cardiovascular system. Evaluation of peripheral vascular tone was performed by means of tetrapolar reography with calculating index of peripheral resistance (IPR). The concentration of serum NO was measured by Griss reaction (USA, «R&D Systems, kit «Total NO/Nitrite/Nitrate»). Serum oestradiol level was measured by enzyme-linked immunosorbent assay (Russia, "Вектор-Бест"). Serum ET-1 level was evaluated beenzyme-linked immunosorbent assay (Austria, "BIOMEDICA GRUPPE"). Index

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Oestradiol and vasoactive endothelial factors in women with polymorphism T-786C (rs 2070744) *eNOS* gene depending on menstrual phase. Medianvalues (Q1;Q3)

Genotypes	Phase					
	Follicular phase			Luteal phase		
	T/T	C/T	C/C	T/T	C/T	C/C
NO.mcmol/l	13.713* (11.706;15.719)	15.53▲ (13.97;17.098)	18.239*▲ (13.21;23.262)	16.804 (12.148;21.459)	16.470 (14.709;18.231)	15.582 (12.386;18.77)
ET-1. fmol/ml	0.62* (0.362;1.00)	0.84▲ (0.39;1.66)	1.24*▲ (0.28; 2.670)	1.227* (0.726;1.728)	0.987▲ (0.758;1.217)	2.51*▲ (0.160;4.87)
NO/ ET-1	22.476 (13.11;28.01)	19.063 (14.40;25.22)	14.84 (8.49;25.412)	19.49 (13.66;25.33)	21.77 (16.96;26.57)	11.15 (6.15;16.15)
Oestradiol. nmol/l	0.218 (0.208;0.228)	0.268 (0.234;0.303)	0.341** (0.13;0.543)	0.308 (0.252;0.364)	0.362 (0.288;0.437)	0.269* (0.166;0.37)

Comments. Significant differences ($p<0.05$): ** - for C/C genotype in follicular and luteal phase; * - between C/C and T/T genotypes; ▲ – between C/C and C/T genotypes.

ratio vasodilator NO to vasoconstrictor ET-1 was calculated (concentration NO/ concentration ET-1). «SPSS statistics» (StatSoft, USA) was used for statistical analyses.

Results and discussion. All alleles and all genotypes of T-786C polymorphism were determined and were not deviated from Hardy-Weinberg Equilibrium. Our study showed that the frequency of T allele was 0,67, C allele – 0,33 and C/C genotype was the rarest. This frequency of alleles and genotypes of T-786C polymorphism of *eNOS* gene is similar to frequency in European population [TheAl. Lete FRE quency Database, 2021, http://alfred.med.yale/edu].

According to literature C allele is associated with low level of NO, but this study demonstrated that higher level of NO was determined in C/C women during follicular phase in comparison with T/T and C/T women. NO level had no significant difference in women with different genotypes of T-786C polymorphism during luteal phase (Table 1).

The level of ET-1 in women with T/T and C/T genotypes was normal during follicular and luteal phase, but in women with C/C genotype the level of ET-1 was higher than the normal reference range during follicular and luteal phase (more than 2,5 times) (Table 1). High level of ET-1 is the factor of imbalance of vasoactive endothelial factors which is confirmed by low index NO/ET-1 in women with C/C genotype. IPR before and after physical test in T/T and C/T women was normal during follicular and luteal phase, IPR in C/C women was above reference interval after physical test during follicular phase and after and before physical test during luteal phase. Probably imbalance of endothelial factors in these women can explain high level of IPR during luteal phase.

The concentration of oestradiol in women with T/T and C/T genotypes was higher during luteal phase, in women with C/C genotype the level of oestradiol was higher in follicular phase compared with luteal phase (Table 1).Correlation analysis between oestradiol and NO level showed absence of significant difference in women with T/T genotype, moderate correlation in C/T genotype during follicular phase (r=0,302; p=0,05) and luteal phase and the strong positive association in case of C/C genotype (r=0,755, p=0,03).

It was demonstrated that allele C in genotype leaded to lower NO levelin comparing with women with T/T and C/T genotype [15]. But our study showed that the highest NO level was determined in C/C women during follicular phase in comparing with women with C/T and T/T genotypes. Apparently it is associated with compensatory function of oestradiol which increases NO level by means of activation *eNOS* by direct phosphorylation of estrogen receptors and subsequent transport of signal through protein kinase cascades, which activates eNOS [12, 16]. Also the genomic way can increase the expression of *eNOS* gene.

So in this study it was determined that the association between oestradiol and NO level appears only on presence of C allele of T-786C polymorphism. The absence of this association in women with T/T genotype, moderate correlation in C/T women and strong correlation in C/C women supports the hypothesis.

Conclusions:

1. The spread of alleles and genotypes of T-786C polymorphism of *eNOS* gene in circumpolar-women is similar to European population. The frequency of T allele was 0,67, C allele – 0,33 and C/C genotype was the rarest.

2. Peripheral vascular tone in women with C/C genotype was above normal value after dosed physical testduring follicular phase, during luteal phase - before and after dosed physical test. Women with T/T and C/T genotypes had normal value of vascular tone during follicular and luteal phase.

3. C/C genotype was correlated with higher NO level during follicular phase and with imbalance of vasoactive endothelial factors (prevalence of vasoconstrictors during both phases of cycle).

4. Correlation analysis between oestradiol and NO level showed moderate correlation in women with C/T genotype and positive association in women with C/C genotype, which demonstrates the positive influence of oestradiol to production of NO.

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FEATURES OF ANEMIA IN PREGNANT WOMEN OF VARIOUS GENESIS IN ETHNIC SAMPLES

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Objective of the Study: to determine in different ethnic samples of pregnant women with anemia of various genesis the factors influencing on its development; perinatal outcomes in anemia of various genesis; features of the production of pro- and antioxidant blood factors.

Material and methods

A prospective cohort study of pregnant women with IDA and ACD was carried out in various ethnic samples. In the Republic of Dagestan, the sample with anemia consisted of 470 women: with IDA (n = 286) and ACD (n = 184). In the sample of pregnant women with anemia in the Republic of Sakha (Yakutia) (n = 284) we also distinguished groups with IDA (n = 186) and ACD (n=98). The control group - 34 healthy pregnant women in the Dagestan population and 42 - in the Yakut one was introduced into the study to compare the indicators in the study of pro- and antioxidant factors.

Research methods included the assessment of a general blood test, serum iron (SI), C-reactive protein (CRP), ferritin, total protein, pro- and antioxidant factors (erythrocyte and blood serum catalase, sulfhydryl groups (SH-groups), ceruloplasmin (CP) and malondialdehyde (MDA) in blood serum), the level of IgG to parasitic infections.

Results

The study showed a variety of risk factors and conditions contributing to the development of anemia on the background of lower iron and lower hemoglobin concentration in various ethnic samples (ecological, biological and social biotopes). True ID was confirmed at low levels of ferritin (100.0%) and serum iron.

Inflammatory diseases of the pelvic organs were twice as common in women with ACD than IDA ($p < 0.05$).

Iron limiting participation for erythropoiesis in ACD was accompanied by an increase (85.6%) or normal serum ferritin level (14.4%), increase in the level of CRP (100,0%), lymphocytes (29.3%), monocytes (22.8%), blood sedimentation rate (ESR)(14.7%).

Pregnant women with true ID were characterized by a balanced increase in the level of pro- and antioxidant factors.

Iron metabolism violations in ACD were accompanied by a pronounced imbalance in the production of hydroperoxides and antioxidant protection factors.

The effect of excess lipid peroxidation products on the placenta in ACD in the Yakut population was accompanied by an evolutionarily accumulated level of endogenous antioxidants (blood plasma and erythrocyte catalase, sulfhydryl groups). A decrease in the compensatory mechanisms of the placenta of pregnant Dagestan women with ACD influenced the higher frequency of morphological and functional immaturity of newborns due to the moderate antioxidant potential. Morphofunctional immaturity of newborns (MFI) in the group with ACD was detected one and

a half times more often in the Dagestan population (p = 0.0005) than in the Yakut population (p = 0.04). Cerebral ischemia was more common among newborns from mothers with ACD – 1.8 times (p = 0.002) and 1.7 times (p = 0.04) than those with IDA in the sample of Dagestan and Yakut women, respectively.

Conclusion. It is shown necessity of correction of risk factors of anemia of different genesis at the preconception stage (replenishment of ID, essential micronutrients, treatment of infections and inflammatory diseases) to improve the hematological status of the mother and pregnancy outcomes.

The nature of placental dysfunction in anaemia of pregnant women is explained by the degree of severity of oxidative stress and the activity of compensatory-adaptive mechanisms. Iron metabolism violation in ACD is accompanied by excessive production of hydroperoxides, a certain decrease in the antioxidant potential in the Dagestan population in comparison with the Yakut population.

Anemia in the population of the Far North proceeds on the background of evolutionary adaptive and homeostatic physiological characteristics of the organism. The increased risk of adverse pregnancy outcomes (low birth weight, cerebral ischemia) was more common in women with ACD.

Key words: iron deficiency, anemia of chronic diseases, ferritin, oxidative cell stress, antioxidant activity

Introduction. According to the WHO, anemia affects about a third of the world's population and more than 800 million women and children, including 38% of all pregnant women [22]. Reducing anemia in women of reproductive age by 50% by 2025 is one of the global nutrition goals [24].

It is reported that the peculiarities of iron metabolism in pregnant women may be due to ethnic and ecological disunity, genetic characteristics of ethnic groups, place of residence and socio-economic factors [17].

The combination of maladaptive reactions from various body systems results in the development of the polar stress syndrome in conditions of the Far North [11].

The development of IDA in the regions of our country is associated with the deterioration of the socio-economic situation, national habits of the population in nutrition, the provision of essential micronutrients, including iron [9].

The study confirms the role of environmental factors in the genesis of IDA, which determine the level of iron in the composition of soil, drinking water, plant and animal products [2,9,10].

The role of social factors in the genesis of IDA is performed by the nutritional traditions of national groups (isomerism, deficiency of protein, iron and other microelements in the diet, mainly carbohydrate foods) [9]. The modern population of Yakutia is distinguished by a carbohydrate-lipid diet (excessive consumption of bread, sugar, confectionery), an excess of protein and fatty foods in the diet was found only in distant uluses [5].

The consequences of maternal anemia (low birth weight, premature birth, unfavorable perinatal outcomes), proved in studies, negatively affect the gene pool of small ethnic groups [21].

The concept of complex iron homeostasis allows us to distinguish anemia of chronic diseases (ACD) associated with impaired proliferation of erythroid precursors on the background of an infectious, inflammatory or autoimmune process and urogenital diseases [16,17]. The development of anemia on the parasitic invasions background is explained by the fact that the republics of Sakha (Yakutia) and Dagestan belong to the zones of natural focal biohelminthiasis [20]. Exceeding the average rate of parasitic diseases, among which the most common are opisthorchiasis, diphyllobothriasis, echinococcosis, was registered in 17 territories of the Republic of Sakha (Yakutia). Parasitoses transmitted through fish, crustaceans, molluscs, amphibians, reptiles and their products remain an important problem. The social prerequisites for the incidence of parasitosis in the population are the hygienic skills of the population (household and behavioral), an increase in the amount of fish and homemade fish products in the diet of the population of coastal cities and villages [8]. Due to the favorable natural and climatic conditions of the lowland and foothill zones, the Republic of Dagestan belongs to the regions with a high incidence of ascariasis (in some areas the indicators exceed the national average by several times) and trichocephalosis [1].

The mechanisms of the ID influence on the body of a pregnant woman and a fetus are different depending on the genesis of anemia. ACD is associated with oxidative stress in erythrocytes, damage to the structure of proteins, carbohydrates, fats, and DNA [12].

The study of the features of iron homeostasis and factors influencing the development of anemia in ethnically different samples is promising from the standpoint of understanding the relationship between perinatal risks and the activity of compensatory-adaptive mechanisms of the pregnant organism.

The objective of the study: to determine in different ethnic samples of pregnant women with anemia of various genesis the factors influencing on its development; perinatal outcomes in anemia of various genesis; features of the production of pro- and antioxidant blood factors.

Material and methods. A prospective cohort study of pregnant women with IDA and ACD was carried out in various ethnic samples. In the Republic of Dagestan, the sample with anemia consisted of 470 women (avarkas, кumychkas, darginkas, lezginkas, lachkas): with IDA (n = 286) and ACD (n = 184). In the sample of pregnant women (yakuts, evenks) with anemia in the Republic of Sakha (Yakutia) (n = 284) we also distinguished groups with IDA (n = 186) and ACD (n=98). The control group - 34 healthy pregnant women in the Dagestan population and 42 - in the Yakut one was introduced into the study to compare the indicators in the study of pro- and antioxidant factors (146 women with IDA and 82 – ACD in each sample).

Inclusion criteria: pregnant women with anemia confirmed by specialists before pregnancy (IDA and ACD), singleton progressive pregnancy. Exclusion criteria: anemia of other types.

The study was conducted with the voluntary informed consent of the participants. The study took into account the provisions of the Helsinki Declaration of the World Medical Association (revised 2008) and the document "International Ethical Guidelines for Biomedical Research with human participation".

Research methods included the assessment of a general blood test, serum iron (SI), C-reactive protein (CRP), ferritin, total protein, pro- and antioxidant factors (erythrocyte and blood serum catalase, sulfhydryl groups (SH-groups), ceruloplasmin (CP) and malondialdehyde (MDA) in blood serum), the level of IgG to zoonotic infections.

The diagnosis of anemia was made on the basis of hemogram indicators (decrease in Hb <110 g/l), iron status (decrease in serum ferritin less than 15 mcg/l among IDA patients). ACD was diagnosed with an increase in C-reactive protein (CRP)) on the background of normal or increased ferritin levels.

In pregnant women with ACD, the level of IgG to echinococcus, trichinella, toxocara and ascaris was determined using test systems by the enzyme-linked immunosorbent assay (ELISA) with the help of standard kits

from "DRG diagnostics" (Germany).

Laboratory tests were carried out at 16-20 weeks of pregnancy.

All pregnant women with anemia were recommended to take preparations containing iron, folic acid (400-800 mg per day), macro- and micronutrients.

Statistical data was processed using the Statistica 10 software package (manufactured by StatSoft Inc., USA), SPSS 12.0. The Mann-Whitney test was used to compare the two independent variables. Significance level (p) when testing statistical hypotheses was taken ($p \leq 0.05$). The data in the text is partially presented as the arithmetic mean and its standard deviation (M ± σ). Student's and Kruskal-Wallis tests were applied. The analysis of intergroup differences in terms of qualitative characteristics was carried out using the $\chi 2$ test (chi-square), less than five – the exact two-sided Fisher test.

Results and discussion. The average age of pregnant women with ACD was 26.8 ± 3.2 years, IDA – 27.3 ± 4.1 years, without significant intergroup differences.

The geographical distribution of pregnant women in different zones influenced the nature of anemia. The number of Dagestani women living on the flat territory of the republic was 68.0% (40.6% with IDA and 59.4% with ACD), on the foothills – 32.0% (65.3% with IDA, 34.7% with ACD) ($p = 0.00$, $\chi 2 = 24.1$).

The study of the premorbid background showed a higher incidence of chronic infectious and inflammatory diseases in both samples in comparison with IDA (Table 1).

Respiratory diseases were noted three times more often in the Dagestan sample ($p = 0.0005$, $\chi 2 = 25.8$), twice more often in the Yakut sample ($p = 0.007$, $\chi 2 = 7.9$), kidney disease – two and a half times ($p = 0.0005$, $\chi 2 = 29.6$) and twice ($p = 0.0003$, $\chi 2 = 14.2$), respectively, sinusitis – 2.6 times ($p = 0.002$, $\chi 2 = 10.0$) and twice ($p = 0.02$, $\chi 2 = 5.5$), respectively, diseases of the upper respiratory tract (pharyngitis, rhinitis) – three times ($p = 0.0005$, $\chi 2 = 38.4$) and two and a half times ($p = 0.00$, $\chi 2 = 22.4$), respectively. More than half of pregnant women with anemia had inflammatory diseases of the female pelvic organs – twice more often in the group with ACD than IDA ($p < 0.05$). When diagnosing parasitic invasions in ACD, enzyme-linked immunosorbent markers were detected in 5.9% of Dagestani women and 9.2% of Yakutia residents.

The diet of the indigenous inhabitants of Yakutia with antibodies to zoonotic infections (echinococcus – 2.0%, Trichinella – 2.0%, toxocara – 2.0%, ascaris – 3.1%) included the consumption of raw meat and fish, the presence of domestic animals and cattle. Pregnant women who were seropositive for parasitic infestations were more common among the rural population, and there were more Yakuts than Dagestanis. The reasons for the infection are non-compliance with the keeping of domestic animals, the consumption of raw meat and fish by the local population of Yakutia, and unsatisfactory processing of vegetables and fruits. The consumption of raw fish remains highly frequent despite the awareness of personal and community prevention measures for helminthiasis. Seropositive reactions for ascariasis are associated with the use of fruits and vegetables contaminated with helminth eggs.

The consumption of macronutrients in the recommended amount for pregnant women was the following: protein – in 19.6% of Dagestani women and 22.9% of Yakut women, fats – 33.8% and 35.6%, respectively, carbohydrates – 34.2% and 38.4%, respectively. Unbalanced nutrition (preference for pasta and bakery products on the background of a deficiency of animal protein, vegetables, fruits and dairy products) forms an insufficient energy value of the diet, vitamins and microelements. The diet of the inhabitants of the northern uluses consists mainly of fishing and hunting products, with a significant shortage of fruits, vegetables and greens.

The delivery time of pregnant women with anemia (17.8% in the Dagestan population and 25.9% in the Yakut population) and the frequency of caesarean section (12.8% and 14.1%, respectively) did not differ between groups. The weight of newborns was lower in the group with ACD than IDA (2850 ± 140 g/l vs 2970 ± 280 g/l in Dagestani women), however, ethnic features of the skeletal structure explain the smaller parameters of children in the Yakut population (2760 ± 160 g/l vs 2850 ± 130 g/l ($p = 0.0005$).

The nature of chronic hypoxia (hemic, circulatory and tissue) and the degree of compensatory-adaptive mechanisms in pregnant women with anemia influenced the adaptation of the newborn to extrauterine conditions of existence (Table 2).

8.6% of children in the Dagestan and 12.9% in the Yakut population had a short gestational period at birth, malnutrition was detected in the group with ACD ($p < 0.05$). Infectious and inflammatory diseases of newborns (omphalitis, conjunctivitis, dacryocystitis, vesiculopustulosis) in the groups with ACD were determined by the high infectious potential of mothers. Signs of morphological and functional immaturity of newborns (MFI) in the group with ACD were detected one and a half times more often in the Dagestan population ($p = 0.0005$, $\chi 2 = 18.8$) than in the Yakut population ($p = 0.04$, $\chi 2 = 4.2$). Cerebral ischemia was more common among newborns from mothers with ACD – 1.8 times ($p = 0.002$, $\chi 2 = 11.0$) and 1.7 times ($p = 0.04$, $\chi 2 = 4.9$) than those with IDA in the sample of Dagestan and Yakut women, respectively.

Features of iron metabolism and hemograms of pregnant women with anemia are presented in Table 3.

True ID was confirmed at low levels of ferritin (100.0%) and serum iron (8.2 ± 2.6 mmol/l). Iron sequestration in macrophages in chronic infectious and inflammatory diseases was accompanied by an increase in CRP and / or a shift in the leukocyte formula, an increase in ferritin (85.6%) or its normative values (14.4%). Pregnant women with ACD had a more pronounced total protein deficiency.

The results of the study of the oxidant blood profile of pregnant women with anemia of various origins are presented in Table 4.

A decrease in erythropoiesis in ACD was accompanied by a pronounced imbalance in the production of hydroperoxides and antioxidant protection factors (catalase of blood plasma, erythrocytes, sulfhydryl groups). Pregnant women with true ID were distinguished by a balanced increase in the level of pro- and antioxidant factors. The content of ceruloplasmin turned out to be statistically significantly higher in ACD than in the group with IDA only in women from Yakutia ($p = 0.01$). The concept of severe damage to placental tissues in pregnant women with ACD in the Dagestan sample was based on excessive MDA (malondialdehyde) production with a moderate antioxidant potential of blood serum (catalase of plasma, erythrocytes, sulfhydryl groups).

Our research has shown the influence of a combination of factors on the development of anemia in pregnant women – the environment (ecological biotope), biological and social [18].

The impact of low temperatures in the Republic of Sakha determines the great need of the body for iron due to

Table 1

Chronic diseases of pregnant women with anemia of various origins

Parameters	Iron- deficiency anemia (IDA) (n=286)	Anemia of chronic diseases (ACD) (n=184)	p, χ^2	Iron- deficiency anemia (IDA) (n=186)	Anemia of chronic diseases (ACD) (n=98)	p, χ^2
	Dagestani women			Yakut women		
Sinusitis	16 (5.6)	27 (14.7)	0.002 (10.0)	22 (11.8)	22 (22.4)	0.02 (5.5)
Rhinitis, nasopharyngitis and pharyngitis	33 (11.5)	66(35.9)	0.0005 (38.4)	33 (17.7)	43 (43.9)	0.00 (22.4)
Respiratory diseases	21 (7.3)	45 (24.4)	0.0005 (25.8)	23 (12.4)	25 (25.5)	0.007 (7.9)
Kidney diseases	41 (14.3)	67 (36.4)	0.0005 (29.6)	40 (21.5)	42 (42.9)	0.0003 (14.2)
Inflammatory diseases of the female pelvic organs	78 (27.4)	99 (53.8)	0.0005 (32.4)	61 (32.8)	64 (65.3)	0.00 (27.5)
Parasitic invasions (total)	-	11 (5.9)		-	9 (9.2)	
Trichinosis	-	-		-	2 (2.0)	
Toxocariasis	-	3 (1.6)		-	2 (2.0)	
Echinococcosis	-	-		-	2 (2.0)	
Ascariasis	-	8 (4.3)		-	3 (3.1)	

Table 2

Morbidity of newborn in groups of women with anemia of various origins

Parameters	Iron-deficiency anemia (IDA) (n=286)	Anemia of chronic diseases (ACD) (n=184)	p, χ^2	Iron-deficiency anemia (IDA) (n=186)	Anemia of chronic diseases (ACD) (n=98)	p, χ^2
	Dagestani women			Yakut women		
Hypotrophy of newborn	59 (20.6)	49 (26.6)	0.2	30 (30.6)	23 (23.5)	0.15
Infectious and inflammatory diseases	14 (4.9)	27 (14.7)	0.001 (12.2)	7 (3.8)	13 (13.3)	0.006 (8.8)
Morphofunctional dismaturity of newborn	47 (16.4)	63 (34.2)	0.0005 (18.8)	36 (19.4)	22 (22.4)	0.54 for ACD – 0.04 (4.2)
Cerebral ischemia of newborn	51 (17.8)	58 (31.5)	0.002 (11.0)	29 (15.6)	26 (26.5)	0.04 (4.9)
Premature newborns	18 (6.3)	20 (10.9)	0.1	16 (8.6)	17 (17.3)	0.03 (4.8)

Table 3

Laboratory parameters of pregnant women with anemia of various origins

Parameters	Iron-deficiency anemia (IDA) (n=286)	Anemia of chronic diseases (ACD) (n=184)	p, χ^2	Iron-deficiency anemia (IDA) (n=186)	Anemia of chronic diseases (ACD) (n=98)	p, χ^2
	Dagestani women			Yakut women		
Decrease in ferritin, mcg/l	286 (100)	0	-	186 (100)	0	-
Normal ferritin level, mcg/l	0	34 (18.5)	-	0	10 (10.2)	-
Increase in ferritin level, mcg/l	0	150 (81.5)	-	0	88 (89.8)	-
C-reactive protein, mg/l	0	184 (100.0)	-	0	87 (88.8)	-
Lymphocytosis, %	28 (9.8)	54 (29.3)	0.0005 (28.4)	12 (6.5)	33 (33.7)	0.00 (35.7)
Monocytosis, %	23 (8.0)	42 (22.8)	0.0005 (19.3)	11 (5.9)	11 (11.2)	0.16
Increase in ESR, mm/h	13 (4.5)	27 (14.7)	0.0009 (13.5)	12 (6.5)	22 (22.4)	0.00 (15.6)
Serum iron, mmol/l	7.8±2.6	8.1±2.3	0.9	6.8±1.7	9.4±1.2	0.2
Total protein, g/l	74.6±4.2	69.4±5.3	0.44	70.6±3.8	65.4±4.2	0.35

Table 4

Pro- and antioxidant factors in samples of pregnant women with anemia of various origins

Parameters	Iron-deficiency anemia (IDA) (n=146)	Anemia of chronic diseases (ACD) (n=82)	Healthy pregnant women (n=34)	p_{1-2}	Iron-deficiency anemia (IDA) (n=146)	Anemia of chronic diseases (ACD) (n=82)	Healthy pregnant women (n=42)	p_{1-2}
	Dagestani women				Yakut women			
Malon dialdehyde, mmol/l	1.3±0.1	1.7±0.1	1.2±0.4	0.005	1,5±0,1	2,0±0,1	1,4±0,6	0,00
Erythrocyte catalase, mcat/l	87.4±2.7	74.9±1.4	74.7±0.9	0.001	1.4±0.6	87,4±2,7	72,4±1,1	0,00
Serum catalase, mcat/l	29.6±2.4	14.8±1.5	15.7±0.5	0.001	0.001	24,2±1,7	17,5±0,3	0,01
Ceruloplasmin, mg/l	369.8±12.5	406.3±14.1	366.9± 13.5	p>0.05	388.5±10.6	414.3±10.6	356.4±9.2	0.01
SH-groups, mmol /l	17.2±1.3	13.3±0.4	12.4±0.4	0.01	16.5±0.5	19.2±1.3	14.4±0.4	0.00

the adaptive activation of the basal metabolism, revealed in the Eskimos, Yakuts, Evens and Chukchi [3]. Probably, the imbalance of the processes of anabolism and catabolism in the indigenous population of Yakutia is the reason for the development of acclimatization ID.

Climatic and geographic conditions of Dagestani women with low oxygen content in the air (in the mountains) are accompanied by a compensatory increase in the number of erythrocytes. Physiological needs for hemoglobin in people living at high altitudes increase on the background of low oxygen concentration in the atmosphere [13]. A study in Myanmar showed a lower possibility of anemia among women living in hilly areas compared to other areas of the country [23].

The effect of the environmental factor was found by us in the Dagestan population: the severity of anemia prevailed in urban women in comparison with rural ones, in residents of flat areas in comparison with those living in mountain villages.

It seems that the influence of environmental factors on microelement disorders and the functional activity of the erythroid blood germ is integral.

We have confirmed the connection between the mother's unsatisfactory nutrition and the formation of antenatal and perinatal risk factors. The lack of animal protein, vegetables, fruits and berries in the diet of pregnant women is associated with a low educational level of mothers who are not sufficiently informed about the needs of expectant mothers.

The development of anemia in pregnant women of the Far North was facilitated by an unbalanced diet, with an increase in the proportion of carbohydrates (refined sugar and starch) and a decrease in animal protein.

The development of ACD on the parasitic invasions background determined the living conditions and eating habits of women of various ethnic groups [17].

The reasons for the infection are non-compliance with the keeping of domestic animals, the consumption of raw meat and fish by the local population of Yakutia, and unsatisfactory processing of vegetables and fruits.

The study of the premorbid background of pregnant women with anemia confirms the need to identify and eliminate controllable risk factors for pregnancy complications.

Identification of biomarkers of inflammation in pregnant women with anemia (acute phase reactions of inflammation, increased C-reactive protein (CRP)) on the background of normal or increased ferritin levels allows to diagnose the development of ACD [15]. The effect of inflammatory processes on the reduction of hemoglobin concentration was noted in a recent BRINDA study [16].

The high perinatal morbidity in women with anemia should be considered as a consequence of the angiopathy of the uterine vessels formed before pregnancy [14].

The consequences of chronic hypoxia were more pronounced in pregnant women with ACD, more significant violations of the molecular mechanisms of protein biosynthesis in whom, in comparison with IDA, determined a more frequent morbidity in newborns [19]. The anthropometric characteristics of the children of the indigenous population of Yakutia, corresponding to the lower centile boundaries of the standards, explain their low weight in the presence of ACD in mothers [4].

A number of physiological changes, called an adaptive shift, in the indigenous inhabitants of Yakutia is accompanied by the activation of peroxide processes in conditions of increased consumption of energy reserves and an increase in the rate of basal metabolism [3]. The excessive LPO activity in the indigenous and newcomer population of the Far North in comparison with the middle latitudes is compensated by a sufficient level of endogenous antioxidants developed by generations of aborigines [6]. The nature of biochemical changes in all pregnant women with ACD exceeds the “adaptive Arctic norm,” however, the degree of reduction in reserve and compensatory capacities turned out to be higher in the Dagestan population [7].

The damaging effect of hydroperoxides in Dagestani women with ACD led to a more significant destabilization of cell membranes, disruption of cell division and growth, depletion of the erythroid germ because of the deficiency of SH-groups, catalase in blood serum and erythrocytes.

Conclusion. The study showed a variety of risk factors and conditions that contribute to the development of anemia against the background of limited iron stores and lower hemoglobin concentrations in various ethnic samples.

The concepts of the adaptive and homeostatic mechanisms of pregnant women with anemia on the background of chronic infectious and inflammatory diseases are formed when studying proteins of the acute phase of inflammation, the ratio of oxidative stress factors and antioxidant activity.

Violation of the regulation of iron metabolism in ACD is accompanied by excessive production of hydroperoxides, a pronounced decrease in the antioxidant potential in the Dagestan population in comparison with the Yakut one. The development of anemia in the population of the Far North proceeds against the background of the

evolutionarily established adaptive-homeostatic physiological characteristics of the organism.

An increased risk of adverse pregnancy outcomes (low birth weight, low body weight for gestational age, cerebral ischemia) was more common in women with ACD.

The reduction of pregnancy complications and newborns’ morbidity in women with anemia is possible with the replenishment of ID, essential micronutrients and the treatment of chronic infectious and inflammatory diseases at the preconception stage.

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POLYMORPHISM OF THE ORGANIC ANION TRANSPORTER PROTEIN 1B1 OATP1B1 RS2306283 GENE IN CHILDREN WITH THYROID DISEASES LIVING IN THE FAR NORTH

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The increased prevalence of iodine deficiency diseases, such as thyroid pathology, is an extremely urgent problem for Russia. Huge part of the country's territory, including the Extreme North regions, is situated in the iodine deficiency zone. Iodine deficiency diseases of the thyroid gland are widespread among prepubescent children living in this area. Polymorphism of thyroid hormone transporter genes, including the organic anion transporter 1B1 protein *OATP1B1* gene is associated with changes in their functional activity. It causes the thyroid pathologies development in children living in the conditions of iodine deficiency in the Far North. **The aim of the work** is to study the polymorphism of the organic anion transporter protein 1B1 *OATP1B1* rs2306283 gene associated with the changes of endocrine regulation in living in the Far North children with thyroid diseases. **Materials and methods**. A clinical and laboratory examination of children living in conditions of iodine deficiency in the Far North was conducted. The observation group consists of 52 children with thyroid diseases (congenital iodine deficiency syndrome, hypothyroidism, thyroid disease, endemic goiter). The comparison group includes 54 children without pathologies of the endocrine system. The iodine content in urine was determined by a unified method using spectrophotometry. The thyroid-stimulating hormone (TSH) level was determined by enzyme immunoassay. The *SNP* of the *OATP1B1* gene (rs2306283) was identified using the real-time PCR technique. **Results.** The results of the clinical and laboratory biological media analysis in the examined children demonstrate a reduced iodine content in the urine of children with thyroid pathology relative to the comparison group and the reference level ($p<0.05$). At the same time, the level of thyroid-stimulating hormone exceeds similar values in the comparison group ($p<0.05$). Polymorphism of the organic anion transporter 1B1 protein *OATP1B1* (rs2306283) gene in children with thyroid diseases is characterized by the increased C-allele frequency relative to the comparison group (OR=1.79 (CI: 1.03-3.09); $p<0.05$). It may be associated with thyroid hormone transport inhibition. **Conclusion.** Thus, the endocrine profile of children with established thyroid pathology living in conditions of iodine deficiency in the Far North is characterized by an imbalance of the pituitary-thyroid system according to the criterion of an increase in TSH content against the background of a decrease in iodine content in urine ($p<0.05$), which indicates a decrease in the functional activity of the thyroid gland. The established increased C-allele frequency of the *OATP1B1* gene (rs2306283) indicates the formation of pathogenetic trends in the transport of thyroid hormones in the presence of thyroid diseases in conditions of natural iodine deficiency. Genotyping of the *OATP1B1* gene (rs2306283) polymorphic markers associated with excessive TSH levels against the background of iodine deficiency in biological media can be used for prevention, early diagnosis and personal therapy of thyroid diseases in the population of iodine-deficient territories.

Keywords: gene polymorphism, thyroid gland, Far North, iodine.

Introduction. The increased prevalence of iodine deficiency diseases such as thyroid pathology is an extremely urgent problem for Russia due to significant part of the country's territory is situated in the iodine deficiency zone. The territory of the Far North is one of the iodine-deficient regions by the reason of permafrost, specific features of the catchment area during snowmelt, insufficient penetration of air masses from the ocean into these territories, which leads to an absolute iodine deficiency in the biosphere [11].

Iodine is a vital trace element that is necessary for normal human growth and development as an integral part of thyroid hormones – thyroxine (T4) and triiodothyronine (T3) [9]. Chronic iodine deficiency leads to the development of hypothyroidism, endemic and nodular goiter, can also cause abnormalities in the neuron development as well as mental and physical retardation in children due to inadequate production of thyroid hormones. In the territories with decreased iodine content in the environment there is an increased incidence of thyroid pathologies such as endemic goiter, hypothyroidism and other thyroid diseases associated with low iodine deficiency. Thus, in the Far North, the incidence of thyroid pathology among prepubescent children is up to 70% [12].

Polymorphic variants of genes are associated with functional changes in expression products and, as a consequence, determine an enzymatic activity level of the corresponding proteins. Therefore, different individuals may have increased resistance or excessive sensitivity to the action of damaging environmental factors, depending on the specific features of their genome and the corresponding functional activity of specific enzymes [1]. The pituitary-thyroid system of the children's population in industrial centers is characterized by an increase in activity and change in the thyroid hormones ratio in order to ensure compensatory reactions of the body in response to adverse environmental factors [4]. Consequently, polymorphism of thyroid hormone transporter genes, including the gene of the organic anion transporter protein 1B1 *OATP1B1* is associated with changes in their functional activity [6], which creates an increased risk of thyroid pathologies in children living in conditions of iodine deficiency in the Far North.

The aim of the work is to study the polymorphism of the organic anion transporter protein 1B1 *OATP1B1* rs2306283 gene associated with changes in endocrine regulation in living in the Far North children with thyroid diseases.

Materials and methods. The clinical and laboratory examination of a biological material (blood, urine, buccal epi-

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thelium) in children living in conditions of iodine deficiency in the Far North was carried out. The observation group consists of 52 children aged 4-10 years with diagnosed thyroid diseases: E00 Congenital iodine deficiency syndrome, E01 Thyroid diseases associated with iodine deficiency and similar conditions; E01.2 Goiter (endemic) associated with iodine deficiency, unspecified; E03.9 Hypothyroidism, unspecified). The comparison group includes 54 children aged 3-10 years without an established endocrine pathology. The groups are homogeneous by ethnicity and social status

The study was carried out in accordance with the norms set out in the Helsinki Declaration of the World Medical Association "Ethical principles of conducting medical research involving people as subjects" of 1975 with additions of 1983, in harmonization with the National Standard of the Russian Federation GOST-R 52379-2005 "Good Clinical Practice" (ICH E6 GCP). Parents or other legal representatives of minors have signed a voluntary informed consent for the examination of children.

Determination of iodine in urine was carried out using a unified technique on a PE-5400UF spectrophotometer ('Ekroschem', Russia). Determination of the thyroid-stimulating hormone level was carried out by enzyme immunoassay ("Hema-medica", Russia) on an Elx808 analyzer ("BioTek", USA). Genotyping by polymorphism T388C of the anion transporter protein *OATP1B1* (rs2306283) gene was carried out by PCR in real time on the CFX96 device (Bio-Rad, USA). Genetic material was extracted from buccal epithelium using the reagents set for DNA extraction from clinical material (Syntol, Russia). The human genotype was determined by the method of allelic discrimination in the specialized TaqMan program.

Methods of parametric (Student's t-test) and nonparametric (Mann-Whitney U-test) mathematical statistics using the Statistica 6.0 application software package (StatSoft, USA) were used for statistical processing of the research results. The results of the study are presented in the form of the arithmetic mean (M) and its standard error (m) studied. The analysis of associations of variant genotypes with the development of thyroid pathology was carried out using the odds ratio (OR) and its confidence interval (CI). The differences between the groups were considered statistically significant at $p<0.05$.

Results and discussion. The biochemical analysis results of biological media in the children's population in the Far North demonstrates that children with thyroid pathologies has significantly reduced iodine content in urine in relation to similar values of the comparison group and to the reference level ($p<0.05$). At the same time, the iodine content in the urine of children in the comparison group is comparable with the lower limit of the reference level (Table 1).

In result of the studying the indicators of endocrine regulation in the examined children by the criterion of thyroid hormone levels, it was found that the content of thyroid-stimulating hormone (TSH) in children of the observation group was 1.2 times higher than the comparison group ($p<0.05$). At the same time, the indicators of both groups are within the reference level (Table 2).

The level of thyroid-stimulating hormone in the blood accurately reflects the functional state of the thyroid gland. An increase in TSH indicates a decrease in the functional activity of the thyroid gland, which is an acute problem for children [2]. However, one of the most discussed issues in modern endocrinology both in our country and abroad is the reference lev-

Table 1

Iodine content in biological media of the Far North child population

Indicator	Reference level	Observation group (n=52)	Comparison group (n=54)
Iodine [urine], mcg/100 cm³	10.00-50.00	6.45±1.06*/**	9.93±2.21

* - differences are significant relative to the reference level ($p<0.05$);
** - differences are significant relative to the comparison group ($p<0.05$).

Table 2

The content of thyroid-stimulating hormone in the blood of the Far North child population

Indicator	Reference level	Observation group (n=52)	Comparison group (n=54)
ТТГ, мкМЕ/см³	0.30-4.00	3.78±0.48*	3.13±0.36

* - differences are significant relative to the comparison group ($p<0.05$).

Table 3

The frequency genotypes and alleles distribution of *OATP1B1* gene in the Far North child population

Gene	Genotypes/alleles	Observation group (n=52)	Comparison group (n=54)
OATP1B1 (rs2306283)	T/T	0.32	0.45
	T/C	0.38	0.40
	C/C	0.30	0.15
	T	0.51*	0.65
	C	0.49**	0.35

Note: * - OR=0,56 (CI: 0,32-0,98);
** - OR=1,79 (CI: 1,03-3,09)

el range of thyroid-stimulating hormone. Determining of the TSH concentration is considered as the main test for assessing the functional state of the thyroid gland. Currently, the TSH level of more than 4-5 mEd/l indicates the presence of a decrease in thyroid function. The reason for the discussion was the recommendations of the National Academy of Clinical Biochemistry of the USA to reduce the upper limit of the TSH level in the blood from 4.0 to 2.0-2.5 mEd/l [8].

In result of analyzing the frequency distribution of alleles of the *OATP1B1* gene (rs2306283) in children with thyroid diseases it was established that the variant C-allele frequency in the comparison group was 1.4 times higher than in the comparison group ($p<0.05$). In the observation group, 32% of children have a homozygous wild-type TT-genotype, 38% of children are carriers of a heterozygous T/S genotype, and 30% of children had a homozygous minor CC-genotype. In the comparison group, 45% of children have a wild-type TT-genotype, 40% of children are carriers of a heterozygous T/S genotype, 15% of children have a variant homozygous C/C-genotype (Table 3).

The *OATP1B1* gene, also known as *SLCO1B1*, encodes a membrane protein that carries organic anions B1. Polypeptides transporting organic anions are a family of membrane transporters regulating cellular uptake of a number of endogenous substances and clinically important drugs. [5]. The OATP1B1 protein is one of the main absorbing transporter proteins in this group and participates in the transport of a number of endogenous and exogenous substances, including thyroid hormones [15]. More than 50 forming various haplotypes during interaction non-synonymous SNPs of this gene have been described in the scientific literature. Some of the most studied SNPs of this gene are c.521T>C/Val174Ala (rs4149056) and c.388A>G/Asn130Asp (rs2306283). These polymorphic variants of the *OATP1B1* gene are in unstable relationship with each other and are combined in different haplotypes. In some investigations the c.388G-521C haplotype is mentioned as a variant with reduced functional activity. It is associated with reduced absorption of a large number of OATP1B1 substrates *in vitro* and a noticeable increase in its concentrations in blood plasma [13, 14].

The frequency meta-analysis of the c.521T>C polymorphism of *SLCO1B1* gene in 941 people from 52 populations from Africa, the Middle East, Asia, Europe, Oceania and America revealed that this variant is widespread all over the world. However, the distribution of its frequencies in different populations is heterogeneous and varies from 1.9% in the population of Sub-Saharan Africa to 24% in the representatives group of indigenous population in America [3]. Results of similar investigation in Russia demonstrate that the TT-genotype frequency of the *SLCO1B1* gene is 64.3% in population, TC is 31.0%, CC is 4.7% [7].

Conclusion. Thus, the endocrine profile of children with established thyroid pathologies living in conditions of iodine deficiency in the Extreme North is characterized by an imbalance of the thyroid system. The reduced iodine content in the urine of the examined children is combined with an excessive thyrotropic hormone content, which indicates a decrease in the thyroid gland functional activity. The established increased C-allele frequency of the *OATP1B1* gene (rs2306283) indicates the formation of pathogenetic trends in the transport of thyroid hormones in the presence of thyroid diseases in conditions of natural iodine deficiency. Genotype polymorphic marker determination of the *OATP1B1* gene (rs2306283) can be used for prevention, early diagnosis and personal therapy of thyroid diseases in the population of iodine-deficient territories.

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FEATURES OF THE COURSE OF INFECTIOUS DISEASES OF VIRAL ETIOLOGY WITH NEUTROPENIA

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The aim of the study is to establish the features of the course of infection of viral etiology with neutropenia. Study included analysis of immunological parameters of 628 people with a viral infection and 359 practically healthy people aged 31-51 years living in Arkhangelsk. It was found that the course of infection of viral etiology against the background of neutropenia is accompanied by a more significant decrease in the percentage of active phagocytes and an increase in the concentration of circulating immune complexes, which occurs against the background of a low content of properdin, which is a risk of a chronic course of the disease. The deficiency of the phagocytic activity of neutrophils in neutropenia is due to the insufficiency of the main chemotaxis factor C5a, which is a product of the enzymatic cleavage of C5. An increase in the content of autoantibodies, which is characteristic of viral pathology, speaks in favor of a more significant level of cytolytic and secretory function of neutrophils in neutropenia.

Keywords: neutropenia, viral infection, phagocytosis, circulating immune complexes, autoantibodies.

Introduction. Neutropenia is not a mandatory hematological manifestation of most diseases. In infectious diseases that do not directly affect the organs of hematopoiesis, neutropenia is not associated with a violation of the processes of maturation and differentiation of neutrophils. In infections, neutropenia is temporary and mostly disappears during recovery. But the presence of neutropenia does not have a positive effect on the course of any inflammatory process, including viral etiology. The questions of neutropenia attract little attention of researchers, but this does not make them less relevant. In the North, where neutropenia is quite widespread and depends on the climatic and geographical conditions of life, the issues of neutropenia become very topical. Neutropenia is often combined with a deficiency of active phagocytes. Neutropenia, in combination with a deficiency of phagocytic protection, creates serious defects of natural and acquired resistance to various factors that adversely affect a person. The frequency of registration of phagocytic defense deficiency in practically healthy children, aged 1-1.5 years on average is 5.56±0.24%, in children 10-12 years, the level of registration of this immunodeficiency increases to 8.39±0.31%, and at the age of 16-19 years, the frequency of phagocytic activity deficiency of neutrophils is already 29.76±0.84% [6]. Based on the data of Almazov V.A. (1981), Dale D.C. (1995) and Lichtman M.A. (1995), the frequency of registration of so-called "spontaneous" neutropenia is quite significant [1, 14, 19]. Neutropenia is registered in the first hours after the introduction of vaccines, when infected with respiratory viruses, with some bacterial infections [2, 4, 5, 10].

The aim of the study is to establish the features of the course of infection of viral etiology with neutropenia.

Materials and methods. The immunological results of the preanalytical and analytical stages of the examination of 628 people with a viral infection aged 31-51 years living in Arkhangelsk, who applied to the professional diagnostics center "Biolam" after a previous illness with a previously established diagnosis, including 126 people with enterovirus infection, 164 – herpes infection, 223 – Acute respiratory viral infections (ARVI), 115 – Grippe, were analyzed. As a comparison group, 359 practically healthy people of the specified age living in Arkhangelsk were examined. The survey was carried out with the written consent of the respondents in compliance with the basic norms of biomedical ethics in accordance with the document "Ethical principles for medical research involving human subjects" (WMA Declaration of Helsinki 1964, amended in 2013).

For the study, peripheral venous blood was taken from the ulnar vein in the morning on an empty stomach. The number of leukogram cells and neutrophil phagocytosis were calculated in blood smears stained by the Romanovsky-Giemsa method; the calculation was performed at the rate of 100 cells. The content of complement system factor P (properdin) (Cloud-Clone Corp., CCC, Wuhan), C4, C3, C5-components of the complement system (AssayPro, USA) was determined in blood serum by enzyme immunoassay (ELISA) with appropriate reagents. Anti-double stranded DNA (Anti-dsDNA) antibodies, Anti-RNP antibodies, and autoleucoagglutinins were determined. Autoantibodies were detected using ELISA using the ENA Profile kits from Bio-Rad (USA) and ORGenTec Diagnostika (Germany). The results were recorded using a Multiskan series spectrophotometer (Finland) and an automatic enzyme immunoassay analyzer "Evolis" from Bio-RAD (Germany). Serum autoantibodies to leukocytes were determined in leukoagglutination reactions, the results of which were taken into account in a "thick drop" type preparation. Leucoagglutinins were determined in dilutions 1/5, 1/20, 1/40, 1/80, 1/60, etc., the titers of which were recorded in log2. The concentration of circulating immune complexes (CIC IgG) was determined by the standard precipitation method using 7.5 % PEG-6000 in blood serum. The reaction was evaluated on an automatic enzyme immunoassay analyzer "Evolis" of the company "Bio-RAD" (Germany). A deficiency in the content of neutrophil granulocytes (neutropenia) was established at a content of < 2.0×109 cells/l. Statistical processing of the obtained data was carried out using the Statistica 10.0 software package (StatSoft, USA). The critical level of significance (p) in the work was taken equal to 0.05.

Results and discussion. The frequency of neutropenia registration in viral infections varies within 12.56-26.96% (19.46±1.23%), it is most often detected with influenza and enterovirus infection. Deficiency of active phagocytes and neutropenia coincide in 78-93% in viral infections (table 1).

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Table 1

Frequency of registration of immune defense defects in viral infections in adults (number / %)

Indicator	Enterovirus infection, n=126	Herpes infection, n=164	ARVI, n=223	Grippe, n=115
Neutropenia	26 / 20.63	29 / 17.68	28 / 12.56	31 / 26.96
Deficiency of active phagocytes	23 / 18.25	25 / 15.24	24 / 10.76	26 / 22.61
Neutropenia and deficiency of active phagocytes	21 / 80.76	24 / 82.76	22 / 78.57	29 / 93.55

Table 2

Immunological parameters of peripheral blood in patients and practically healthy people with neutropenia and normal neutrophil granulocytes (M±m)

Studied parameters	Viral infection		Practically healthy persons	
	Neutropenia, n=114	Normal neutrophil content, n=125	Neutropenia, n=134	Normal neutrophil content, n=225
	1	2	3	4
Neutrophils, 109 cells/l	1.62±0.25	2.29±0.19	1.83±0.17	2.68±0.22
% of active phagocytes	35.32±1.32 ***1-3	49.28±1.05 ***2-4	41.34±1.93	54.27±1.26
Properdin, g/l	0.33±0.03**1-3	0.27±0.04 ***2-4	0.67±0.05	0.89±0.07
C4, g/l	0.52±0.01	0.51±0.06	0.62±0.09	0.59±0.05
C3, g/l	1.61±0.08**1-3	1.54±0.07**2-4	0.62±0.09	0.53±0.09
C5, g/l	0.32±0.04 ***1-2	0.68±0.05	0.28±0.08**3-4	0.49±0.06
CIC IgG, g/l	3.89±0.09**1-3	2.36±0.07	2.83±0.09	2.23±0.12
Autoleucoagglutinins, $\log_2$	2.32±0.02*1-3	2.86±0.08*2-4	1.49±0.07	1.36±0.09
Anti-dsDNA, IU/ml	49.60±1.26 **1-2	38.67±1.35	39.71±1.11	35.32±1.03
Anti-RNP, IU/ml	0.79±0.04	0.69±0.06	0.57±0.08	0.89±0.13

* p<0.05, ** p<0.01, *** p<0.001

The infection is accompanied by an increase in the CIC content in the blood; statistically significant differences were found relative to the CIC IgG, whose concentrations are higher in patients with neutropenia (table 2).

A decrease in the percentage of phagocytic neutrophils in viral infections, regardless of the etiology of the infectious disease, occurs against the background of a low content of properdin, an activator of the alternative pathway of the complement system, as well as an increase in C3 concentrations. Without going into the details of the functional activity of the complement system, we will mention only the basic concepts related to the analyzed results. The classical complement activation pathway begins with the binding of C1q to the Fc fragment of complement-binding immunoglobulins (IgM, IgG1-3) and the formation of either their aggregates or complexes with an antigen. After C1, C4 and C2 are activated, and only after that C3 convertase is formed. An alternative or properdin activation pathway immediately begins with the formation of active C3a and C3b without the participation of C1, C4 and C2 [17, 28]. Low concentrations of C4 and slight fluctuations in its concentrations indicate the predominance of activation of the complement system by an alternative route. Properdin (from the Latin perdition – destruction, factor P) was discovered by L. Pillemer in 1954, electrophoretically – it is a gamma-globulin of blood serum. A long-term low content of properdin is a poor prognostic sign, as well as the risk of a prolonged or chronic course of the disease [3, 9]. Non-complement-binding IgA and Fab fragments of all classes of immunoglobulins, which can aggregate not only antigens, are also able to immediately activate C3

The deficiency of the content of phagocytic granulocytes is combined with neutropenia not only in viral infections, but also in practically healthy individuals; in patients with neutropenia, the content of phagocytic neutrophils is noticeably lower (p<0.01). The reason for the decrease in phagocytic activity in neutropenia, in our opinion, is the predominant exocytic activity of neutrophils. Immediately after contact with the object, first part of the granules merges with the outer surface of the cell membrane, then breaks or is thrown out of the cell, and phagocytosis occurs much later. The release of pyrogen is the earliest reaction of activated neutrophils in tissues and entails the aggregation of granules, the release of cationic proteins from lysosomes, the marginal standing of cationic proteins under the cell membrane and their secretion into the intercellular medium [11]. The decrease in the level of active phagocytes during the activation of the secretory function of neutrophils is confirmed by a sufficiently large number of convincing facts [7, 8, 12, 18, 20, 22, 25, 35].

Both in patients and in practically healthy individuals, neutropenia is combined with a low content of C5 (p<0.001), which is quite understandable since the chemotaxis factor C5a is formed mainly by an enzyme in the lysosomal granules of polymorphonuclear leukocytes. Activation of the serum complement leads to the enzymatic cleavage of C3 and C5 into fragments of C3a and C5a, which contribute to the release of histamine, but only C5a is a true chemotactic factor for granulocytes [15, 21].

If there is a sufficient concentration gradient of the chemoattractant, the location

of the receptors on the surface of the cell membrane becomes asymmetric, concentrates on one of the poles in the form of a cap (capping) and determines the direction of its movement [13]. Well-studied chemotactic agents are components of activated complement or short peptides with N-terminal formyl-methyl residues. Activation of the complement system can be induced by bacterial endotoxins, bacterial cell walls (zymosan), various proteases. Bacterial growth products stimulate chemotaxis because, unlike eukaryotic cells, bacteria initiate the synthesis of products with an N-terminal formyl-methionyl group [26]. The number of such newly discovered chemotactic peptides in recent years has numbered several hundred and their number continues to increase, but, most likely, all these substances react with the same, common neutrophil membrane receptor. At elevated concentrations of chemoattractant, the activity of chemotaxis may even decrease. At high concentrations of various chemotaxis factors, there is a decrease in the activity of signal transmission and the mechanism of receptor concentration on pseudopods with a parallel increase in the secretion of hydrolases, metalloproteases and free radical production. At the same time, the activity of chemokinesis does not decrease, which is manifested by the absence or decrease in the severity of the pointed front of cell movement in agarose [24, 36]. The speed and number of moving neutrophils significantly decreases by 10 and even 100 times at low concentrations of granulocytes [23].

So, with neutropenia, the content of C5 in the blood is lower, which is formed mainly by the enzyme of lysosomal granules of polymorphonuclear leukocytes, which leads to a low formation of the product of its enzymatic cleavage of C5a – the main factor of granulocyte chemotaxis. The content of C5 in practically healthy and sick people with neutropenia is noticeably lower in these cases, the differences in their concentrations in the blood of patients and healthy people are actually not significant. In addition to reducing the content of the main chemotaxis factor in neutropenia, their chemokinesis is also lower.

The adhesion of the object to the phagocytosis wall (opsonization) is provided by the treatment of the object with the complement system enzyme C3b and immunoglobulins. Opsonins have been known since 1903 [34]. They act as ligands between the object and the phagocyte [32]. The adhesion of the object to the phagocyte wall causes changes in the cell membrane, leading to the organization of contractile proteins and the movements of the membrane around the phagocytosis object [29, 30].

The possibility of an insufficient effect of opsonins on the deficiency of phagocytic protection in neutropenia is hardly real. Opsonins act on the object of phagocytosis as ligands. The most important opsonins are C3 (C3b), activated both by the classical and alternative pathways, and immunoglobulins [16, 27, 30-33]. Complement-binding immunoglobulins, as well as non - complement-binding IgA, IgE and Fab fragments of immunoglobulins of any classes capable of aggregating antigens, play only a predominantly initiating role. Opsonization, in all probability, does not suffer from neutropenia, since the serum content of C3, the source of C3b, does not actually change with neutropenia (1.61±0.08 and 1.54±0.07 g/l). It should be noted that the activity of autoantibody formation in northerners is significantly higher than in people living in favorable climatic conditions and an excessive increase in autoantibodies can cause low concentrations of neutrophils. Thus, in neutropenia, the content of autoleucoagglutinins in persons with a viral infection is higher than in practically healthy people (2.32±0.02 and 1.49±0.07 log2). The concentrations of Anti-dsDNA in viral infections on the background of neutropenia are noticeably higher than their level in patients with normal neutrophil content in peripheral venous blood. In itself, the fact of an increase in the content of Anti-dsDNA in a viral infection is not surprising and, most likely, is the result of the cytopathic effect of viral infection of the cell. An increase in the content of Anti-dsDNA against the background of neutropenia may be the result of the predominance of cytolytic and secretory activity of neutrophils in the conditions of neutropenia. Cytolysis and phagocytosis are a mechanism for protecting organs and tissues from the damaging influence of factors and actions that activate the complement system.

Conclusion. The course of infection of viral etiology against the background of neutropenia is accompanied by a more significant decrease in the % of active phagocytes and an increase in the concentration of CEC. The deficiency of the phagocytic activity of neutrophils in neutropenia is due to the insufficiency of the main chemotaxis factor C5a, which is a product of the enzymatic cleavage of C5 formed by enzymes of lysosomal neutrophil granules, as well as a decrease in the activity of their chemokinesis. An increase in the content of autoantibodies, which is characteristic of viral pathology, speaks in favor of a more significant level of cytolytic and secretory function of neutrophils in neutropenia.

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EVALUATION OF ANTITUMOR ACTIVITY OF BENZIMIDAZOLE DERIVATIVE ON MODELS OF EXPERIMENTAL TUMORS

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The effect of dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole on the growth and metastasis of transplanted allografts of melanoma B16 and epidermoid lung carcinoma Lewis with intraperitoneal administration was investigated. Antitumor effect was established in relation to primary epidermoid carcinoma of Lewis lung and its metastases to the lungs, as well as in relation to metastatic lung damage for melanoma B16 mice.

Keywords: experimental B16 melanoma, epidermoid Lewis lung carcinoma, dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole, anticancer activity, antimetastatic activity, intraperitoneal administration.

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Introduction. Despite the wide range of modern drugs for medical cancer therapy, their high toxicity necessitates the search for anticancer agents that selectively suppress or inhibit the growth of tumor cells.

Over the past decades, many benzimidazole derivatives have been reported to have pronounced anticancer activity due to their structural similarity to naturally occurring nucleotides (El Rashedy AA, 2013). Benzimidazole-based drugs have been developed and introduced into clinical practice for cancer chemotherapy. Thus, Veliparib (ABT-888), a benzimidazole-based drug, was assigned the status of an orphan drug for non-small cell lung cancer by the FDA in 2016 (https://adisinsight.springer.com/drugs/800028802). Its mechanism of action is to inhibit poly (ADP-ribose) polymerase (PARP) -1 and -2, thereby inhibiting DNA repair and potentiating the cytotoxicity of DNA damaging agents (Penning TD, 2009).

Recent studies have shown the activity of various substituted benzimidazole derivatives with their antiproliferative value against various cancer cell lines such as HCT116, MCF7, HeLa, HepG2, A549 and A431. (Tahlan S, 2019). Anticancer and antimetastatic effect of a benzimidazole derivative dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole was reported (Komarova EF, 2017; RF Patent 2016). Intragastric administration of the pharmacological substance dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole to mice caused minor inhibition (48.7%) on the growth of experimental B16 melanoma at a dose of 220 mg/kg, without affecting the survival of animals with tumors. However, a pronounced inhibiting effect of dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole on metastatic nodes in the lung was revealed (the metastasis inhibition index was 75.5%).

The purpose of this study was to analyze the effect of intraperitoneal administration of dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole on the growth and metastasis of experimental transplantable tumors.

Material and methods. The study included 96 female C57Bl6j mice weighing 18-20 g (the protocol of the bioethical commission of Rostov Research Institute of Oncology No. 18 from 10.09.2015). Animals were obtained from the vivarium of the Andreevka branch of the Scientific Center of Biomedical Technologies (Moscow region). All manipulations with animals and their withdrawal from the experiment were carried out in accordance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes.

The experiment used two strains of transplantable murine tumors: B16 melanoma (EG1) and epidermoid Lewis lung carcinoma (LLC; EG2). The solution of the studied substance in the physiological solution for the administration to animals was prepared ex tempore and injected intraperitoneally once a day for 10

days, 48 hours after subcutaneous tumor transplantation to animals in the single doses were 6.15 (subgroup 1), 30.75 (subgroup 2) and 61.5 (subgroup 3) mg/kg (1/40, 1/8 and 1/4 of LD50, respectively). Control groups (CG1 for B16 melanoma and CG2 for LLC) included animals with tumors who received intraperitoneal injections of physiological saline in similar doses and regimens, instead of the studied solution.

Some of the animals in all groups were euthanized in a CO2 chamber on day 25 after tumor inoculation, and necropsy was performed. The anticancer and antimetastatic activity of the substance was studied in accordance with the Guidelines for the experimental (preclinical) study of new pharmacological substances of the Federal Service for Surveillance in Healthcare and Social Development of the Russian Federation (Mironov, 2013) and the Order of the Ministry of Health of the Russian Federation No. 199n from 01.04.2016.

Anticancer and antimetastatic activity of the studied substance was evaluated by standard parameters: tumor volume, survival, and the number of metastatic nodes. The survival improvement (T/C, %), tumor growth inhibition (TGI, %), and metastasis inhibition index (MII, %) were calculated.

Table 1 presents the experiment design.

Statistical analysis of results was performed using the STATISTICA 12.0 program (StatSoft Inc., USA). The results were checked for a normal distribution by the Shapiro-Wilk and Kolmogorov-Smirnov tests. The significance of differences between the means of the independent samples was assessed using the Student's t-test. Differences were considered significant at $p<0.05$.

Results. The study of an effect of RU-185 intraperitoneal administration on the growth and metastasis of experimental B16 melanoma showed influence on the survival of animals depending on the dose (Table 2). According to the quantitative criteria for the substance activity, intraperitoneal administration of a dose of 30.75 mg/kg improved the survival of animals with B16 melanoma (T/C = 151.3%), and other doses did not significantly affect this indicator.

Intraperitoneal administration of RU-185 did not cause a pronounced inhibiting effect on the growth of subcutaneous B16 melanoma (Table 2). On the 7th day after the end of treatment in subgroups 1 (6.15 mg/kg) and 2 (30.75 mg/kg) EGI, a slight decrease in the volume of the primary tumor node was found, which maintained by day 14 only in subgroup 2 (TGI=23.6%).

Intraperitoneal administration RU-185 changed the studied parameters of anticancer effect on experimental lung carcinoma depending on the substance dose (Table 3). Significant improvement of survival and decreased tumor sizes were registered in EG 2, subgroup 2 (T/C=171.6%). The volumes of the prima-

Table 1

Design of the experiment

Main indices	Animal groups							
	EG1			EG2			CG1	CG2
	1	2	3	1	2	3		
Number of animals in the group AC/AM	12 6/6	12 6/6	12 6/6	12 6/6	12 6/6	12 6/6	12 6/6	12 6/6
Administered substances	dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole						physiological saline	
Single doses, mg/kg	6.15	30.75	61.5	6.15	30.75	61.5		
Injected volumes	0.3 mL/day							
Period of administration	10 days							
Rout of administration	intraperitoneal							

Note: EG1 – experimental group with transplanted B16 melanoma, EG2 – experimental group with transplanted epidermoid Lewis lung carcinoma, CG1 and CG2 – control groups of animals with transplanted B16 melanoma and epidermoid Lewis lung carcinoma, respectively, AC -evaluation of anticancer effect, AM - evaluation of antimetastatic effect.

Table 2

Effect of intraperitoneal dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole on B16 melanoma growth dynamics

Single dose, mg/kg	T/C, %	Tumor volume (cm3), M±m (TGI,%)		
		days after the end of treatment		
		1	7	14
6.15	126.9	4.3 [3.1-5.1]	26.9 [16.3-37.5] (15.9)	51.3 [50.5-60.9]
30.75	151.3[1.2]	3.8 [2.6-6.0] (7.3)	26.1 [15.7-37.2] (16.1)	35.9 [35.2-46.5] (23.6)
61.5	84.7	3.9 [1.4-5.3] (4.9)	29.9 [18.9-34.1] (3.5)	43.1 [35.3-54.1] (4.5)
Controls	0	4.1 [1.5-5.6]	31.1 [20.9-37.6]	47.1 [34.9-55.2]

Note: 1 – differences were significant compared to controls ($p<0.05$); 2 - differences were significant compared to subgroups of the experimental group ($p<0.05$). Differences were determined using the Student's t-test.

Table 3

Effect of intraperitoneal dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole on LLC growth dynamics

Single dose, mg/kg	T/C, %	Tumor volume (cm^3), M±m (TGI, %)		
		days after the end of treatment		
		1	7	14
6.15	83.3	26.4 [21.9-34.6]	66.9 [53.9-71.1] (12.8)	91.1 [85.6-95.2] (12.1)
30.75	171.6[1.2]	8.1 [6.9-9.1][1.2] (56.2)	37.1 [31.7-45.6][1.2] (51.8)	56.1 [51.2-60.3][1.2] (45.9)
61.5	110.7	15.6 [11.3-19.9] (14.8)	51.4 [46.8-57.1][2] (32.9)	82.1 [73.8-90.6] (20.8)
Controls	0	18.3 [13.9-24.2]	76.7 [73.1-84.2]	103.6 [90.5-121.4]

Table 4

Effect of intraperitoneal dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole on metastasis of B16 melanoma and LLC

Indices		EG1	EG2
Number of metastases per 1 animal	6.15	5.6±1.0[1]	13.1±1.0[1]
	30.75	4.6±0.6[1.2]	10.6±0.6[1.2]
	61.5	12.7±2.9	23.7±0.9
	Controls	14.2±6.2	27.6±1.2
MII, %	6.15	60.2±4.3[2]	63.1±5.1[2]
	30.75	74.5±4.8[2]	79.6±5.6[2]
	61.5	15.8±4.1	16.9±3.9

Note: 1 – differences were significant compared to controls ($p<0.05$); 2 – differences were significant compared to subgroups of the experimental group ($p<0.05$).

ry subcutaneous tumor nodes were 2.3 times lower already on the 1st day after the end of treatment, compared to the control ($p<0.05$), and this effect persisted up to the 14th day (the tumor volume was decreased by 2.1 and 1.9 times on days 7 and 14, respectively, at $p<0.05$).

The next stage of the study was to assess the antimetastatic effect of intraperitoneal dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole against the studied experimental tumors (Table 4).

The substance administration in EG1 reduced the number of metastases in subgroups 1 and 2 by 2.5 and 3.0 times, respectively ($p<0.05$), compared to controls, and did not influence the number of metastases in subgroup 3. The frequency of metastasis in the subgroups was high: 60.4% in subgroup 1 and 74.5% in subgroup 2. Similar results on antimetastatic activity were obtained in EG2. The number of metastases in subgroups 1 and 2, EG2, was decreased by 2.1 and 2.6 times, respectively ($p<0.05$), compared to controls, and did not differ from the number in controls in subgroup 3. MII was higher in EG2 than in EG1 and was 63.1 and 79.6 for subgroups 1 and 2, respectively.

The results demonstrated that intraperitoneal administration of RU-185 at a total dose of 307.5 mg/kg had the inhibitory effect on the growth of the primary epidermoid Lewis lung carcinoma and did not affect the growth of the primary B16 melanoma in mice. However, a significant antitumor effect of intraperitoneal dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole at a total dose of 61.5 mg/kg and 307.5 mg/kg was revealed relative to metastasis of both studied strains, since the number of metastases and the frequency of metastases in the lungs decreased.

Our earlier research of anticancer activity of intraperitoneal RU-185 showed its pronounced inhibitory effect against lung metastases from B16 melanoma without any effect on the growth of the primary subcutaneous B 16 melanoma, and an inhibition of subcutaneously transplanted epidermoid Lewis lung carcinoma (Комарова 2017; Комарова 2021-вторая и патент). The results of this and previous studies on the anticancer activity of dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole suggest that the mechanism of its antitumor action is associated with metabolic changes in the lung tissue. Tissue metabolism of various tumors plays an important role for their growth and development (Кит 2015,2014). The growth of a metastatic tumor in the lungs of rats was reported to be accompanied by an increasing imbalance of the main metabolic systems: free radical, hydrolytic, and kallikrein-kinin ones, and a change in the hormonal tissue status, which contributes to the malignant progression in the lung tissue (Комарова - диссертация). However, identification of pathogenetic factors involved in the antimetastatic action of dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole showed in this experiment requires further research.

Conclusion. Intraperitoneal administration of dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole showed its anticancer effect against primary epidermoid Lewis lung carcinoma and its metastases to the lungs, as well as against lung metastases from B16 melanoma in mice.

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THE LEVEL OF STEROID HORMONES IN THE BODY OF WRESTLERS AT DIFFERENT PERIODS OF THE TRAINING CYCLE IN THE CONDITIONS OF THE NORTH

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The aim: to assess the level of steroid hormones in the Yakut freestyle wrestlers in the pre-competitive and recovery period in the spring season. The levels of testosterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate and cortisol in the blood serum of highly qualified athletes and university students who go in for physical education at least 2 times a week were studied. The lower testosterone content in wrestlers revealed before the competition indicates the intensity of training loads and psycho-emotional stress. A slight increase in testosterone levels after 7-10 days and its excess of the basal level after 30 days after the competition indicates the adequacy of recovery. The level of cortisol is characterized by a significantly lower content before the competition, and a continuing decrease after the competition in the second period (p=0.027; p=0.003) than in the control group. A similar character of changes in the level is also observed in relation to DHEAS. Levels of all steroid hormones 30 days after the competition, exceeding their pre-competition levels, indicates adaptation to stress and shows the recovery of the body. The growth of the T/K index in athletes 7-10 years after the competition indicates the beginning of recovery processes in the body. A higher level of testosterone, cortisol and DHEAS (p = 0.003) - the hormone of the precursor of these hormones one month after the competition indicates a moderate activation of the pituitary-adrenal system to balance the processes of anabolism and catabolism.

Keywords: steroid hormones, cortisol, testosterone, DHEA, wrestlers, training cycle period.

In modern sports, growing physical activity increases neuropsychic stress. Their joint influence with climatic and environmental factors of the North on the body of athletes causes the summation of stress effects that activate metabolic processes. In such conditions of training, an adequate process of adaptation to physical loads becomes relevant for maintaining the performance of athletes and achieving high results.

An important role in maintaining homeostasis in the process of adaptation to physical activity is played by the endocrine system, which regulates anabolic and catabolic processes in the body, where sex hormones play an important role.

Anabolic processes mean the processes of synthesis of substances necessary for the organs and systems of the body. Regenerative processes and anabolism of muscle tissue are dependent on the level of hormones, including testosterone. Its main role is to induce the synthesis of contractile proteins in muscles undergoing strenuous exercise. Also, during competition, testosterone may be needed to mobilize functionality [17].

In parallel, catabolic processes occur in the body - the breakdown of cells and tissues, the decomposition of complex structures with the release of a large amount of energy. Strong physical loads during training and competitive periods can become catabolic stress, causing changes in the hormonal status of the body [12]. An excessive increase in the level of cortisol causes the breakdown of muscle cells, disrupts the delivery of amino acids to them, thereby reducing the athlete's performance. It is known that the nature of hormonal changes depends on the level of fitness of the body, load parameters and the duration of the recovery period [1, 6].

Excessive activation of the pituitary-adrenal system can cause disruption in the functioning of organs, imbalance of various systems and depletion of the functional reserves of the body. Therefore, it is necessary to evaluate the effect of physical activity on the body in different periods of the training cycle [4].

The purpose of this study was to assess the level of steroid hormones in Yakut freestyle wrestlers in the pre-competitive and recovery period.

Material and research methods. The study was conducted in the spring period from March to April 2019. A total of 40 young men aged 17 to 23 were examined. The first group consisted of 18 freestyle wrestlers, candidates for master of sports (CMS) of the Republican School and the College of the Olympic Reserve. The average age was Me-18 (18; 19). The second group included 22 NEFU students. M.K. Ammosov, who go in for physical education at least twice a week. The average age was Me-19 (18; 22).

Blood sampling from all subjects was carried out in the morning hours (8-10 hours) on an empty stomach from the cubital vein into a vacutainer with a coagulation activator, in a state of relative muscle rest. The athletes were examined at different periods of the training cycle, the

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1st stage - 10-14 days before the competition, the 2nd stage after 7-10 and the 3rd stage 30 days after the competition. Students involved in physical education 2-3 times a week, blood sampling was carried out once in the interval between the beginning of the recovery period of athletes. The analysis was carried out in blood serum by enzyme-linked immunosorbent assay (ELISA) using standard kits, on a Uniplan photometer (Pikon, Russia). Determination of the level of hormones cortisol (K), testosterone (T) and dehydroepiandrosterone sulfate (DHEA-s) was carried out using standard kits "AlkorBio" (Russia) and dehydroepiandrosterone (DHEA) - DBC company (Canada), according to the manufacturer's instructions.

The study was approved by the decision of the Local Ethics Committee at the Federal State Budget Scientific Institution "YSC CMP" and carried out with the informed consent of the subjects in accordance with the ethical standards of the Declaration of Helsinki (2000).

Statistical processing of the obtained data was carried out using the SPSS Statistics 26 statistical software package. Continuous values were presented as a median (Me) and an interquartile range of 25 and 75%. To identify the relationship between the studied indicators, the method of correlation analysis of data was used with the calculation of coefficients and Spearman's rank correlation. Significance of differences was determined by Student's t-test and ANOVA for independent groups. The critical value of the level of statistical significance of differences (p) was taken equal to 5%.

Results and discussion. Analysis of the obtained data showed that the average values of steroid hormones in all the examined groups were within the reference values (table 1). It was found that the content of anabolic hormones testosterone and DHEA did not have significant differences in all groups, but the range of DHEA concentrations in some athletes, especially at the pre-competitive stage, was slightly higher than in the group of students. However, in wrestlers at the pre-competition stage (10-14 days before the competition), the testosterone level tended to be lower in comparison with its content in the student group and after the competition stages after 7-10 and 30 days (Table 1).

Freestyle wrestling belongs to the group of martial arts, where mainly the speed-strength qualities of athletes are developed. At the pre-competitive stage of training, athletes train harder and perform longer exercises, the nature of which stimulates a decrease in testosterone. A number of authors noted a decrease in testosterone levels in men during prolonged physical exertion [15, 20, 21]. In addition, an increase in the level of testosterone in the blood serum was not observed in athletes during endurance training [9]. In the work of Nikanorov A.A. the average serum testosterone level in young Yakut men (18–28 years old) with a normal BMI (18.5–24.9 kg/m^2) was 22.9 ± 8.24 nmol/l [11].

Synthesis and secretion of testosterone are regulated by luteinizing (LH) and follicle-stimulating hormones FG of the pituitary gland. Prolonged exercise or exercise has been shown to increase cortisol levels while maintaining LH levels while decreasing testosterone levels in men. When modeling a stressful state with reduced physical activity (immobilization), a decrease in testosterone secretion occurs along a different pathogenetic pathway. In this case, corticoliberin blocks luliberin cells, which, accordingly, leads to inhibition of the synthesis of LH and testosterone. One of the possible mechanisms for reducing the testosterone content, not associated with the secretion of gonadotropins, is considered to be a shift in metabolism towards catabolic processes over anabolic ones as a result of cortisol hypersecretion [3].

It is assumed that if athletes whose physical activity requires endurance continue their training sessions, testosterone concentration decreases as a result of dysfunction of the hypothalamus or an increase in cortisol levels, which suppresses cortisol secretion [17].

At the second and third stages, 7-10 and 30 days after the competition, there is a tendency to increase the level of testosterone, compared with the pre-competition period, which is probably associated with a decrease in training loads and psycho-emotional stress at the recovery stage (Table 1). With intense physical activity and adequate recovery, an increase in testosterone levels and a decrease in cortisol levels were recorded [13]. In one study, an increase in testosterone levels in the recovery period relative to baseline was noted in skiers [2]. In the absence of normal recovery, the level of both total testosterone and its free fraction decreases.

The level of DHEA-S at the pre-competition stage for 10-14 days did not have significant differences with the group of students, but was significantly reduced at the second stage of the training cycle 7-10 days after the competition by 14.2%, compared with the group of students (p= 0.041) and increased at stage 3 30 days after the competition by 32.2% compared with stage 2 p=0.003 (Table 1).

Analysis of the data obtained did not reveal significant differences in the content of cortisol in the blood serum of wrestlers at different stages of the training cycle (Table 1). The average level of cortisol in the group of wrestlers before (for 10-14 days) and after the competition (after 7-10 days) was lower in comparison with the group of students (p=0.027; p=0.003, respectively) (table). Our data do not contradict the literature data. One study showed that a decrease in fasting serum cortisol levels after submaximal cycling in wrestlers compared to skiers and control subjects was noted, this is due to the fact that in this case, physical activity led to a decrease, providing, possibly, elimination hormones from the blood. And later, throughout the entire period of the study, the concentration of

Table 1

Indicators of the level of steroid hormones in wrestlers and students Me (25%Q1 -75%Q3)

Hormones (reference values)	Students (n =22)	Wrestlers		
		Stage 1 (n =18)	Stage 2 (n =17)	Stage 3 (n =17)
T (12,1-38,3 nmol/l)	30.64 (26.06; 36.83)	25.18 (19.26; 32.84)	29.42 (26.40; 34.19)	33.44 (21.54; 37.02)
K (150,0-660,0 nmol/l)	568.84 (516.77; 624.70)	540.28$^+$ (490.27; 559.82) p=0.027	522.14$^+$ (426.94; 542.00) p=0.003	560.21 (531.25; 603.00)
DHEA (3,0-11,0 mcg/ml)	5.10 (4.33; 5.89)	5.91 (4.56; 8.25)	4.77 (3.92; 7.57)	5.91 (4.51; 7.27)
DHEA-S (1,0-4,2 mcg/ml)	2.46 (2.09;3.43)	2.41 (2.07; 3.35)	2.11$^+$ (1.56; 2.38) p=0.041	3.11* (2.08; 4.06) p=0.003

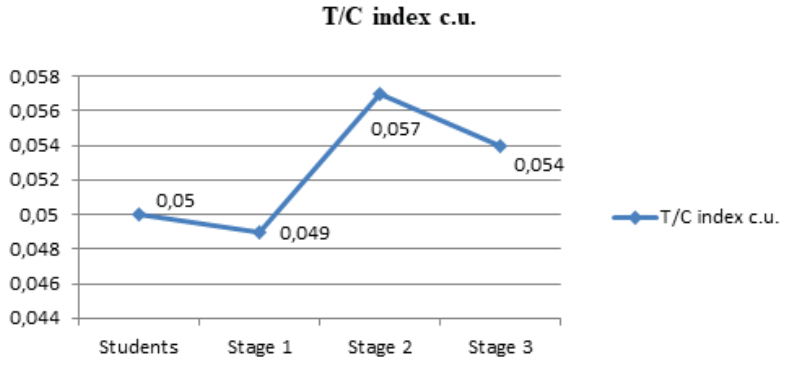
Note: + in comparison with the control group, * - in comparison with the 2nd stage, after the competition in 7-10 days.

cortisol in the blood serum on an empty stomach in wrestlers was significantly lower compared to the background [2].

In the group of wrestlers, a slight increase in the level of cortisol was noted at the 1st pre-competition stage 7-10 days before the competition and the 3rd recovery stage 30 days after the competition, compared with the 2nd post-competition period (after 7-10 days) (Table 1.). A higher value of cortisol at the pre-competitive stage of training is an adaptive response and a good indicator of the fitness of the body and is associated with the psycho-emotional state of some athletes. There are publications that indicate the relationship between pre-competitive cortisol concentration and good performance in martial arts [16], as well as a positive correlation with the psycho-emotional state, self-confidence and anxiety [14, 19]. The previous increase in cortisol concentration, most likely, reflects the psychological mechanisms that provide an increase in the athlete's precompetitive excitement and are part of the mechanism for increasing readiness to overcome the stress associated with the upcoming fight. A slight increase in cortisol contributes to increased physical performance and performance. Its excessive activation is an unfavorable factor and has a negative impact on the athlete's body, leading to the tension of adaptive reserves and showing fatigue and overtraining. In addition, an excessive increase in cortisol affects bone and muscle tissue, sleep, the cardiovascular system, immunity, endocrine regulation, weight change, and glucose regulation. As a result, with significant overloads and overtraining syndrome, the ratio of anabolism and catabolism hormones (testosterone/cortisol) changes with the prevalence of the latter [8].

Taking into account all these data, in order to identify the degree of stress of the studied body systems and its regulatory systems in the recovery process at different periods of the training process, the testosterone/cortisol index was determined. There is an increase in the ratio of the T/K index among athletes during the recovery period, after the competition (after 7-10 days) in comparison with the group of students and the period 10-14 days before the competition (p=0.013; p=0.024).

Correlation analysis showed a direct relationship between testosterone levels and cortisol levels (r = 0.363; p = 0.001), T / C index (r = 0.761; p = 0.000) and DHEA (r = 0.330; p = 0.004), a direct relationship was also revealed concentrations of DHEA with the level of



Changes in the T/K index of wrestlers at different stages of the training cycle:
+ in comparison with students, * in comparison with the 1st stage, before the competition (10-14 days)

Table 2

Dependence of steroid hormones in young wrestlers and students

Hormones	Ro Spearman	T	K	T/K	DHEA	DHEA-S
T	Correlation coefficient Value (two-sided) N	1.000 . 74	0.363** 0.001 74	0.761** 0.000 74	0.380** 0.001 74	0.121 0.306 74
K	Correlation coefficient Value (two-sided) N	0.363** 0.001 74	1.000 . 74	-0.155 0.188 74	0.454** 0.000 74	0.159 0.177 74
T/K	Correlation coefficient Value (two-sided) N	0.761** 0.000 74	-0.155 0.188 74	1.000 . 74	0.141 0.232 74	0.90 0.446 74
DHEA	Correlation coefficient Value (two-sided) N	0.380** 0.001 74	0.454** 0.000 74	0.141 0.232 74	1.000 . 74	0.540** 0.000 74
DHEA-S	Correlation coefficient Value (two-sided) N	0.121 0.306 74	0.159 0.177 74	0.90 0.446 74	0.540** 0.000 74	1.000 . 74

Note: ** Correlation is significant at the 0.01 level (two-tailed); *correlation is significant at the 0.05 level (two-tailed)

cortisol (r=0.454; p=0.000) and DHEAS (r=0.540; p<0.000), which confirms the regulation of anabolic processes over catabolic ones is associated with an increase in steroid hormones (Table 2).

DHEA is a hormone with androgenic activity, has an anabolic effect and is responsible for the development of secondary sexual characteristics. 90% of the hormone is produced in the adrenal cortex, the remaining 10% is synthesized in men in the testes, in women in the ovaries. The precursor of DHEA is cholesterol. In turn, DHEA is converted into other steroid hormones. In the body of men, DHEA is converted into stronger androgens: testosterone and androstenedione [7].

Neurosteroids (DHEA) and its sulfated form (DHEAS) are mainly synthesized by the adrenal cortex and partly in the brain tissue and are of great interest. [5,18]. In the brain, DHEA and DHEA-S regulate glucocorticoid activity and protect nervous tissue from high doses of cortisol. Activation of the hypothalamic-pituitary-adrenocortical system leads to the release into the systemic circulation of many steroid hormones, including DHEA, which is metabolized to DHEA-S with a pronounced antiglucocorticoid effect. It has been reliably confirmed that DHEA has such effects as anti-stress, antidepressant, immunomodulatory, which are essential for a person to maintain health and active longevity. Since DHEA is a biochemical substrate for the further synthesis of sex steroid hormones (testosterone and estrogens) and undergoes intracrine metabolism with the formation of testosterone and/or estradiol in the cells of a number of organs

and tissues, some authors suggest that DHEA deficiency in men can lead to testosterone and estrogen deficiency. [10].

Low DHEA values are more often associated with insufficient adrenal function. Chronic stress and disease can lead to a decrease in DHEA, indicating adrenal stress syndrome. DHEA works in many ways as a synergistic twin of another stress hormone, cortisol. This helps the body adapt more effectively to stress. Stress can be anything: physical, mental and emotional, but its impact is always long-term. For example, studying that is given to a person with difficulty or exhausting conditions at work can become a source of serious health problems.

DHEA-S is synthesized primarily as the sulfate ester from the cholesterol sulfate ester. DHEA-S undergoes hydrolysis, thereby maintaining a constant level of DHEA in the blood plasma.

Conclusion. The results of the study of the dynamics of the hormonal response to physical and mental stress at different stages of the training cycle revealed the features of the adaptive restructuring of the hormonal background, in connection with the sports activities of wrestlers. At the pre-competition stage (10-14 days before the competition), when wrestlers adapt to psychophysiological and physical loads, the level of steroid hormones with anabolic effect testosterone, DHEA and DHEAS remains unchanged, the cortisol level decreases p=0.027, in comparison with the group of students involved in physical education 2 times a week, which indicates a high level of physical fitness and good adaptation of the body. At the recovery stage (after 7-10 days of the competition) there is a significant increase in the T/K index p=0.013 and a significant decrease in the level of cortisol in athletes, in comparison with the control group, p=0.003 and the pre-competitive stage p=0.024, which indicates an increase in anabolic effects and efficiency of recovery processes in the body. A relatively high level of steroid hormones testosterone, DHEA, a significant increase in DHEAS (p = 0.003) and an insignificant decrease in the T/K index in comparison with the recovery stage in wrestlers 30 days after the competition indicates a high adaptation of the body to physical exertion and moderate activation pituitary-adrenal system to balance the processes of anabolism and catabolism.

Assessment of hormone levels in athletes in different periods of the training cycle requires an individual approach to identify ambiguous changes in the stress of adaptive capabilities, fatigue and overstrain.

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GENDER DIFFERENCES IN THE CONTENT OF THYROID HORMONES IN DIFFERENT GROUPS OF THE POPULATION OF THE ARCTIC

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The study of the gender characteristics of the thyroid gland functional activity take on particular significance in light of the increasing frequency of detecting various thyroid dysfunctions, especially in the Northern regions. Aim: to carry out a comparative analysis of the thyroid profile due to sex, taking into account the population groups of the North. Materials and methods. We examined 338 people born and living or wandering near the villages in the Arctic zone of the Russian Federation. The examined persons were divided by gender (men, women), age (21-44; 45-59 years) by gender and, population group (nomadic aborigines, sedentary aborigines, local Caucasoid population). The serum levels of thyroid hormones were determined by the method of enzyme immunoassay. Results and discussion. Analysis of sex differences in thyroid status by age groups showed a higher thyrotropin level in women of different age groups (p = 0.049; p = 0.048) compared with men (1.94 and 2.08 μIU/L and 1.60 and 1,81 μIU/L, respectively). In addition, in the age group 21-44 years, there was an increase in thyroxine level (107.31 and 97.70 nmol/L, p <0.001) and a decrease in the content of free triiodothyronine in women (4.79 and 5.36 pmol/L, p = 0.002) compared to men. There were shown a higher content of thyrotropin and thyroxine in the female aboriginal population compared with the male population. A higher level of thyroxine in women may be due to its reserve functions in relation to free fractions of iodothyronines, which play an important role in the reproductive health of women. The lower content of free fractions of triiodothyronine and thyroxine was shown in women belonging to the local Caucasoid population compared with men. Free fractions of thyroxine were lower in women - sedentary aborigines in relation to men of this group. The higher content of free fractions of iodothyronines in men may be due to longer-term effects from cold temperatures when working outdoors. Conclusion. Consequently, gender differences in the content of thyroid hormones among the local Caucasoid population are in the content of free fractions of iodothyronines, while the indigenous population has differences in the content of thyrotropin and total fractions of thyroxine. The sedentary aboriginal population, in addition to its own distinctive features characteristic, acquires the characteristics of the Caucasoid population with distinctive gender characteristics according to the free fractions of iodothyronines.

Keywords: thyroid gland, thyreotrophin, thyroxine, triiodothyronine, men, women, North.

Introduction. Thyroid pathologies occupy a leading position among diseases of the endocrine system, both in the world and in the Russian Federation, with a steady increase in the frequency of thyroid dysfunction registration in recent decades [6, 12]. It is well known about the age-related increase in the prevalence of thyroid diseases in both sexes, which in women is more often associated with an autoimmune response [10, 11]. There are also shown gender differences in the content of hormones of the hypothalamic-pituitary-thyroid axis. Some authors indicate that the TSH level is higher in the female population [11], and there were no gender differences in its content in population aged 65 years or over [10]. Free fractions T3 and T4 were higher in the female population than in the male [10, 11]. In residents of the European North of Russia (Arkhangelsk), the contents of total T4 and T3 were higher in women than in men without significant differences in the TSH level [7].

The thyroid gland is involved in the maintenance of the body's metabolism [11], and therefore, human adaptation to the conditions of the North is undoubtedly associated with the stress of the thyroid gland function, which increases when moving to the North, and can lead to the development of its dysfunction [4, 9]. One of the methods for diagnosing thyroid dysfunction is to determine the levels of TSH, total and free fractions of iodothyronines. However, not all developers of test systems in the recommended standards for determining indicators of thyroid activity take into account the sex of the examined persons. In addition, the activity of the thyroid gland is mainly determined by both the geographical latitude of residence [9] and the racial or ethnicity of the surveyed individuals [3, 5, 10]. At the same time, in recent decades, the traditional way of life of northern peoples has changed, that is associated with their transition from a nomadic to a sedentary way of life [1]. In connection with the heterogeneous information available in the literature on gender differences in the content of thyroid hormones and the practical absence of such data among persons leading different lifestyles, the aim of the study was: to conduct a comparative analysis of the thyroid profile in different sexes, taking into account the population groups of the North.

Material and methods. An analytical cross-sectional uncontrolled study of 388 people (aged 21-59 years) born and permanently residing in villages in the Arctic zone (village of Nelmin Nos NAO, village of Sovpolye, village of Soyana, village of Dolgoshchelye of the Mezensky district of the Arkhangelsk region (AR), village of Seyakha, village of Tazovsky, village of Gyda of the YaNAO), or wandering near these villages and the village of Pinega (AR)) of the Russian Federation was carried out. The surveyed were divided into groups according to the sex, age (21-44 and 45-59 years old), and groups of the population of the North (nomadic

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aborigines, sedentary aborigines, local Caucasoid population). The expeditions were carried out during the period of increasing daylight hours (March) from 2009 to 2016. The study was carried out in accordance with the Declaration of Helsinki of the World Medical Association "Ethical principles of scientific medical research with human participation." At the time of the study, those examined were not registered with an endocrinologist, had no exacerbations from cardiovascular and acute respiratory diseases. Blood collection was performed in the morning on an empty stomach after filling out the questionnaire and examining the doctor. On automatic plate analyzer ELISYS Uno ("Human GmbH", Germany) by enzyme immunoassay the serum concentrations of thyrotropin (TSH), total triiodothyronine (T3), total thyroxine (T4), free triiodothyronine (fT3), free thyroxine (fT4) were determined using test systems of LLC "Company AlcorBio" (Russia). The results were statistically processed using Statistica 10. The hypothesis of normal distribution was tested using the Shapiro – Wilk test. In accordance with the results, the medians and 10-90 percentile intervals of the studied hormones in the groups were determined. Comparison of groups was performed using the Mann-Whitney U-test.

Table 1

The content of hormones of the hypothalamic-pituitary-thyroid system in the blood of residents of the Arctic territories, taking into account gender and age

Variable	Men		Women	
	21-44 years old	45-59 years old	21-44 years old	45-59 years old
	1	**2**	**3**	**4**
	Me (10-90 %)	Me (10-90 %)	Me (10-90 %)	Me (10-90 %)
N	86	26	183	76
Age	41.0 (27.0; 44.0)	53.0 (45.0; 59.0)	41.0 (28.0; 43.0)	54.0 (46.0; 58.0)
TSH 0,23-3,4 uIU/mL	1.60 (0.60; 3.56)	1.81 (0.89; 3.04)	1.94 (0.90; 4.05) * **(1)**	2.08 (1.13; 7.22) * **(2)**
T3 1,0-2,8 nmol/l	1.76 (1.20; 2.62)	1.70 (1.01; 2.45)	1.70 (1.20; 2.68)	1.77 (1.20; 2.30)
T4 53-158 nmol/l	97.70 (63.2; 120.9)	103.50 (75.1; 122.5)	107.31 (82.5; 131.6) *** **(1)**	105.10 (71.8; 131.0)
fT4 10,0-23,2 pmol/l	14.80 (11.9; 20.1)	14.60 (11.6; 17.5)	14.40 (11.5; 18.1)	14.65 (10.9; 18.9)
fT3 2,5-7,5 pmol/l	5.36 (3.8; 7.0)	5.23 (3.7; 7.5)	4.79 (3.5; 6.4) ** **(1)**	4.80 (3.5; 7.2)

Notes: * - p <0.05; ** - p <0.01 **; *** - p <0.001 - reliability of differences in relation to the data of the corresponding column in the table. The column number is given in bold.

Table 2

The content of hormones of the hypothalamic-pituitary-thyroid axis in the blood of residents of the Arctic territories according to gender and population group

Variable	Men			Women		
	nomadic aborigines	local Caucasoid population	sedentary aborigines	nomadic aborigines	local Caucasoid population	sedentary aborigines
	1	**2**	**3**	**4**	**5**	**6**
	Me (10-90 %)	Me (10-90 %)	Me (10-90 %)	Me (10-90 %)	Me (10-90 %)	Me (10-90 %)
N	33	56	23	32	118	109
Age	42.0 (28.0; 54.0)	46.0 (33.0; 53.0)	44.0 (25.0; 56.0)	43.0 (24.0; 56.0)	47.0 (34.0; 57.0)	44.0 (28.0; 59.0)
TSH 0,23-3,4 uIU/mL	1.73 (0.90; 4.30)	1.45 (0.62; 2.97)	1.94 (0.79; 3.04)	2.47 (0.90; 4.36)	1.50 (0.80; 4.29)	2.15 (1.21; 4.90) * **(3)**
T3 1,0-2,8 nmol/l	1.70 (1.20; 3.10)	1.80 (1.24; 2.40)	1.48 (1.13; 1.93)	1.80 (1.40; 3.24)	1.70 (1.20; 2.10)	1.70 (1.10; 2.90)
T4 53-158 nmol/l	88.65 (60.9; 116.0)	102.40 (71.6; 122.5)	101.70 (68.8; 120.6)	108.45 (70.7; 125.4) ** **(1)**	101.12 (70.0; 119.8)	110.10 (88.5; 134.4) ** **(3)**
fT4 10,0-23,2 pmol/l	13.50 (11.6; 17.2)	15.65 (12.5; 20.7)	15.53 (13.2; 19.3)	14.45 (11.3; 18.3)	14.70 (11.4; 18.9) * **(2)**	14.50 (11.5; 17.3) * **(3)**
fT3 2,5-7,5 pmol/l	5.32 (3.9; 7.9)	5.43 (3.8; 7.1)	4.23 (3.2; 5.6)	5.23 (3.6; 8.9)	4.85 (3.5; 6.3) ** **(2)**	4.60 (3.4; 6.1)

Notes: * - p <0.05; ** - p <0.01 - reliability of differences in relation to the data of the corresponding column in the table. The column number is given in bold.

Results and discussion. Analysis of sex differences in thyroid status by age groups showed a higher TSH level in women of different age groups (p = 0.049; p = 0.048) compared with men. In women aged 21-44 years were shown an increase in the T4 level (p <0.001) and a decrease in the content of fT3 (p = 0.002) compared with men (table 1).

Depending on the group of population a similar pattern of an increase in the TSH level in women compared with men was noted among the sedentary aboriginal population (p = 0.037) (table 2). An insignificant increase in TSH level was noted in women - nomadic Aborigines and no increase in it - among the Caucasoid population. Increased T4 levels in women compared to men were recorded in nomadic (p = 0.008) and sedentary aborigines (p = 0.004). There were no differences in the content of T4 in persons of different sexes among the Caucasian population. There was shown a decrease in fT3 level in Caucasoid women compared with men (p = 0.002). Despite the absence of reliable gender differences in the content of fT4 when analyzed taking into account gender and age, analysis depending on the population group and gender showed a decrease in fT4 in the female population - sedentary aborigines (p = 0.024) and the local Caucasoid population (p = 0.030).

Thus, in nomadic and sedentary aborigines, similar gender differences were revealed, consisting in higher levels of total thyroxine and TSH in the female population compared to the male population. Free thyroxine in women were lower than in men both in the sedentary Aborigines and in the local Caucasoid population, as were the free T3 fractions, the greatest differences in which were noted in the local Caucasoid population.

The presence of a higher T4 level in the female aboriginal population compared to men can be explained by its ability to be a deposition of blood free fractions of iodothyronines, which are active forms and provide the body's metabolism, which is especially important when adapting to cold temperatures. The reserve of iodothyronines is especially important for the woman's body, which by its nature must ensure the formation and growth of the fetus [8, 12]. It has been shown that an increase in estrogen is combined with an increase in TSH in the blood and a decrease in the concentration of fT4 [10], and a decrease in estrogen in postmenopausal women is accompanied by an increase in thyroid dysfunction [11]. Probably, it is precisely due to the difference in the content of sex hormones that the greatest gender differences in the levels of thyroid hormones were revealed in the period of 21-44 years of age. Free fractions of iodothyronines are active forms that have a direct effect on various tissues and organs. There is information in the literature about the presence of sex differences in their content [11]. At the same time, it is known that their concentrations increase when exposed to cold [2]. One of the possible reasons for the higher levels of free fractions of iodothyronines in the male population of the North may be a longer exposure to low temperatures when working outdoors, which is accompanied by an activation of thyroid hormone metabolism with a decrease in the reserve of iodothyronines, namely, their total fractions [2].

Conclusion. In the population of the Arctic regions, gender differences in the content of hormones of the hypothalamic-pituitary-thyroid system were shown, consisting in a higher content of TSH, T4, a lower level of free fractions of iodothyronines in the female population compared to the male. Gender differences in the content of thyroid hormones among the local Caucasoid population are in the content of free fractions of iodothyronines, while the aboriginal population has differences in the content of TSH and total fractions of T4. The sedentary aboriginal population, in addition to the distinctive features of the content of TSH and T4, acquires the particular qualities of the Caucasoid population with distinctive gender characteristics by the free fractions of iodothyronines.

The data obtained are of interest in connection with the change in the lifestyle of indigenous peoples, with the possible impact of iodine deficiency conditions in the studied regions, and necessitate further studies on a representative sample on a large scale.

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DIAGNOSTIC AND TREATMENT METHODS

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MODERN SURGICAL TREATMENT OF ELDERLY PATIENTS WITH CHOLEDOCHOLITHIASIS AND MECHANICAL JAUNDICE

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A prospective analysis of diagnosis and treatment of the elderly and senile patients with acute cholecystitis complicated by choledocholithiasis and mechanical jaundice is carried out. Ultrasound scan, multispiral computed tomography, MRI and endoscopic retrograde cholangiopancreaography were used in complex diagnosis. The tactics of a double step-by-step approach in surgical treatment of these patients was performed, the first stage required minimally invasive methods of decompression of bile ducts, including endoscopic. The second stage was preferably carried out by minimally invasive surgical operation. The duration of pre-operative preparation and choice of the method of the operation depended on the morphology of acute cholecystitis and degree of the patient's physical condition. Due to the double step-by-step stage approach of the surgical tactics in such patients the level of postoperative complications decreased up to 9.1% and postoperative lethality reduced up to 6.8%.

Keywords: acute cholecystitis, choledocholithiasis, elderly and senile age, risk factors, level of the severity of the physical condition, mechanical jaundice, cholecystectomy, microcholecystostomy, magnetic resonance (MR) cholangiography, endoscopic retrograde cholangiopancreaography, lythoextraction, laparoscopy, laparoscopic cholecystectomy, cholecystectomy.

Introduction. Cholelithiasis is one of the prevalent diseases, from 10% to 40% of the total world population suffer from it depending on the age and sex, the total numbers showed 23 million people in 2016. The cases of cholelithiasis in the Russian Federation are similar to the numbers worldwide [13]. The surgical practice most commonly, as a rule, deals with the complicated forms of cholelithiasis, which refers to 40% of all the cases. Most common complication is choledocholithiasis, which is caused by concrement migration into the bile duct lumen resulting in mechanical jaundice in 25% of the cholelithiasis cases. The concurrent pathologies like obesity, ischemic heart disease, arterial hypertension and chronic pathologies of the respiratory system inevitably result in outcomes of the surgical treatment [7,8,14].

Most prevalent non-invasive methods of diagnosis are ultrasound scan (US) and magnetic resonance imaging (MRI) of the bile ducts. Sensitivity of the ultrasound scan in the diagnosis of the mechanical jaundice is 87-90%, in cholelithiasis – 98.3-99%, tumors of the bile ducts – 63.9-70%, total specificity – 85.4-90% [12,15,16,20]. Magnetic resonance imaging (MRI) is still the most informative and non-invasive method of choledocholithiasis diagnosis. This method reveals the bile duct stones of the size up to 2 mm in diameter, the sensitivity is 100% and specificity is 96-98.5% [1,11].

The main cause of mortality in the elderly patients with acute cholecystitis complicated by acute cholecystitis and mechanical jaundice is progression of the hepatic failure after the surgical intervention. The elderly patients suffering from different concomitant diseases, as we have described above, are at a high risk in a case of urgent surgery [9,10,17].

A variety of therapeutic and diagnostic measures, which include consequent approach and total volume of the medical intervention are realized in two step-by-step stages for such patients [2,3,4,16,18,19]. The first stage is realized by conservative elimination of the source of the cholestasis by means of endoscopic or X-ray endobiliary interventions. Non-surgical removal of the cholestasis in the bile ducts and bile intoxication with the following hepatic failure helps restore the functions of such vital organs as the liver and the pancreas. The delayed operation is performed with a minor risk for the patient and in most cases it requires lesser scope of work [6].

Objectives of the work are to analyze the results of the double step-by-step approach surgical treatment in the elderly and senile patients with acute cholecystitis complicated by choledocholythiasis and mechanical jaundice.

Methods and materials. The controlled cohort analysis of the results of the surgical treatment of 87 (100%) elderly and senile patients, with complicated forms of the cholelithiasis at its different degrees, is represented. The patients were admitted to the surgical department of the Republican hospital #2, the Center for urgent care in Yakutsk within the period of 2016-2020 (table 1).

A great prevalence of the patients are the women - 55 (63.2%), the men – 32 (36.8%). Concomitant diseases of the patients are represented in the table 2. The most common pathologies were disorders of the cardiovascular, respiratory, urinary systems and diabetes which was

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closely associated with a high rate of the postoperative mortality [5,6]. Nonetheless, the objective picture of the severity of the case can be represented only together with the factors of the operative and anesthetic risks taking into account somatic pathologies (table 2).

Postoperative lethality is associated with these diseases [5,6]. However it should be underlined again that age and concomitant diseases do not fully reflect the severity of the physical condition of the patient [4].

Magnetic resonance cholangiography (MR cholangiography) was preferable in diagnosing choledocholithiasis. MR cholangiography is a highly informative method to diagnose the location of the concrement in the bile ducts, and it is associated with the total volume of the intervention, outcome and prognosis of the disease. The sensitivity and specificity of MR angiography method is estimated by 94.3% and 100% respectively [1,11]. Thus, the morphologic forms of acute cholecystitis were revealed according to the results of clinical examination and the results of the ultrasound scan and MR cholangiography: catarrhal form in 25 (28.7%), destructive (phlegmonous) in 62 (71.3%) (table 3).

There are 4 (I,II,III and IV) categories of the severity of the patient's physical condition. It is determined that the prolonged cases of the jaundice could precisely determine the severity of the condition out of all the clinical signs of cholelithiasis complications. Thus, almost all the cases lasting for more than 2 weeks are included into the III and IV categories of the severity.

Results and discussion: The choice of the therapeutic tactics in a case of acute cholecystitis is performed with the help of the scored rating of the surgical risks depending on the severity of the patient's condition [4]. The score rating helped diagnose and treat complicated cases of cholelithiasis. Such tactics allowed optimum volume of minimally invasive surgical operations by means of endoscopic retrograde cholangiopancreaography (ERCP), endoscopic papillosphincterotomy (EPST) with lythoextraction, ultrasound guided microcholecystostomy, laparoscopic cholecystectomy, cholecystectomy by a mini approach [5,6].

Endoscopic retrograde cholangiopancreaography (ERCP) was performed in 47 (54%) cases, 17 (46%) patients suffered from multiple choledocholithiasis, 5 (10.4%) cases were complicated by acute suppurative cholangitis, 11 (23.1%) had peripappilary diverticulum in the area of major duodenal papilla, and 7 (16.1%) patients had adenoma of the papilla. The size of the gallstones varied from 1.0 to 2.2 cm.

The diagnostic stage was followed by an attempt of endoscopic papillosphincterotomy or balloon dilatation of major duodenal papilla, after which they underwent lithotripsy and removal of the concrements which was successful in 40 (85%) cases. 5 (11%) patients underwent secondary bile stone removal (lithoextraction), 2 (4%) patients had very large concrements in the hepatocholedoch, endoscopic manipulations for them were ineffective. They had laparoscopic choledocholithotomy to extract the stones.

Volume of the endoscopic interventions directly depended on the clinical and anatomical conditions of each patients, size and amount of the concrements, their localization and concomitant pathology of the gallbladder, major duodenal papilla and pancreas. In "standard" cases endoscopy included endoscopic papillosphincterotomy (EPST) and lythoextraction, in non-standard (complex) anatomical conditions a balloon dilatation,

Table 1

Age and severity distribution of the patients

Age, years	Patients, total n(M±m%)	Including: category of the condition severity n(M±m%)			
		I	II	III	IV
60-69	41(47.2)	3(25.0)	23(56.1)	11(22.0)	4(28.5)
70-79	37(42.5)	9(75.0)	14(34.1)	7(14.0)	7(50.0)
80 and older	9(10.3)	-	4(9.8)	2(10.0)	3(21.5)
Total	87(100.0)	12(100.0)	41(100.0)	20(100.0)	14(100.0)

Table 2

Concomitant diseases in (87) patients with acute cholecystitis, complicated by the mechanical jaundice

Concomitant diseases	The number of the patients
Coronary heart disease with changes in ECG	27
Myocardial infarction, dated back from 9 to 17 days	3
Postinfarction aterosclerotic cardiosclerosis with the disturbance in the rhythm and conduction	29
Morbus hypertonicus, I-II degree	32
Cardiovascular collapse, II-III degree	5
Bronchial asthma	16
Diabetes mellitus	13
Chronic kidney disorders	6
Acute stroke dated back 3-5 days	1
Residual effects after stroke	4
Chronic and non-specific pulmonary disorders	10
Others	4

Table 3

Prevalence of the cases according to morphological form of gallbladder inflammation and the level of its severity

Type of gallbladder inflammation	Patients, total n (M±m%)	Including: category of the condition severity n (M±m%)			
			II	III	IV
Catharal	25(28.7)	7(38.8)	13(33.3)	3(14.2)	2(22.3)
Phlegmonous gangrenous	62(71.3)	11(61.2)	26(64.9)	18(85.8)	7(77.7)
Total	87(100.0)	18(100.0)	39(100.0)	21(100.0)	9(100.0)

lithotripsy, nasobiliary drainage and hepatocholedoch stenting were engaged.

If there is a destructive cholecystitis complicated by choledocholithiasis and mechanical jaundice the surgical operation can cope inflammatory process in the gallbladder, thus preventing urgent laparotomy to decompress the gallbladder. Ultrasound guided cholecystostomy is a less traumatic operation, it is characterized by lesser rate of the following complications [4].

Double step-by-step stage surgical interventions were performed only in the cases of catarrhal form of acute cholecystitis complicated by choledocholithiasis and mechanical jaundice in 25 (28.7%) patients. After endoscopic corrections of choledocholithiasis 11 of these patients were diagnosed with I-II categories of the severity, they underwent laparoscopic cholecystectomy afterwards. A single-stage laparoscopic cholecystectomy and choledocholythotomy with lythoextraction was performed in 6 patients. Out of the total 25 cases that underwent step-by-step surgical interventions in its total volume, only 1 case required a wide laparotomy. 4 patients had postoperative complications. No lethal cases were registered.

The vast majority of the elderly and senile patients 62 (71.3%) suffering from acute cholecystitis and mechanical jaundice was diagnosed with destructive (phlegmonous) cholecystitis morphologically. Out of these cases 37 patients with the categories I and II underwent laparoscopic cholecystectomy with choledocholithiasis which resulted successfully.

18 cases (29.03%) of destructive cholecystitis were diagnosed with the III category of the severity. The patients of this group had ultrasound-guided microcholecystomy a day or two before the radical surgical intervention in order to decompress the gallbladder and prevent mechanical jaundice. As a result, endoscopic cholecystectomy was performed after 24-48-hour of previous endoscopic papillotomy and lythoextraction. There were 2 cases of the wide laparotomy. Acute cardiovascular insufficiency caused a lethal case of 1 patient.

There were 8 cases (12.9%) with the IV category of the severity of condition. The total volume of the surgical intervention was similar to the III category: all the patients underwent initial decompression of the gallbladder to prevent mechanical jaundice and cholemia by means of microcholecystostomy with the following endoscopic pappilothomy and lythoextraction of choledocholithiasis by the end of the second day. 3 lethal cases out of 8 were registered, they were mostly caused by acute hepatorenal insufficiency in 2 cases; and 1 died of sepsis effects and pulmonary embolism.

Conclusion. Thus, geriatric patients with acute cholecystitis complicated by choledocholithiasis and mechanical jaundice compose a particular group of the patients which requires specific diagnostic and therapeutic approaches. Their treatment is characterized by a double step-by-step approach, where the first stage is performed by ultrasound quided microcholecystostomy of the gallbladder to prevent mechanical jaundice, cholemia and hepatic failure which is followed by the second stage, i.e. the radical operation as endoscopic cholecystoctomy.

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APPROACHES TO PHYSICAL REHABILITATION OF PATIENTS WITH SPINOCEREBELLAR ATAXIA TYPE 1 IN THE CLINIC OF YSC CMP

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The aim of the study was to search for approaches to physical rehabilitation of patients with spinocerebellar ataxia type 1 (SCA1) using kinesitherapy. Gradual activation of motor activity is the main condition for improving the psychological and physical health of patients with SCA1. In our article, physical rehabilitation is specially directed use of physical exercise as a means of treating a disease and improving body functions that are disrupted or lost due to SCA1's neurodegenerative processes.

Keywords: kinesitherapy, physical rehabilitation, spinocerebellar ataxia type 1, Republic of Sakha (Yakutia).

Introduction. Studies of hereditary diseases of the nervous system are becoming more relevant in the world due to severe clinical manifestations, disability and social maladaptation of patients.

In 1991, dynamic mutations, which are the cause of a large group of diseases of the human nervous system, were described, among which polyglutamine diseases with an increase in the number of CAG repeats and various clinical manifestations, such as Kennedy's disease, Huntington's Chorea and spinocerebellar ataxia of types 1, 2, 3, 6, 7 and 17 are distinguished [10].

Spinocerebellar ataxia type 1 (SCA 1) belongs to the group of neurodegenerative diseases with late manifestation. The mutation causing SCA1 is located on the p arm of chromosome 6 and represents a pathological increase in trinucleotide CAG repeats, therefore SCA1 is also classified as a disease with dynamic mutations. The prevalence of SCA1 varies in different populations of the world [5,8].

In the last two decades, scientific and clinical interest in the use of physical exercises for the treatment of mobility problems in persons with neurodegenerative pathology has sharply increased. Advances in basic scientific research suggest neurochemical and neuroplastic changes after physical exertion, an increasing number of high-quality studies document specific aspects of improving mobility after physical exertion [6,7,9,11].

Individuals suffering from type 1 spinocerebellar ataxia are usually demotivated to engage in recreational physical exercise. The most common obstacles are external barriers: the lack of an accessible environment for people with disabilities, feelings of awkwardness and embarrassment in public, anxiety, frustration and anger. Patients with SCA1 are also demotivated by muscle weakness, stiffness, balance disorders, and fear of injury [9].

One of the forms of exercise therapy is kinesitherapy - a new direction in medicine based on the restoration of the human ability to move normally. A person, performing active and passive movements and certain exercises of therapeutic gymnastics, achieves a definitive improvement in his condition. Kinesitherapy as a specialty has a scientific and applied nature, which combines medicine, pedagogy, physiology and biochemistry. It contributes to the psychoemotional and physical comfort of the individual [2].

The aim of the study was to search for approaches to physical rehabilitation of patients with spinocerebellar ataxia type 1 (SCA1) using kinesitherapy.

Materials and methods. The medical examination of patients with SCA1 and the curation of the Republican medical and genetic register of hereditary and congenital pathology has been conducted in the Medical and Genetic Center of the Republican Hospital No. 1 - NMC since 2001, and in 2019, a Center for Neurodegenerative Diseases was organized in the Clinic of the YSC CMP on the order of the Ministry of Health of the Republic No. 01-07/184 dated 02/14/2019. "On the procedure for routing neurological patients suffering from neurodegenerative diseases at the outpatient and hospital stages" [1,3].

The study was conducted within the framework of the research "Exercise therapy in the rehabilitation system of patients with spinocerebellar ataxia type 1 in the Republic of Sakha (Yakutia)", agreed by the local Committee on Biomedical ethics at the YSC CMP (extract from Protocol No. 53 of April 13, 2021)

The study included patients with SCA1 who were treated in the clinic of YSC CMP during 2021. A total of 14 patients were examined, of which 2 were men and 12 were women; 28% of the examined were young people from 20 to 30 years old; 35% were middle-aged (31-50 years); 35% were elderly patients from 51 to 75 years old. All patients had gait disorders to varying degrees. We used the Morse Fall Scale assessment, which is used to assess the probability of falling risk due to the presence of hereditary or acquired risk factors.

Results and discussion. One of the main clinical signs of SCA1 are gait disorders of the patient, due to damage to peripheral nerves, spinal cord roots, loss of sensitivity in the legs. In addition, with cerebellar ataxia, disorders of motor coordination are present, and patients are concerned about loss of balance, frequent falls [5,6]. In our study, gait disorders were assessed: the majority of patients (86%) receiving maintenance

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therapy at the YSC CMP clinic had mild gait disorders. This is due to the fact that patients with severe gait disorders or using a wheelchair rarely come to the YSC CMP clinic due to the lack of conditions (wheelchair lift / elevator).

We analyzed how SCA1 patients move from their self-reports. In our study, only 28% of patients moved by themselves without support, while the majority walked with the help of a cane (35%) and leaning on furniture and walls (35%)

The assessment of falls was carried out using a standard Morse Fall Scale in points, the frequency of falls of patients with SCA1 was estimated for three months. It turned out that half of our patients (50%) suffered involuntary falls in various situations.

Currently, the Russian system of therapeutic/adaptive physical education faces the task of scientifically substantiating the physical rehabilitation of disabled people for their professional and social adaptation. Specialists in the field of rehabilitation of patients with spinal cord disorders distinguish the following forms of physical education:

- independent physical exercises according to methodological instructions, walking, walks in the outside;
- group classes under the guidance of an instructor in medical institutions and rehabilitation centers [4,6]

Another additional method is the use of demonstrational physical exercises in the online Zoom program. So, in 2021, for the first time, we held a webinar for patients with SCA1 on the topic "The importance of physical education for patients with SCA1".

The main conditions for practicing SCA1 physical therapy are: methodical and daily exercise; exercise should bring pleasure to the patient; it is necessary to adhere to the principle "from simple to complex" (Fig.1).

Gradual activation of motor activity is the main condition for improving the psychological and physical condition of patients with SCA1. At the same time, all types of motor activity are effective: physical exercises, walking, dancing, and practicing suitable sports. Significant emotional stresses, physical exercises requiring intense attention and continuous changes in response to changing conditions are contraindicated in patients with SCA1, it is important to avoid overwork and keep your condition under control [9,11].

We have developed a "Self-monitoring Diary" for patients with SCA1 in the form of a notebook, where patients are offered to perform two sets of simple exercises daily, it also contains recommendations for observing the daily schedule, nutrition, graphs for daily control of heart rate and blood pressure (Fig. 2).

Thus, at this initial stage of research, we are searching for approaches and

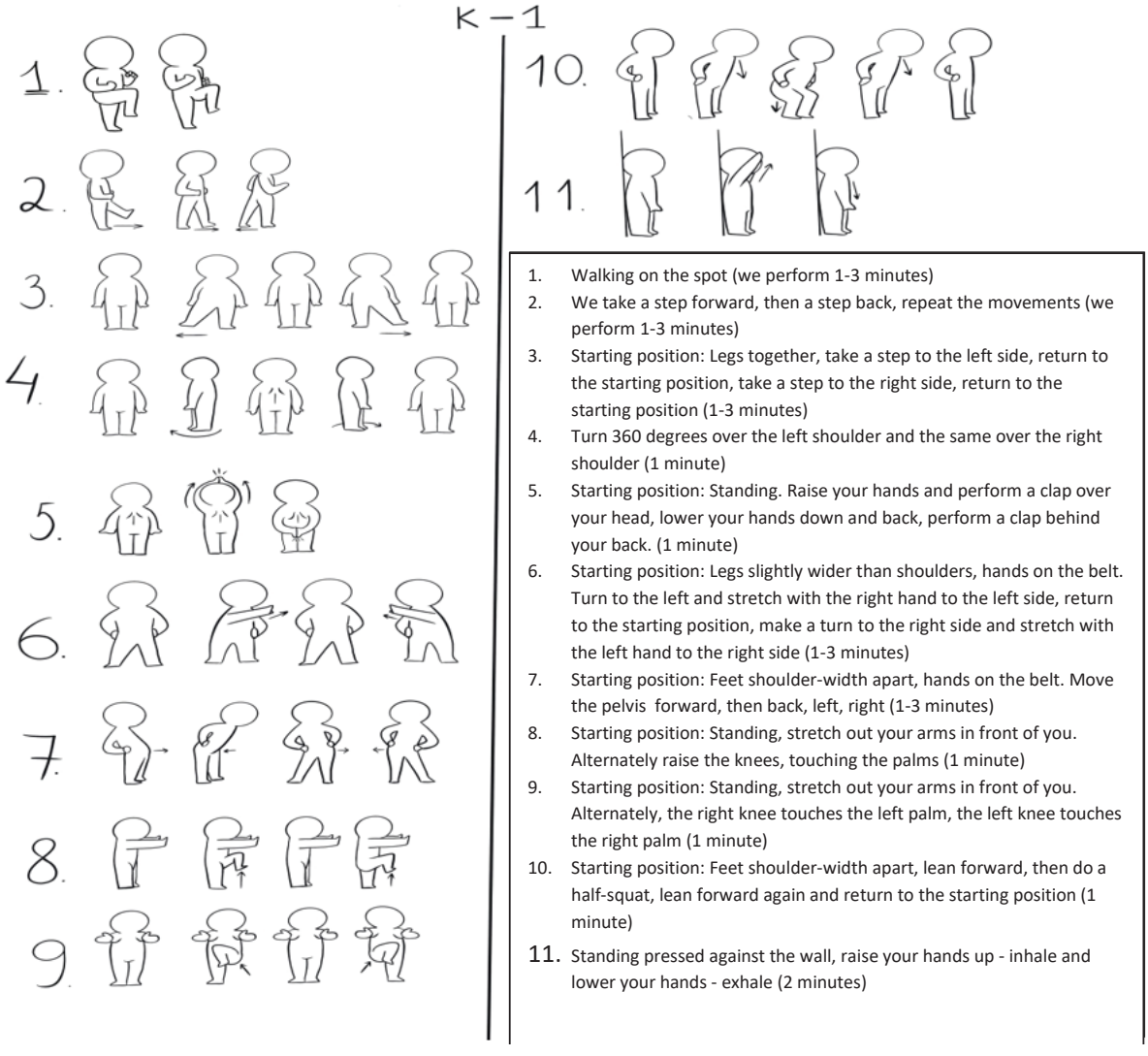

Fig. 1. A set of simple exercises for the development of coordination in patients with SCA1

Fig. 2. Self-monitoring diary for patients with SCA1

methods to the physical rehabilitation of a complex patient group - patients with SCA1. The difficulty lies in the fact that spinocerebellar ataxia type 1 is an incurable and progressive disease of the nervous system. The very awareness of this fact demotivates patients to engage in physical exercise, additional professional psychological assistance is needed for patients receiving maintenance therapy in the clinic.

Conclusion. Taking into account the urgency and sparseness of source material on problems of physical rehabilitation of patients with persistent and progressive health disorders, in the article we describe the first results of kinesitherapy treatment on patients with SCA1. In our article, physical rehabilitation is specially directed use of physical exercise as a means of treating a disease and improving body functions that are disrupted or lost due to SCA1's neurodegenerative processes. At the first stages of our research, we set the tasks of using simple sets of physical exercises so that, firstly, they have a health-improving and restorative effect on the body; secondly, they strengthen weakened muscles, improve coordination of movements. At the next stage, patients with SCA1 will be divided between case and control groups, we will also apply research methods to develop scientific justifications for physical rehabilitation: pedagogical experiment, questionnaire, stabilometry, goniometry, dynamometry, etc.

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DIAGNOSTICS AND DYNAMIC OBSERVATION OF CONGENITAL MALFORMATIONS OF THE URINARY SYSTEM ORGANS IN FIRST-YEAR CHILDREN

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Introduction. Congenital malformations of the urinary system occupy a leading place in the progression of children chronic kidney disease. Therefore, the purpose of our study was to monitor the abnormalities of children kidney defects and to determine the tactics of managing patients with obstructive malformations in a polyclinic. **Materials and methods.** We analyzed the data of 126 children medical records for the period from 2014 to 2020, in whom ultrasound changes in the kidneys and urinary tract was detected in the first month of life. Obstructive variants of renal defects was recorded in 102 (80.95 ± 3.50 %) children. Depending on the presence of urinary syndrome. Children with obstructive defects were ranked into two groups: Cohort I included 30 (29.41 ± 4.51%) children with kidney anomalies in whom a urinary tract infection was registered, and Cohort II included 72 (70.59 ± 4.51 %) a child with kidney abnormalities without changes in urine tests. **Results.** Pyelectasias prevail in the structure of kidney anomalies in infants – in 65.08 ± 4.25% of cases, which disappear spontaneously in 68.63 ± 4.59 %. The negative echographic dynamics of defects was significantly more often recorded in children with the addition of urinary tract infections ($\chi 2 = 5.47$, with $p = 0.01$). For children with obstructive variants of kidney anomalies, early accession of urinary tract infection is characteristic – at 6 months with a frequency of exacerbation 2 times a year. Conclusions. If pyeloectasia is detected at the age of 1 month, it is necessary to conduct a sonographic study in dynamics at 3 and 12 months, and at 6 months – to prescribe a general urinalysis and bacteriological examination of urine

Keywords: infants, congenital malformations of the urinary system, urinary tract infection, ultrasound diagnostics, pyeloectasia.

Introduction. Despite the significant advances in modern medicine in the diagnosis of diseases, the problem of congenital malformations does not lose its importance [4,13]. The most common types of defects include congenital anomalies of the kidney and urinary tract (CAKUT), which accounts 20 to 50% of all reported cases [5,10,11]. It is well known that congenital malformations of CHI are the cause of chronic kidney disease (CKD) and end stage renal failure (ESRD) in children, affecting their growth, development and socialization [5,10,11]. Accession of urinary tract infection (UTI) in patients with structural abnormalities of the CAKUT leads to earlier scarring and thinning of the renal parenchyma and, as a consequence, a decrease in glomerular and tubular renal function [5,8].

The method of ultrasound prenatal diagnostics allows to prevent the birth of children with uncorrected malformations, to detect kidney anomalies in the early stages of the disease, but its effectiveness, according to various sources, ranges from 0.6 to 14% [7,8]. Therefore, in the Russian Federation, in the first month of life, all children undergo a planned ultrasound examination of the kidneys, which makes it possible to diagnose CAKUT that have not been verified in the antenatal period. For example, when conducting mass neonatal screening in the Chuvash Republic, it was found that the share of CAKUT not detected at the stages of prenatal diagnosis is 15.5% among the entire child population of the region [9]. According to Vito Antonio Caiulo et al (2012), as a result of mass postnatal screening of 17,783 infants carried out over eighteen years, the proportion of congenital malformations of the kidneys was 0.96% [12]. Yinv Gong et al (2018), during an ultrasound examination of 12,350 newborns over five years, diagnosed CAKUT in 1180 (13.4%) people [10]. It should be noted that today there is no unified approach to interpreting the results of sonograms in relation to the size of the pyelocaliceal system (PCS) in children. Most of the studies are devoted to the postnatal management of children with prenatally diagnosed variants of kidney and urinary tract defects, but there is practically no work on assessing the dilatation of the pyelocaliceal system, if abnormalities of the pyelocaliceal system were detected in the first months of a child's life during routine examination [7,8]. Therefore, the purpose of our study was to monitor congenital kidney defects in children and determine the tactics of managing patients with obstructive malformations in a polyclinic.

Materials and research methods. An analysis of 1256 outpatient medical records (form No. 112 / y) were carried out among the clinics of Vladivostok for the period from 2014 to 2020, of which 126 (10%) children at the age of 1 month during the first screening examination revealed ultrasound changes in the kidneys and urinary tract. 65 girls (51.59 ± 4.45%) and 61 boys (48.41 ± 4.45%) took part in the work, and then all children were followed–up until they reached one year of age. All patients underwent a standard clinical and laboratory examination, and underwent ultrasound diagnostics at the age of 1, 3, 6 and 12 months. Statistical processing was carried out using the Statistica version 10.0 software. The assessment of the significance of the factors was carried out using X2 Pearson. Differences were considered statistically significant at $p < 0.05$.

Results and its discussion. In children with congenital anomalies of the kidney and urinary tract, pyeloectasias prevailed, which were registered in 82 (65.08 ± 4.25%) children, in second place was hydronephrosis – in 15 (11.90 %) children; pyelocaliceal system (PCS) – in 9 (7.14 %), hydrocalicosis – in 5 (3.97%), vesicoureteral reflux (VUR) – in 5 (3.97 %), renal hypoplasia – in 3 (2.4%), renal agenesis – in 2 (1.59 %), in isolated cases such pathologies as: horseshoe kidney, polycystic kidney disease, lumbar

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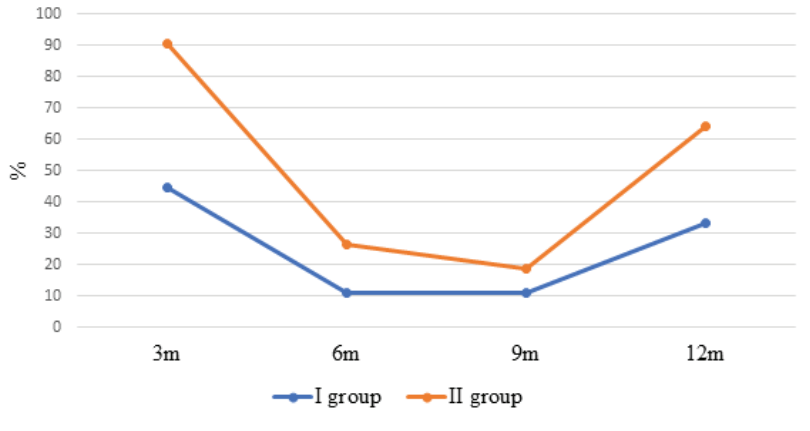
dystopia, combination of iliac dystopia and hypoplasia of the kidney, a combination of hydronephrosis and kidney cysts (0.79 %). In 7 (5.56 %) children, renal and urinary tract anomalies were diagnosed in the antenatal period: of these, pyelectasis was detected in 2 cases, renal hydronephrosis also in two children, in one case – iliac dystopia with hypoplasia of the left kidney and polycystic kidney disease.

Congenital anomalies of the kidney and urinary tract were combined with minor cardiac anomalies (opened oval window, Eustachian valve of the inferior vena cava, additional chord of the left ventricle) in 21 (41.18 ± 6.89%) children, with pathology of the hepatobiliary tract (deformation of the biliary bladder, kink of the gallbladder) – in 17 (33.33 ± 6.60%), with orthopedic pathology (torticollis, varus or valgus deformity of the feet) – in 7 (13.73%), with umbilical hernias – in 6 (11.76%).

Obstructive variants of kidney defects in the form of pyeloectasia, hydronephrosis and hydrocalicosis were recorded in 102 (80.95 ± 3.50%) cases. Depending on the presence of urinary syndrome, they were ranked into two groups: cohort I included 30 (29.41 ± 4.51%) children with UTI combined with renal abnormalities, and cohort II included 72 (70.59 ± 4, 51%) of a child with kidney abnormalities without changes in urine tests. In the group of children with UTI against the background of congenital malformations, girls were significantly more often recorded than in the second (70.00 ± 8.31% and 38.89 ± 5.75%, respectively, $\chi 2$ = 8.211, with p = 0.0042), which agrees with the literature data – the risks of developing UTI against the background of the CAKUT are 30% higher in girls and in children with grade 3–4 hydronephrosis [8,14]. In the first cohort, the mean age of UTI manifest was 6.17 ± 0.67 months, and the frequency of exacerbations was 2.07 ± 0.28 times per year of observation. Pathogenic microorganisms were isolated in 10 (33.33%) children in bacteriological analysis of urine, in 70% of cases uropathogens of the Enterobacteriaceae family were found.



Dynamics of spontaneous resolution of CHS dilatation in children with congenital malformations of OMS according to echographic examination data

Of great importance in the obstructive uropathy diagnosis in children during the first months of life is the determination of the dilatation of the PCS; in the works of various authors, the size of the pelvis is considered to be from 0.2 to 0.7 cm [1,6]. In group I, the sizes of the PCS of the right and left kidney during ultrasound diagnosis of pyeloectasias did not differ statistically and were determined in the range – 0.51 ± 0.04 cm and 0.52 ± 0.03 cm, respectively (p> 0.05), and in children with hydronephrosis recorded a more significant dilatation of the pelvis on the left than on the right – 1.35 ± 0.17 cm

Table 1

Sizes of the kidneys in group I, depending on the age of the child, (M ± m)

Age, months	Right kidney			Left kidney			p
	Length, sm	Width, sm	Parenchyma thickness, mm	Length, sm	Width, sm	Parenchyma thickness, mm	
1	4.44±0.12	2.16±0.03	9.76± 0.12	4.67±0.12	2.2±0.06	9.61± 0.13	>0.05
3	5.19± 0.08	2.51±0.07	10.15±0.19	5.43± 0.13	2.54± .08	10.04±0.26	>0.05
6	5.51 ± 0.11	2.61± 0.05	10.2 ± 0.19	5.79± 0.14	2.62±0.06	10 ± 0.22	>0.05
9	5.94 ± 0.19	2.61± 0.08	10.71± 0.18	5.98± 0.24	2.64± 0.12	10.5 ± 0.22	>0.05
12	6.29 ± 0.14	2.75± 0.07	10.96± 0.18	6.5 ± 0.14	2.8 ± 0.08	11.14 ± 0.2	>0.05

Table 2

Sizes of the kidneys in group II, depending on the age of the child, (M ± m)

Age, months	Right kidney			Left kidney			p
	Length, sm	Width, sm	Parenchyma thickness, mm	Length, sm	Width, sm	Parenchyma thickness, mm	
1	4.37±0.06	2.09±0.02	9.49 ± 0.09	4.54±0.07	2.11±0.02	9.53 ± 0.09	>0.05
3	4.91±0.06	2.28±0.02	10.02±0.06	4.97±0.07	2.33±0.04	10.03± 0.06	>0.05
6	5.61±0.09	2.43±0.04	10.16±0.14	5.63±0.09	2.43±0.04	10.23±0.14	>0.05
9	6.24±0.29	2.81±0.13	10.86±0.26	6.26±0.31	2.8±0.13	10.86 ± 0.26	>0.05
12	6.33±0.09	2.83±0.04	11.03±0.13	6.45±0.11	2.83±0.04	11.12± 0.12	>0.05

and 0.78 ± 0.1 cm, respectively, with p = 0.0233. In group II, the size of the PCS with pyeloectasia on the right averaged 0.51 ± 0.04 cm, and on the left – 0.57 ± 0.02 cm, which does not statistically differ from the data in patients of the first cohort (p> 0.05). In hydronephrosis in children with CAKUT without UTI attachment, the average sizes of the pelvis of the right and left kidney were determined at the level of 0.54 ± 0.03 cm and 0.9 ± 0.1 cm, respectively (p> 0.05). It is noteworthy that the expansion of the PCS in children with UTI against the background of hydronephrosis on the right and on the left was more significant than in patients of group II (p <0.05).

Most experts are of the opinion that in 50% of cases, hydronephrosis detected at the stages of prenatal diagnosis can independently resolve by one year of life [7,8]. In our study, spontaneous regression of enlarged renal PCS according to the results of sonograms in group I was observed in 18 (60%) children, of which: after 3 months in 8 (44.45%), after 6 months – in 2 (11.11 %), after 9 months – in 2 (11.11%) observed patients, by 12 months – in 6 (33.33%) (Pic. 1). No dynamics was revealed in 5 (16.7%) children, negative echographic changes were recorded in 7 (23.3%) patients, as a result of which 4 children underwent surgical treatment. In the second group, the regression of PCS expansion was documented in 52 (72.2%) children, of which: after 3 months in 24 (46.1%) children, after 6 months – in 8 (15.4%), after 9 months – in 4 (7.7%) patients, by 12 months – in 16 (30.8%). In 15 (20.8%) children, no dynamic changes were noted throughout the observation period, and in 5 (7%) patients, negative dynamics was documented by 12 months of age.

According to the literature, the presence of recurrent UTIs can adversely affect the functional state of the renal parenchyma in children with congenital anomalies of the kidney and urinary tract and increase the need for surgical treatment [5,8], which is also confirmed by the data of our study – in the group of UTIs with a combination of concurrent malformations, more negative dynamics than in the comparison group ($\chi 2 = 5.47$, with a significance level of p = 0.01), and pyeloureteroplasty was indicated for children only from cohort I. When ultrasound examination of the kidneys state, it is necessary to assess not only the expansion of the PCS, but also the length, width, and thickness of the renal parenchyma [2,3,8]. We analyzed the ratio of sizes between the right and left kidneys in the study groups. 4 children were excluded from the first cohort, because due to negative echographic dynamics (PCS more than 25 mm), the children underwent pyeloureteroplasty. The results of the study showed that in both groups there was no significant difference when comparing sizes of the right and left kidneys (Tables 1 and 2).

It is believed that the thickness of the parenchyma in children during the first six months of life is in the range of 8–11 mm, from six to twelve months – 9–12 mm [2]. In our study, according to the results of sonograms, in patients of both groups, the parenchyma thickness corresponded to age norms.

Conclusions

1. In the structure of the kidneys and urinary tract anomalies in infants, pyelectasias prevail in 65.08 ± 4.25% of cases (with an average dilatation of the PCS of 0.5 cm).

2. Spontaneous regression of the expansion of the PCS is characteristic of 68.63 ± 4.59% of the subjects.

3. Negative echographic dynamics is reliably more often recorded when UTI is attached ($\chi 2 = 5.47$, with a significance level of p = 0.01)

4. For children with CAKUT early addition of UTI is characterized – at 6 months with a frequency of exacerbation 2 times a year.

5. In the presence of an obstructive type of kidney anomalies, it is necessary to carry out a dynamic sonographic study at 3 and 12 months of life, and at 6 months – to prescribe a general urine analysis and a bacteriological study of urine.

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NEUROLOGICAL DEFICIT SCALE FOR ASSESSMENT OF ISCHEMIC STROKE IN EARLY CHILDHOOD

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The article discusses the data of an original study on development of a clinical scale for neurological deficits severity assessing in children with arterial ischemic strokes (AIS) under the age of 2 years old (SANDYc). The relevance of SANDYc development is caused by inability to use pedNIHSS scale in children under 2 years of age and limitations of the PSOM using in the acute and subacute IS stages in young children. The study presents clinical features of IS course in 31 children aged up to 2 years old, being treated at children's clinical hospital N5 named after N.F. Filatova from 2005 to 2021. The statistical analysis data are presented, showing statistically significant correlations between the assessment results according to SANDYc and the values obtained according to the PSOM and BMRC scales. Additionally, statistical analysis demonstrated correlation between allelic variants A / C and C / C of the MTHFR A1298C gene (p = 0.044) in the examined children and milder clinical course of AIS as assessed by SANDYc.

Keywords: neurological deficits severity assessment scale, ischemic stroke, children, acute stage, clinical assessment.

Introduction. Despite significant progress in diagnostic and treatment methods improvement, arterial ischemic strokes (AIS) in children remain a potential threat of severe neurological disorders development, in some cases with disabling or fatal outcome.

The variety, and on frequent occasions non-specificity, of clinical manifestations significantly complicate timely diagnosis of AIS, especially in young children, which is partly caused by focal symptoms masking with common, non-focal ones [5, 9]. Fast AIS diagnosis in children gives an opportunity to influence clinical course severity and outcome favorability due to the earlier initiation of pathogenetically oriented treatment. At the same time, the accuracy of neurological deficits severity verification significantly increases when using standardization principle [1, 3, 11] in the form of clinical assessment scales, which allows us to avoid subjectivity factor, as well as reflect dynamics of neurological status deviations with greater sensitivity and specificity.

Supposedly because of the difficulties with young children examination, especially in the acute and subacute AIS stages, a generally accepted scale for neurological deficits assessing in this age group has not been developed yet. The pediatric modification of the US National Institutes of Health Stroke Scale (pedNIHSS) [5] has limitations for use in children under 2 years of age, and Pediatric Stroke Outcome Measure (PSOM) [8] is more intended for use in the recovery stage.

The aim of the present study was to develop a scale for neurological deficits severity assessment in children with cerebrovascular accidents (arterial ischemic strokes) in the age group up to 2 years old.

Materials and methods: from 2005 to 2021 we performed the clinical picture analysis of the acute (first 5 days of stroke) and subacute (up to 21 days from the moment of initial manifestations) stages of AIS in 31 children aged up to 2 years old, being treated at children's clinical hospital N5 named after N.F. Filatova.

The minimum age was 6 months, the maximum one 1 year 11 months. In all age groups male predominance was observed (Table 1).

The diagnosing criterion was acute focal neurological symptoms in the clinical picture, persisted for more than 24 hours. Also a mandatory requirement was the presence of changes corresponding to ischemic stroke (IS) according to neuroimaging data (CT, MRI) [2, 6, 12].

All the examined children underwent a routine somato-neurological examination in dynamics, their life and medical histories were studied.

Clinical assessment of neurological disorders severity was conducted according to the developed scale for neurological deficits assessing in young children (SANDYc). Additionally, clinical verification was performed with the PSOM (Pediatric Stroke Outcome Measure) and the six-point scale for muscle strength assessing of the British Medical Research Council (British Medical Research Council, BMRC) [10].

Molecular genetic testing of blood for polymorphism of thrombophilia genetic markers was performed in 17 children with IS using PCR. Real-time allele-specific PCR and restriction fragment length polymorphism technique (RFLP), with polyacrylamide gel electrophoresis and visualization under UV light, were used.

Statistical analysis. Statistical processing of the obtained data was carried out using the programs "Statistica 12.0" (StatSoft, USA), Microsoft Excel-2010 with nonparametric criteria. For each group, a number of statistical parameters were calculated: symptom incidence rate and incidence error, mean value, standard deviation, median, 95% confidence interval for the median. Because of the abnormal distribution the Spearman's rank correlation test was used. To standardize the statistical assessments results the critical values for all studied parameters were defined at the significance level ($p < 0.05$), common for biomedical research.

Results and discussion. The clinical picture analysis enabled definition of 8 main groups of neurological manifestations (indicators) of AIS course in children under 2 years of age.

The groups of common non-focal cerebral symptoms and epileptic disorders were entirely new, not found in the PSOM and pedNIHSS scales when assessing

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neurological deficits in children. The list of groups of clinical manifestations in children with ischemic stroke is given in Table 2.

In all children AIS occurred in carotid artery territory with more frequent involvement of the left internal carotid artery (ICA) (19 children, 61.3%), less often – the right ICA (12 children, 38.7%). Lenticulostriate branches of the middle cerebral artery were mainly affected (29 children, 93.5%), two children had cerebral infarct in anterior choroidal artery territory (6.5%). Ischemic injury area included the internal capsule (25 children, 80.6%), the caudate nucleus (19 children, 61.3%), the lenticular nucleus (19 children, 61.3%), the thalamus (18 children, 58%), and the centrum semiovale (1 child, 3.2%). In all children the clinical picture was presented by motor symptoms in the form of central hemiparesis, in 24 cases combined with facial central palsy (77.4%). The assessment of muscle strength using the BMRC scale in the acute stage of stroke was performed in 26 children, because of the difficulties with its use in infants. The average paresis degree in the upper limb was 2.2 ± 1.05, in the lower limb – 2.5 ± 1.3 points. All children underwent the assessment of neurological deficits severity according to the PSOM scale, the average score was 1.24 ± 0.6, with a minimum score of 0.5, a maximum of -3.0 points.

Based on the clinical picture analysis, a scale for neurological deficit assessing in young children with stroke (SANDYc) was developed. The gradation of parameters changes was carried out in accordance with previously developed criteria [3, 4, 11, 13].

For each group of symptoms neurological disorders severity was assessed from 0 points – absence, to 4 points – the most severe neurological manifestations. When choosing the parameters, assessability of every specific clinical sign in the acute and subacute AIS stages in children of the younger age group was considered. Regression (loss of previously acquired skills) was assessed in the following subgroups: speech skills, fine motor skills and self-care skills. Epileptic disorders included clinical and electrophysiological characteristics. The detailed description of the assessment parameters is presented in Table 3.

The criteria for assessment of regression severity of acquired speech skills, fine motor skills, and social interaction and self-care skills for different age groups will be presented in separate publication due to the large amount of material.

Using the developed scale, we assessed neurological status of 31 examined children with AIS in the acute and subacute stages. The average value of neurological deficit indicator in points was 10.8 ± 3.4, with boundary values of 6 and 18. The interquartile range extends from 8 to 13 points. The distribution and graphical display of the values ranges are shown in Figures 1 and 2.

For additional assessment of neurological disorders severity the PSOM scale was used in all children of the study group (Fig. 3).

The statistical analysis was performed with nonparametric methods because of a lack of normal distribution of the data obtained and the study group size. The Spearman's rank correlation test revealed statistically significant direct relationships between the values of SANDYc and PSOM ($r = 0.45$, $p = 0.0103$, with a threshold value of < 0.05). Also, statistically significant inverse correlations were found between the SANDYc and the BMRC indicators in the subacute AIS stage, for the upper limb $r = -0.634$, $p = 0.0005$, for the lower limb $r = -0.630$, $p = 0.0006$. Negative correlation coefficients are explained by multidirectionality of the scales (maximum deficit severity according to the BMRC scale is 0, and according to SANDYc – -43 points).

Additional statistical analysis made it possible to find an inverse correlation between neurological deficit severity according to SANDYc and the MTH-

Table 1

Age and gender distribution of children with IS under the age of 2 years, total number, n = 31

	Age group		
	6-12 months	1-1.5 years	1,5-2 years
Male	7 (22.6)	7 (22.6)	4 (12.9)
Female	6 (19.4)	4 (12.9)	3 (9.7)
Total number	13 (41.9)	11 (35.5)	7 (22.6)

Table 2

Группы клинических проявлений (показателей) у детей с ОНМК по ишемическому типу в возрасте до 2 лет

Indicators	Number of children with deviations, n (%)
Consciousness level (CL)	1 (3.2)
Common non-focal cerebral symptoms (CNFC)	18 (58.0)
Visible active movements limitation (VAML)	31 (100)
Movement disorders prevalence (after 60 weeks postmenstrual age) (MDP)	31 (100)
Hyperkinesis (H)	13 (2.0)
Cranial nerves (including facial palsy due to central lesions) (CN)	24 (77.4)
Skills regression (degree) (SR) (change in skills acquired before stroke is assessed)	20 (64.5)
Epileptic disorders (in the acute and subacute stages) (E) NB! Repeated paroxysms without epileptiform changes, managed with AET (antiepileptic treatment) during 7 days – 2 points	2 (6.45)
Ataxia (A) Not evaluated in paretic limbs with predominance of movement disorders. In case of hyperkinetic disorders dominance in the examined limb(s), ataxia is also not assessed	0

Table 3

Parameters of neurological deficits assessment in children with stroke according to SANDYc

Indicator	Assessment	Points	Description	Primary source of modification
1	2	3	4	5
CL	Normal	0	Wakefulness, normal arousal response, normal quantity and quality of motor responses	J.J. Volpe, 2008
	Slight stupor	1	Sleepy appearance, arousal response diminished (slight), quantity of motor responses diminished (slight), quality – at high level	
	Moderate stupor	2	Child asleep, arousal response diminished (moderate), quantity of motor responses diminished (moderate), quality – at high level	
	Deep stupor	3	Child asleep, arousal response absent, quantity of motor responses diminished (marked), quality – at high level	
	Coma	4	Child asleep, arousal response absent, quantity of motor responses diminished (marked), or absent, quality – at low level	
CS	No	0		
	One of the symptoms: short-lived headache less than 30 minutes (or its signs), nausea, lack of appetite, general weakness (lack of energy), drowsiness, restlessness	1		
	Single vomiting episode, or presence of two symptoms, headache for more than 30 minutes	2		
	Two vomiting episodes, presence of three or more symptoms, combination of a symptom with a headache lasting more than 30 minutes	3		
	Repeated episodes of vomiting, presence of other symptoms	4		
VAML	No limitations	0	*** assessment is carried out in the limb with the most severe motor deficit** **Mild:** minor active movements limitation, notable to a great extent because of reduced active movements range – compared to the opposite side, or muscle strength in pre-stroke period. Able to hold the limb poised in the air for more than 5 seconds, to stand up, to stand unsupported. **Moderate:** significant active movements limitation, able to hold the limb poised in the air up to 5 seconds (moving against gravity), poor grip strength, short unsupported standing (less than 5 seconds). **Severe:** low-amplitude limb movements, not able to grasp and hold a toy, to stand unsupported. Minimal movements, no power to act against gravity. **Plegia:** complete absence of motor activity in the limb.	Medical Research Council (Great Britain), 1976
	Mild paresis	1		
	Moderate paresis	2		
	Severe paresis	3		
	Plegia	4		

Continuation of the table 3

1	2		3	4	5
MDP	No		0		
	Monoparesis		1		
	Para-/hemiparesis		2		
	Threeparesis		3		
	Tetraparesis		4		
H	No		0		A.A. Skoromets et al., 2012
	Dystonia / Hyperkinesis in one limb, or one muscle group (discrete, short-term)		1		
	Dystonia / Hyperkinesis in several limbs, or muscle groups (intermittent)		2		
	Dystonia / Hyperkinesis in several muscle groups, or limbs, regular		3		
	Prolonged generalized hyperkinesis (including transition from focal forms), choreo-/athetosis		4		
CN	Normal		0		A.A. Skoromets et al., 2012
	1 nerve damage		1		
	2 nerves damage		2		
	Multiple nerves paresis (incl. Bulbar palsy)		3		
SR	Speech	Norm	0		
		Mild	1		
		Moderate	2		
		Severe	3		
		Mutism	4		
	Fine motor skills	Norm	0		
		Mild	1		
		Moderate	2		
		Severe	3		
		Complete loss	4		
	Self-care skills (if acquired before), social interaction	Norm	0		
		Mild	1		
		Moderate	2		
		Severe	3		
		Complete loss	4		
Э	No		0		
	Single epileptic seizure		1		
	Repeated epileptic seizures without epileptiform changes on EEG / single convulsive seizure with persistent epileptiform changes on EEG		2		
	Recurrent seizures with epileptiform changes on EEG, need for basic AET		3		
	Status epilepticus		4		

End of table 3

1	2	3	4	5
A	Mild	1	**Points are scored if one of the signs is present:** minimal tremor when trying to reach an object (toy), slight unsteadiness (up to 5 seconds) in standing and (or) sitting position	
	Moderate	2	Moderate intention tremor when trying to reach a toy, and (or) occasional failed attempts to grasp a toy leading to final successful grasping. Moderate unsteadiness in standing and (or) sitting position (more than 5 seconds, still able to keep balance unsupported)	
	Severe	3	Severe intention tremor, able to grasp an object only with help. Unsupported standing and sitting for less than 5 seconds	
	Complete lack of movements coordination, voluntary movements present	4	Lack of movements coordination, complete loss of balance in standing and sitting positions	
Total		Max = 43		

Note. Criteria for assessing the severity of regression of acquired speech skills, fine motor skills, social interaction and self-service for different age groups will be presented in a separate publication due to the large volume of material.

FR A1298C gene mutation (p = 0.044), allelic variants A / C and C / C. The obtained results may suggest milder clinical course of AIS in children of the younger age group with the MTHFR A1298C polymorphism.

Conclusions. The practical significance of SANDYc lies in the possibility to quantify and ensure objectivity of neurological symptoms severity in children under 2 years of age in the acute and subacute stages of AIS. The obtained strong statistical correlations between the neurological deficit sum scores according to SANDYc and the indicators of generally accepted scales (the PSOM, the 6-point BMRC scale) suggest diagnostic significance of SANDYc for neurological deficit assessment in young children with AIS. The use of additional, previously not applied for comprehensive assessment, parameters, such as common non-focal cerebral symptoms and epileptic disorders, expands diagnostic capabilities of the scale in neurological deficit sum score calculating, and also makes it more accurate and personalized for each individual case of AIS. In case of common non-focal cerebral symptoms severity prevalence over focal ones SANDYc shows higher scores of neurological deficit compared to the PSOM, thus, makes it possible to more accurately assess the clinical picture of AIS acute stage in young children.

Taking into account the small sample of patients in the present study, SANDYc testing in a larger group of children will make possible assessing of its widespread use in various types of stroke, which is already available in multicenter studies. It may prove to be promising to use the scale in children up to 3 years of age, that is include an additional number of children with IS into the comparison group.

Scoring of neurological deficit would enable more accurate dynamic observation of children with IS, use of the results in research work, and continuity of assessment at various stages of medical care. SANDYc practical application in other types of stroke, including hemorrhagic strokes, requires separate study, and verification with existing scales.

The correlation between milder course of IS in children of the younger age group and the MTHFR A1298C gene mutation requires additional research.

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ALGORITHM FOR DIAGNOSIS OF EXTRAORGAN RETROPERITONEAL CYSTS

In order to determine the optimal diagnostic tactics in patients with extra-organ cysts of the retroperitoneal space, the results of examination of patients who received treatment at the Tver Regional Clinical Oncological Dispensary in 2013 - 2020 were analyzed. The informative value of a set of diagnostic methods was assessed according to the following criteria: determination of the type of cystic formation and identification of complications. It was found that the optimal set of diagnostic methods: ultrasound, CT and / or MRI of the abdominal cavity, small pelvis and retroperitoneal space, diagnostic cyst puncture under ultrasound control followed by cytological examination, excretory urography

Keywords: extraorgan cysts of the retroperitoneal space, true and false cysts, diagnostic puncture under ultrasound control, cytological examination.

Background. Extraorgan cysts of the retroperitoneal space (ECRS) are cysts located in the retroperitoneal fatty tissue that are not associated with any mature anatomical structures, except for loose connective tissue [1, 2]. There are true ECRS with epithelial lining, and false ones, the wall of which is not lined with epithelium [4]. Until now, there are no unified approaches to the choice of diagnostic tactics and treatment method [3, 5].

The development of diagnostic capabilities in medicine makes it possible to increase the detection rate of rare pathological conditions, to which numerous researchers refer to ECRS [3, 5, 6]. At the same time, there is a tendency towards an increase in the incidence [1- 3]. It is important to note that the increase in incidence is mainly due to false cysts.

The aim of the study is to determine the optimal diagnostic tactics in patients with ECRS.

Material and methods. The results of examination of 61 patients aged 31 to 70 years were analyzed, of which 39 (63.9%) were men, 22 (36.1%) were women who received treatment at the Tver Regional Clinical Oncological Dispensary in 2013 - 2020. The age group from 51 to 70 years old accounted for 54/61 (88.5%) patients. The age structure of patients is presented in more detail in table. 1.

In accordance with the research methods, the patients were divided into 3 groups: 32 (52.5%), 19 (31.1%) and 10 (16.4%) people (Table 2). In the first group, patients underwent ultrasound, CT and / or MRI of the abdominal cavity, small pelvis and retroperitoneal space. In the second group, in addition to the methods of examining the patients of the first group, diagnostic puncture of the cyst under ultrasound control and cytological examination of the cystic contents were also performed. In the third group, in addition to the examination methods, patients from the first and second groups also underwent excretory urography (EU). The informativeness of a set of diagnostic methods was assessed according to three criteria: determination of the type of cystic formation; identification of complications of the disease; determination of the belonging of cysts to extraorganic formations at the diagnostic stage.

Results. When assessing the dynamics of the incidence of CKD, attention is drawn to the fact of an increase in the number of detected false cysts, mainly due to lymphocele (Fig. 1).

Complaints were noted in 14 (23%) patients, of which the most frequent was abdominal discomfort (6 (9.8%) patients), urinary retention was also noted (3 (4.9%) patients), body temperature rise to 38 ° C and higher (2 (3.3%) patients), pain syndrome (2 (3.3%) patients), of which 1 pa-

Table 1

The age structure of patients with extraorganic retroperitoneal cysts

Age	Gender of patients				Total	
	Males		Females			
	n	%	n	%	n	%
31 – 40	-	-	1	1.6	1	1.6
41 – 50	2	3.2	3	5	5	8.2
51 – 60	20	32.8	15	24.6	35	57.4
61 – 70	16	26.2	3	5	19	31.2
70 and older	1	1.6	-	-	1	1.6
Total	39	63.9	22	36.1	61	100

Table 2

The distribution of patients in the comparison groups

Research method	Comparative groups			Total n (%)
	I n (%)	II n (%)	III n (%)	
Ultrasound	32 (52.5)	19 (31.1)	10 (16.4)	61 (100)
CT	22 (36.1)	11 (18.0)	8 (13.1)	41 (67.2)
MRI	10 (16.4)	8 (13.1)	4 (6.6)	22 (36.1)
Diagnostic puncture	-	19 (31.1)	10 (16.4)	29 (47.5)
Cytological examination	-	19 (31.1)	10 (16.4)	29 (47.5)
Excretory urography	-	-	10 (16.4)	10 (16.4)
Amount of patients in the group	32 (52.5)	19 (31.1)	10 (16.4)	61 (100)

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tient had girdle pains, another 1 had pain in the left iliac and lumbar regions with irradiation to the right lower limb.

By localization, most of the cysts were pelvic (below the iliac arteries) - 39 (63.9%) cases. Among other localizations, infrarenal left-sided - 9 (14.7%), infrarenal right-sided - 6 (9.8%), suprarenal left-sided - 2 (3.3%), peripancreatic (prevailing component in the retroperitoneal space) - 2 (3, 3%), suprarenal right-sided - 1 (1.6%), parapancreatic (the prevailing component in the abdominal cavity) - 1 (1.6%) and central - 1 (1.6%) observation.

Complications developed in 8 (13.1%) patients: unilateral subrenal block - in 4 (6.6%), bilateral subrenal block - in 2 (3.3%), cyst suppuration - in 2 (3.3%), secondary pyelonephritis - in 1 (1.6%) patient with unilateral hydronephrosis.

Instrumental studies are presented in table. 3. The dimensions of the VKZP varied from 39 mm to 152 mm in the largest dimension. Large cysts (more than 100 mm) were noted in 4 (6.6%) cases.

Puncture and cytological examination made it possible to obtain data on the type of neoplasms (primary or secondary cyst): 18/19 and 9/10 patients. Without puncture, the cyst type was identified only in 13 (40.6%) / 32 patients. The belonging of formations to extraorgan cysts at the diagnostic stage was determined in 27 (87%) / 31, 16 (84.2%) / 19, 8 (80%) / 10 cases, respectively (p> 0.05).

The belonging of formations to extraorgan cysts at the diagnostic stage in the first group was determined in 27 patients, in the second group - in 16, in the third - in 8 (p> 0.05).

In 1/29 (3.4%) of cytological examinations of cystic contents, atypical cells of the transitional epithelium were revealed, which was an indication for the appointment of a number of additional examinations: plain radiography and CT of the lungs, as well as cystoscopy. No pathology of the bladder or lungs was found.

Discussion. In the previously encountered works of both domestic and foreign authors, the diagnosis and treatment of ECRS is presented in the form of sporadic observations [7, 8, 9]. Some clinicians consider ECRS either in combination with extra-organ retroperitoneal tumors, or with cysts of the retroperitoneal space, which have an organ affiliation, which does not allow tracing the optimal diagnostic algorithm [3, 5, 7].

It should be noted that the absence of early symptoms creates difficulties in diagnosis [8]. Today, modern diagnostic capabilities provide us with full information about the patient's condition, using mainly non-invasive research methods [9]. However, not always the correct diagnosis can be made before surgery [1, 11, 12]. Due to the anatomical features of the retroperitoneal space and the absence of a specific clinical picture of its cystic lesion, differential diagnosis of retroperitoneal cysts remains difficult even during surgical intervention, and in some cases the answer to the question of the organ belonging of the cyst can only be provided by histological examination.

Diagnostic laparotomy was one of the first methods for diagnosing ECRS, widespread at the beginning of the 20th century [13]. Ultrasound is widely used to diagnose liquid formations of the retroperitoneal space, both organ and extraor-

Table 3

Diagnostic tools conducted before treatment

Research method	Gender				Total	
	Males		Females			
	n	%	n	%	n	%
Ultrasound	39	63.9	22	36.1	61	100
CT	26	42.6	15	24.6	41	67.2
MRI	11	18.0	11	18.0	22	36.0
Excretory urography	4	6.6	6	9.8	10	16.4
Diagnostic puncture with ultrasound	16	26.2	13	21.3	29	47.5
Cytological examination	16	26.2	13	21.3	29	47.5

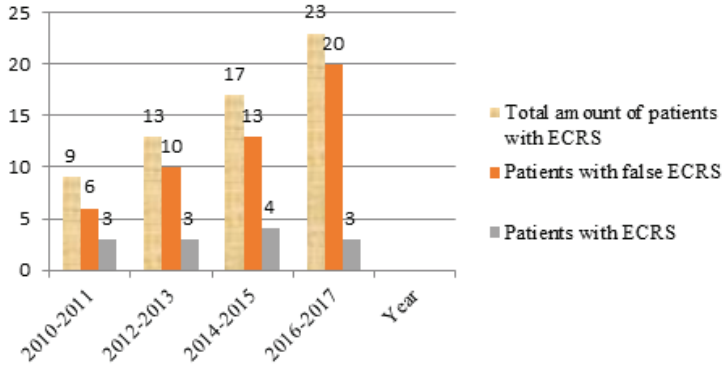

Fig. 1. The dynamics of the incidence from 2010 to 2017

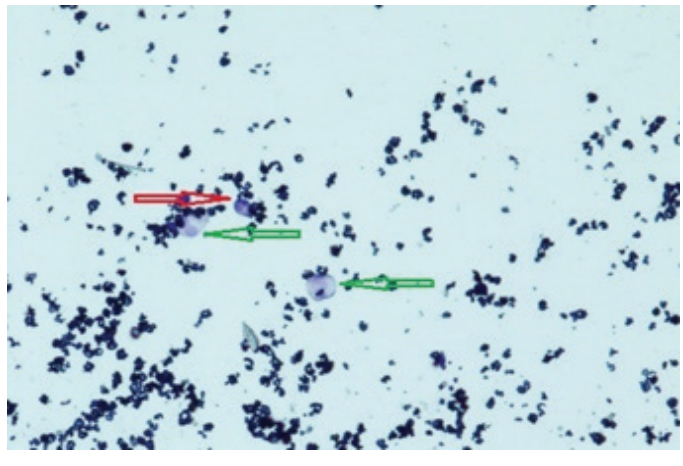

Fig. 2. Photocytogram of the cystic content of a secondary EORC. Coloring by Pappenheim. Magnification × 200. Among a large number of erythrocytes the single macrophages (green arrows) and neutrophils (red arrow) are found. Epithelial cells are absent.

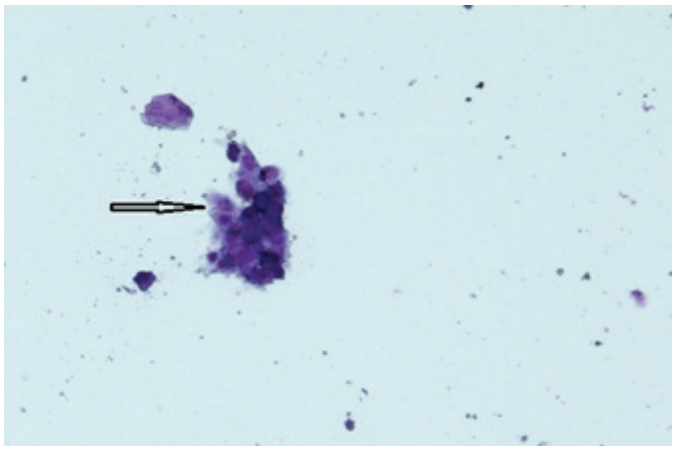

Fig. 3. Photocytogram of the cystic content of a primary EORC. Coloring by Pappenheim. Magnification × 200. The arrow indicates the accumulation of cells of the cubic epithelium, indicating the presence of an epithelial lining

ganic origin [3]. The advantages of ultrasound are undoubtedly the possibility of multiple studies (dynamic observations), availability and relatively high information content [4]. The widespread use of CT and MRI in medicine has significantly improved the diagnosis of neoplasms, namely, to determine their more accurate localization, relationship with surrounding organs and structures, density and size, which made it possible to increase the detectability of retroperitoneal cysts [1, 2, 13]. Another research method is excretory urography (EU), which has minimal diagnostic value, but with large cysts it helps to assess renal function [1, 8, 13].

Undoubtedly, conducting a diagnostic puncture of ECRS under ultrasound control followed by cytological examination before starting treatment of the patient in most cases allows to determine the nature of the cystic formation. In the studied literature sources, the puncture of the ECVP is described in one of the observations [8]. The rare use of puncture at the diagnostic stage may be due to the lack of a unified diagnostic algorithm.

There were no differences between the groups in the diagnostic aspect of identifying complications of ECRS ($p > 0.05$).

From the results obtained, it should be noted that diagnostic puncture under the control of ultrasound and cytological examination of cystic contents (groups II and III) significantly increases the reliability of determining the presence or absence of the epithelial lining of cystic formation: 18 (94.7%) and 9 (90%) observations against 13 (40.6%) ($p < 0.05$).

The cellular composition of the cystic contents makes it possible to assess the type of cyst - true or false (Fig. 2 and 3). Thus, the presence of epithelial cells during cytological examination indicates the presence of an epithelial lining.

Diagnostic puncture under ultrasound control followed by cytological examination of the cystic contents did not improve the rates of complications detection and determination of the formation belonging to ECRS at the diagnostic stage. It is important to note that the results of EU (group III) did not affect the determination of the type of cyst, its complications or organ affiliation, but supplemented the information picture when choosing the scope of treatment.

Conclusion. The results obtained showed that for clinical use in the diagnosis of ECRS, the most appropriate is a list of studies of diagnostic groups II and III, namely ultrasound of the abdominal cavity, small pelvis and retroperitoneal space, CT and / or MRI of the abdominal cavity, small pelvis and retroperitoneal space. diagnostic puncture of the cyst under ultrasound control, cytological examination of cystic contents and EI, which made it possible to obtain more accurate information about the nature of cystic formations.

Particular attention should be paid to diagnostic puncture under ultrasound control, followed by cytological examination of the cystic contents, since this study allows you to determine not only the origin of the cyst, but also the presence or absence of atypical cells.

EI, although it did not affect the definition of the main diagnosis, significantly supplemented the information picture of the functional state of the kidneys.

The above diagnostic measures can become the basis of a modern diagnostic algorithm for detecting cysts of the retroperitoneal space.

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ANALYSIS OF SURGICAL TREATMENT TACTICS AND TREATMENT RESULTS FOR COMMON PURULENT PERITONITIS IN A MULTIDISCIPLINARY SURGICAL HOSPITAL

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The aim of the study was a retrospective analysis of the choice of surgical treatment tactics and the results of CPP treatment in a multidisciplinary urgent surgical hospital. **Material and methods.** The study is based on a retrospective analysis of the results of complex treatment of 253 patients with CPP who were treated in the emergency surgical departments of the Republican Hospital №2 - Emergency Medical Aid Center (RHN№ 2-CEMA) of the Republic of Sakha (Yakutia) in the period from 2015 to 2022. Results. In the clinic under consideration, the CPP tactic was most often used for CPP – 47,4%, while the share of ROD accounted for at least 27,7%, which is largely due to the profile of the clinic (Center for Emergency Medical Aid of the third level), but already at 31,4 In% of cases, after ROD, the transition to RAP was carried out, which led to a low mortality rate even with HS and SS – 16,7%. Moreover, in more than 91,7% of cases with CPP, as a rule, no more than two or three sanitizing relaparotomy were performed. The widespread introduction into surgical treatment practice of integral scales for assessing the severity of the general condition and the nature of damage to the abdominal organs – APACHE II, SOFA, MIP and ACI made it possible to more objectively assess the clinical situation and choose surgical treatment tactics. **Conclusion.** The results of the clinical study presented by us allow us to conclude that the use on an ongoing basis of the currently existing systems for assessing the severity of the condition and the nature of damage to the abdominal organs, along with intensive therapy, can reduce the level of postoperative mortality to 20-30% even with the development of HS.

Keywords: common purulent peritonitis, relaparotomy, surgical treatment tactics.

Introduction. Despite the advances in modern medicine, common purulent peritonitis (CPP) is still one of the topical problems of modern urgent abdominal surgery [9, 12, 14]. According to the generalized data of leading specialists of domestic and foreign clinics, the mortality rate in CPP over the past decade does not have a significant tendency to decrease and ranges from 10-60%, and with the development of severe abdominal sepsis, septic shock and multiple organ failure it can reach 70-80 % and more [2, 5, 15]. An equally important circumstance in the list of problems in the treatment of CPP is the high incidence of postoperative complications, the level of which reaches 10-30% and has not changed significantly in recent years [3]. The main role, according to a number of researchers [13, 17], is played by ineffective surgical debridement of the site of infection, ongoing peritonitis, untimely re-intervention, underestimation of the severity of the condition and inadequacy of intensive therapy.

Currently, for the treatment of CPP, four main strategies of surgical intervention at the end of primary laparotomy are most widely used: the traditional (closed) method, when, upon completion of all stages of the operation, the abdominal cavity is sutured tightly; staged operations using half-open / half-closed technologies (relaparotomy "according to plan" or according to the program (RAP), relaparotomy "on demand" (ROD)); combined (a combination of the traditional method with programmed endoscopic sanitation of the abdominal cavity); open abdomen (laparostomy) [8, 9, 18].

The currently existing surgical therapeutic tactics of sanitizing relaparotomies, according to the conclusion of a number of researchers, have a number of known advantages and disadvantages [8, 11, 16], therefore, the timing, volume and procedure of these interventions are currently not standardized and vary widely. The disadvantages of traditional methods of surgical treatment, first of all, are: the danger of incomplete elimination of the source of peritonitis in the course of one operation, late diagnosis of developing local and systemic complications, and, as a consequence, untimely decision-making on the need for re-intervention with subsequent radiotherapy [1]. Evaluation of the effectiveness of various surgical strategies is also difficult due to the heterogeneity of the compared groups of patients under study and the equipment of specific medical institutions [12, 19]. To some extent, these problems can be avoided by using the method of repeated (programmed) interventions, which is one of the most popular among others in modern surgery for CPP [4]. As indicated in their works [1, 6], RAP give the surgeon the opportunity to establish complete control over the course of the inflammatory process in the focus of infection and the abdominal cavity as a whole, to carry out complete and timely elimination of emerging complications. However, it should be noted that in this case, too, the issue of indications for programmed interventions, the timing of their implementation and an objective assessment of the degree and nature of damage to the abdominal organs has been insufficiently worked out [10, 7].

The **aim** of the study. Retrospective analysis of the choice of surgical treatment tactics and the results of treatment of common purulent peritonitis in a specific multidisciplinary urgent surgical hospital of the third level.

Material and methods. The presented work is based on a retrospective analysis of the results of complex treatment of 253 patients with CPP who were treated in the emergency surgical departments of the Republican Hospital №2 - Emergency Medical Aid Center (RHN№ 2-CEMA) of the Republic of Sakha (Yakutia) in the period from 2015 to 2022. The diagnosis of

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CPP was verified on the basis of a comprehensive examination, which included data from physical, laboratory, instrumental and apparatus research methods. The average age of patients was 33,2 ± 6,5 years, with 156 men (61,7%), women – 97 (38,3%). Of 253 patients with CPP, only primary laparotomy was performed in 63 (24,9%) patients, 70 (27,7%) patients were operated on in the ROD mode and 120 (47,4%) patients with CPP who underwent staged surgical treatment in the RAP mode.

The initial severity of patients was assessed using the APACHE II scale (Acute Physiology And Chronic Health Evaluation). The Mannheim Peritonitis Index (MIP) and the Abdominal Cavity Index (ACI) were used to assess the severity and nature of abdominal lesions. The presence and severity of multiple organ failure at baseline and over time was determined using the SOFA (Sequential Organ Failure Assessment) scale. When assessing the severity of the systemic inflammatory response syndrome (SIRS) adhered to the definitions presented by the consensus conference of the American College of Pulmonologists and the Society of Critical Medicine Specialists – ACCP / SCCM.

Statistical processing of this material was carried out using the MS EXCEL software package for the Microsoft Office 2010 operating system. The calculation of the indicators of the variation series with the calculation of the arithmetic mean and standard deviation (M ± σ) was carried out using the wizard of functions (fx). The assessment of the significance of differences (p) was determined by the Student's t-test. Differences were considered significant at p <0,05.

Results and discussion. During the statistical processing of the obtained clinical data aimed at identifying the causes of the development of CPP, the predominant cause was postoperative peritonitis, recorded in 87 (34,4%) treated patients, in second place, destructive appendicitis – in 58 (22,9%) patients, third place, destructive pancreatitis – in 34 (13,5%) patients. Somewhat less often, the reasons for the development of CPP were: acute intestinal obstruction – in 26 (10,3%) patients, perforation of the small intestine, usually caused by foreign bodies in the form of metal wire or nails, as well as fish bone – in 16 (6,3%) patients , trauma to the abdominal organs (damage to parenchymal organs with the formation of hematomas, suppuration and subsequent breakthrough into the abdominal cavity) – in 14 (5,5%) treated patients, destructive cholecystitis – in 10 (3,9%) patients, perforated gastroduodenal ulcer – in 5 (2,0%) patients, colon perforation (Crohn's disease and ulcerative colitis (NUC)) – in 3 (1,2%) patients.

The results of the analysis of the data show that the main nosologies that required reoperations in the ROD and RAP modes were: postoperative peritonitis – in 87 (100%) patients, colon perforation (Crohn's disease and NUC) – in 3 (100%) patients, perforated gastroduodenal ulcer – in 4 (80,0%) patients, destructive cholecystitis – in 7 (70,0%) patients, destructive pancreatitis – in 23 (67,6%) patients, destructive appendicitis – in 37 (63,8%)) patients, acute intestinal obstruction – in 16 (61,5%) patients. Somewhat less frequently, such reasons were: perforation of the small intestine – in 8 (50,0%) patients, trauma of the abdominal organs – in 5 (35,7%) patients. In total, the need to perform ROD and RAP arose in 190 (75,1%) patients (table 1). At the same time, the indications for ROD and RAP were: persistent or progressive peritonitis – in 109 (57,4%) patients, the emergence of new sources of peritonitis – in 24 (12,6%) patients, including incompetence of the sutures of the hollow organs – in 19 (10,0%) patients, abscesses (single or multiple) of the abdominal cavity – in 15 (7,9%) patients, eventration – in 7 (3,7%) patients, non-resolving intestinal paresis – in 2 (1,0%)) patients, adhesive intestinal obstruction – in 11 (5,8%) patients, intra-abdominal bleeding – in 3 (1,6%) patients.

It should be noted that in most cases, the use of the ROD regimen for CPP required the use in cases when an unfavorable course of the infectious process was not predicted during the primary operation or was due to the profile of the clinic (regional level, Emergency Medical Center - CEMP), patients were evacuated from others surgical hospitals of regional hospitals and the city of Yakutsk. At the same time, one surgical intervention to stop CPP was sufficient only in 63 (24,9%) patients. At the same time, in 70 (27,7%) patients, therapy was required to relieve widespread peritonitis and eliminate intra-abdominal complications. Of these, 22 (31,4%) patients ultimately required a transition to the programmed mode of abdominal management. According to some authors [1, 5, 11], which is also confirmed by our studies, unfortunately, as a result of one operation, it is not always possible to perform a full sanitation of the abdominal cavity and achieve complete control over the focus of infection. In such clinical cases, for dynamic control and active influence on the infectious process in the abdominal cavity with CPP, RAP is performed. At the same time, traditional and non-traditional indications, as well as various integral systems and scales for assessing the degree of damage to the abdominal cavity and the severity of the patient's condition, are used to select the program mode for the abdominal cavity management. A similar surgical tactic was used in 120 (47,4%) patients. At the same time, in more than half of these patients – 71 (59,2%), one-time sanitation of the abdominal cavity was required to stop the main manifestations of CPP, and only 21 (17,5%) required 3 or more RAP (table 2).

Table 1

Characteristics of patients due to the development of CPP and the chosen surgical treatment tactics

The cause of common purulent peritonitis and the number of patients (n)*	Abdominal guidance technique			
	Relaparotomy "on demand"		Relaparotomy "by program"	
	abs.	M±σ	abs.	M±σ
Postoperative peritonitis (n=87)	19	21.8±8.8	68	78.2±4.7
Destructive appendicitis (n=58)	16	27.6±8.5	21	36.2±8.0
Destructive cholecystitis (n=10)	2	20.0±8.9	5	50.0±7.1
Destructive pancreatitis (n=34)	16	47.1±7.3	7	20.6±8.9
Perforated gastroduodenal ulcer (n=5)	3	60.0±6.3	1	20.0±8.9
Acute intestinal obstruction (n=26)	6	23.1±8.8	10	38.5±7.8
Small bowel perforation (n=16)	3	18.8±9.0	5	31.3±8.3
Colon perforation (Crohn's disease and NUC) (n=3)	1	33.3±8.2	2	66.7±5.8
Abdominal trauma (n=14)	4	28.6±8.4	1	7.1±9.7
Total for groups of ROD and RAP modes	70	100%	120	100%

* Significance of differences between group I in relation to group II at least p <0.05

With the management of the abdominal cavity by a semi-open method, the lowest mortality was observed when performing one program sanitation – 2,8% of patients. With an increase in the number of programmed readjustments, the mortality rate also increased: 17,9% of patients with two RAP, 54,5% with three RAP and 80,0% with 3 or more RAP.

During the analysis of the material, some differences were found in the severity of the initial manifestations of systemic inflammation in patients with CPP, depending on the surgical treatment tactics used. Thus, severe manifestations of abdominal sepsis (the stage of heavy sepsis (HS)) were more often diagnosed in patients who underwent RAP – in 84 (70,0%) patients. At the same time, RAP was more often performed in the stage of septic shock (SS) – in 10 (14,3%) patients. With less severe manifestations of SIRS (SIRS-3 and SIRS-4), both ROD and RAP were used almost equally often – in 20 (28,6%) and 25 (20,8%) patients.

Abdominal sepsis (SIRS 3-4, HS, SS) was initially observed in 190 (75,1%) patients with CCP. At the same time, there was a direct relationship between the presence and severity of abdominal sepsis and mortality. In the absence of HS events, mortality was minimal – in 4 (8,9%), in the presence of HS and SS symptoms, mortality was already 19,4% and 80,9%, respectively. In the absence or unexpressed initial manifestations of systemic inflammation in patients with CCP, there were no significant differences in mortality rates with different surgical treatment tactics. In patients with initial HS during program sanitation, mortality was significantly lower than in the semi-closed method – in 9 (7,5%) patients, and with initial manifestations of SS, the mortality did not depend on the chosen surgical treatment tactics – 8,6% and 9,2% respectively. The overall mortality rate was 45 (23,6%) (table 3).

The analysis of the initial severity of the condition of patients with different surgical treatment tactics showed that significant differences were noted both in the severity of the general condition (according to the APACHE II scale), and in the severity of multiple organ failure syndrome (MOFS) (according to the SOFA scale), and in the degree and nature of abdominal lesions – MIP and ACI. Speaking about the possible differences in the mortality rate in the groups of patients with CPP, depending on the surgical tactics used, it should be remembered that the initial severity of the condition, the severity of the MOFS, the degree and nature of damage to the abdominal organs, as well as the severity of the initial manifestations of SIRS were significantly higher in patients. with RAP. At the same time, mortality in CPP directly depended on the severity of the course of peritonitis. With MIP less than 21 points, mortality was 11,1%, with MIP 21-29 points – 12,1%, with MIP 29 or more points – 28,1%. Accordingly, with ACI less than 14 points, the mortality rate was 11,1%, and with ACI 14 or more points – 27,6%.

When analyzing the mortality rate of patients with different surgical tactics, depending on the severity of CCP according to MIP, significant differences can also be noted in patients with the use of ROD and RAP with MIP values of 21-29 points – 20,0% and 8,7%, respectively, and MIP more than 29 points – 44,6% and 19,5%, respectively. Significantly higher mortality rates were observed in patients with ROD in terms of the severity of ACI in the ACI group of less than 14 points – it was 20,0%. At the same time, in patients with RAP, the mortality rate in this group was no more than 4,0%. Also, with ACI of 14 or more points in the group of patients with staged sanitization of the abdominal cavity, the mortality rate was two times lower than with semi-closed administration – 21,1% and 40,0%, respectively. When analyzing mortality according to the integral scales APACHE II and SOFA, a fairly clear relationship was traced, the higher the scores, the greater the percentage of mortality was observed. However, when comparing the predicted mortality rates according to the above-described scales indicated by the developers, a higher mortality rate can be noted in the group of patients with ROD (table 4).

Table 2

Characteristics of the chosen surgical treatment tactics in patients with CPP

Surgical treatment option	Number of patients		Mortality	
	abs.	M±σ	abs.	M±σ
Semi-closed method				
ROD reoperation	48	68.6±5.6	18	37.5±7.9
ROD reoperation with transition to RAP	22	31.4±8.3	6	27.3±8.5
Total for the group of the ROD mode	70	100%	24	34.3%
Semi-open method				
1 programmed relaparotomy	71	59.2±6.4	2	2.8±9.9
2 programmed relaparotomies	28	23.3±8.8	5	17.9±9.1
3 programmed relaparotomies	11	9.2±9.5	6	54.5±6.7
More than 3 RAP	10	8.3±9.6	8	80.0±4.5
Total for the group of the RAP mode	120	100%	21	17.5%

Table 3

Clinical characteristics of abdominal sepsis depending on the severity of SIRS and abdominal management technique

Clinical syndrome	Abdominal guidance technique				Mortality Σ (ROD и RAP) n (M±σ)
	ROD n (M±σ)	Mortality n (M±σ)	RAP n (M±σ)	Mortality n (M±σ)	
SIRS-3	13 (18.6±9.0)	1 (1.4±1.4)	5 (4.1±9.7)	–	1 (5.6±5.4)
SIRS-4	7 (10.0±9.5)	2 (2.9±2.0)	20 (16.7±8.4)	1 (0.8±0.8)	3 (11.1±6.0)
Heavy sepsis	40 (57.1±6.5)	15 (21.4±4.9)	84 (70.0±5.5)	9 (7.5±2.4)	24 (19.4±3.5)
Septic shock	10 (14.3±9.3)	6 (8.6±3.3)	11 (9.2±9.5)	11 (9.2±2.6)	17 (80.9±8.6)
Total for ROD and RAP groups	70 (100%)	24 (34.3%)	120 (100%)	21 (17.5%)	45 (23.6%)

Table 4

Clinical characteristics of the initial severity of the condition and methods of abdominal management in patients with CCP

Diagnostic scales	Abdominal guidance technique				Mortality Σ (ROD и RAP) n,%
	ROD, n	Mortality n,%	RAP, n	Mortality n,%	
APACHE II less than 19 points	10	1 (10.0%)	11	1 (9.1%)	2 (9.5%)
APACHE II 20-29 points	21	8 (38.1%)	25	3 (12.0%)	11 (23.9%)
APACHE II more than 30 points	39	15 (38.5)	84	17 (20.2%)	32 (26.0%)
SOFA less than 3 points	18	6 (33.3%)	22	2 (9.1%)	8 (20.0%)
SOFA more than 3 points	52	18 (34.6%)	98	19 (19.4%)	37 (24.7%)
ИБП less than 14 points	20	4 (20.0%)	25	1 (4.0%)	5 (11.1%)
ИБП 14 or more points	50	20 (40.0%)	95	20 (21.1%)	40 (27.6%)
МИП less than 21 points	13	1 (7.7%)	5	1 (20.0%)	2 (11.1%)
МИП 21-29 points	10	2 (20.0%)	23	2 (8.7%)	4 (12.1%)
МИП more than 29 points	47	21 (44.6%)	92	18 (19.5%)	39 (28.1%)
Total for ROD and RAP groups	70	24 (34.3%)	120	21 (17.5%)	45 (23.6%)

Thus, the main publicly available options for surgical treatment tactics in CPP remain staged operations using half-open / half-closed technologies – ROD and RAP. At the same time, the use of the RAP method allows timely detection and complete sanitation of all foci of the infectious process in the abdominal cavity. The analysis showed that the most rational use of the RAP method in patients with CPP at the stage of the process – HS and SS and with the severity and nature of the lesion of the abdominal organs – MIP more than 20 points, ACI 14 and more points, when this tactic is much more effective than ROD. At the same time, it must be remembered that surgery itself is an undoubted factor aggravating the course of systemic inflammation. This is confirmed by a significant increase in the mortality rate with an increase in the number of sanitary relaparotomies. Therefore, when managing patients with the RAP method, it is optimal to perform two or three relaparotomies. Based on this, the most promising direction in the optimization of surgical treatment tactics in CPP are tactical and therapeutic measures aimed both at reducing the number of sanitation interventions and at reducing the severity of systemic inflammation.

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A PERSONALIZED APPROACH TO DETERMINING THE NEEDLE IMMERSION DEPTH DURING MANDIBULAR ANESTHESIA

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We have studied a personalized approach determining the depth of needle immersion during mandibular anesthesia. For this, new devices developed by the authors were used for measuring the ramus width for mandibular anesthesia, as well as a special table determining the individual depth of needle immersion.

The personalized approach to determining the depth of needle immersion has significantly changed the technology of performing classical mandibular anesthesia and improves the efficiency and safety of anesthesia.

Keywords: mandibular anesthesia, mandible, branch width, temporal crest, needle immersion depth, efficacy and safety.

Relevance. Today the priority of health care development is to improve the delivery of medical care. Despite the wide study of dental diseases their prevalence remains at a high level among the population. It is an urgent medical and social problem, since chronic foci of oral infection contribute to the development of foci-conditioned diseases in the organism [9, 11]. At the same time, the provision of therapeutic and preventive care remains the most massive type of medical care for patients with dental diseases, where its quality depends on the effectiveness of local anesthesia [1, 3, 4, 10, 15].

It should be noted that the technological features of classical mandibular anesthesia techniques take into account complex anatomical-topographic landmarks in the maxillofacial region. Meanwhile, the dentist in his daily practice encounters anatomical and age-specific features of different patient groups, where the performance of mandibular anesthesia requires a personalized approach [5, 6, 7, 14]. Different scientific, theoretical and practical researches are conducted to improve local anesthesia in dentistry [8, 13]. Thus, we have studied the personalized approach to determining the needle immersion depth during mandibular anesthesia.

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Material and methods. Anatomical-topographic study of the mandible (n=110) was performed according to the method of V.P. Alekseev, G.F. Debitz (1964). We used our developed devices for measuring the ramus width (patent №196101 from 09.12.2019) and mandibular anesthesia (patent №184398 from 04.10.2018), and developed a special table to determine the individual needle immersion depth (patent №2695896 from 29.07.2019) to substantiate the clinical effectiveness and safety of the mandibular anesthesia method with a personalized approach in determining the depth of needle immersion. The efficacy of anesthesia in patients (n=148) was evaluated by the Sokhov's method and analysis of the electroodontodiagnostics results. A comparative characteristics of efficiency and safety of the developed method of mandibular anesthesia (main group - MG, n=107) and the classical palpatory method of mandibular anesthesia (comparison group - CG, n=41) was performed.

At first we placed the extraoral working part of the device in the form of the end arch section with a groove on the posterior edge of the mandibular ramus in the area of the greatest concavity (Pic. 1) and fixed it with the middle finger of the left hand to perform our new mandibular anesthesia with a personalized approach in determining the needle immersion depth. Then the rod was pulled back using the holder and the device was placed in the patient's oral cavity, where the intraoral working part in the form of a saddle was placed on the anterior edge of the mandibular ramus in the area of the greatest concavity (Pic. 2).

Then the rod was fixed on the set position with the help of the screw fixer and the device was taken out of the oral cavity. In this case, the index in the graduated scale of the device shows the width of the mandibular ramus in mm (Pic. 3).

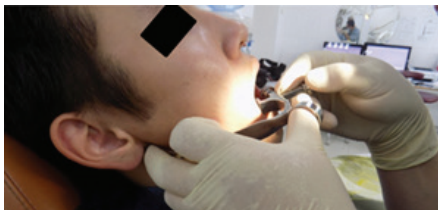
The depth of needle immersion depending on the mandibular ramus width is set using the movable limiter on the mandibular anesthesia device (Pic. 3).

The mandibular anesthesia device is then placed in the patient's mouth, where the fixator of the device is placed in the oral cavity in the area of the greatest concavity of the anterior edge of the mandibular ramus (Pic. 4, 5). The handle of the device is positioned vestibularly from the dentition, pushing the corner of the mouth and cheek outward at the level of interocclusal height. Then the carpule syringe with anesthetic and needle is placed parallel to the device at the level of premolars on the opposite side.

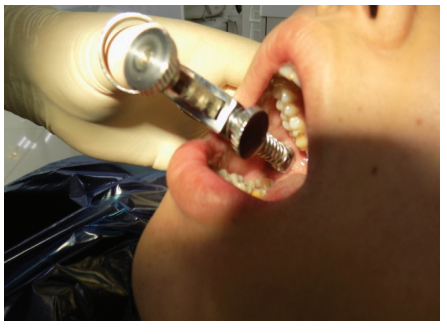
The needle is placed between the limiter plates, which is advanced into the tissue until it reaches the bone, where 0.3 ml of anesthetic is injected to disable the lingual nerve, then the syringe is moved to the frontal teeth and the needle is advanced to the back without losing contact with the bone until it stops at the pre-set limiter, where the needle reaches the target point and an aspiration test is performed with further 1.5 ml of the remaining anesthetic dose injected. Anesthesia occurs in 5-7 minutes, with the anesthetic zone corresponding to the standard technique.

Statistical processing of the research data was performed using the software package "SPSS", version 22, correlation and factor (by Varimax method) analysis of clinical material with determination of Pearson coefficient (r). The obtained results were grouped according to the same features.

Results. Comparative analysis of anesthesia efficiency of the developed and palpatory methods of mandibular anesthesia revealed the presence of peculiarities (Table 2). Thus, the obtained data characterize a rather high level of anes-

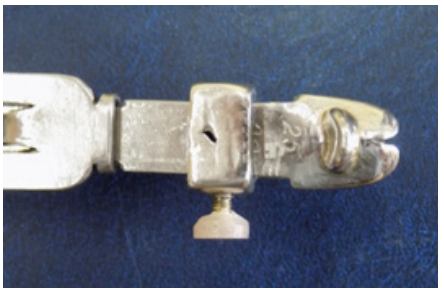


Pic. 1. Fixation of the extra-oral working part of the device to the posterior edge of the mandibular ramus with the middle finger of the left hand.

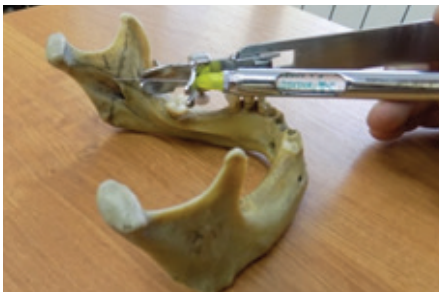


Pic. 2. Fixation of the intraoral working part in the form of a saddle to the anterior edge of the mandibular ramus in the area of greatest concavity

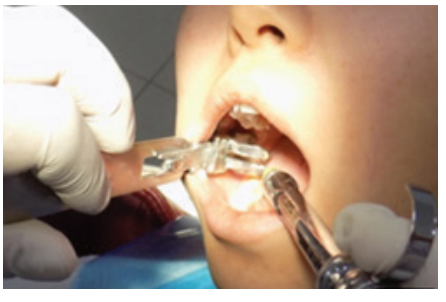
Pic. 3. Registration of mandibular ramus width using a graduated scale



Pic. 4. Fixation of distance values between the anterior edge of the mandibular ramus and the target point on the Ushnitsky-Chakhov's device for mandibular anesthesia



Pic. 5. Mandibular anesthesia device location on the mandibular bone



Pic. 6. Mandibular anesthesia device location in the oral cavity

thetic effect of the presented methods. The rate of onset of lower lip numbness ranged from 54 to 327 seconds in the main group, and the comparison group - from 63 to 431 seconds. (p> 0,05). At the same time, the rate of onset of anesthesia in the tongue region was 41-463 and 48-533 sec, respectively. (p>0,05). A similar situation is determined in indicators of tongue anesthesia duration. Meanwhile, in the data of the duration of anesthesia of the lower lip there is a significant difference in the main group, where the index is greater by 26.10 minutes (p<0.05). In addition, there is a 0.24 lower score in the Sokhov's analgesic effect score compared to the comparison group (p<0.05). Meanwhile, the average EOD before anesthesia in both groups was 3.64±0.46 μA, and the analgesic efficiency 7 minutes after anesthesia was higher by 5.07 μA in the main group. Meanwhile, no cases of positive aspiration test were detected in the main group, while in the comparison group this indicator was 4.88%, including a case of mandibular contracture. At the same time, the efficiency of anesthesia was 97.19% in the main group, and 95.12% in the comparison group. In our opinion, this is due to a closer approach of the needle tip to the nerves by to the use of the special Ushnitsky-Chakhov's table which takes into account the individual depth of needle immersion based on the mandibular ramus width, as well as the use of the Ushnitsky-Chakhov's device for mandibular anesthesia, which ensures precise approach of the needle tip to the target point.

The stated facts proved the results of the Pearson correlation analysis, where we revealed a marked connection of the minimal width indices of the mandibular ramus with the distances between the anterior edge of the ramus and the target point (r=0,69) (the depth of needle immersion), the anterior edge of the ramus and the temporal ridge (r=0,51), temporal ridge and the target point (r=0,54), which determines a relationship between the depth of needle immersion and the individual width of the lower jaw ramus. At the same time, the indicators of anesthetic effect according to Sokhov's method depend on the rate of lower lip (r=0,73) and tongue (r=0,70) anesthesia, EOD (r=0,82), duration of lower lip (r=0,73) and tongue anesthesia (r=0,55). The identified features also confirmed the results of the factor analysis according to the "Varimax" method with Kaiser normalization (Fig. 5), which characterizes that the needle immersion depth when performing mandibular anesthesia depends on the individual dimensions of the mandible (mandibular ramus width, mandibular body length, distance between the target point and the front edge of the mandible ramus) and the soft tissue thickness.

Discussion. The palpatory method of mandibular anesthesia in clinical dentistry is based on the palpation of bony landmarks, such as the anterior edge of the mandibular ramus and the temporal ridge. At the same time there are no concrete data about the depth of needle immersion, depending on the individual indices of mandibular ramus width, and the

Table 1

Determination of needle immersion depth depending on mandibular ramus width (mm)

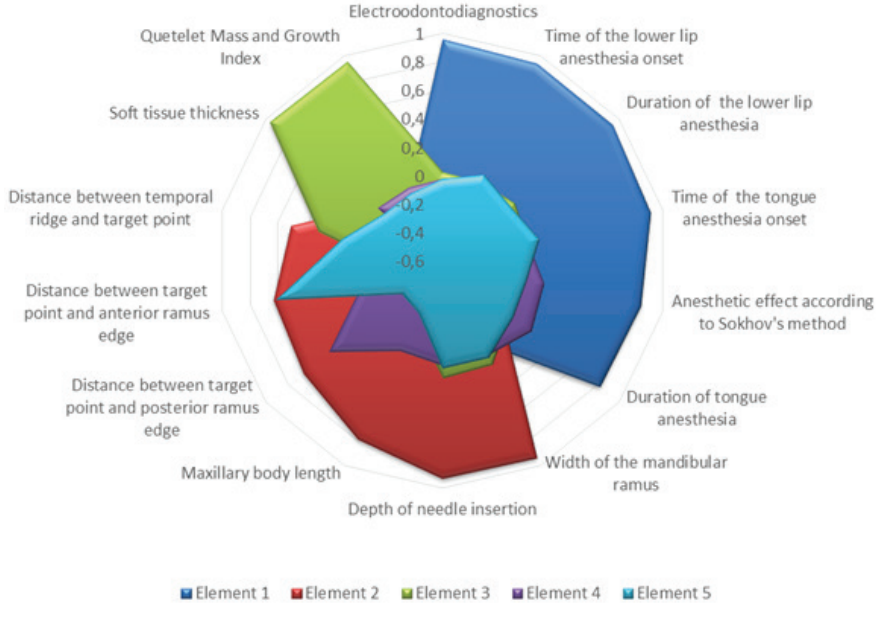
Indicators of the device for determining the width of the mandibular ramus	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
Indices of the depth of needle immersion	15.3	15.9	16.5	17.1	17.7	18.3	18.9	19.5	20.1	20.6	21.2	21.8	22.4	23.0	23.6	24.2	24.8	25.4	26.0	26.5

Table 2

Comparative characteristics of the effectiveness of the Ushnitsky-Chakhov method of mandibular anesthesia and the palpatory method of mandibular anesthesia

Group	Speed onset anesthesia (sec.)		Duration anesthesia (min.)		Analgesic effect	
	Lower lip	Tongue	Lower lip	Tongue	EOD (mA)	By Sokhov (points)
Main (n=107)	157.0 ± 21.07	175.23 ± 23.67	252.22 ± 6.63	234.10 ± 7.29	127.43 ±1.53	1.15 ±0.11
Comparison (n=41)	194.45 ± 25.31	213.72 ± 22.38	226.12 ± 5.52	222.44 ± 6.68	122.36 ±1.72	1.39 ±0.10
P	> 0.05	> 0.05	< 0.05*	> 0.05	< 0.05*	< 0.05*

Note: * – the presence of reliability when comparing the parameters of the main and comparison groups



Pic. 7. Factor analysis of the effectiveness of the Ushnitsky-Chakhov's mandibular anesthesia method (according to the Varimax method)

standardized index of the depth of needle immersion from the temporal ridge is 2,0-2,75 cm (Robustova T.G., 2003). Meanwhile, the width of the mandibular ramus according to V.P. Alekseev and G.F. Debitz (1964) varies from 23,2 to 42,4 mm. At the same time the use of standardized parameters of the needle immersion depth for a patient with mandibular ramus width of 23,2 mm may lead to such complications as trauma of the mandibular neurovascular bundle and facial nerve. It should also be noted that the temporal ridge is not always well defined by palpation and is characterized by inconsistent topography. Therefore, the use of this anatomical landmark to determine the injection point and depth of needle immersion may cause some difficulties.

A comparative analysis of clinical data revealed no cases of positive aspiration test in the main group, while in the comparison group this indicator was 4.88%. The efficiency of anesthesia was 97.19% in the main group, while it was 95.12% in the comparison group. Thus, the personalized approach to determining the needle insertion depth during mandibular anesthesia has advantages in the efficiency and safety of anesthesia.

Conclusion. The developed method of mandibular anesthesia significantly changed the technology of standard anesthesia in the form of devices and a special table, which takes into account individual anatomotopographic features of the mandible with a personalized approach in determining the depth of needle immersion and contributes to increased efficiency and safety of anesthesia.

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HEALTHY LIFESTYLE. PREVENTION

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SCIENTIFICALLY BASED EDUCATIONAL PROGRAM ON HEALTHY DIET: FEATURES OF NUTRITION TO MINIMIZE HARM TO HEALTH CAUSED BY ADVERSE (EXTREME) NATURAL AND CLIMATIC CONDITIONS

A scientifically based nutrition education programme has been developed covering nutrition peculiarities for people living on territories with extreme natural and climatic conditions. Adequate and balanced diet that takes aforementioned peculiarities into account makes a significant contribution to preserving health of both indigenous people and newcomers. Systemic informing and teaching provided for people regarding principles of healthy diet seems a promising trend in activities implemented within the 'Demography" National project.

Keywords: education programme, nutrition, natural and climatic conditions, Far North, Arctic zone.

Introduction. Climate is a long-term weather pattern that is typical for a given territory. In the Russian Federation there are several climatic zones including arctic, sub-arctic, moderate, and sub-tropic one. A big part of the country territory is located in the Far North (or areas that are considered similar to it); natural and climatic conditions there are adverse (extreme) [15,16]. These territories include Murmansk region, Arkhangelsk region, Tyumen region, Irkutsk region, Kamchatka, Magadan region, Sakhalin, Komi Republic, Karelia, Tyva, Sakha (Yakut Republic), Krasnoyarsk region, Khabarovsk region, Khanti-Mansi Autonomous Area, and Chukotka. All these RF regions are conditionally divided into Asian North and European North. Some of them are included into the Arctic zone [8]. Population is made up of various groups: natives from various ethnic groups; indigenous Caucasians (the second or older generation); migrants or newcomers who have been living in the zone for rather a short time (the 1st or the 2nd generation); shift workers who have been working there in shifts for a year or several years [16].

Both indigenous people and newcomers can preserve their health to a larger extent due to adequate and balanced diet, certain peculiarities taken into account. But still, data available in scientific literature indicate that actual nutrition consumed by indigenous people does not conform to principles of healthy diet and doesn't take climatic peculiarities into account. Thus, though food rations consumed by pre-school and school children contain fats and carbohydrates in sufficient quantities, some components are in deficiency, such as proteins, including animal ones (11-20%), vitamin C (20-36%) and A (22-89%), calcium, iodine (up to 75%) and other essential ones [23]. Rations consumed by young males (aged 17-21) who lived in the north-eastern regions in Russia (Magadan and Chukotka) tended to have low quantities of proteins and fats including polyunsaturated fatty acids and, on the contrary, high quantities of carbohydrates (up to 68%); dietary fiber was almost absent. Vitamin-mineral profile of consumed food products is apparently poor [1]. Moreover, basic rations consumed by sportsmen who live and train in the Far North can't satisfy daily energy needs and provide optimal macronutrient ratio; it should be noted that such rations should take into account not only overall dietary principles but also a specific kind of sport, a season, physical loads intensity and stages in a training process [5].

Products with high biological values do not occur frequently enough in food rations consumed by adult people [4,23]. For example, milk is daily consumed only by 47% respondents; fresh vegetables, greenery, and fruit, by not more than 16%; and fish, only by 3% (49% respondents consume it 1-2 times a week). On the contrary, sugar is consumed too often since it occurs in daily rations of 77% respondents [29]. Comparative analysis of

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actual daily food products consumption and recommended levels reveals deficiency of milk products, vegetables, potato, and fruit, and excessive quantities of confectionary [20,23,27]. Although local population consume meat in relatively significant quantities (owing to deer-raising products and hunting season), average annual quantity is 240 g/day and it is lower than in other RF regions [26]. Indigenous people, as opposed to newcomers, consume sour milk products, milk, and cheese in much smaller quantities and it results in lower calcium contents and its improper ratio with phosphor. Vegetable products deficiency leads to the body being poorly provided with water-soluble vitamins, first of all, vitamin C [20].

A share of carbohydrates reaches 60% in the structure of energy value, proteins and fats account for 20% each [13]. Some researchers state that nutrition becomes carbohydrate-lipid and carbohydrate in its essence with refined products being consumed in large quantities but low contents of vitamins, minerals, and dietary fiber [9,16,23]. This trend occurred more than 20 years ago when a share of products brought to the Far North from other regions started to grow [10,19].

Therefore, even native people tend to consume food rations that are close to conventional Caucasian ones; such rations are unable to satisfy all physiological needs of people who live under adverse (extreme) natural and climatic conditions. The existing situation requires intense activities aimed at raising people's awareness about principles of healthy diet and implementing up-to-date tools for spreading scientific knowledge including peculiarities of nutrition typical for a relevant ethnic group.

To implement activities within the "Demography" National project regarding "Population health improvement", the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor) developed the Concept for creating teaching (educational) programs on healthy diet. According to the Concept, eight scientifically substantiated programs are to be developed. Among them there is a program on healthy diet for people living on territories with peculiar exposures to environmental factors (macro- and micronutrient deficiency, climatic conditions).

Our research goal was to develop a scientifically substantiated teaching program on healthy diet covering nutrition peculiarities for people living on territories with extreme natural and climatic conditions.

Data and methods.A section in the teaching program on nutrition peculiarities to minimize health hazards caused by adverse (extreme) climatic conditions consists of two theoretical elements. The first one dwells on peculiarities of extreme climate and its influence on the body. The second one covers principles of healthy diet and its peculiarities for a relevant population group. Practical work is accomplished to strengthen knowledge and acquire relevant skills and abilities (Table 1).

To create theoretical sections in the teaching program, we analyzed research papers with results of fundamental and applied scientific research that were available in conventional citation databases (CyberLeninka, eLibrary, Google Scholar, Web of Science, Scopus, RSCI, Higher Attestation Commission etc.) and were considered relevant to the topic.

When implementing the teaching program, it is advisable to stick to a conventional algorithm that involves creating a multi-level system for continuous education provided for population (with participating medical and non-medical organizations) [7].

Results and discussion. *Peculiarities of extreme climate at high latitudes (the Far North).* Climate at high latitudes is influenced by three basic interacting factors; they are radiation, that is, solar heat income and consumption on the earth surface and in the atmosphere; circulation, that is, movement of air masses (either sea or continental ones); heat and moisture moving vertically in the atmosphere and over underlying surfaces (topsoil, plant cover, top water, snow cover, ice cover over the sea etc.) [8].

As a result, climate in the Far North is characterized with certain adverse conditions (Table 2). They include a set of non-specific meteorological factors (low temperature, high relative and low absolute humidity, and high air mobility) that tend to fluctuate drastically [8,28,30]. Apart from these meteorological factors, there are other specific exposures in the Far North such as peculiar photoperiodicity (polar days and nights) and differential air pressure. Additionally, the body is influenced by intense natural electromagnetic background created by both earth and cosmic factors. Thus, the geomagnetic field is by 25% higher than in the central European part of the country; still, since this field has weaker protective capabilities than at middle and low latitudes, alternating currents from ion- and magnetosphere produce significant effects related to solar activity [24]. Low mineralization of drinking water is another peculiarity in the Far North owing to the existing microelement structure of soils and dilution with melted snow [8,11,30]. Another adverse factor is that settlements are located far from each other in this zone and therefore transport communications are scarce and irregular between them.

All the aforementioned natural and climatic conditions are adverse and even extreme as per certain parameters

Table 1

Structure of the section in the teaching program on healthy diet regarding its peculiarities for people living on territories with extreme natural and climatic conditions

Program elements	Expected results		
	Instant		Prospect
	knowledge	skills and abilities	
Peculiarities of extreme climate and its influence on the body	- peculiarities of extreme climate - influence exerted by extreme climate on the body	- to assess whether it is necessary to correct one's food ration - to correct a food ration if necessary - to develop rational eating habits	- decreasing prevalence of alimentary-dependent diseases - decreasing prevalence of micronutrient deficiency - growing healthy life expectancy, - growing number of people who pursue healthy lifestyle
Principles of healthy diet and its peculiarities	- peculiarities of diet under extreme climatic conditions at high latitudes		
Practice	- drilling		

making higher demands to functional systems in the body even if it is adapted to them; influence on health is hardly avoidable. It is well-known that morbidity among population (both overall and primary) is higher among population living in the Far North than on average in Russia; many diseases occur at younger ages, their clinical course in non-specific and involves a lot of complications; there is also premature ageing and a decrease in life expectancy by 10-15 years [15,16]. Vitamin D deficiency and alimentary-dependent diseases (obesity, type 2 diabetes, and cardiovascular pathology) are more widely spread in the Far North than in other regions [10,20]. It is advisable to use approaches that involve hazard identification to quantitatively assess health risks [31].

When people live permanently (indigenous natives from various ethnic groups and indigenous Caucasians) on territories with extreme (and sub-extreme) cold climate, their bodies are usually well-adapted (Figure). Adaptation mechanisms are fixed by evolution in their genotype and become apparent in ontogenesis [2]. Key components in adaptation are aimed at preserving heat balance due to greater heat production under cold stress. These components are, first of all, an increase in basal metabolism determined by hyperfunction of the thyroid gland and changes in all types of metabolism including protein, fat, carbohydrate, vitamin, macro- and microelements. Vasodilatation induced by cold also helps the body to preserve heat [13,14,25]. Basal metabolic rate (BMR) corresponds to energy costs necessary to maintain vital activities (functioning of the cardiovascular, respiratory, excretory and other systems as well as heat production) when the body is at relative rest. BMR is by 10-15% higher for people living at high latitudes than for their counterparts who live at middle and low latitudes [22,17,18]; according to some other authors, the difference can reach 30% [16,25]. However, there are studies revealing that the value has already decreased down to 5% due to, among other things, changes in diets [14].

Energy metabolism switching from carbohydrate to lipid one is the most characteristic change in metabolism; thus, a so called "polar metabolic type" is created [21,22,25]. Prevalence of lipid metabolism is necessary for heat formation and heat exchange maintenance since the body prefers to oxidize fatty acids due to them having higher caloric coefficient (1 gram provides 9 kilocalories) thus preventing proteins from being spent on energy needs [13,22]. Besides, lipids participate in changing viscosity of cell membranes which is also important for adaptation to low temperatures [12].

This metabolic type results in elevated contents of very low density lipoproteins (VLDLP) and low density lipoproteins (LDLP) in blood of an adapted person. By the way, they have certain atherogenic properties. However, atherosclerosis doesn't occur since high density lipoproteins (HDLP) are also contained in blood in elevated quantities and it creates a balance between atherogenic and anti-atherogenic lipid fractions. Besides, elevated quantities of VLDLP and LDLP that contain apolilipoprotein B with contrinsular effects lead to a decrease in dextrose absorption by body tissues and lower reabsorption threshold in the kidneys. Under such conditions gluconeogenesis in the liver involving dextrose formation out of proteins and fats becomes the primary source of carbohydrates necessary for tissue nutrition. Physiological standards (homeostasis levels) are significantly different from those in the central European part of the country. Dextrose concentration in blood goes down to a value corresponding to the bottom limit of the physiological standards against lower concentrations of insulin [22].

Since lipoprotein metabolism is significantly higher under extreme climatic conditions, it creates great loads on liver macrophages. Bearing in mind that primary function of these cells is to create an immune response, we can assume that inhibited functioning of key cells in the immunity makes people living in the Far North more susceptible to communicable diseases [21,22].

Given changes in lifestyle and socio-economic structures including diet transformations, there is failure in adaptation to traditional living conditions of indigenous people. Occurring dyslipidemia and depleting functional and receptor activity of β-cells in the pancreas determine further metabolic disorders and chronic non-communicable diseases (obesity, type 2 diabetes, ischemic heart diseases, primary hypertension, and others); prevalence of such diseases has grown over the last decade [6,13].

Newcomers have to face significant loads on their adaptation system since it requires complicated structural changes in regulatory, physiological, and metabolic processes, and so called "the winter-over syndrome" occurs [15]. The circulatory system is among the fastest to react. Peripheral vascular spasm is necessary to prevent heat loss but it can also cause primary hypertension occurrence. Morphofunctional changes in the pulmonary circulation are considered to underlie chronic non-specific lung diseases ('Magadan pneumopathy"). The respiratory system is under significant functional strain that is related, among other things, to the necessity to preserve temperature homeostasis in respiratory sections [28]. Cold air with absolute humidity requires more secretion to moisten mucosa and it makes for greater moisture losses, up to 1.500 ml per day (instead of 500 ml typical for the central European part of the country), with exhaled air [30]. Moisture also evaporates on skin surface and it results in its weakened protective capabilities and changes in the overall heat exchange of the body. When liquid is excreted via extra-renal way, it results in more intense external breathing and oc-

Table 2

Natural and climatic peculiarities in the Far North

Factors that determine natural and climatic peculiarities in the Far North	Natural and climatic peculiarities in the Far North	
	non-specific	specific
Solar radiation (solar heat income and consumption on the earth surface and in the atmosphere)	- low temperature (-40-70 0C) - high relative humidity (65-95%) - low absolute humidity (1-3 g/m3) - significant air mobility (up to 40 m/sec)	- changes in photoperiodicity (polar night lasts up to 125 days; polar day, up to 140 days) - intense electromagnetic (geomagnetic and cosmic) field - air pressure differential (70-80 gPa in winter, 40-60 gPa in summer) - low mineralization of drinking water (selenium, fluorine, and calcium deficiency)
Movement of air masses		
Heat and moisture moving vertically in the atmosphere and over underlying surfaces		

currence of “polar shortness of breath” (it can occur due to strong wind combined with frost). Changes in external breathing involve greater respiratory minute volume, respiratory volume, respiratory rate, oxygen consumption; lower vital capacity of lungs, inhalation and exhalation reserve volumes, and maximum lung ventilation; large bronchial tubes widen but there is spasm in the middle-sized and small ones. Similar changes occur in external breathing when hands and to a greater extent feet are cold [28].

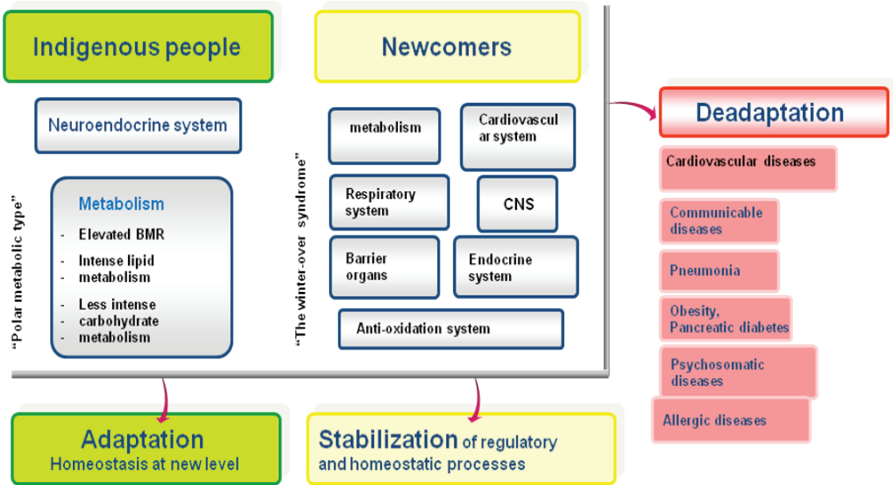
Drastic rises and drops in air pressure (10 times higher than threshold values) result in similar drastic fluctuations in partial density of oxygen (an actual quantity of oxygen molecules in inhaled air) and developing hypoxia [28,30]. All these changes undoubtedly influence metabolism. Hypoxia stimulates more intensive lipid peroxidation and it exerts negative membrane-tropic impacts. Exposure to cold leads to stronger oxidation of deposited fats and glycogen but dextrose contents in blood go down (by 40-45%). The latter results in an increase in renal “carbohydrate barrier” and functional disorders in the pancreas [9].

Basal metabolism increases by 13-17% at an early stage in adaptation during the whole polar day. Newcomers’ long staying in these new conditions, polar nights, as well as shorter periods of time spent outside in the frost lead to a decrease in BMR by 10% [22]. These changes occur owing to endocrine-metabolic shifts including activation of the sympathetic system, greater production of glucocorticoids, high contents of free fatty acids, LDLP and VLDLP, that is, atherogenic forms [21].

Insufficient UV-radiation due to the Sun standing low over the horizon and changes in spectrum of solar radiation lead to “ultraviolet hunger”, vitamin D deficiency, and disorders in phosphor-calcium metabolism. Strained electromagnetic field (direct and alternating) creates changes in tissue respiration caused by slower transfer of electrons along the respiratory chain and natural decrease in ATP synthesis (energy substrate in the body) [30].

In case an outcome is favorable, regulatory and homeostatic processes stabilize and synchronize but this, by the way, can take as long as 10 years [25]. Probably due to it hereditary adaptation mechanisms of newcomers’ children can’t ensure long preservation of their health [15].

When reserve capabilities are depleted and overall adaptation costs are higher than functional and morphological



Scheme showing influence exerted on the body by natural and climatic conditions at high latitudes

limits, it results in deadaptation which can be considered a borderline state between health and illness or a disease itself [3]. Its basic components are oxidation stress, insufficient detoxification and barrier organs failure, disorders of polar metabolic type, northern tissue hypoxia, immune deficiency, blood hypercoagulation, polyendocrine disorders, regenerating and plastic deficiency, electromagnetic homeostasis disorders, functional dissymmetry of intrahemispheric relations, desynchronosis, psychoemotional strain, and meteopathy [15]. Cardiovascular diseases, diseases of the nervous and respiratory system, and communicable diseases occupy leading places in the structure of morbidity [9,28]. Chronic non-communicable diseases occur and develop in large measure due to the alimentary factor, that is, excessive consumption of carbohydrate food, refined sugar, and products rich with saturated fatty acids; vitamin and mineral deficiency as well as deficiency of essential amino acids. We should note that technogenic and anthropogenic environmental contamination in the Far North deteriorates adaptation capabilities and additionally makes for occurrence of multiple diseases including allergies and immune pathologies [9].

Basic principles of healthy diet

- Rations should be energy-adequate, that is, their energy value should correspond to energy costs borne by the body.

- Basic food products should be consumed in quantities within physiologically adequate ranges and ratios between them.

- Food rations should include variable food products: bakery and grocery (flour, bread, cereals, beans, and macaroni), milk and milk products, meat and meat products, fish and fish products, vegetables, potato, fruit, eggs, vegetable oil, as well as sugar and confectionary.

- Nutrition regime should be optimal.

Nutrition peculiarities under adverse (extreme) natural and climatic conditions at high latitudes

- Energy value of a ration should be by 10-15% higher than in other climatic zones [17,18,22]. The reason is that people living in the Far North tend to spend more energy in general since it is necessary to both increase heat production (due to BMR) and to cope with additional physical loads (walking on snow in heavy winter clothing, resisting winds, etc). The farther from the equator, the greater are energy costs on doing the same work [9].

- Protein and fat components should appear in food in sufficient quantities due to energy metabolism switching from carbohydrates to lipids. Recommended ratio of proteins, fats, and carbohydrates is 1:1:3, that is, a share of proteins should not be lower 15%; fats, 35-36%; carbohydrates, 46-50% [23]. Animal proteins should account for not less than 60% of the overall quantity, and animal fats, not less than 60-90%.

It is extremely important to use locally manufactured food when creating rations for indigenous people. Priority products include reindeer meat and fat; meat of Yakut horses, elk, and hare; bird game (partridge, heath-cock, wood-goose, wild duck, and wild goose); codfish and whitefish (Siberian salmon, grayling, navaga, red salmon, sterlet, burbot, herring, pike, perch, etc.); as well as meat of sea animals (walrus, seal, or whale). These products are rich with irreplaceable amino acids, polyunsaturated fatty acids, fat-soluble vitamins, and antioxidants [9,16,26].

- Simple carbohydrates should be con-

sumed in smaller quantities since carbohydrate metabolism changes and tissues consume dextrose in smaller quantities. Dextrose income is provided due to gluconeogenesis in case proteins and fats are consumed in sufficient quantities.

- Vitamins should be consumed in sufficient quantities. Less intensive carbohydrate metabolism decreases (but doesn't eliminate) body needs in water-soluble vitamins. Use of low-mineralized water leads to lower assimilation of not only minerals but also vitamins and to developing vitamin deficiency. Therefore, there is almost twice as high need in various vitamins [9]. More intense lipid metabolism increases demand for fat-soluble vitamins.

A food ration should necessarily include vegetables, fruit, local wild plants (wild sorrel, wild garlic, Iceland moss) and berries (cowberries, cloudberries, cranberries, blackberries, blueberries, honeysuckle, rose hips, etc.).

- There should be additional macro- and microelements intake. Mineral deficiency occurs in the body mainly due to low mineralization of water in local rivers and selenium and fluorine deficiency. Radiation exposure results to radioactive strontium accumulation in bones. A food ration should include products rich with calcium that makes for strontium elimination [9]. Zinc and copper should also be consumed in sufficient quantities since they are necessary for functioning of cytochrome chain enzymes, anti-oxidation system, and neuroendocrine regulation [26].

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGYAND MEDICAL ECOLOGY

A.V. Timonin, S.V. Shirokostup, N.V. Lukyanenko

OPTIMIZATION OF THE SYSTEM OF PLANNING MEASURES FOR EPIDEMIOLOGICAL CONTROL OF THE INCIDENCE OF TICK-BORNE ENCEPHALITIS AND SIBERIAN TICK TYPHUS IN REGIONS WITH COMBINED FOCI OF THESE INFECTIONS

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The article presents the results of the multidimensional factor analysis, with the help of which the leading factors influencing epidemic processes of tick-borne viral encephalitis and Siberian tick-borne typhus in the territories of Altai Krai with combined foci of these natural focal infections in the period from 2000 to 2019 were determined. The relationships between individual predictors have been established, allowing them to make a significant contribution to the formation of the incidence rate as a single factor. The degree of influence of each of the leading factors on the morbidity level according to these nosologies in the studied territories was identified. The results of multiple and dual regression are presented carried out for the purpose of estimating the perspective value of the analyzed controlled factors necessary for the subsequent optimization of the planning system for the measures of epidemiological control of morbidity of tick-borne viral encephalitis and Siberian tick-borne typhus in the studied territory, which will also allow to form a planned trend of morbidity dynamics towards a decrease in its indicators.

Keywords: combined foci, natural focal infections, tick-borne viral encephalitis, Siberian tick-borne typhus, endemic territories, determination of leading factors, multidimensional factor analysis.

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Introduction. The incidence of Siberian tick-borne typhus (STT) and tick-borne viral encephalitis (TVE), as well as other tick-borne infections, is currently high and depends on multiple influence of a large number of factors characterizing epidemic processes of these vector-borne natural focal infections [1, 2, 3, 9, 10]. Such factors may be expressed as an independent phenomenon beyond the control of others or may consist of a different number of predictors forming a general, meaningful impact on the epidemic process of these infections [5, 6, 7, 11].

The multidimensional factor analysis of the effects of various predictors on the TVE and STT incidence will allow inducing the “latent” relationship between individual predictors acting as a single factor, while the effect of each predictor individually on the resulting trait was considered as statistically insignificant [4, 8, 12]. Identification of leading factors with determination of predictors in their structure allowed assessing each factor by its contribution to formation of incidence rate of these infections in the territory of the endemic region by means of the multidimensional factor analysis [13, 14, 15].

The **aim of the study** was to optimize the system for planning measures of epidemiological control of tick-borne viral encephalitis and Siberian tick-borne typhus incidence in regions with combined foci of these infections.

Materials and methods. The study was conducted using the data of the of-

ficial sources: statistical reporting forms No. 2 "Information on infectious diseases" in Altai Krai for 2000–2019, data of the Federal Statistics Service for Altai Krai for 2000–2019, information from the State reports "On the state of sanitary and epidemiological well-being of the population in Altai Krai" for 2000–2019. The study was carried out in Statistica 12.0, during which the absolute, relative and average indicators were calculated, as well as the coverage errors (±m). The calculation of significance of differences was carried out using the Fisher test (f). The multidimensional factor analysis was carried out using the principal component method with the rotation of factor loads Varimax. Leading predictors were determined using the Kaiser criterion.

Results and discussion. A set of predictors was selected empirically characterizing the territories of Altai Krai with combined foci of STT and TVE annually differing in the region's high incidence rates of these infections among the local population. After selection, all predictors were systematized into three groups according to their ability to influence the trend in the dynamics of incidence rates of current infections. **Group 1** included predictors consisting of data reflecting the frequency of contacts of population of endemic territories with causative agents of these infections: these are indicators of the prevalence of ticks with rickettsia (STT pathogens), infected ticks, the number of ticks per 1 km of the way, as well as indicators of the population at risk: children up to the age of 17, working-age population and older, occupational risk cohort. **Group 2** was formed from predictors designed to ensure a change in the direction of the trend in the incidence rate of current infections towards its decrease: these are data reflecting the level and availability of medical care in the study territory (the number of medical institutions of various levels), as well as data of such preventive measures as indicators of areas of acaricide treatment, indicators of emergency seroprevention and preventive vaccination of TVE.

The predictors included in **group 3** reflected the anthropogenic change in the natural system within the boundaries of the region's territories with combined foci of STT and TVE: these are indicators of the area of perennial plantings, seed cultures, indicators of the number of cattle and small ruminants in farm and personal subsidiary holdings, the length of auto-roads. This group of predictors contributed to the creation and maintenance of the activity of anthropurgic foci of these infections.

After the distribution of the selected predictors into groups, in the course of the multidimensional factor analysis, the "leading" predictors were determined in each of them. Establishment of the leading predictors in each group was carried out taking into account the Kaiser criterion, according to which, the "leading" predictors are those that are greater than or equal to 1.0 using the own calculated values of the analyzed predictors. If the own calculated values of the predictors turn out to be less than 1.0 in the course of factor analysis, they will be considered "background", i.e. unable to have a significant impact on the resulting sign; in this case, it is the incidence of STT and TVE in the study areas.

Further, using the multidimensional factor analysis and principal component method, the selected leading predictors were ranked taking into account the criterion of their share of total variance (%) and factor loads. Thus, the contribution of each of the analyzed predictors to the formation of the incidence rate of current infections was assessed. In addition, it was found that there is a hidden relationship between some of the analyzed predictors allowing them to influence the incidence rate as part of a single factor. Thus, **Factor 1** included predictors having a dependent effect on the incidence of current infections and reflecting the availability of medical care, as well as indicators of the population at risk. **Factors 2–7** consisted of one predictor independent of the others. Thus, two groups of factors were obtained: specific and non-specific. Specific **Factors 1–3** had the ability to simultaneously affect two infections of different nosologies: STT and TVE, while non-specific **Factors 4–7** had the ability to affect the incidence of only one nosology: either TVE or STT. The data are presented in the Table.

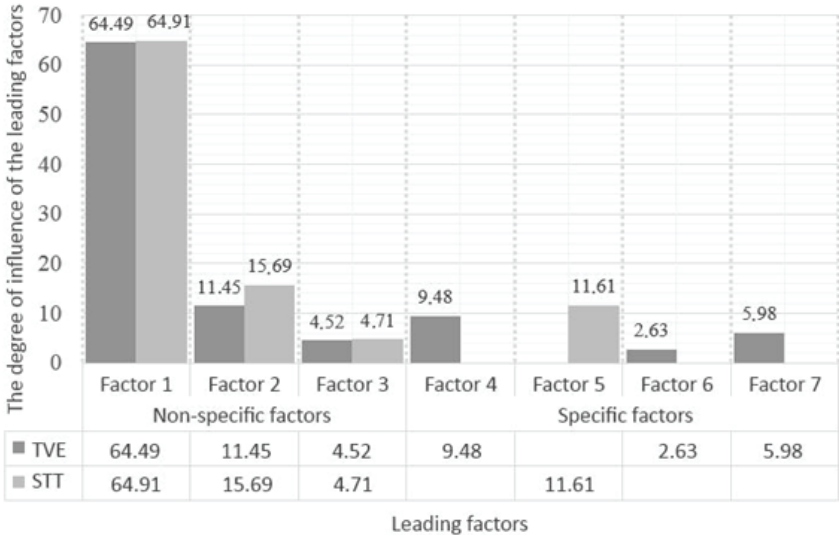
The degree of influence of each of the identified leading factors on the incidence of STT and TVE was heterogeneous, as the group of non-specific factors that simultaneously influence the incidence of both nosologies was characterized by the degree of influence on TVE in 80.5%, STT – 85.31%. This group of factors reflected the availability of treatment and prophylactic care for the population, the number of ticks per 1 km of the way, the area of acaricide treatment (ha), and the population at risk. The group of specific factors influencing the incidence rate of only one infection was characterized by the degree of influence on TVE – 18.09% (infected ticks, rates of vaccination of the population and emergency seroprevention), on STT – 11.61% (the prevalence of ticks with rickettsia).

Factors reflecting preventive measures (preventive vaccination and seroprevention of TVE, acaricide treatment of territories) have a degree of influence on the TVE incidence in 13.13%. For STT, there was a factor in the section of preventive measures that included an indicator of the area of acaricide treatment with a degree of influence on the incidence of this infection of 4.71%. The data are shown in the Figure.

The degree of influence of measures

List of analysed predictors forming factors

Factor group	Factor name	List of predictors included in the factor
Non-specific factors	Factor 1	- the number of children under 17; - the number of occupational risk cohort; - the number of population older than the working age; - the number of medical organizations
	Factor 2	the number of ticks per 1 kilometer of the way
	Factor 3	the area of acaricide treatment (ha)
Specific factors	Factor 4	infected ticks (%)
	Factor 5	the prevalence of ticks with rickettsia (%)
	Factor 6	vaccination rate against TVE
	Factor 7	emergency seroprevention of TVE in affected individuals from a tick bite



Influence of the leading factors on the trend of the dynamics of the STT and TVE incidence typical for the local population of Altai Krai territories with their combined foci (%).

of specific and non-specific prevention on the formed level of TVE and STT incidence characteristic of region's territories with combined foci may have been due to the insufficient volume of measures carried out.

For the studied period of 2000–2019, the average long-term incidence rates of TVE and STT in certain territories of Altai Krai characterized by the presence of combined foci of these infections significantly exceeded similar incidence rates in the region as a whole; for TVE, this difference was 1.5 times (reaching 4.3±1.09 0/0000, while corresponding figures in Altai Krai were within 2,86±0,34 0/0000); for STT, indicators exceed 2.8 times (reaching 87,8±4,90 0/0000, while the same indicator in the region was 31,77±1,11 0/0000) (p≤0,001).

In order to from the tendency to decrease in the STT and TVE incidence in areas with combined foci, the assessment of the perspective values of measures of epidemiological control of the incidence rate of these nosologies was carried out using the method of multiple regression. Using this method, it was possible not only to confirm the existence of a connection between the resulting trait (TVE and STT incidence) and the factors affecting it, which are implemented as measures of epidemiological control (the indicator of preventive vaccination and emergency prevention with immunoglobulin against TVE, the area of acaricide treatment), but also to assess the perspective value of the analyzed factors necessary for formation of a planned trend of incidence dynamics.

Thus, the coefficient of the multiple regression equation for the preventive vaccination factor was -0.00074, which means a decrease in the TVE incidence rate by 0.74 0/0000 (p<0.001) with an increase in the preventive vaccination level by 1000 0/0000, i.e. 33.6% (to 3979.1 0/0000) compared to the previous year. The coefficient of the multiple regression equation for the factor of emergency prevention with immunoglobulin was -0.0085, which means a possible decrease in the TVE incidence rate by 0.85 0 /0000 in case of an increase in the emergency immunoprophylaxis level by 100.0 0/0000, i.e. by 24.6% compared to the previous year (to 507.0 0/0000 (p<0.001)). The coefficient of the multiple regression equation for the area of acaricide treatment factor regarding TVE was -0.00016, which means a possible decrease in the incidence rate by 0.16 0/0000 as a result of an increase in the area of acaricide treatment by 1000 ha, i.e. 45.4% (up to 3203 ha) compared to the previous year (p<0.001). For STT, this dual regression coefficient for this factor was -0.0156, indicating a possible decrease in the STT incidence by 15.60 0/0000, i.e. 15.74% (p<0.001) compared to the previous year with the same increase in the volume of acaricide treatment (by 1000 ha, i.e. by 45.4% up to 3203 ha) within the areas with combined foci of these infections.

The identified leading factors characterizing epidemic processes and ensuring formation of the TVE and STT incidence rate in areas of the region with combined foci of these infections show the significant contribution of indicators of the population at risk (children under 17, population older than the working age, and occupational risk cohort) to the positive trend in incidence dynamics. A large number of cases of TVE and STT in the areas under study is recorded in these population groups due to the higher susceptibility to infections (children under 17, population older than the working age) and the high frequency of contact with natural and anthropogenic foci among persons from the occupational risk group. The unidirectional effect on the incidence indicators trend provided by a predictor reflecting the availability of medical care together with predictors of risk groups among the population is explained by a higher level of diagnosis and laboratory confirmation of the disease.

The relatively low degree of influence of leading predictors reflecting preventive measures against TVE and STT among the population of the studied territories may be due to the low volume of measures in Altai Krai in general, as well as specifically among the population of risk groups. It is the small amount of preventive measures in relation to these nosologies and their non-rational implementation among the population or territories that could be one of the main reasons for the existing level of morbidity.

Conclusion. Thus, thanks to the carried out multidimensional factor analysis, it was possible to establish the presence of leading factors having a significant impact on the formation of the incidence rate of STT and TVE, registered among the local population in the territories of Altai Krai with combined foci of these infections. A low degree of influence of factors reflecting preventive measures for specific and non-specific prevention of these infections was established, which could be due to the insufficient volume of these measures implemented in the areas of the region with combined foci. The insufficient amount of these measures in the study areas is also confirmed by the long-term average incidence of population of these areas, which is 1.5 times higher for TVE than the same indicator for the region in general making 4,3±1,09 0/0000 and 2,8 times higher for STT making 87,8±4,90 0/0000.

It was possible to establish the perspective value of the analyzed factors necessary for the formation of the planned trend of incidence dynamics. Thus, if to increase the volume of vaccination against TVE by 33.6%, increase the volume of emergency prevention with immunoglobulin against TVE by 24.6%, and increase the volume of acaricide treatment by 45.4% in the territories of the areas of Altai Krai with combined foci of TVE and STT, it will be a success to get a possible decrease in the incidence rate by 40.7% to 2.55 0/0000 for TVE and

15.74% to 83.5 0/0000 for STT among the population in these areas.

Conflict of interest: The authors declare no conflict of interest.

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S.S. Sleptsov, S.S. Sleptsova, T.E. Burtseva

MORTALITY ANALYSIS OF THE WORKING-AGE POPULATION OF YAKUTIA

The article analyzes the government statistics data on mortality of able-bodied population in the Republic of Sakha (Yakutia) in the period from 1995 to 2020, together with the structure of the main causes of death in this category. The dynamics of changes in the mortality structure of urban and rural residents with gender division is studied, the impact of the new coronavirus infection on the work of the health care system in Yakutia is shown. Mortality rate of the population of the Republic of Sakha (Yakutia) of working age decreased significantly during the study period, but the proportion of deaths in this group to the total number of deaths is still higher than the all-Russian figures. It is also shown that the mortality rate of men is 3.6 times higher than that of women. Since 2011, the mortality rate in rural areas has become significantly higher than that in urban areas, especially among the female population, which is largely determined by the reduction of bed capacity. The trend towards reducing the number of inpatient beds is certainly typical not only for Russia, but also for most European countries, but the negative consequences of this are largely offset by the opening of prevention and rehabilitation centers locally, where progressive treatment technologies are used. But this approach does not take into account the main regional peculiarities of Yakutia - its extensive territory and low population density. The problem is also exacerbated by environmental conditions, the negligent attitude of many citizens to their health and unfavorable socio-economic factors, especially pronounced in rural areas. But it must be recognized that in recent years the republic has carried out significant work to improve its healthcare system, including through the construction of new medical facilities, large-scale preventive work and the introduction of "Zemskiy Doctor" and "Zemskiy Feldsher" programs, thanks to which qualified personnel are sent to the remote corners of the republic to work. However, receiving quality and prompt medical care is still difficult for remote rural settlements.

Keywords: mortality; able-bodied population; main causes of death; coronavirus; Yakutia.

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Introduction. Increasing life expectancy is one of the national development goals of Russia until 2030. [1]. However, the achievement of this goal is still hindered by the high mortality rate of people of working age. According to even the average version of the UN forecast [6], calculated even before the COVID-19 pandemic, by 2050 the number of Russians aged 25-64 will decrease by 28% (from 82,808,000 to 59,623,000 people). This may cause a shortage of labor resources and lead to an increase in the demographic load factor.

Objective of the study. To conduct a comparative analysis of the mortality rate

Table 1

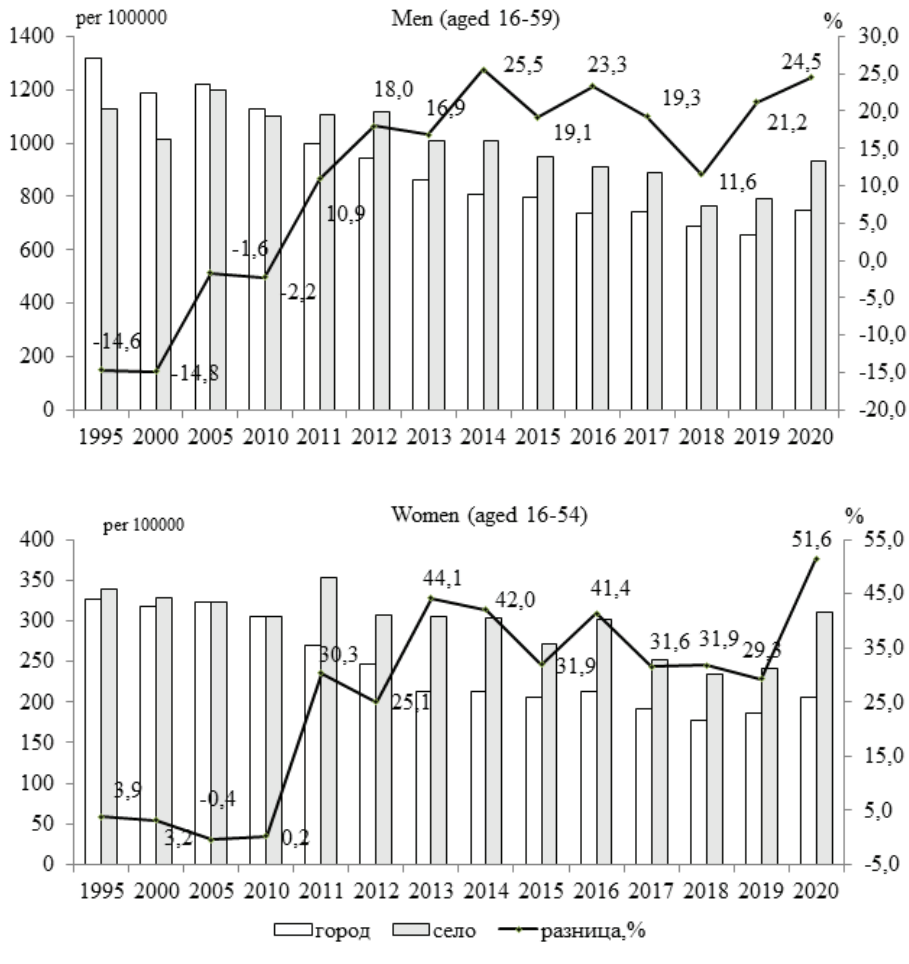
Dynamics of the number of deceased in the working age in the Republic of Sakha (Yakutia) from 1995 to 2020

Indicator	Year								
	1995	2005	2010	2015	2016	2017	2018	2019	2020
Mortality rate of working-age population, per 100000	829.2	773.6	725.5	552.8	532.2	516.7	468.8	465.2	538.4
including male mortality rate	1259.8	1209.9	1118.2	848.7	794.4	790.9	713.2	697.7	806.9
including female mortality rate	330.3	322.9	305.8	226.5	241.0	210.6	194.9	203.4	236.6
Proportion of deaths in working age in relation to the total number of deaths, %	50.6	48.2	46.9	38.8	37.5	36.9	34.5	33.7	33.9

of the working-age population of the Republic of Sakha (Yakutia) for the last 25 years (from 1995 to 2020). Data of the territorial body of the Federal State Statistics Service in the Republic of Sakha (Yakutia) on the death rate of the working-age population (men 16-59 years, women 16-54 years) by major causes of death were analyzed: certain infectious and parasitic diseases (A00-B99), neoplasms (C00-D48), cardiovascular diseases (I00-I99), respiratory diseases (J00-J99), digestive diseases (K00-K93) and external causes of death (V01-Y98) from 1995 to 2010 and from 2011 to 2020. The materials of the state report "On the state of population health and organization of health care in the Republic of Sakha (Yakutia) according to the results of activity for 2020" were also used. [3]. Statistical processing of the data was performed using Microsoft Office spreadsheets.

Results: According to official statistics, the mortality rate of Russians of working age is gradually decreasing. Not an exception is the Republic of Sakha (Yakutia). As Table 1 shows, while in 1995 this rate per 100,000 population was 829.2 people, by 2019 it has decreased by 43.9%, i.e. to 465.2 people. (Increase in mortality in 2020, due to the COVID-19 pandemic). For comparison, in 2019 the mortality rate for working-aged people was at 470 for the Russian Federation and 593 for the Far Eastern Federal District.

But it is worth noting that in Yakutia to this day the share of working-age deaths is still over 30% of the total number of deaths, while the average value for Russia in 2019 was at 21.1% (1,800,683 people died, including 379,883 working-aged. Second, even taking into account differences in the age range between the sexes, there is a significant gender difference - on average, the mortality rate of men is 3.6 times higher than that of women.



Mortality rates of the working-aged people of the Republic of Sakha (Yakutia) in rural and urban areas (1995-2020)

Thirdly, in recent years there has been a pronounced difference between mortality in rural and urban areas (Fig. 4). Thus, while before 2010 the mortality rate in rural areas was lower or was at the level of indicators in urban settlements, since 2011 it has been significantly higher than that in urban areas, especially for the female population. For example, in 2020 the difference was 51.6% (Fig. 1).

One of the reasons for the previously mentioned difference between the mortality rates of the rural and urban population is a significant reduction in the number of beds. So, from 1995 to 2020, this indicator for the Republic of Sakha (Yakutia) decreased from 155 to 96 beds/10 000 population, or, in absolute terms - from 16080 to 9305 units (-42,1%). When comparing the number of budget beds with the calculated difference in

Table 2

Distribution of causes of mortality of rural and urban residents of working-age residents in the Republic of Sakha (Yakutia) for 1995-2010 and 2011-2020

ICD	Population							
	Urban				Rural			
	1995-2010		2011-2020		1995-2010		2011-2020	
	M	F	M	F	M	F	M	F
	чел./100 тыс. населения							
V01-Y98	472.2	90.5	259.2	50.3	564.6	103.6	416.2	88.1
I00-I99	388.1	97.2	291.7	65.3	293.9	98.2	291.8	86.6
C00-D48	115.9	52.1	80.9	38.6	78.5	43.0	91.3	46.7
A00-B99	29.0	7.6	24.5	8.0	20.4	9.3	17.0	6.6
J00-J99	49.2	12.9	28.4	7.7	26.3	11.1	20.2	6.3
K00-K93	81.8	28.8	56.8	24.2	48.8	20.5	40.6	19.9
Прочие	78.0	29.6	55.8	18.3	77.6	38.4	70.9	34.1
	%							
V01-Y98	38.9	28.4	32.5	23.7	50.9	32.0	43.9	30.6
I00-I99	32.0	30.5	36.6	30.7	26.5	30.3	30.8	30.0
C00-D48	9.5	16.3	10.1	18.2	7.1	13.3	9.6	16.2
A00-B99	2.4	2.4	3.1	3.8	1.8	2.9	1.8	2.3
J00-J99	4.1	4.0	3.6	3.6	2.4	3.4	2.1	2.2
K00-K93	6.7	9.0	7.1	11.4	4.4	6.3	4.3	6.9
Others	6.4	9.3	7.0	8.6	7.0	11.8	7.5	11.8

urban and rural population mortality, we found a pronounced inverse correlation (r = -0.8...-0.9). It should be taken into account that the dynamics of the reduction of beds in Yakut villages is much higher than in the city. For example, if from 2008 to 2020 the last indicator has decreased by 12.4%, the reduction of beds in rural areas has been registered by 40.2%, or from 3134 to 1873 units. In other words, in 2020 there were on average 3.2 beds per one rural settlement of the republic, whereas in 2010. (i.e. before the difference in mortality between the rural and male populations), the figure was 4.7 beds.

The new coronavirus infection COVID-19, which emerged in 2020, has made a significant change in public health. According to the State Report "On the state of public health and organization of health care in the Republic of Sakha (Yakutia) according to the results of 2020" in 2020 the hospitalization rate decreased by 23.7% compared to 2019, the volume of inpatient care - by 24%, the intensity of use of beds in hospitals - by 14.8%. There was also a significant reorganization of 24-hour beds. Primarily by increasing the number of infectious disease beds for adults (from 264 to 1691) the number of therapeutic (by 40.9% or from 1377 to 814), tuberculosis (by 29.1% or from 731 to 518), neurology (by 35.8% or from 386 to 248), gynecology (by 35.6% or from 388 to 250), pediatric somatic (by 34.9% or from 708 to 461) and other beds were reduced. This aggravated the deplorable situation in healthcare, especially in distant from the center, where transport infrastructure is extremely difficult, lack of qualified personnel, necessary medicines, equipment, etc.

The problem is exacerbated by Yakutia's severe environmental conditions, the careless attitude of many citizens toward their health, unfavorable socio-economic factors, such as low income or unemployment, deteriorating nutrition, etc. According to a medical and social survey we conducted in 2020 among the residents of rural areas of Namsky District diagnosed with chronic viral hepatitis, we found that only 20.8% considered their income high enough, 54.5% of respondents were burdened with consumer loans, 50.6% lived in poorly equipped houses, 46.8% considered the consumed food intake to be insufficient. Only 15.5% of men and 40.9% of women fully followed their physician's prescriptions [4].

In 1995-2000, a significant proportion of the working-aged malepopulation died of external causes (V01-Y98). But over the past decade, positive changes have been observed, especially in the urban population, where the mortality rate has decreased by 44.4-45.1%. This reduction is caused mainly by the decrease in the number of murders (from 241 to 116 cases/year) and suicides (from 340 to 168 cases/year), the total share of which in the structure of external causes varied from 28.1% to 39.8% depending on the year. The number of deaths caused by transport injuries also decreased significantly (from 160 to 76 cases/year). But the mortality rate due to alcohol poisoning is still high - a total of 601 people died in the country between 2011 and 2020, including 468 men and 133 women. In general, the mortality rate of rural residents from external causes is always significantly higher than that of urban residents - 39.5% for men and 47.3% for women.

The data in Table 2 show that of the diseases influencing high mortality in working-aged people, the leading place is occupied by diseases of the circulatory system (I00-I99). At the same time, in recent years, urban residents have seen an obvious decrease in mortality from this cause (by 24.8-32.8%). Rural residents have not seen such pronounced positive changes. According to calculations for 2011-2020, the most frequent causes of death were coronary heart disease (27.8%), cerebrovascular disease (17.6%) and acute myocardial infarction (10.3%). Today in the Sakha Republic there is Regional Vascular Center No. 2 on the basis of the State Institution of the Republic of Sakha (Yakutia) Republican Hospital No. 1-National Medical Center, which provides care for cerebrovascular disease, Regional Vascular Center No. 1 on the basis of the State Institution of the Sakha Republic (Yakutia) Republican Hospital No. 2-Emergency Medical Care Center, and 4 primary vascular departments in Mirny, Neryungri, Nyurba and the village of Maya of the Megino-Kangalassky District. Pre-hospital thrombolysis by ambulance services is carried out to reduce mortality from acute coronary syndrome, work on early detection of patients with high and very high cardiovascular risk is carried out, etc. [3]. In April 2022 it is planned to put into operation the republican cardiovascular center for 150 places, equipped with the most up-to-date equipment.

The mortality rate from neoplasms (C00-D48) among the urban population also decreased significantly (by 25.9-30.2%), and, on the contrary, among men in rural areas increased by 16.3%. From 2011 to 2020 the absolute number of those who died of neoplasms in the work-

ing-aged people in the Republic of Sakha (Yakutia) amounted to 3663 people, including 2538 men and 1125 women. Proceeding from the urgency of the problem, Yakutia is working to create a network of outpatient cancer care centers. At present, such centers have been opened in Aldan, Vilyui, Mirny, Megino-Kangalassy, Neryungri, Nyurba, Lensk, Olekminsky, Khangalassy uluses and in Yakutsk. It is also planned to open 2 centers in Amga and Verkhnevilyuysky uluses on the basis of the Central Regional Hospital. Besides, in the regional capital, under the regional program "Fighting cancer in the Republic of Sakha (Yakutia)", the construction of a new Oncoclinic center is being completed, the Internet project initiated in 2020, operates for early cancer diagnostics. Yakutsk Republican Oncological Dispensary. Since its launch, about ten thousand people have been surveyed on the platform, and about seven thousand of them have been examined.

The share of infectious and parasitic diseases (A00-B99) in the total structure has ranged from 1.8 to 3.8% for all years. But it should be borne in mind that only some intestinal infections and tuberculosis are included in this category. And those who died of complications of viral hepatitis depending on the diagnosis are classified as those who died of diseases of the digestive organs or neoplasms. Coronavirus infection is also included in a separate group, from which 1784 people died from the beginning of the pandemic till December 31, 2021, including 1073 in 2021.

The mortality rate from respiratory diseases (J00-J99) became much lower - for urban dwellers by 40,3-42,4%, for rural women by 43,2%, for men by 23,2%.

Conclusion: in recent years Yakutia has made significant efforts to improve the health care system, including the construction of new health care facilities, large-scale preventive work, as well as the implementation of the "Zemskiy Doctor" and "Zemskiy Paramedic" programs, thanks to which qualified personnel are sent to remote parts of the republic to work. Nevertheless, for a significant part of the population, especially in rural areas, it is still difficult to obtain high-quality and prompt medical care.

Despite a steady decline in the mortality rate of the working-age population in Yakutia over the past 25 years, including from external causes, the share of deaths in the working-aged people to the total number of deaths is still high, even compared to the national data. In Yakutia, 2,500-3,000 people of working age die annually for various reasons. Moreover, the male mortality rate is 3.6 times higher than the female mortality rate. In addition, since 2011 a significant difference in mortality between rural and urban populations began to emerge. The calculations showed that one of the main reasons for this was the reduction in the number of beds, especially after the emergence of a new coronavirus infection. However, in the target indicators of the state program of the Republic of Sakha (Yakutia) "Development of healthcare of the Republic of Sakha (Yakutia) for 2020 - 2024 years", approved on December 12, 2019 (N 887), this most important indicator was not included, which we consider a great omission [2]. Undoubtedly, the downward trend in the number of inpatient beds in general hospitals is typical not only for Russia, but also for most European countries, and its negative consequences are largely compensated by the opening of prevention and rehabilitation centers in the field, where advanced treatment technologies are used [5]. But in the Far East, particularly in Yakutia, which is characterized by its unique natural and territorial conditions and low population density, this approach is ineffective, and this is confirmed by state statistics.

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TOPICAL ISSUE

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IMPROVEMENT OF PERINATAL RESERVES IN WOMEN WITH EXTRAGENITAL DISEASES

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Risk factors were determined and a prognostic model of adverse perinatal outcomes was constructed in a sample of pregnant women with extragenital diseases (EGD) (anemia, chronic pyelonephritis, chronic arterial hypertension) by logistic regression. The search for prognostic criteria is optimal in the comprehensive examination of pregnant women with EGD (assessment of microbiome, immune status, utero-fetal-placental blood flow and placental pathomorphology).

The morphology of the placenta reflects the fullness of embryo- and fetogenesis of women with EGD, mediated by the resources of the mother's body, optimal in the dogestational recovery and prevention of placental insufficiency in the early gestation. Prediction of the risks of perinatal outcomes and morbidity in pregnant women with EGD – anemia, CP and CAG is realizable using logistic regression model resources.

Keywords: extragenital diseases, risk factors, adverse perinatal outcomes.

Improving the reserves of perinatal outcomes in women with extragenital diseases (EGD), such as chronic pyelonephritis (CP), anemia, chronic arterial hypertension (CAH), presents great difficulties due to the high frequency of pregnancy complications in women with EGD and violations of maternal-fetal-placental interaction [1].

The analysis of the completeness of the examination of pregnant women with EGD seems to be manageable from the standpoint of identifying and monitoring high-risk groups of gestational complications [7,14]. It is known that a vicious circle of pathological changes is created in the "mother-placenta-fetus" system of pregnant women with EGD, however, the nature and degree of compensatory-adaptive reactions are poorly understood [3]. The inconsistency of data on the state of the fetoplacental complex is associated with EGD duration, as well as medical tactics before and during pregnancy. The focus of scientific attention is the analysis of perinatal risks based on expanding the diagnostic capabilities of the features of uterine-fetal-placental blood flow, homeostasis, microbiota and immune status of pregnant women with EGD [6,8].

The lack of study of the morphofunctional viability of the fetoplacental complex (FPC) in pregnant women with EGD and high infectious potential confirms the prospect for identifying predictors of placental dysfunction under conditions of endogenous intoxication and immune dysregulation. The search for highly informative clinical, instrumental and laboratory markers that allow to predict suboptimal pregnancy outcomes antenatally will contribute to the pathogenetic therapy and the choice of an adequate method of delivery for women with EGD.

The aim of the study was to determine risk factors and prognostic criteria for adverse perinatal outcomes in pregnant women with extragenital diseases (EGD) (anemia, chronic pyelonephritis, chronic arterial hypertension).

Material and methods. The study population – 576 pregnant women with EGD (anemia (n = 62), CP (n = 135) and CAG (n = 376)) were retrospectively divided into groups depending on the results of the placental pathomorphological study.

Inclusion criteria: singleton progressive pregnancy; the woman's informed consent for the use of biological material for scientific purposes, extragenital diseases found before pregnancy and confirmed by specialists (CP, anemia).

Groups: I – pregnant women with high infectious risk (graduation was carried out on the basis of data from history, a complex of laboratory and instrumental studies) (n = 182) and PI (116 – with subcompensation, 64 – compensation); II – with compensation PI (n = 126); III – subcompensation of PI (n = 143); IV – without PI (n = 122).

Placental insufficiency was morphologically verified in 451 out of 576 examined.

Determinants of pregnancy complications and adverse perinatal outcomes were determined depending on the presence of PI.

Methods of research: assessment: lower genital microbiota (smear microscopy for the degree of purity (Gram stain), bacteriological inoculation of cervical discharge for flora and sensitivity to antibiotics, polymerase chain reaction (PCR study), molecular genetic research (Femoflor), microscopy and culture examination of urine for flora and sensitivity to antibiotics, cellular link of immunity (CD3+, CD20+, CD4+, CD16+, CD8+, CD95+, HLA-DR+)).

Immunoreactivity was studied based on the results of ELISA-detected Probably of pathology, an enzyme-linked immunosorbent assay of the number and affinity of individual embryotropic autoantibodies interacting with embryogenesis regulatory proteins (Biopharm – test LLC).

During the screening period and according to the indications, sonography and blood flow in the mother-placenta-fetus system, cardiotocography (CTG) of the fetus were carried out. Pathomorphological examination of the placenta was carried out according to a standard scheme.

The degree of reliability and approbation of the results of the work. The statistical analysis was carried out using the IBM SPSS Statistics 23 program, parametric analysis methods in accordance with the results of checking the compared masses for the normality of distribution, descriptive statistics (arithmetic mean (M), mean error of the mean (m), Student's t-test, odds ratio (OR), confidence interval (CI, 95%).

The analysis of intergroup differences in qualitative characteristics was carried out using the criterion $\chi 2$, less than five – the exact two-sided Fischer test. The significance level (p) when testing statistical hypotheses was taken to be $p \leq 0.05$.

The construction of a predictive model for calculating the risk was performed us-

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ing the binary logistic regression method according to the formula:

$$P = \frac{1}{1+e^{-z}}, z = a0 + a1x1 + a2x2 + \\ + a3x3 + \ldots + anxn,$$

where p is the probability of the outcome, x1… xn are the values of the predictors in a nominal, ordinal or quantitative scale, a1… an are the regression coefficients, using Wald statistics. The effectiveness (the proportion of correctly predicted cases of the presence and absence of the studied pathology), sensitivity (the presence of pathology), specificity (the absence of pathology), the prognostic value of a negative result (PVNR) and a positive one (PVPR) were determined, ROC analysis (receiver operating characteristic) of the error curve was done. The Area Under Curve (*AUC*) under the ROC curve was calculated.

Results and discussion. The condition of newborns from mothers with extragenital diseases (EGD) turned out to be worse than that of healthy women (p <0.05). The need to transfer newborns to the intensive care unit (ICU) was 16.6%; at the second stage of nursing – 15.8% vs 5.9% with physiological pregnancy (p> 0.05); at home discharge – one and a half times less often (66.8% vs 94.1%, p <0.05).

The morbidity of newborns in the sample of women with a high infectious risk was higher than with subcompensation of placental insufficiency (PI): hypotrophy and morphofunctional immaturity – twice (35.7%, p <0.05) and 4.5 times (7.9%) – with PI compensation; cerebral ischemia – one and a half times (46.2%, p <0.05), prematurity – twice (22.5%, p <0.05), infectious and inflammatory diseases (omphalitis, conjunctivitis, vesiculosis) – three times (12.6%, p <0.05).

In order to identify risk factors and predict unfavorable perinatal outcomes, the method of logistic regression was used. The calculation results are shown in Table.

The effectiveness of the prognostic model for identifying the contingent of pregnant women with EGD when calculating the risks of unfavorable perinatal outcomes is reflected by the following data: regression coefficient B – 1.11; Wald statistics χ2 – 1.0; Exp B – 3.0, Nagelkerke index – 0.79.

The calculation was carried out according to the formula:

$$P = \frac{1}{1+e^{-z}}, z = a0 + a1x1 + a2x2 + \\ + a3x3 + \ldots + anxn,$$

Risk factors for adverse perinatal outcomes on the EGD background

Factors	Regression coefficient B	Wald statistics, χ^2	Value p	Exp B
Chronic pyelonephritis exacerbation	2.377	6.433	0.011	10.770
Bacterial vaginosis (BV) relapses + contamination of the cervical canal loci, urine	3.012	10.367	0.001	20.337
Hyporeactivity according to ELI-P test	2.405	7.522	0.006	11.078
Absence of pregravid phase / PI prevention or delayed therapy	2.015	3.822	0.047	7.500
Index "CD 4 + / CD 8+"> 1.0	1.625	4.529	0.033	5.078
Violation of hemodynamics 1B, 2nd degree	4.057	7.800	0.005	57.781
Untypical cardiotocography (CTG) type	1.608	5.084	0.024	4.992
Thinning of the placenta by sonography in the first half of pregnancy	-3.463	6.098	0.014	0.031
Weak compensatory changes in the placenta	-4.795	14.171	0.000	0.008
Inflammatory changes in the placenta	-2.563	5.928	0.015	0.077
>60% non-functional zones	2.371	5.968	0.015	10.708
Dystrophic changes in the placenta	2.871	13.267	0.000	17.661
Constant	1.112	1.047	0.03	3.039

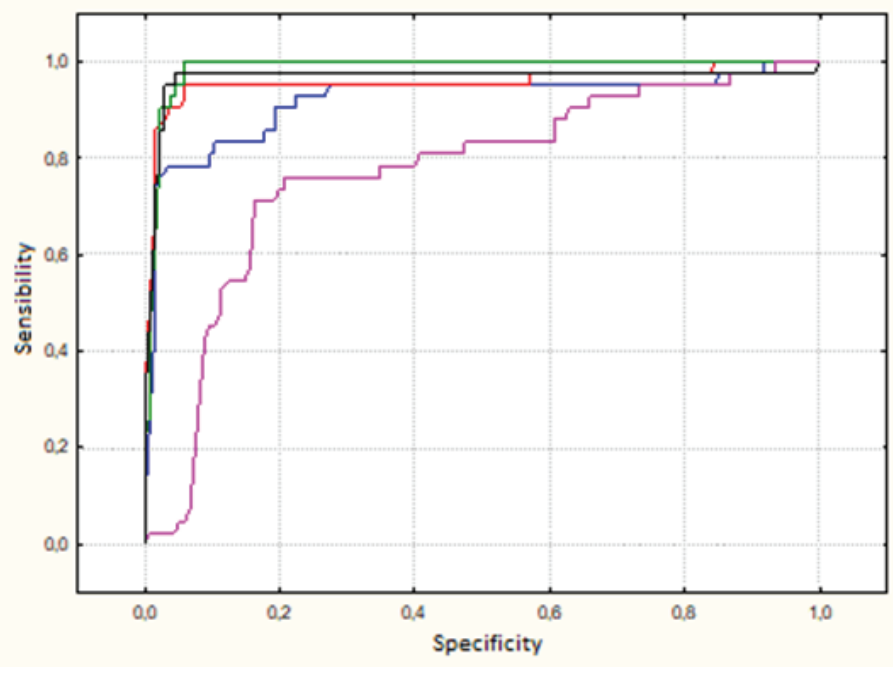
where p is the probability of the outcome, x1 ... xn are the predictor values measured on a nominal, ordinal or quantitative scale, a1 ... an are the regression coefficients (Figure).

The area under the AUC curve 0.97 allows us to regard it as reliable.

The cut-off criterion ("cut-off" – 0.6) is a sign of high prognostic effectiveness of the model, which is realized when the index is more than 0.6. The high predictive value of the model with identified risk factors is proved by the following criteria: sensitivity – 96.5%, specificity – 82.0%, diagnostic efficiency – 93.2%, positive predictive value (PPV) – 96.5%, negative predictive value (NPV) – 82.0%.

A negative effect on perinatal outcomes was found in the absence of pregravid recovery and / or placental insufficiency (PI) prevention (or delayed therapy, after the completion of the second wave of placentation) (χ2 = 3.8; p = 0.04).

Recovery at the pregravid stage



ROC analysis of the prognostic model (the area under the AUC curve is 0.97) for predicting unfavorable perinatal outcomes on the EGD background

among women with EGD was least often carried out in the group with a high infectious risk (17,6%): in comparison with the stage of PI subcompensation (28.7%) – 1.6 times (p = 0.02), compensation (78.6%) – 4.5 times (p = 0.005). PI prevention in early pregnancy took place among 81.0% women with EGD, twice less often – with subcompensation of placental dysfunction (40.6%) (p = 0.0005), a high infectious risk – 3.5 times (24.2%) (p = 0.0005).

Exacerbation of chronic pyelonephritis (CP) ($\chi2$ = 6.4; p = 0.01) with a temperature reaction in inflammatory urine sediment negatively affected the fetal-placental interaction only in the absence of regular urine monitoring and treatment of asymptomatic bacteriuria (AB). Exacerbation of CP with bacteriuria occurred in 35.4% of pregnant women with a high infectious risk, 5.3% with PI compensation (p = 0.001) and 19.3% with subcompensation.

The probability of developing unfavorable obstetric outcomes with the lack of rational management tactics for pregnant women with CP was confirmed by other authors. The expediency of treating urinary tract infections [16], the prevalence of which in pregnant women reaches 10%, is explained by the risk of CP exacerbation [11].

AB requires treatment to avoid the risk of developing acute pyelonephritis in 25-30% [10]. The formation of a focus of inflammation in persistent infection is determined by the ability of uropathogenic strains to synthesize virulence factors and damage kidney tissues [15]. Bacterial contamination (pathogenic and / or conditionally pathogenic flora in a titer> 104) of several loci simultaneously (in the cervical canal, vagina, urine sediment) was detected in a third of pregnant women with a high infectious risk (32.4%), three times less often – with PI compensation (p = 0.02)). During PCR testing, pregnant women with a high infectious risk were distinguished by infection of the cervix with herpes simplex virus (HSV2) (17.6% vs 7.3% with PI, p = 0.05), gardnerella (26.4% vs 12.4% on average, p = 0.0008) and genitalium mycoplasma (20.3% vs 15.4% with PI subcompensation, p = 0.002). When calculating the factors affecting perinatal outcomes, the cumulative infection of the cervical canal, urine, and recurrence of bacterial vaginosis (BV) were identified ($\chi2$ = 10.4, p = 0.001).

The role of monitoring the immunological homeostasis of pregnant women with EGD in predicting gestational complications – PI, prematurity as a consequence of a maladaptive state uncorrected at the pregravid stage – turns out to be important [12]. Violation of the immune response in pregnant women with a high infectious risk was determined by a high level of embryotropic autoantibodies production (81.9% vs 55.3% with PI subcompensation, 47.9% with its compensation). Hyporeactivity (54.9% vs 45.5%, p = 0.0005) in pregnant women with PI subcompensation was detected more often than a hyperreactive response (36.8% vs 9.8%, p <0.05). This fact proved the prognostic significance of hyporeactivity in fetal outcomes ($\chi2$ = 7.5, p = 0.006), as well as the immunoregulatory index "CD4 + / CD8 +" at a value above 1.0 ($\chi2$ = 4.5, p = 0.033).

Obviously, a decrease in immunoresistance in pregnant women with a high infectious risk is the pathogenetic basis for disorders of the uterine-fetal-placental interaction [2]. Various researches prove the prospect of a comprehensive study of the systems providing the activity of the fetoplacental complex (FPC) and the degree of maladaptation of the homeostasis mechanisms in pregnant women with EGD.

Among sonographic stigmas, placental thinning has prognostic potential in women with EGD in the first half of pregnancy ($\chi2$ = 6.1, p = 0.01).

Low activity of the uteroplacental complex (UPC) in groups with a high infectious risk and PI subcompensation [5,13] contributed to the identification of predictors of unfavorable perinatal outcomes in pregnant women with EGD: hemodynamic disorder 1B, 2nd degree ($\chi2$ = 7.8, p = 0.005) and an untypical CTG type ($\chi2$ = 5.1, p = 0.02).

Hemodynamic disorders correlated with the discrepancy between the plastic resources of the placenta and the needs of the growing fetus, most pronounced with PI subcompensation. The disruption of protein synthesis that contributes to the transformation of spiral arteries into tortuous sinusoidal vessels, progressing in the second half of pregnancy, reflects a different degree of adaptive and homeostatic resources in women with EGD.

A comprehensive assessment of the metabolic resources of the FPC (Doppler and CTG) allows us to predict the morphostructure of the placenta: the violation of the biophysical profile of the fetus corresponded to "functionally inactive zones" – thrombosis, placental infarctions and pathology of the villous tree.

The features of the placenta of pregnant women with a high infectious risk were determined in comparison with PI subcompensation: dystrophic changes in villi –100.0% ($\chi2$ = 13.267, p = 0.000); dissociation of their development (87.4%) – almost twice as often (p = 0.0005); calcifications (77.5%) – 1.3 times (p = 0.0005); pseudoinfarctions (37.9% vs 17.5%, p = 0.0007) and dyscirculatory disorders (49.5% vs 25.9% p = 0.0005) – twice. Inflammatory changes in the placenta (basal deciduitis, membranitis, interllusitis) ($\chi2$ = 5.9, p = 0.01) were identified as predictors of a low neonatal health index, 6.6 times more often in the group with a high infectious risk than with subcompensation (87.4%, p <0.05); weak compensatory reactions ($\chi2$ = 14.2; p = 0.000); the presence of "> 60% of non-functional zones" ($\chi2$ = 5.9, p = 0.01).

Weak compensatory reactions in a high infectious risk and PI subcompensation corresponded to the peculiarity of metabolism under stressful conditions, with a decrease in placental mass [4,9]. The discrepancy between the characteristics of the placenta and the trophic needs of the fetus was confirmed by low weight, purulent-septic diseases of newborns and unfavorable perinatal outcomes [17,18,19].

Conclusion. Thus, the morphology of the placenta reflects the usefulness of embryo and fetogenesis in women with EGD, mediated by the resources of the mother's body, optimal in the dogestational recovery and prevention of placental insufficiency in the early gestation. Prediction of the risks of perinatal outcomes and morbidity in pregnant women with EGD – anemia, CP and CAG is realizable using logistic regression model resources.

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CHARACTERISTICS OF THE MAIN LINKS OF IMMUNITY AND ENDOMETRIAL CYTOKINES IN WOMEN WITH REPRODUCTIVE DISORDERS

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Introduction. The involvement of many systems and levels of regulation in the processes of fertilization and gestation makes one pay attention to the changes occurring at all its levels.

Aim: to study and analyze changes in the indices of general and local immunity in women of reproductive age for the pathogenetic substantiation of therapeutic measures for reproductive disorders.

Materials and methods. The study included 50 patients with and reproductive disorders. Thirty-one healthy women with preserved fertility entered the control group included. All respondents underwent a questionnaire survey; general clinical, gynecological and laboratory-instrumental examination was carried out. The study followed the ethical principles and was approved by the local Committee on Biomedical Ethics. Statistical processing of the data obtained was performed using the StatSoft Statistica 6.1 (USA).

Results. Evaluation of indicators of cellular and humoral links of immunity showed a significant increase in the concentration of CD3 + (T-lymphocytes), CD3 + CD8 + / CD45 + (T-suppressors), phagocytic activity of neutrophils, NST -test sp., Ig M, and an increase in the studied pro- and anti-inflammatory cytokines. In the endometrium, with persistence of an infectious agent, a significantly high concentration of IL-8 and a decrease in IL-1 (β) were revealed.

Conclusions. The presence of the pathogen in the endometrium is characterized by a significant activity of the pro – inflammatory cytokine IL-8 and a decrease in IL-1(β). A decrease in progesterone, cortisol, NST sp., an increase in CD3 + CD8 + / CD45 +, IL-6, IL-8 can be attributed to the markers of reproductive disorders.

Keywords: immunity, endometrium, cytokines, reproductive disorders.

Introduction: The study of the problem of reproductive disorders is one of the important directions in reproductology. The percentage of infertility is constantly growing [2], miscarriage does not tend to decrease [6]. From a clinical point of view, pregnancy loss or their absence is becoming an increasingly significant problem in reproductology. The implantation process is very sensitive and requires compliance with a number of important conditions: a high degree of coordinated action between normal anatomical conditions, normal functioning of sex cells, an adequate hormonal environment of the embryo in the endometrium [8]. Taking into account the complexity of the process, the ambiguity of the pathogenetic mechanisms of reproductive disorders becomes obvious [4,3]. Adequate pregravid restructuring of the endometrium is the key to successful implantation. Multiple paracrine and autocrine regulatory factors are involved in the regulation of endometrial decidualization. The spatiotemporal regulation of the decidual process is strictly controlled by a variety of substances, such as growth factors, cytokines produced by various cellular structures of the endometrium including epithelial cells, stromal cells, local immune cells, and the vasculature [5,7].

Materials and methods: A cross-sectional study was conducted in the period 2011-2013 on an outpatient basis according to the patients' referral. When women were included in the study, the ethical principles set forth by the World Medical Association Declaration of Helsinki (1964, 2000) were followed. This study was approved by the local Committee on Biomedical Ethics. Eligible women participated after they signed an informed consent. This work was performed with the use of equipment of Collective research centre "Center for the development of progressive personalized technologies for health" SC FHHRP, Irkutsk.

A survey of 327 women of fertile age who complained of reproductive dysfunction was carried out. The patients underwent examination according to the standards of examination of infertile married couples (Kulakov V.I., 2006); the examination included general clinical, gynecological and laboratory-instrumental examination.

The criteria for inclusion in the group with reproductive disorders (RD) were: absence of pregnancy in patients with regular sexual activity without contraception for a year or more or miscarriage during the last year, or failure in assisted reproductive technologies programs. As a result, 223 (68%) women were diagnosed with infertility: primary infertility in 38% (125), secondary infertility in 30% (98), miscarriage was detected in 32% (104) women.

Criteria for inclusion in the control group: regular menstrual cycle, absence of neuroendocrine disorders and severe somatic pathology, presence of a pregnancy that ended in childbirth within the last year. The control group included 31 healthy women with preserved fertility.

Subsequently, there was formed a group of women (100 women) with suspected chronic endometritis who underwent minimally invasive manipulation - a pipel biopsy of the endometrium on the 4th-9th days of the menstrual cycle (middle proliferative phase) using a disposable intrauterine probe (Taizhou Kechuang Medical Apparatus Co., Ltd ", China) followed by a pathohistological examination (PHI) of endometrial tissue to verify or exclude the presence of signs of chronic inflammation of the endometrium. Finally, according to the results of the pathohistological examination, two groups were formed: the 1st group in-

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cluded 50 patients with reproductive disorders and chronic endometritis (mean age 30.5 ± 0.6 years), the 2nd group included 50 patients with reproductive disorders without chronic endometritis (mean age 30.2 ± 0.7 years).

This analysis included 50 women of fertile age with reproductive disorders (ICD 10 - N97.9, O03) and 31 women from the control group. The average age in the groups did not differ, it was comparable and was 30.2 ± 0.7 years (respectively, in the group of fertile women, 30.7 ± 5.9 years) (p≥0.05). The main criteria for inclusion in the main group were: the absence of pregnancy in patients with regular sexual activity without contraception for a year or more, miscarriage during the last year, absence of chronic endometritis based on the results of histopathological examination, and signing of informed consent. Exclusion criteria: presence of endocrine, genetic, hemostasiological, immunological causes, including the male factor, and the diagnosis of chronic endometritis verified by the results of a pathohistological examination (PHE) of the endometrium.

The main group, patients with reproductive disorders, was divided into two subgroups:

- a subgroup of 16 patients with RD with an infectious agent isolated from endometrial tissue
- a subgroup of 34 patients with RD with no infectious agent in the endometrial tissue.

Laboratory diagnostics for the presence of STIs (*N. gonorrhoeae, T. vaginalis, Ur. Urealyticum, M. hominis, M. Genitalium. Chl. Trachomatis*) was performed using the culture method. The polymerase chain reaction (PCR) method was used to diagnose a viral infection (HPV, HSV, CMV) in the material taken from the cervical canal. Microbiological studies of the vaginal biotope were carried out according to the guidelines (Order of the Ministry of Health of the USSR No. 535 of April 22, 1985 "On the unification of microbiological (bacteriological) research methods used in clinical and diagnostic laboratories of medical and preventive institutions". Ultrasound examination of the pelvic organs was performed using an Aloka-5500 machine with a 7 MHz vaginal transducer in two-dimensional imaging mode. Ultrasound examination of the pelvic organs was performed using an Aloka-5500 machine with a 7 MHz vaginal transducer in two-dimensional imaging mode. The concentrations of cytokines (IL - 1β, INF - γ, TNF - α, IL - 4,6,8,10) were determined in the endometrial tissue using the "Protein Contour" test systems (St. Petersburg), on the basis of the "sandwich" method using the enzyme immunoassay analyzer "Multiscan EX" (Germany) and expressed in PG / ml.

Blood sampling for hormonal studies was carried out on an empty stomach, from the 3rd-9th days of the menstrual cycle and in the second phase from the 20th-24th days of the menstrual cycle in accordance with generally accepted requirements. Determination of the concentration of prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH) was carried out by radioimmunoassay using the analyzer "Immunotest" (kits of LLC "Dias", Russia). Enzyme immunoassay was used to determine the levels of testosterone ("Alcor Bio" kits, Russia); progesterone ("DRG ELIAS" kits, USA). The concentration of hormones PRL, LH, FSH was expressed in ng / ml; cortisol, testosterone - in pmol / l; progesterone - in nmol / l.

Statistical processing of the data obtained was performed using the StatSoft Statistica 6.1 application software package (USA) (the license holder is the Federal State Budget Scientific Institution "Scientific Centre for Problems of Family Health and Human Reproduction"). The distribution pattern (normality) was evaluated by Kolmogorov-Smirnov methods. Absolute and relative indicators (shares,%) were used for qualitative indicators. The significance of differences in unrelated samples was assessed using the Mann-Whitney criterion. For quantitative variables, the data in the tables are presented as M ± m, where M - the mean, m - the error of the mean. The difference was considered significant with a 95% confidence level ($p<0.05$). The analysis of the intragroup relationship of quantitative characteristics was carried out by the nonparametric Spearman correlation method. The relative risk (RR) was calculated using the criterion $\chi 2$ for a four-field table and one degree of freedom.

Results: As a result, 81 women with reproductive disorders, aged from 18 to 45 years agreed to participate and were surveyed. In the course of the survey, information was obtained about past diseases, somatic and gynecological morbidity. In the group of women with RD, there was a high rate of ovarian dysfunction 68% (ICD - 10, E28.9), the presence of chronic salpingo-oophoritis in 28% (ICD - 10, N70), scanty and rare menstruation was noted by 12% (ICD-10, N91) of respondents. Ten percent each accounted for heavy, frequent and irregular menstruation (N 92), primary dysmenorrhea (N 94.4), chronic inflammatory diseases of the cervix (N 72).

Comparative analysis of the concentration of pituitary hormones and sex hormones in patients with RD in comparison with those in women in the control group showed a significant increase in the concentration of prolactin, testosterone and a significant decrease in progesterone (Table 1).

Thus, the hormonal background in patients with reproductive disorders was characterized by the presence of hypoprogesteronemia, significant increase in PRL, cortisol, and testosterone. The concentrations of these indicators did not go beyond the reference values offered by the manufacturers of test systems for their determination.

The analysis of data on previous diseases in the examined women is presented in Table 2.

Compared with the control group, patients with RD were significantly more likely to have a history of kidney diseases ($p(\chi 2) = 0{,}021$), endocrine system diseases ($p(\chi 2) = 0.001$), allergic diseases ($p(\chi 2)=0.015$), surgical interventions on the pelvic organs ($p(\chi 2) = 0.0001$).

No significant differences were found in the structure of concomitant somatic pathology.

Anamnestic data showed that women with RD had ureaplasmosis in 50%, trichomoniasis in 36%, HSV in 32%, and chlamydia in 30%. Twenty-eight percent ($n=14$, $p(22) = 0.03$) of patients at the time of examination had conditionally pathogenic microflora in the cervical canal. In 9 women, it occurred as a monoinfection; mixed infection with predominance of two types of microorganisms was noted in 5 women. The most frequently observed were: low-risk HPV in 8%, Ur. Urealiticus, G. vaginalis, Candida, Staph. Epidermidis, E. Coli, Citrobacter spp., high-risk HPV 4% each. The number of microorganisms was in the range of 10^3–10^4 CFU / ml.

In 32% ($n = 16$, $p(\chi 2) = 0.0001$) of the patients, an infectious agent was detected from the uterine cavity; its content was in the range of 103-104 CFU / ml, E. coli was found with the highest frequency - in 12%, Candida - in 6%; Enterococcus faecalis, Staph. Epidermidis, Klebsiella 4% each.

Ur. urealyticum, Candida, E. coli, M. hominis, Streptococcus, Citrobacter spp., Enterococcus faecalis, low-risk HPV were detected in the control group as a monoinfection in isolated cases.

The results obtained in the study of Moreno I, Cicinelli E, Garcia-Grau I et al. (2018) show similar rates of pathogen

detection in patients with both chronic endometritis (CE) and in its absence (CE: 24/40 versus without CE: 14/25 [22]. Some studies have shown that 53% of women with infertility and miscarriage were observed to be completely free of lactobacilli [13].

The indicators of cellular and humoral immunity were determined and analyzed taking into account the presence and absence of an infectious agent in the endometrial tissue.

The results of the indicators characterizing the cellular and humoral immune response in patients in both study groups are presented in Table 3.

Evaluating the results of cellular and humoral immunity in patients with RD in comparison with the corresponding blood parameters of healthy women, there was a significant increase in the concentration of CD3 + (T-lymphocytes), CD3 + CD8 + / CD45 + (T-suppressors), a decrease in the phagocytic activity of neutrophils, NST - test sp., Ig M. Correlation analysis showed the presence of a strong positive relationship between IgM-IgA (r = + 0.77), which clearly indicates a decrease in immunity from the mucous membranes, and also showed the presence of a strong negative relationship between CD3 + CD4 + / CD45 + and CD16 + 56 + / CD45 + (r = - 0.77), which indicates the relationship of T-helpers and natural killers.

When comparing the indicators of the cellular and humoral links of immunity within the group, in the presence of an infectious agent and in its absence, no significant differences were found.

The state of local immunity was assessed by the levels of cytokines determined in the endometrial tissue. The results are presented in Table 4.

A 1.4-fold increase in the level of pro-inflammatory cytokines *IL-1 (β), INF - γ* was found in the endometrial tissue of women with reproductive disorders in comparison with similar indicators in healthy women. There was a 2.5-3 fold increase in *IL - 6, 8, 10; IL - 4* increased only in the group with no infectious agent. Assessing the cytokine status for the isolated infectious agent in the compared groups, a decrease in the concentration *of IL – 1(β), 6* and an increase in *IL – 8* were noted.

Using the discriminant equation, the contribution of the studied indicators was calculated, among which the following indicators were identified: a decrease in progesterone, cortisol, NBT sp., an increase in CD3 + CD8 + / CD45 +, IL-6, IL-8, which, with a high degree of probability, made it possible to include patients in the group with RD without chronic endometrial inflammation.

Table 1

Concentration of pituitary hormones and sex hormones in patients with reproductive disorders and control group

	Group with reproductive disorders n=50	Control group n=31
Prolactin (ng / ml)	424.1±213.22* 369 (155 и 914)	297.81±100.14* 274 (150 и 520)
LH (ng / ml)	4.67±2.84 4 (0.6 и 18.4)	4.2±1.43 3.8 (1.9 и 7.2)
FSH (ng / ml)	6.46±1.77 6.3 (3.3 и 10.2)	6.92±1.77 6.9 (3.7 и 10)
Estradiol (pM/l)	354.1±225.57 317.5 (90 и 987)	276.19±157.58 243 (110 и 980)
Progesterone (nmol/l)	43.05±19.69* 42.7 (3 и 84)	74.19±13.17* 75 (38.4 и 98)
Testosterone (pmol/l)	1.98±1.07* 1.8 (0.22 и 4.4)	1.41±0.88* 1.2 (0.6 и 3.7)
Cortisol (pmol/l)	644.2±242.77* 588.5 (148 и 1256)	387.74±97* 388 (214 и 589)

Significance level - * p <0.05.

Table 2

Characteristics of the previous diseases in women of the main and control groups

Premorbid background	group with RD абс./% *n* = 50	Control group abs./% *n* = 31	Significance level *p*(χ2)
Diseases of the ENT organs	5/10	5/16	
Gastrointestinal diseases	9/18	3/10	
Kidney diseases	6/12	1/3	0.021
Diseases of the endocrine system	11/22	2/6	0.001
Pathology of the thyroid gland	2/4	0/0	
Allergic diseases	6/12	1/3	0.015
Surgical interventions on the abdominal organs	6/12	2/6	
Surgical interventions on the pelvic organs	4/8	0/0	0.0001
Diseases of the cardiovascular system	3/6	2/6	

Discussion: The endometrium is tissue that undergoes monthly cyclical changes leading to menstruation, proliferation, secretion and decidualization under the influence of ovarian steroid hormones. There is a finely coordinated interaction between the circulating steroid hormones of the ovaries and the corresponding receptors in a variety of endometrial cell types [16,17]. Many researchers say that many factors involved in implantation have not yet been fully studied and, apparently, the endometrium plays a much more relevant role than other well-known factors [9, 11]. The endometrium contains a large number of immunocompetent cells, natural killer (NK) cells, macrophages, T cells and neutrophils whose composition and density fluctuate periodically [19,12]. Cycle-dependent changes in these subpopulations of leukocytes and their mediators are likely to play a significant role in implantation [11].

In addition, morphological changes in the endometrium are normally accompanied by focal activation of matrix metalloproteinases (MMPs) at the sites of menstrual lysis [20], by the enhancement of local expression of inflammatory mediators in the endometrium, for example, cyclooxygenase-2 (COX-2) [21], cytokines / chemokines (for example, cytokines-8 (IL-8), CCL-2) [5,1], as well as an increase in the level of local synthesis of prostaglandin [18].

An increase in the concentration of IL-1(β) stimulates the development of a whole complex of protective reactions of the body. The pro-inflammatory activity of IL-1(β) includes stimulation of lym-

Table 3

Characteristics of indicators of cellular and humoral links of immunity in patients with reproductive disorders taking into account the presence and absence of an infectious agent and in patients in the control group

indicators of Immunity	Patients with an isolated infectious agent, n= 16	Patients in the absence of an infectious agent, n=34	Control group n=31
CD3+/CD45+	75.33± 6.9	73.71±6.7	71.09±4.6
CD3+	*2057.88 ±454.9**	*2132±521.7**	*1462±348.4**
CD3+CD8+/CD45+	*30.33 ±5.02**	*29.45±5.07**	*22.25±3.4**
CD3+CD4+/CD45+	42.00 ±4.47	48.8±5.7	45.93±5.3
CD3+CD4+CD8+/CD45+	0.55 ±0.72	0.45±0.77	0.74±0.17
CD16+56+/CD45+	*10.77± 6.18*	*11.7±5.38*	*13.6±4.7*
CD19+/CD45+	*11.44 ±4.3*	*12.4±3.1*	*12.13±3.4*
Phagocytosis	*57.44 ±12.64**	*53.8±10.1**	*61.45±8.3**
NST-test sp.	*5.55 ±4.44**	*7.1±5.2**	*9.29±7.7**
NST-test ind.	27.88± 14.11	32.7±12.6	32.35±11.8
Ig G	12.85 ±3.89	14.3±4.9	14.26±4.2
Ig A	*2.12± 1.10*	*2.08 ±1.1*	*2.3±1.1*
Ig M	*2.30 ±0.82*	*1.88±0.9**	*2.6±0.8**
Circ.immune complexes	38.33± 11.13	41.4±16.6	40.74±14.1
T Help./ Suppres.	*1.41± 0.21*	*1.48±0.34*	*2.12±0.4*

Note: *p1-2<0.05. **p1/a-1/б<0.05

Table 4

Concentrations of cytokines in endometrial tissue in women with reproductive disorders and control groups depending on the presence or absence of an infectious agent

Indicators of local immunity local immunity	Patients with an isolated infectious n=16	Patients in the absence of an infectious agent n=34	Control group n=31
IL-1(β), pg/ml	34. 22± 37.72**(*)	44.46± 44.49**(*)	23.64±3.37*
IL-4,pg/ml	14.38 ± 12.98**	41.54 ± 81.22**(*)	13.71±1.93*
IL-6, pg/ml	83.85± 45.6**(*)	100.56 ± 98.13**(*)	39.53±3.81*
IL-8, pg/ml	99.55 ±102.56**(*)	81.31 ±71.82**(*)	23±2.42*
IL-10, pg/ml	70.4± 2.51*	76.51 ± 51.01*	26.67±4.61*
INF-γ, pg/ml	45.33± 70.01*	44.50± 50.21*	25.75±4.24*
TNF-α, pg/ml	16.33± 14.43	14.42 ± 20.24	9.48±0.85

phocytes, synthesis of prostaglandins, chemokines, and expression of endothelial adhesion molecules. Chemokines, in particular, a significant increase in IL-8 in the group of patients with an isolated infectious agent, enhances the migration of leukocytes to the site of inflammation and, together with other cytokines, increase their functional activity aimed at eliminating the pathogen and limiting the spread of the inflammatory process [10, 13, 20]. At the same time, pro-inflammatory cytokines activate connective tissue metabolism, stimulate the proliferation of fibroblasts and epithelial cells necessary for healing and restoration of tissue integrity [1], which contributes to maintaining a healthy endometrium.

Hypoprogesteronemia noted in patients with RD, in turn, enhances the local effect of cytokines and prostaglandins (PG) on endometrial stromal cells [15]. Previously published data from studies conducted on decidualized stromal cells of human endometrium in vitro, demonstrated the induction of inflammatory mediators, including IL-6, chemokines CCL11, CCL2, CXCL10 and CXCL8, and granulocyte macrophage colony stimulating factor (GM-CSF) in response to a decrease in progesterone levels. This cellular response is controlled by the action of the transcription factor NF-kB [10].

In addition, the lack of progesterone reduces the secretion of TGF-beta, a protein (a representative of cytokines) that controls proliferation, cell differentiation and other functions in most cells, is involved in the immune response by epithelial endometrial cells and, indirectly, acts on the stromal cells of the endometrium causing an increase in the production of PRL and integrin 3 necessary for decidualization, which we observe in patients with RD in relation to PRL [14]. In our study, similar results were obtained: a decrease in progesterone revealed an increase in the pro-inflammatory cytokine IL-6 and chemokine-IL-8 ($p<0.05$) as a specific cytokine-chemoattractant-responsible for the movement of white blood cells in the endometrium (recruitment, migration and activation) [1]. A significant increase in IL-10 and the normal concentration of IL-4 in patients with RD noted by us are due to the suppressive effect on the response of monocytes to endotoxin, in particular, by affecting the production of INF-γ by T-lymphocytes and, consequently, reducing the cytotoxicity of NK cells by inhibiting the reactions of cellular immunity [14].

On the part of the general link of the immune system, the revealed negative relationship of T-helpers and natural killer cells may be due to an increase in the production of inflammatory cytokines involved in the activity of NK cells, which play a decisive role in the local immune response at the early stages of implantation. The results obtained in the study indicate changes in the immune response characteristic of the immunological failure of the endometrium associated with reproductive disorders. The state of the endometrium in women with RD without CE can most likely be considered as an intermediate state between a "healthy" and "diseased" endometrium.

Conclusion: Reproductive disorders are accompanied by changes in the reactivity of the immune system in women at different levels of the immune response. The cytokine status in the presence of the pathogen in the endometrium is characterized by a significant activity of the pro – inflammatory cytokine IL-8 and a a low content of IL-1(β). A decrease in progesterone, cortisol, NST sp., an increase in CD3 + CD8 + / CD45 +, IL-6, IL-8 can be attributed to markers of reproductive disorders in the absence of chronic endometrial inflammation.

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LIPID PEROXIDATION IN THE DEVELOPMENT OF SOME SYMPTOMS OF POST-COVID SYNDROME

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The relationship of lipid peroxidation with sleep disturbance, anxiety and depression in residents of Yakutsk who recovered from COVID-19 was studied. It has been established that oxidative stress in COVID-19 due to an increase in the level of reactive oxygen species (ROS) in the body can lead to hypoxia and psycho-emotional disorders, such as anxiety and depression.

Keywords: COVID-19, malondialdehyde, lipid peroxidation, post-COVID effects, hypoxia, sleep, anxiety, depression, oxidative stress.

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Introduction. A novel coronavirus infection that causes severe acute respiratory syndrome COVID-19 has become a global pandemic with high morbidity and mortality [4,5].

The impact of the SARS-CoV-2 virus on the human body occurs primarily in the lungs, which causes pneumonia. Penetrating into the lower parts of the respiratory tract (small bronchi and alveoli) and begins damage to lung cells, provoking a strong inflammatory reaction, due to which the lungs cannot provide all organs and systems with sufficient oxy-

gen, which leads to hypoxia. Studies by many authors indicate the existence of a directly proportional relationship between the severity of COVID-19 disease and hypoxia [3,8,11].

Hypoxia leads to excessive production and accumulation of ROS, therefore, to the initiation of lipid peroxidation (LPO) and the development of oxidative stress. Reactive oxygen species produced during cellular metabolism play an important role as signal transmitters [9]. The activation of cells that provide antimicrobial immunity, neutrophils and macrophages, and the production of pro-inflammatory cytokines largely depend on ROS [11]. The optimal level of ROS in the body is controlled by the antioxidant defense system (AOD) of cells, which includes enzymatic and non-enzymatic links. With insufficient activity of antioxidant protection, a phenomenon occurs as oxidative stress, where TBA-active products, including malondialdehyde (MDA), are a marker. In addition, hypoxia causes clinical signs, such as a change in the properties of hemoglobin, a decrease in the bioavailability of nitric oxide (NO), vasoconstriction, an increase in the synthesis of leukotrienes and prostaglandins, cytokines, etc. Prolonged hypoxic state during illness, in our opinion, may be the cause of the development of post-COVID symptoms, such as anxiety and depressive disorders, insomnia, etc.

The aim of the study is to evaluate the association of lipid peroxidation with sleep disorders, anxiety and depression in people who have recovered from COVID-19.

Material and methods. The study involved 164 residents of Yakutsk aged 20 to 72 who recovered from COVID-19. Of these, 96 women (58.18%), men 68 (41.46%). The mean age was 51.07±0.97 years.

Informed consent for the study was obtained from all participants in the study (according to the protocol of the Ethical Committee of the YSC CMP No. 52 dated March 24, 2021). All the persons examined by us had extracts in which there were data from biochemical and morphological blood tests, computed tomography.

An oral survey was conducted with all the subjects, on the basis of which a questionnaire was filled out on the state of health, sleep, and a test was also performed on the HADS anxiety and depression scale. The material of the study was venous blood, which was taken on an empty stomach from the cubital vein. The initiation of free radical oxidation was assessed in blood plasma by the accumulation of malondialdehyde concentration [1]. The measurements were performed using an AgilentCary 100 UV-Vis spectrophotometer. Complete blood count was performed on a BC-3600 Mindray automatic hematology analyzer.

Statistical processing of our own research results was carried out using the Microsoft Excel application package and the IBM SPSS Statistics 24 statistical program. The Kolmogorov-Smirnov criterion was used to test the normality of the distribution. The original quantitative variables are presented as a median with an interquartile range (25% - 75%). To compare two independent samples, the Mann-Whitney U-test was used. When comparing groups, differences were considered statistically significant at $p<0.05$. When analyzing the relationship of features, the Spearman correlation method was used.

Results and discussion. All participants in the study had certain complaints about the state of health after the illness - COVID-19 [2]. Our data indicate that the parameters of the general and biochemical blood tests significantly change during the disease and after 8 months. In Table 1, we compared some indicators of the complete blood count during illness and 8 months after illness with control (persons who did not have COVID-19).

A comparative analysis (Table 1) of changes in the parameters of the general blood test at the time of the coronavirus disease and after 8 months, compared with the control group, indicates that inflammatory processes and lack of oxygen are observed in the body of patients during the disease. During the active struggle of the body with coronavirus, the content of leukocytes increases - 1.1 times, lymphocytes - 1.1 times, and the erythrocyte sedimentation rate (ESR) - 1.6 times in the blood. The level of erythrocytes decreases by 2.3 times from the norm (4.3-6.2 * 1012/l), the hemoglobin content also decreases by 1 times compared with the control group. 8 months after discharge from the hospital, the main indicators of the general blood test are normalized.

The results of our study show that in the body of residents of the city of Yakutsk, with a coronavirus infection, hypoxia develops. Intensive inflammatory processes were also going on in the body, as evidenced by an increase in the number of lymphocytes, leukocytes and sedimentation rate of erythrocytes.

It is known from the literature that COVID-19 causes diffuse damage to the endothelium of the alveolar capillaries, leading to a pathological process - hypoxia, which, in fact, is the cause of multiple organ dysfunction and death in patients with the SARS-CoV-2 virus [6]. The pathogenesis of COVID-19 has the following chain of flow in the body: 1-introduction of the pathogen into the alveolar cells of type II of the lungs, 2-development of diffuse alveolar damage, 3-reduction in the area of "breathing" alveoli, 4-diffuse lung compaction, 5-hypoperfusion in the capillaries of the lungs and the formation of

Table 1

Some indicators of the general blood test of those who recovered from COVID-19 (during the illness and after 8 months from the moment of discharge from the hospital) and the control group (persons who did not have COVID-19)

Blood cells	Control group	During COVID-19	After 8 month
	Me (Q1-Q3)		
Red blood cells	4.640 (4.270-4.990)	2.000 (2.000-4.430)	4.650 (4.360-4.975)
p		0.012	0.684
Hemoglobin	135.000 (120.000-151.000)	131.000 (118.000-142.000)	136.000 (128.000-146.000)
p		0.098	0.575
Leukocytes	5.600 (4.800-6.600)	5.810 (4.810-8.190)	5.600 (4.700-6.900)
p		0.160	0.758
Lymphocytes	33.400 (27.500-38.650)	33.650 (28.480-46.580)	30.000 (26.250-36.000)
p		0.464	0.001
Sedimentation rate of erythrocytes	10.000 (6.000-16.000)	18.500 (9.000-29.000)	16.000 (9.000-23.000)
p		0.000	0.000

Table 2

MDA scores on the HADS anxiety and depression scale in patients with coronavirus infection

Correlation coefficient	Levels of anxiety and depression	MDA indicators		
		1	2	3
r=0.177 **p=0.040**	Median anxiety	0.114 (0.068-0.256)	0.153 (0.100-0.229)	0.321 (0.153-0.500)
	p1-2 p1-3 p2-3	0.400 0.017 0.033		
r=-0.021 p=0.805	Median depression	0.140 (0.080-0.290)	0.137 (0.091-0.243)	0.168 (0.066-0.483)
	p1-2 p1-3 p2-3	0.881 0.919 0.665		

Note: 1 - normal, 2 - subclinically expressed anxiety and depression, 3 - clinically expressed anxiety and depression.

erythrocyte sludge, 6-intrabronchial and intraalveolar hemorrhages, 7-reduction of oxygen diffusion into the bloodstream, 8-hypoxemia and hypoxia of endothelial cells of the branches of the pulmonary arteries and veins, 9-hyperfibrinogenemia and thrombus formation, 10-inflammation [3]. From this chain of events, it can be seen that this pathogenetic chain has a hypoxic orientation, and most damage in the body is a consequence of hypoxia, and inflammation is naturally accompanied by oxygen starvation [8].

It is known that prolonged hypoxia affects the human central nervous system, and uncontrolled initiation of free radical processes can aggravate the effect of hypoxia, in this regard, we considered the concentration of MDA in the blood plasma (one of the end products of lipid peroxidation), in relation to the scale of anxiety and depression (HADS) developed by AS ZigmondR P.Snalth in 1983. The test is easy to use and process, which allows it to be used in general medical practice for the primary detection of anxiety and depression in patients. The data analyzed using this test is presented in table 2.

According to this scale, severe anxiety was observed in 6%, subclinically expressed anxiety - in 12%, and the norm was in 65% of people with post-COVID syndrome. The correlation coefficient showed a significant relationship between anxiety and the level of MDA in blood plasma. Significant differences in the concentration of MDA were found by us when comparing clinically expressed anxiety with the norm and subclinical anxiety.

Clinically expressed depression was noted in 4%, subclinically expressed depression in 15% and the norm was detected in 64% of the residents. Assessment of depression on the HADS scale showed no dependence on the concentration of MDA in blood plasma (table 2).

When comparing the level of MDA in those who recovered from COVID-19 without sleep disturbance (0.158 (0.087-0.297)) with those who complained of disturbances in the rhythms of life (insomnia, sleep inversion, excessive sleepiness) (0.186 (0.115-0.296)) the level of MDA was higher by 15%.

Our data confirm that oxidative stress in COVID-19 due to increased levels of ROS in the body can lead to psycho-emotional disorders. This is evidenced by works that say that an increased level of oxidative stress exacerbates the severity of COVID-19 and can later cause neurological disorders, as one of the options for post-COVID consequences [7,10,12]. There is an opinion that patients with COVID-19 may experience delirium, depression, anxiety and insomnia [13]. Coronaviruses can cause psychopathological consequences through direct viral infection of the CNS or through an immune response [14].

We also considered such a concept as the odds ratio of those who recovered from COVID-19, who had sleep disorders, anxiety and depression, with indicators of erythrocyte sedimentation rate and hemoglobin in the blood. The data obtained are presented in table 3.

An analysis of the odds ratio showed that people who recovered from coronavirus infection COVID-19 with a high level of SRE in the blood have significantly more sleep disorders, and with a decrease in hemoglobin, the frequency of sleep disorders increases (p = 0.030). Changes in SRE and Hb did not reach the level of statistical significance in anxiety and depression.

Table 3

Of the odds ratio of the incidence of sleep disturbance, anxiety and depression with 95% confidence intervals in people who have had COVID-19 with SRE and Hb

Sedimentation rate of erythrocytes (SRE)		
Sleep	OR	2.000 (0.912-6.023)
	χ^2	**3**
	P	**0.072**
	F	**0.054**
Anxiety	OR	0.873 (0.397-1.920)
	χ^2	0.113
	P	0.736
	F	0.444
Depression	OR	1.710 (0.753-3.882)
	χ^2	1.668
	P	0.196
	F	0.137
Hemoglobin (Hb)		
Sleep	OR	0.307 (0.096-0.982)
	χ^2	**4.253**
	P	**0.039**
	F	**0.030**
Anxiety	OR	1.341 (0.502-3.583)
	χ^2	0.344
	P	0.557
	F	0.364
Depression	OR	0.604 (0.216-1.690)
	χ^2	0.930
	P	0.334
	F	0.239

Conclusion. The findings highlight the importance of oxidative stress in COVID-19, especially the role of lipid peroxidation. According to the data we received, residents of Yakutsk who recovered from coronavirus infection were found to have sleep disturbances and an increased sense of anxiety, which can later lead to more serious disorders. Thus, we recommend monitoring the state of health after suffering COVID-19 until the complete disappearance of post-COVID symptoms.

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

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FEATURES OF THE CLINICAL COURSE OF COVID-19 CORONAVIRUS INFECTION IN CHILDREN OF THE REPUBLIC OF SAKHA (YAKUTIA)

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The article presents the results of retrospective analysis of the clinical histories of children hospitalized from March 23, 2020 to December 27, 2020 in the Republic of Sakha (Yakutia) "Children's Infectious Clinical Hospital" with the diagnosis of “Coronavirus infection caused by COVID-19" (ICD-10 code U07.1, U07.2). The features of the clinical course of a new coronavirus infection in 358 children were described. It was shown that during the first and second waves of COVID-19 in the Republic of Sakha (Yakutia) 56% of hospitalized children had respiratory tract infections. 36% were cases of pneumonia without respiratory failure. In 2 cases, a multisystem inflammatory syndrome with symptoms of incomplete Kawasaki syndrome was observed. In the remaining cases coronavirus infection caused by COVID-19 occurred against a background of intestinal infections of different etiology and concomitant diseases. Accumulation of epidemiological and clinical data will make it possible to find ways to prevent and treat the new infection, taking into account regional and population characteristics.

Keywords: coronavirus infection (COVID-19), pneumonia, children, North, Arctic, Yakutia.

Introduction. According to many authors, the clinical course of COVID-19 in children has its own peculiarities. The disease is often asymptomatic or has a subtle clinical picture [3,4,8]. The most common clinical manifestations are cough, febrile fever, and catarrhal manifestations [1]. According to the results of large-scale clinical and epidemiological studies, the main clinical manifestations of COVID-19 in children are upper airway lesions, pneumonia without or with respiratory failure, acute respiratory distress syndrome, sepsis, septic shock [6,7,8,9]. One of the most severe manifestations of COVID-19 in children is considered to be the occurrence of multisystem inflammatory syndrome [5].

The lack of etiotropic treatment and prophylaxis for COVID-19 in children is of concern. Only symptomatic therapy and instrumental means for managing patients with severe manifestations of the disease are available. There is enough information about the peculiarities of the pathogenesis and clinical course of COVID-19 in children. However, there are few studies in the literature devoted to the peculiarities of the course of coronavirus infection in harsh conditions of

circumpolar regions of the world, which makes it important to further summarize and analyze the results of scientific studies concerning the problem of COVID-19 in children in the Far North.

Materials and methods. The work was performed on the basis of the State Budgetary Institution of the Republic of Sakha (Yakutia) "Children's Infectious Clinical Hospital", Yakutsk, which is the head institution for children with COVID-19 in the Republic of Sakha (Yakutia). All 358 cases of children hospitalized at the Yakutsk Children's Clinical Hospital with the diagnosis of "Coronavirus infection caused by COVID-19" (ICD-10 codes U07.1, U07.2) during the period from March 23, 2020 to December 27, 2020 were included in the analysis. From the case histories, anamnesis data, complaints, description of clinical picture, results of laboratory and instrumental methods of examination, information on treatment and outcomes of each case were entered into the database.

Statistical processing of the material. Statistical calculations were performed using IBM SPSS Statistics 22 software. Pearson's criterion $\chi 2$ was used to compare groups. Quantitative variables were presented as median and interquartile range in Me format (Q1-Q3). The critical value of the significance level for statistical hypothesis testing was assumed to be 5%.

Results

In 2020, according to the Department of the Federal Service for Supervision of Consumer Rights Protection and Human Welfare in the Republic of Sakha (Yakutia), 24441 people (21151 adults and 3288 children) fell ill with coronavirus infection. The primary incidence was 2,531.0 per 100,000 of the population (3,015.2 in adults and 1,244.5 in children, respectively). Among the pediatric population, the highest incidence rates per 100,000 population were in adolescents (1,792.0), followed by children under one year old (1,444.7) and children 7-14 years old (1,249.8).

According to the routing scheme during the first wave of coronavirus infection, all children with a respiratory infection clinic and PCR-positive results for COVID-19 were hospitalized at the Children's Infectious Clinical Hospital of the Republic of Sakha (Yakutia). From 23.03.2020 to 27.12.2020 there were 358 children with coronavirus infection (ICD-10 codes U07.1, U07.2) undergoing hospital treatment. Among them there were 21 children from districts of the republic and 2 from other regions of Russia.

Analysis of the age structure showed

Table 1

Characteristics of patients by age and sex

Age group	Boys N=201		Girls N=157		Both boys and girls N=358	
	n	%	n	%	n	%
to 1 year	22	14.0	36	17.9	58	16.2
from 1 to 3 years	21	13.4	22	10.9	43	12.0
from 3 to 7 years	23	14.6	36	17.9	59	16.5
from 7 to 10 years	22	14.0	25	12.4	47	13.1
from 10 to 14 years	26	16.6	35	17.4	61	17.0
14-18 years old	43	27.4	47	23.4	90	25.1
P	0.762					

Note: p- reached significance level of differences (Pearson's criterion $\chi 2$).

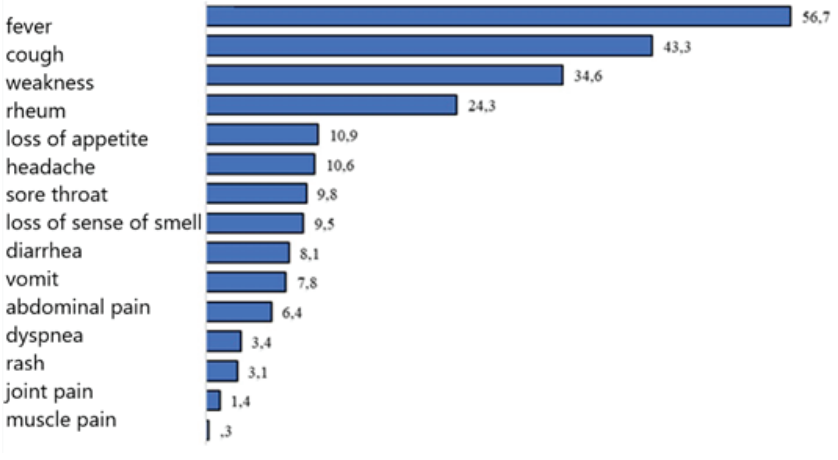

Fig.1. Frequency of patient complaints on admission (%)

Table 2

Symptoms detected during objective examination on admission

Symptoms	N (%)
Subfebrile body temperature (37-38°C)	51 (14.2)
Febrile body temperature (38-39° C)	26 (7.3)
Pyretic body temperature (39-40°C)	5 (1.4)
Nasal discharge	45 (12.6)
Pale skin	23 (6.4)
Sloppy stools	20 (5.6)
Bloating or painfulness on palpation	17 (4.8)
Enlarged lymph nodes	16 (4.5)
Abnormal muscle tone	11 (3.1)
Rattling in the lungs	9 (2.5)
Conjunctival hyperemia	8 (2.2)
Cyanosis	7 (2.0)
Liver enlargement	6 (1.7)
Dyspnea	4 (1.1)

that 25% of them were adolescent children (Table 1). There were no statistically significant differences in the age structure depending on sex (p=0.762). There was a history of exposure in 255 patients (71.2%). In 245 cases it was family contact, in 7 cases it was school contact, and in 3 cases it was contact in a place of temporary stay of children. The virus was identified in 344 (96.1%) cases (ICD-10 code: U07.1). The median duration of inpatient treatment was 12 (10-13) bed-days. 74 patients spent 14 to 31 days in the hospital.

The most common complaints on admission (Fig. 1) were fever (203), cough (155), rheum (87), and symptoms of general intoxication: weakness, lethargy (124), loss of appetite (39), headache (38), sore throat (35), and loss of sense of smell (34). In 133 of 155 cases of cough, patients and their parents noted dry cough.

On admission, the condition of 259 (72.3%) children was assessed as moderate severity, and 5 (1.4%) as severe. On examination, 82 (22.9%) children had elevated body temperature (Table 2). Some children showed signs of gastrointestinal disturbances: fluid stools (5.6%), bloating or painfulness when palpating the abdomen (4.8%). Intestinal bacterial infection (ICD-10 codes: A02.0; A04.0; A04.8; A04.9), and viral enteritis (ICD-10 codes: A08.0; B34.1; A08.1; A08.4; A08.2) were found in 16 children as concomitant diseases.

56% of children with COVID-19 had signs of respiratory tract involvement (Table 3). In 56 (16%) patients, only the upper respiratory tract was affected. Acute nasopharyngitis (pharyngitis) was the most common.

126 cases involved only lower airways, including bronchitis (8), laryngotracheitis (4), and pneumonia (114). In 17 children there was a combined lesion of the upper and lower respiratory tracts.

Computed tomography of the chest organs in 130 children (36.3%) revealed pneumonia (Fig. 2). Pneumonia was more frequently observed in older children, probably due to the fact that children of this age were hospitalized with more pronounced symptoms of the disease.

In 65 (50%) cases pneumonia was bilateral, in 28 (21.5%) - left-sided, 37 (28.5%) - right-sided. The degree of severity of pneumonia in all patients was defined as "moderate", without respiratory failure. In 120 (92.3%) patients with pneumonia the virus was identified.

Two children had multisystem inflammatory syndrome with symptoms of incomplete Kawasaki syndrome. At that, in a 4-year-old girl COVID-19 virus was identified, CT scan revealed signs of fluid in the pleural cavities on both sides against the background of no fresh focal and infiltrative changes. The second case of Kawasaki-like syndrome was detected in a 6-month-old boy, COVID-19 virus was not identified. The child had a clinic of acute bronchitis.

Outcome analysis showed that 211 children were discharged with recovery, 134 with improvement, 13 children were transferred to other departments (5 of them to the ward for patients with mild COVID-19, 8 to the main disease).

Conclusion. According to the results of our study in children hospitalized in the State Budgetary Institution of the Republic of Sakha (Yakutia) "Children's Infectious Clinical Hospital" from 23.03.2020 to 27.12.2020 with the diagnosis "Coronavirus infection caused by COVID-19" the main clinical symptoms were increase in body temperature and signs of lesions of upper and lower respiratory tract. On admission to the hospital, common clinical manifestations were catarrhal symptoms, increased body temperature, and general intoxication. It should be noted that often enough gastrointestinal manifestations were revealed: liquid stool, vomiting and abdominal pain or discomfort in the abdominal area.

COVID-19 was associated with respiratory lesions in 56% of cases. In 16% of cases only upper airways were affected, in 36.3% of cases it was pneumonia without respiratory failure. Two cases of multisystem inflammatory syndrome with symptoms of incomplete Kawasaki syndrome were detected. In the remaining cases coronavirus infection caused by COVID-19 virus occurred against the background of intestinal infections of different etiology and concomitant diseases.

Pneumonia in children was bilateral only in half of the cases. According to the literature, changes on radiographs or computed tomography of the lungs observed in children infected with SARS-CoV-2 include mostly bilateral lesions [3].

The data obtained characterize the

Table 3

Signs of airway lesions in children with COVID-19

Condition/Sign	N (%)
Frequency of individual conditions	
Acute rhinitis	13 (3.6)
Acute sinusitis	1 (0.3)
Acute nasopharyngitis	48 (13.4)
Acute pharyngitis	9 (2.5)
Acute tonsillitis	5 (1.4)
Acute laryngitis (laryngotracheitis)	4 (1.1)
Acute bronchitis	8 (2.2)
Acute pneumonia	130 (36.3)
Level of involvement	
Signs of lesions of the upper respiratory tract only	56 (15.6)
Signs of lower respiratory tract involvement only	126 (35.2)
Combined upper and lower respiratory tract involvement	17 (4.8)
Signs of upper or lower respiratory tract involvement, or both	199 (55.6)

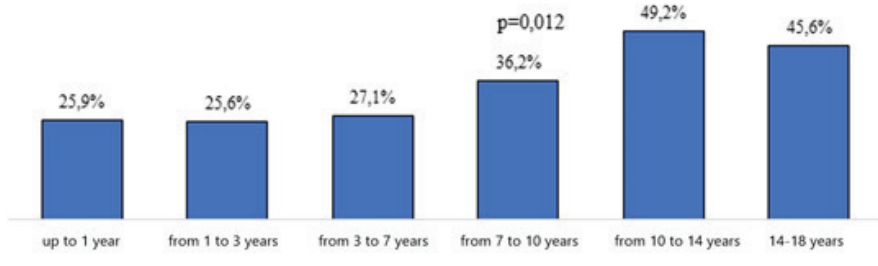

Fig. 2. Frequency of pneumonias as a function of patient age: p- reached significance level of differences (Pearson's criterion χ2)

course of new SARS-CoV-2 coronavirus infection in children of the Republic of Sakha (Yakutia) during the first and second waves of COVID-19. Accumulation of epidemiological and clinical data will make it possible to find ways of preventing and treating the new infection, taking into account the peculiarities of the region and the population.

The work was performed within the research theme "Monitoring of the state of health of children in the Republic of Sakha (Yakutia)" (State Registration No. 0120-128-07-98), within the state assignment of the Ministry of Science and Education of the Russian Federation (FSRG-2020-0016).

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CARDIOVASCULAR PATHOLOGY AND COVID-19 IN RESIDENTS OF YAKUTSK

A study was conducted on 161 citizens of Yakutsk who had a new coronavirus infection in the period from March to December 2020. A high incidence of arterial hypertension, obesity, and lipid-metabolic disorders was revealed. The relationship of lipids, glucose and uric acid in blood serum, arterial hypertension, waist circumference with the severity of the new coronavirus infection was shown. The high prevalence of cardiovascular pathology and its risk factors among study participants requires long-term follow-up of patients with post-COVID syndrome, which prevents premature death from diseases of the circulatory system.

Keywords: cardiovascular pathology, arterial hypertension, lipid disorders, new coronavirus infection, COVID-19, Yakutsk.

In recent years, the world has been agitated by the prolonged outbreak of the new coronavirus infection COVID-19, causing huge social and economic losses. At the time of submission of the article on 02/03/2022, there are 388,100,320 confirmed cases of the disease in the world, 5,713,256 people died [3]. In Russia, 12,284,564 cases were confirmed, 333,357 people died [2]. Numerous studies demonstrate the influence of cardiovascular pathology on the severity of COVID-19, causing high mortality among these patients [6;7;8]. There is also evidence of cardiovascular complications after COVID-19. The pandemic affected the course of the existing pathology or contributed to its appearance, causing long-term consequences in the form of the post-covid syndrome. The relevance of the research is to identify the aggravating effects of COVID-19 on human health in order to develop new recommendations for the management of patients with post-covid syndrome in order to prevent cardiovascular disasters.

The aim of the study was to research cardiovascular pathology in residents of Yakutsk who had suffered the new coronavirus infection COVID-19.

Materials and methods of research. A pilot single-stage study was conducted in March 2021 of residents of Yakutsk, geographically attached to the YSC CMP clinic, with a history of new coronavirus infection COVID-19 in the period from March to December 2020 (1st wave). The response rate was 78%. The object of the study were 161 people, 68 of which were men (42.2%), and 93 were women (57.8%). The average age was 51 [44, 57] years for men and 54 [48, 57] years for women.

Inclusion criteria: adult population of Yakutsk from 30 to 70 years old, attached to the Clinic of the YSC CMP, with a history of COVID-19, voluntary consent to the study.

Exclusion criteria: malignant neoplasms, acute infectious diseases, exacerbations of chronic diseases, acute myocardial infarction, acute cerebrovascular accident.

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The examination program included: a questionnaire survey to assess symptoms and quality of life, an anthropometric study measuring height, weight, waist circumference (WC) and hips circumference, resting ECG, spirometry, blood sampling from the ulnar vein in the morning on an empty stomach for general clinical, biochemical and immunological studies, clinical examination by a cardiologist. Blood pressure (BP) was measured by an automatic tonometer "OMRON M2 Basic" (Japan) twice in a sitting position with the calculation of average blood pressure with a limit of permissible measurement error of ± 3 mm Hg (ESH/ESC, 2018). Informed consent to conduct an examination, questionnaire, and blood collection for further analysis of the results was obtained from all participants of the study according to the protocol of the Ethics Committee of the YSC CMP (Protocol No. 52 of 03/24/2021).

The abdominal obesity (AO) is exposed to the value of the waist measurement (WM) ≥ 80 cm on women, ≥94 cm on (VNOK, 2009).

The blood pressure level of ≥140/90 mmHg or the use of antihypertensive drugs was taken for hypertension. According to degrees of severity, they were divided into: stage 1 AH - BP 140-159/90-99 mm Hg, stage 2 AH - BP 160-179/100/109 mmHg, stage 3 AH - BP ≥180/≥110 mmHg [4].

Laboratory methods of the research included analysis of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL Cholesterol), low-density lipoprotein cholesterol (LDL Cholesterol), very low-density lipoprotein cholesterol (VHDL Cholesterol), levels glucose, uric acid, immunoglobulins class M and G to coronavirus SARS-CoV-2.

When judging the incidence of disorders of the blood lipid profile in a population, we used the Russian recommendations of the VII revision of Society of cardiology of Russian Federation, 2020, into account the European recommendations, 2019. Hypercholesterolemia (HCS) is the level of TC ≥ 5,0 mmol/l (190 mg/dl) taking into account the risk of cardiovascular death on the SCORE scale, the high LDL Cholesterol level >3,0 mmol/l (115 mg/dl) with low, > 2.6 mmol/l with moderate, >1,8 mmol/l with high, > 1,4 mmol/l with very high and extreme risk, the low HDL Cholesterol level <1,0 mmol/l on men; <1,2 mmol/l on women, the hypertriglyceridemia (HTG) is the TG level is >1,7 mmol/l. The atherogenic index (IA) was determined by the formula: IA (cu) = (TC - HDL Cholesterol) / HDL Cholesterol (Klimov A.N., Nikulcheva N.G., 1999). A

Characteristics of patients according to the degree of lung damage

	CT-0	CT-1	CT-2	CT-3	CT-4
Abs. number	27	60	42	26	6
%	16.8	37.3	26.1	16.1	3.7

Note. CT - computed tomography.

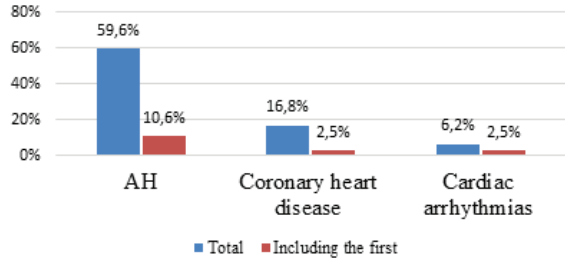

Fig.1. The frequency of cardiovascular pathology in people after COVID-19

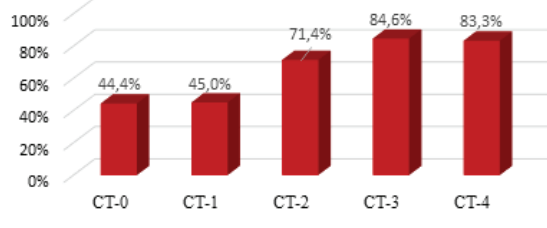

Fig.2. The frequency of arterial hypertension depending on the degree of lung damage

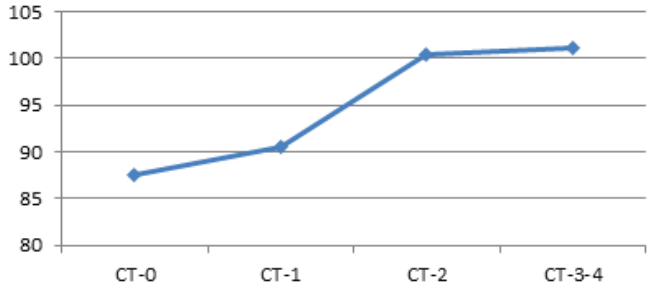

Fig.3. The relationship of waist measurement with the severity of COVID-19 (according to CT picture) (cm)

hyperglycemia (HG) on an empty stomach (a glucose in a blood plasma on an empty stomach > 5,6 mmol/l). Respondents with these disorders also included participants receiving specific medication for these conditions.

The degree of lung damage and its severity were assessed according to the results of computer tomography (CT): CT-0 – absence of viral pneumonia, CT-1 lung lesions less than 25%, CT-2 – 25-50%, CT-3 – 50-75%, CT-4 >75% lung damage in the form of "ground-glass opacities".

Statistical processing of the results was carried out using the standard SPSS 22.0 package. The arithmetic mean (M), the error of the mean (m), median (Me) and the 25th and 75th quartiles (Q1, Q3) were calculated. The intergroup differences were assessed using variance analysis or nonparametric criteria. The correlation analysis was carried out by Spearman's correlation coefficient. The differences were considered statistically significant at p<0.05

Results and discussion. The largest number of respondents (63.4%) had a mild to moderate infection with CT-1 and CT-2 lung damage. Their characteristics according to the severity of the suffered COVID-19 (CT picture) are presented in Table 1.

After suffering the new coronavirus infection, the most frequent complaints

were shortness of breath, which was observed in 43 people (26.7%), discomfort in the area of the heart (n=32 or 19.8%), 24 respondents complained of palpitations (14.9%), 19 people of chest pain (11.8%), 18 - of extrasystole (11.2%).

The majority of the study participants had diseases of the cardiovascular system (97 people or 60.2%), mainly represented by arterial hypertension (AH) (96 people. or 59.6%), 27 of them had coronary heart disease (16.8%). After COVID-19, pathology was first diagnosed in 22 people (13.6%), including hypertension in 17 (10.6%), in 4 - coronary heart disease (2.5%). Cardiac arrhythmias were registered in 10 people (6.2%), represented by sinus tachycardia, sinus bradycardia, supraventricular extrasystole, of which 4 (2.5%) were registered for the first time. The mechanism of arrhythmias has not yet been clarified and remains controversial. It is possible that cytokine inflammation provoked arrhythmias, or that they were a side effect of drugs, or were not properly diagnosed earlier before the infection. The same applies to newly diagnosed hypertension and coronary artery disease.

It should also be noted that 23 respondents had type 2 diabetes and accounted for 14.3% of the total, for 1 person it was registered for the first time. Our data is consistent with the research conducted by domestic and foreign scientists. Thus, 56.6% of 5,700 patients from New York, Long Island and Westchester County (USA) had hypertension, 509 (49%) of 1,043 patients from Milan, Italy had hypertension and 17% - DM, 30.5% of patients from Wuhan, China, had hypertension and 14.4% - DM [5; 8; 9]. The conducted study of the AKTIV international registry, which included 5808 patients from the Russian Federation, the Republics of Belarus, Armenia, Kazakhstan and Kyrgyzstan, showed a high incidence of hypertension (55.41%), ischemic heart disease (20.6%), type 2 diabetes (17.5%) [1].

The analysis of the relationship between glucose and uric acid levels in all respondents with a CT picture of a new coronavirus infection was carried out. It was shown that the levels of blood glucose (r=0.162, p=0.041) and uric acid (r=0.160, p=0.043) positively correlated with the severity of the infection.

The study of the relationship of systolic blood pressure (SAD) with the severity of the infection was carried out. We obtained a strong correlation (r=0.373, p=0.000). That is, the higher the SBP indicators, the more severe is the course of COVID-19. The level of SBP was also strongly correlated with IgG titer (r=0.307, p=0.000), and no relationship was obtained with IgM titer (r=0.070, p=0.380).

Analysis of the conjugacy of infection with hypertension was carried out. It was revealed that persons with hypertension were exposed to a more severe course of COVID-19 in the anamnesis. If the mild course of the disease was registered almost equally in both hypertensive and normotonic patients, then the average and severe course was mainly found in individuals with hypertension from 71.4 to 84.6% (χ 2=18.49, p=0.001) (Fig.2). The stage of hypertension also had a correlation with the severity of COVID-19 (r=0.386, p=0.000).

A study of lipid metabolism disorders in the participants of the pilot project was conducted. In more than half of both men and women, high cholesterol was detected - 54.5% and 59.4%, respectively, there was no statistical difference (p=0.552). Atherogenic HCV was most often registered in men (65.4%) compared with women (56.3%) (p=0.386), a reduced level of HDL cholesterol was also detected in more than half of the respondents (55.6% and 58.9%, respectively), there was no significant difference (p=0.687). TG concentrations were significantly higher in men (62.2%) compared to women (41.2%) (p=0.028).

The analysis of the relationship of the lipid spectrum with the severity of COVID-19 was carried out. The average lipid values had no statistical difference between men and women, except for the concentrations of HDL cholesterol (0.90±0.03 in men and 1.12±0.04 in women, p=0.000) and LDL cholesterol (0.69±0.05 and 0.50±0.03, respectively, p=0.002).

In the postcovid period, an average correlation was revealed between the severity of the infection (according to CT of the lungs), total cholesterol (r=0.187, p=0.018), LDL cholesterol (r=0.142, p=0.073), TG (r=0.251, p=0.001), HDL cholesterol (r=0.056, p=0.479). Comparing by gender, it was revealed that men's CT picture had a correlation with mean values of total cholesterol (r=0.278, p=0.022), LDL cholesterol (r=0.251, p=0.039). Women had a correlation with the level of TG (r=0.294, p=0.004). Lipid metabolism disorders often accompany cardiovascular pathology, which is most common in participants of the pilot study with a more severe course of COVID-19.

Abdominal obesity (AO) plays an important role in the development of cardiovascular pathology and type 2 diabetes mellitus. There was a high incidence of AO in both men (75%) and women (71%). There was a strong correlation between WC and the degree of lung damage in COVID-19 (r=0.348, p=0.000), the more WC, the worse the disease progressed.

Thus, we have proven a conjunction of arterial hypertension and the new coronavirus infection, most pronounced in severe infection. The relationship of lipid, carbohydrate metabolism disorders and obesity with the severity of the disease is also presented. Diabetes mellitus may also have been a background comorbid disease that affected the course and outcome of the disease.

Conclusion. A pilot study of the attached population of Yakutsk with a history of the new coronavirus infection showed a high probability of its long-term consequences, which were a possible trigger for the development or complications of existing diseases of the cardiovascular system. A high frequency of arterial hypertension, obesity and lipid-metabolic disorders was revealed. The relationship of arterial hypertension, waist circumference, lipids, glucose and uric acid of blood serum with the severity of the new coronavirus infection is presented. The high prevalence of cardiovascular pathology and its risk factors among the study participants requires long-term follow-up of patients with postcovid syndrome, which prevents premature death from diseases of the circulatory system. The activities include the development of clear algorithms for medical examination, the organization of a remote way of consulting patients, the popularization of a healthy lifestyle, the correction of modifiable risk factors such as dyslipidemia, hypertension and obesity.

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ARCTIC MEDICINE

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DETERMINATION OF VITAMIN D CONCENTRATION OF 25(OH) IN THE WORKING-AGE POPULATION OF THE NORTHERN REGION

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УДК 577.161.2 + 612.017.2

The study examined working-age population of the North region to determine 25 (OH) vitamin D concentrations and compared insufficient subjects (Group 1) with those having the proper/optimal vitamin D concentration (Group 2) in terms of main indicators of physical development, cardiovascular system, biochemical and trace element picture.

Material and Methods: fifty-five men of working age (mean age was 37.4±0.5 yr.) all Caucasians residing in the territory of Magadan region participated in the research. We used photometric, immunochemiluminescent and spectrometric methods of investigation, as well as standard cardiovascular and anthropometric measurements. Study Results: 42% (Group 1) tested low for vitamin D while 58% (Group 2) had the proper vitamin amounts. Group 1 was up to 78% made up of high body mass index men versus 40% of subjects exceeding standard range of this index in Group 2. Cardiovascular system and circulation values tended to be increasingly stressed and high thyroid-stimulating hormone indicated the development of preclinical hypothyroid pathology with Group 1 examinees. They were more atherogenic in lipid pictures in comparison with Group 2 northerners who showed a shift towards healthier lipid profiles. Moreover, vitamin D deficient subjects proved to also lack vitamin B12 and were low in trace elements.

Conclusion: Subjective vitamin D deficits develop disorders in physical development, cardiovascular system, as well as biochemical and trace element profiles. Our study can be applied for making recommendations on correcting vitamin D deficiency/insufficiency in residents of Russia's northeast.

Keywords: men of working age, 25 (OH) vitamin D, North, physical development, cardiovascular system, biochemical picture, trace elements.

Introduction. Vitamin D insufficiency has become a pandemic health problem [24] since it is common in a third of the world's population, even in Earth's tropical and subtropical regions [16]. It can be invasively assessed in blood serum 25-hydroxyvitamin D (25(OH) vitamin D) concentration [27]. In addition to significantly influencing calcium and phosphorus metabolism, thereby bone health and muscle strength, vitamin D deficiency has been recently reported to develop non-skeletal disorders like cardiovascular [20] and autoimmune diseases, cancers [19], higher blood pressure, depression, as well as overall mortality [34]. Some authors have investigated the relationship between low blood 25(OH) vitamin D and chronic diseases, including insulin resistance [21] and type 2 diabetes mellitus [18].

Vitamin D deficit is a variable which the patient's mineral picture can also be referred to. Therefore, vitamin D control is crucial for the body mineral imbalance management [37]. Trace elements are known to be involved in metabolic activities. They promote vascular tone, nervous and immune functioning at the enzymatic level. Unlike blood or urine, hair is known to constantly accumulate chemicals as the hair shaft grows and is supplied with blood [36]. Therefore, hair elemental composition reflects longer exposure to the chemicals owing to the hair biomonitoring abilities to keep past changes in metabolism as well as environmental effects [1,7,13].

The role of vitamin D in maintaining the proper blood calcium and phosphorus levels has been commonly reported [3] for it ensures bone tissue mineralization and enhances the re-absorption of calcium in kidneys. Extremely low levels of vitamin D can provoke improper calcium and phosphate metabolism, which causes bone tissue impairment. Insufficient absorption of calcium in the intestine results in accelerated release of calcium from bones, which decreases the bone density and increases the risk of fractures [8]. Vitamin D deficiency is often accompanied by shortage of thyroid-specific elements such as cobalt, iron, magnesium, selenium, copper, and zinc, which can be seen under the goiter endemic conditions. The so called northern deficit in essential macro- and microelements owing to the biogeochemistry of the region, as well as poor soils and weakly mineralized drinking waters can develop insufficient absorption of the vitamin, even being taken as a supplement. The specific light regime of the

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northern territories suggests a long dark period in winters, which inhibits the vitamin D absorption and leads to its chronic deficiency.

Thus, hair mineral analysis is a non-invasive, painless, and easy to collect method for determining biomarkers, which requires no special storage conditions [39]. Sampling the hair should be also considered as an indicator of nutrition deficiencies [11]. This study was the first investigation performed in Magadan region to comparatively assess the main indicators of physical development, cardiovascular system, biochemical and trace element pictures in Russia's far north residents with insufficiency or the optimal concentration of vitamin D.

Materials and Methods. Fifty-five male residents (mean age was 37.4 ± 0.5 yr) of Magadan region, Caucasians by origin, participated in the survey within the framework of psychophysiological monitoring of people of the working age under conditions of the North-East of Russia entitled "Arctic. Man. Adaptation" carried out with the Arktika SRC, FEB RAS (Magadan) as part of state assignment. Blood serum samples were taken to study 25 (OH) vitamin D with the Unicel DXi 800 automated immunochemical analyzer (Beckman Coulter, USA) using ACCESS-ELISA technology on submicron paramagnetic particles as a solid phase and enzymatically enhanced chemiluminescence as a detection method.

In this research, insufficient and optimal blood serum 25 (OH) vitamin D concentration values were taken to be less or more than 50 nmol/L [5], respectively, in accordance with the criteria of the Clinical Recommendations of the Russian Association of Endocrinologists (2016). Further, two groups of subjects were formed: Group 1 were subjects who demonstrated a deficiency of 25 (OH) vitamin D (n=23, 42%) and Group 2 were those with the optimal amounts of 25 (OH) vitamin D (n=32, 58%).

The participants' anthropometric characteristics, body length and body mass, were measured to calculate the body mass index (BMI, kg/m^2) was calculated. Using the AIST software package of the Diamant-AIST body impedance analyzer (Diamant, Russia), the total fat content (in % of the body mass) was determined. Systolic (BP_S, mmHg) and diastolic (BP_D, mmHg) blood pressure and heart rate (HR, beat p min) were also measured on the forearm area with the Nessei DS-1862 automated tonometer (Japan).

The variables for total cholesterol (TChol, mmol/L), triglycerides (TG, mmol/L), high-density lipoprotein cholesterol (HDL, mmol/L) and low-density lipoprotein cholesterol (LDL, mmol/L) were determined by colorimetric photometric method using AU 680 (Beckman Coulter, USA). Dyslipidemia of the analyzed variables was determined based on the criteria of the Russian Recommendations of the VII Revision of 2020 [4] and based on the Report of NCEP experts [30].

The amounts of vitamin B_{12} (pmol/L) and thyroid-stimulating hormone (TSH, mcME/mL) were determined with the immunochemiluminescent method using the IMMULITE 2000 XPI Siemens healthcare diagnostics immunochemical analyzer (USA - Germany).

Hair samples were cut from the occipital part of the head to study and analyse amounts of micro- and macroelements (ME): Co, Cr, Fe, I, Mg, Mn, Se, V, Zn, Cu, P, and Ca. This analysis was performed with the laboratory of Micronutrients LLC (Moscow) using the NexION 300 ICP-MS device (Perkin Elmer, Shelton, CT, USA) with the inductively coupled plasma spectrometric method.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki for medical research involving human subjects, including research on identifiable human material and data (2013) [40], with the informed consent of voluntary participants. The study protocol was approved by the Bioethics Commission of the IBPN, FEB RAS (No. 001/019 dated 29.03.2019).

The results of the studies were statistically processed using the Statistica 7.0 software package. The distribution of measured variables was tested for normality using the Shapiro-Wilk test. The results of parametric processing methods were presented as the mean value (M) and its error (±m). The statistical significance of differences was determined using the Student's test *t*. The critical level of significance (p) was assumed to be 0.05; 0.01; 0.001 [2].

Results. The results in Table 1 show subjective variables of physical development, cardiovascular system, and biochemical picture when insufficient (Group 1) and optimal (Group 2) vitamin D examinees are compared. The data indicate statistically significant differences in 17 of the 26 analyzed indicators. Low 25 (OH) vitamin D participants, regardless of their ages, exhibited significantly higher variables of body mass, total body fat, body mass index, systolic and diastolic blood pressure, and heart rate. Biochemical picture analysis revealed higher amounts of B_{12} and D vitamins in Group 2 individuals, with significantly lower values of thyroid-stimulating hormone, total cholesterol, low-density lipoprotein cholesterol, and triglycerides observed in this group. Table 2 presents microelement pictures in subjects with insufficient and the optimal vitamin D concentrations. The results indicate more pronounced trace element deficits observed in Group 1. Figure 1 shows correlation patterns of the studied indices for physical development, cardiovascular system, biochemical and trace element pictures, which are seen to differ depending on the body vitamin D supply.

Discussion. Data in Table 1 show significantly higher body weight, total body fat amount, and body mass index exhibited by insufficient vitamin D subjects. Body mass index (BMI) is known to be the world's recommended indicator for overweight and obesity. In addition, BMI specifies nutritional status and, according to some authors, strongly correlates with the total body fat and risks for developing metabolic and cardiovascular diseases [32]. The relationship between BMI and total body fat is however reported to not be strong enough to accurately assess the obesity in a particular case since the use of BMI in obesity assessment does not consider body composition [38]. Thus, the total body fat value is a true risk factor for cardiometabolic health and human life expectancy, while the use of BMI is rather approximate and insufficient [32].

Total body fat content has a potential advantage in more accurate identifying the metabolic phenotype than BMI [22]. Group 1 of those with vitamin D deficiency tended to be mostly made up with men with a BMI exceeding the range for normal body mass (25 kg/m^2) which is more common in insufficient (up to 78%) than in optimal vitamin D examinees (40%). That was also investigated by T.L. Karonova who has reported that patients with normal BMI had a higher level of 25 (OH) vitamin D than overweight and obese patients (52.5 ± 2.8 and 44.8 ± 2.0 nmol/L, $p<0.05$) [26]. Obesity results in decreased blood serum vitamin D concentration [10]. It worsens bioavailability of vitamin D from food and impairs its synthesis in the skin [26]. Thus, we identified Group 2 of 25 (OH) vitamin D deficit subjects as having worse physical development owing to the obtained somatometric variables.

As seen from Table 2, we found 49% of volunteers to be low in Vanadium, which can be accompanied by decreased cholesterol and increased levels of triglycerides, liver lipids and phospholipids in blood plasma, as well as higher hematocrit, which may cause the risk for atherosclerosis and diabetes mellitus. Table 2 shows significant differences

in chromium amounts between the two groups. Chromium imbalance can develop atherosclerosis, obesity, and worsen thyroid generative function. In addition, it is a mediator of the insulin signal in insulin-dependent tissues. Since that, when being low, chromium is consistently accompanied by impaired glucose and lipid metabolism and decreased insulin sensitivity [31].

By cardiovascular system analysis, we identified insufficient blood serum vitamin D subjects as tension in the circulatory system activity and significantly higher systolic and diastolic blood pressure which have been reported to correlate with lowered 25 (OH) vitamin D concentrations [35].

By biochemical study of lipid metabolism, we revealed significantly higher levels of total cholesterol, low-density lipoproteins and triglycerides with Group 1 subjects with no differences observed about high-density lipoproteins. A high frequency for lipid profile disorders was also seen in insufficient blood serum vitamin D subjects who demonstrated hypertriglyceridemia (38% of cases), hypercholesterolemia (69%), increased LDL (95%) versus those of Group 2 who showed hypertriglyceridemia in 10%, hypercholesterolemia in 53% and increased LDL in 75%.

Thus, during this study, a more atherogenic lipid picture was typical for insufficient vitamin D Group 1 examinees whereas the optimal vitamin D concentration subjects reported a healthier lipid profile.

Vitamin B_{12} deficiency is a worldwide public health concern, especially in developing countries, where it affects the population of all ages [25]. In developed countries, vitamin B_{12} deficiency is most common in the elderly, however the prevalence in younger people is higher than previously thought [25]. As a result, a wide range of neurological, hematological and neuropsychiatric disorders can happen [23]. In addition, the vitamin deficiency indirectly effects on cardiovascular system [15]. The blood serum vitamin B_{12} concentration is considered to be deficient or low when being below 200 pg/mL (147 pmol/L) or below 400 pg/mL (296 pmol/L), respectively [12]. Based on these criteria, insufficient vitamin D Group 1 participants were diagnosed with the deep B_{12} deficiency in 25% of cases, 69% of them were low in the vitamin, and 6% only showed its optimal level.

Subjective B_{12} variables within Group 2 suggested that the vitamin deficiency was common in 12% of the sample, 63% were considered as insufficient while 25% were defined as the optimal level. Low vitamin B_{12} levels are associated with high body fats in healthy adults who are not obese [9], which complies with our studies owing to higher BMI and total fat amounts in individuals with significantly low vitamin B_{12} values. Therefore, the data indicated that Group 1 participants with vitamin D deficiency tended to be low in vitamin B_{12} as well.

The study revealed cobalt deficiency as a common north-related trace element picture in 78% of the examinees which causes impairment in synthesis of vitamin B_{12}, as well as endemic weakness in thyroid functioning (hypothyroidism), develops cardiovascular diseases, anemia, central nervous system disorders and depression.

Thyroid function is mostly monitored by measuring thyroid-stimulating hormone (TSH). Subclinical hypothyroidism is defined as the TSH level above the reference ranges while the level of thyroid hormones remains within the normal range [29].

Our results suggested that TSH of both examined groups were significantly lower than currently used world's reference upper values being equal to as high as 4.2 mcME/L [17], but for Group 1 with vitamin D deficiency, the average TSH values highly exceeded the threshold of 2.5 mcME/L, which was proposed by the NACB

Table 1

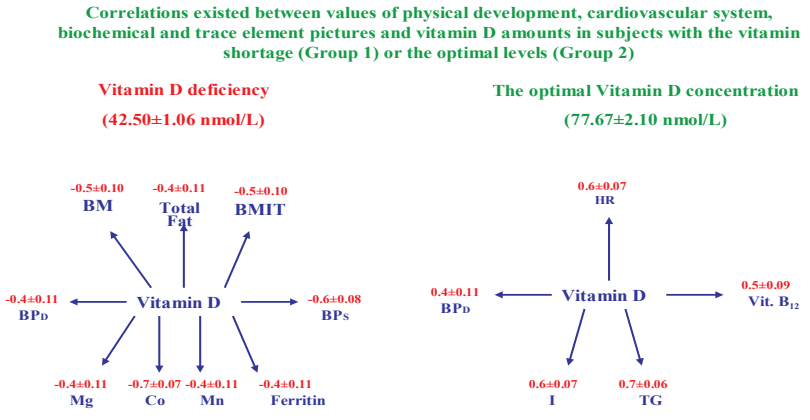
Indicators of physical development, cardiovascular system, biochemical pictures in subjects with insufficient and optimal amounts of vitamin D

Indicator	Insufficient Vitamin D	Optimal Vitamin D	Levels of Significance of Differences
Age, yr	37.2±1.2	37.5±1.0	p=0.82
Body Mass, kg	86.6±1.5	82.7±1.2	p<0.05
Total Fat Amount, %	20.2±0.8	17.7±0.7	p<0.05
BMI, kg/m^2	26.8±0.4	25.6±0.3	p<0.01
BPS, mmHg	128.0±1.8	122.4±1.7	p<0.05
BPD, mmHg	84.3±1.9	78.1±1.6	p<0.05
HR, bpm	69.1±2.3	62.7±1.8	p<0.05
Vit B12, pmol/L	189.80±9.71	251.10±18.30	p<0.05
Vit D, nmol/L	42.50±1.06	77.67±2.10	p<0.001
TSH, mcME/mL	2.75±0.15	2.31±0.10	p<0.05
Cholesterol, mmol/L	6.25±0.19	5.62±0.14	p<0.01
HDL, mmol/L	1.41±0.05	1.42±0.07	p=0.91
LDL, mmol/L	4.26±0.16	3.73±0.18	p<0.05
TG, mmol/L	1.80±0.19	1.16±0.12	p<0.01

Table 2

Microelement pictures in subjects with insufficient and optimal amounts of vitamin D

Indicator	Insufficient Vitamin D	Optimal Vitamin D	Level of Significance of Differences	Reference Values [6]
Co, mc/g	0.008±0.001	0.011±0.001	p<0.01	0.004-0.3 mc/g
Cr, mc/g	0.46±0.04	0.40±0.03	p=0.23	0.04-1 mc/g
Fe, mc/g	29.58±4.47	18.13±1.57	p<0.05	7-40 mc/g
I, mc/g	0.22±0.02	0.56±0.05	p<0.001	0.15-10 mc/g
Mg, mc/g	31.20±1.20	39.64±3.60	p<0.05	20-200 mc/g
Mn, mc/g	0.38±0.03	0.46±0.03	p=0.07	0.15-2 mc/g
Se, mc/g	0.50±0.03	0.61±0.05	p<0.05	0.25-2 mc/g
V, mc/g	0.03±0.00	0.02±0.00	p=0.10	0.005-0.1 mc/g
Ca, mc/g	280.0±26.6	301.8±27.0	p=0.54	200-2000 mc/g
Zn mc/g	181.56±13.97	182.57±11.88	p=0.96	125-400 mc/g
Cu, mc/g	12.06±0.73	12.26±0.99	p=0.84	9-40 mc/g
P, mc/g	172.8±7.8	189.6±6.8	p=0.72	120-200 mc/g



Note: MB is for body mass, kg; Total Fat is body total fat amount, %; BMI is body mass index, kg/m²; BPs is systolic blood pressure, mmHg; BPD is diastolic blood pressure, mmHg; HR is heart rate, bpm; TG is for triglycerides, mmol/L

Analysis of correlations existed between indices of physical development, cardiovascular system, biochemical and trace element pictures in insufficient and optimal vitamin D subjects

for determining preclinical hypothyroidism [14]. In this study we determined the relationship of increased TSH levels with subjective high serum lipids and risks for atherosclerosis [33], which was obviously exhibited by Group 1 lipid picture. In addition, Iodine deficiency demonstrated by vitamin D insufficient subjects can develop hypothyroidism, cardiovascular and reproductive impairments, physical and mental problems, worsened cognitive functions, especially under conditions of the previously observed endemic goiter.

Table 2 shows mineral pictures of the surveyed participants with significant differences in bioelement amounts through both groups. Group 1 subjects exhibited imbalanced magnesium and manganese [28], vanadium and selenium [29], known as important in metabolism of carbohydrates and fats.

By correlation analysis (Fig. 1), we revealed stronger negative intersystem correlations typical for insufficient vitamin D subjects' physical development, cardiovascular system, as well as biochemical and trace element profile. The negative correlations that exist with deficient chemicals can indicate the dysregulation in the relationships. The less stable a system is the more correlations can develop within it. Strong correlations of magnesium and manganese with deficient vitamin D can indicate the risk for neurosis-like conditions, impaired glucose metabolism, osteodystrophy, and bone fragility, especially with low calcium and phosphorus amounts typical for this group. For northern men with the optimal blood vitamin D concentration, a different picture of intersystem correlations could be seen, with no relationships with indicators of physical development apparently owing to subjective healthier values of BMI and total body fat in Group 2. Negative correlations occurred between 25(OH) D and BMI (r=-0.17, p=0.03) were also reported by T.L. Karonova [26]. Furthermore, the direct correlations with the indicators of systolic and diastolic blood pressure, the concentration of vitamin B_{12}, the level of blood triglycerides, and the body iodine concentration were observed with the examinees of this group.

Conclusion. Thus, by comparative analysis, we determined significant differences in the surveyed northern men's functional status, as well as their biochemical and trace element pictures depending on vitamin D levels. Group 1 of those tested low for the blood vitamin D levels exhibited significantly high BMI and total body fat values, which can be considered as a sign of deterioration in physical development. A more atherogenic lipid picture was typical for this group, and dyslipidemia in LDL and TChol values, as well as triglyceride concentration was more common in Group 1 of low 25(OH) vitamin D examinees. Group 2 of northerners tested for the optimal vitamin D concentration demonstrated healthier lipid pictures.

The study confirmed that the deficiency group reported deficit in both D and B_{12} vitamins. By cardiovascular analysis, we could see insufficient blood serum vitamin D subjects having significantly higher (vs. the other group) systolic and diastolic blood pressure, which indicated circulatory system tension, as well as higher thyroid-stimulating hormone values, which we considered to be Group 1 subjects' symptom of the developing preclinical hypothyroidism.

In the surveys, subjective vitamin D, depending upon its levels, differently correlated with the values of physical development, cardiovascular system, as well as indicators of biochemical and trace element pictures. By intersystem analysis we determined that low vitamin D concentration caused dysregulation with examinees diagnosed with its deficiency since they exhibited strongly negative relationships.

We consider the results of this survey to be useful for assessment of either vitamin D supply or other functional parametric values as predictive markers of vitamin D deficiency that do not require invasive and costly research methods. Based on the research, specific recommendations can be created for people diagnosed with vitamin D deficiency, as well as for those working shifts under extremes of the northeast of Russia.

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SCIENTIFIC REVIEWS AND LECTURES

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EFFECT OF PHYSICAL STRESSORS ON NEUROENDOCRINE RESPONSE IN CRITICALLY ILL PATIENTS

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A critical condition is a complex of changes that require replacement of the functions of vital organs and systems to prevent death. The set of reactions can be considered as a gradual development of physiological and pathological reactivity. The most important role in the formation of reactivity in critical conditions is played by the neuroendocrine and neuroimmune systems. The concept of the neuroendocrine system includes connections between the endocrine and central nervous systems and their relationship in the control of homeostasis. Stimulation of the immune system to a complex neuroimmunoendocrine interaction in order to avoid development of a critical condition. Cytokines and afferent pathways of the vagus nerve activate the hypothalamic-pituitary-adrenal system, as a result of which the increased secretion of glucocorticoids suppresses the activity of the immune system. The main action of thyroid hormones is manifested at the genomic level by stimulating the synthesis of many structural proteins of the body and suppressing the expression of neuronal NOS. The sympathetic link of the autonomic nervous system leads to a decrease in the release of pro-inflammatory cytokines, while the synthesis of anti-inflammatory cytokines does not change. In turn, glucocorticoids have a powerful anti-inflammatory effect by reducing the transcription of cytokines by suppressing the nuclear factor "kappa-bi" - a universal transcription factor that controls the expression of genes for the immune response, apoptosis and the cell cycle. At the same time, in critical conditions, a high level of cortisol is observed against the background of a suppressed level of ACTH. This fact is explained by glucocorticoid resistance.

The relationship between the immune system and the central nervous system when exposed to stressors leads to stereotyped responses that include autonomic, endocrine and behavioral components. But despite the extremely important role of neuroendocrine factors in the implementation of critical conditions, their significance, as well as indications and measures of influence on them, have not yet been studied in detail. Further study and the concept of endocrinopathies of critical conditions in the future will be the basis for assessing the endocrine status in order to resolve the issue of the need for substitution therapy.

Keywords: critical condition, endocrinopathy, reactivity thyroid hormones, TSH, cortisole, ACTH.

Introduction. A critical condition is a complex of pathophysiological changes in the body that require replacement of the functions of vital organs and systems to prevent imminent death. Severe physical stressors that cause a critical condition include multiple trauma, cerebral strokes, myocardial infarction, acute respiratory failure, sepsis, and various types of shock [15].

The set of complex adaptive reactions of the human body, aimed at eliminating or maximum limiting the action of various factors of the external or internal environment of the body, is presented in the form of a homeostatic algorithm, which can be considered as a step-by-step development of physiological and pathological reactivity [2]. Physiological reactivity of the organism determines its subtle differentiated response to the action of environmental factors, that is, it determines the quantitative and qualitative features of the response [2]. In this case, pathological reactivity is understood as a special form of reactivity, characterized by a relatively stable, perverted form of the body's response to the corresponding stimulus. This is reflected in new responses that do not take place under conditions of physiological reactivity, in their unusual intensity and duration [5]. Pathological reactivity can be a rescue operation or a destructive mechanism, or it can be both for the body.

In critical conditions, the most important role in the formation of the development of the physiological, and subsequently pathological reactivity of the organism, is played by the neuroendocrine and neuroimmune systems.

The concept of the neuroendocrine system includes multiple connections between the endocrine and central nervous systems (CNS), their relationship in the control of homeostasis, as well as in the formation of responses to environmental stressors [5].

At the same time, stimulation of the immune system by means of foreign pathogens leads to a complex neuroimmunoendocrine interaction in order to avoid development of a critical state. It is formed through the integration of the inflow of information from the vagus nerve, peripheral cytokine interactions with receptors in the region of organs surrounding the cerebral ventricles, cerebral vessels, and local formation of cytokines within the central nervous system. This leads to a complex neuroimmunoendocrine response during the development of a critical state [12].

The leading systems of the brain are involved in the control of homeostasis. *The hypothalamus* is the key integrative center for homeostatic regulation of neuroimmunoendocrine response. The hypothalamus is able to analyze information received from the cortex, hippocampus, thalamus, basal ganglia, reticular formation, nuclei of the medulla oblongata and spinal cord, assess the composition of cerebrospinal fluid, blood and form coordinated responses by changing the efferent innervation of the key regulatory points, which include the adenohypophysis and the neurohypophysis, brain, premotor and motor neurons of the brain stem and spinal cord, as well as autonomous preganglionic neurons [12].

The hypothalamus is a small area of the brain that is part of a neural continuum that extends from the midbrain to the basal regions of the telencephalon and is closely related to the phylogenetically ancient olfactory system [11].

The interaction of the hypothalamus with a huge number of different parts of the nervous system through afferent and efferent connections is necessary in order to coordinate all autonomic processes in the body [3, 19]. In turn, the autonomic nervous system (ANS), acting in conjunction with the endocrine system and

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various nuclei of the brain stem, regulate vital functions necessary to maintain the constancy of the internal environment of the body within narrow boundaries [3]. *The thymus, the central organ of lymphocytopoiesis and immunogenesis,* is also under the influence of the ANS, with the exception of the spleen, adrenal glands, smooth muscles of the vessels of the skin, sweat glands. They are influenced only by the sympathetic nervous system, which determines their role in the immediate stress response [3].

Limbic system. The main biological purpose of the limbic system is the formation of behavior that increases the chances of survival of an individual [3].

One of the main structures of the limbic system are the structures of the brain - the hippocampus and the amygdala. The amygdala provides important behavioral functions such as anxiety and fear. The hippocampus plays an important role in the formation of learning and memory and allows you to compare present stress with past experience, providing the most adequate response to stress. The influence of the hippocampus and amigdala on the hypothalamus and ANS is carried out through the fornix, which is the main efferent bundle of the hippocampus. The presence of a high density of glucocorticoid receptors in the hippocampus enables it to suppress the synthesis of corticotropin-releasing hormone. At the same time, one of the biological purposes of the amigdala is to activate the hypothalamic-pituitary system [5].

Catecholaminergic neurons. One of the important systems of the brain stem involved in the regulation of mind control includes catecholaminergic neurons: dopaminergic, noradrenergic, and adrenergic systems [9, 17].

Neurons containing norepinephrine are concentrated in the brain stem. Their main location is the blue spot, which also includes the nucleus of the solitary tract, the dorsal motor nucleus of the vagus nerve. Axons of blue spot cells are directed towards the cerebral cortex, hippocampus, amigdala, thalamus, hypothalamus [9].

Some of the neurons of the dopaminergic system are localized in the hypothalamic nuclei, the axons of which end in the median eminence [37]. Axons of the other part of neurons are located in the periventricular space in the region of the third and fourth ventricles and are projected onto the brain stem and diencephalon [9, 21].

The efferent pathways of adrenergic neurons are located in the medulla oblongata and go to the dorsal nucleus of the vagus nerve, the nucleus of the solitary pathway, the blue pathway, the periventricular gray matter of the pons and midbrain, the hypothalamus and paraventricular nuclei [29].

Thus, the entire homeostatic system depends on the close interaction of the limbic system, which recognizes and analyzes the danger, with the hypothalamic, noradrenergic systems, which directly modulate metabolic, immune and hemodynamic responses.

"Windows" of the blood-brain barrier. Organs surrounding the ventricles of the brain serve as an important link between peripheral metabolic signals and groups of brain cells that regulate coordinated endocrine, autonomic and behavioral responses. These are specialized structures located along the midline of the brain along the third and fourth ventricles [12, 27, 35]. They include the vascular organ of the terminal plate, the subfornical organ, the median eminence, the neurohypophysis, the subcommissural organ, and the most posterior field. These brain structures are devoid of the blood-brain barrier and are "windows for the blood circulation system", allowing molecules such as proteins, peptide hormones, cytokines, lipopolysaccharides to penetrate relatively freely into the brain tissue. Thus, neurons and glial cells (microglia and astrocytes) located in the organ surrounding the brain ventricles have access to macromolecules. Some of the organs surrounding the cerebral ventricles have neuronal contacts with groups of hypothalamic nuclei that regulate homeostasis [12].

The relationship between immunoreactivity and organs surrounding the ventricles of the brain is performed due to the expression of components of the innate and adaptive immune system on its surface, such as toll-like receptors, CD14 and cytokine receptors, including receptors for interleukin (IL) 1β, IL6 and tumor necrosis factor (TNF) α [22, 25, 32].

The hypothalamic-pituitary system is a humoral component of the complex nervous and endocrine system that reacts to the effects of internal and external stressors. The activation of the central sympathetic tract begins in the amigdala, which are zones of anxiety and stress, as well as in the numerous nuclei of the hypothalamus and reticular formation. This path, passing the midbrain, the bottom of the IV ventricle descends into the lateral horns of the spinal cord - into the first neurons of the sympathetic nervous system [3]. Increased sympathetic activity leads to a state of physical tension and readiness for stress. The influence of physical stressors begins with the activation of the adrenal medulla, secreting norepinephrine and adrenaline, which have a sympathetic effect on the peripheral vascular bed [3].

The secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland is under the control of corticotropin-releasing hormone and, to a lesser extent, of antidiuretic hormone. ACTH stimulates the secretion of cortisol and other adrenal steroids, including aldosterone. Cortisol has several important physiological effects on metabolism, cardiovascular function, and the immune system [16]. The metabolic effects of cortisol include increase of glucose concentration in blood by activating the key elements of gluconeogenesis in the liver and inhibiting glucose uptake by peripheral tissues. In vascular smooth muscle, cortisol increases sensitivity to vasopressor agents such as catecholamines and angiotensin II. These effects are partially mediated by increased transcription and expression of receptors for these hormones [12].

Cytokines and afferent pathways of the vagus nerve activate the hypothalamic-pituitary-adrenal system, as a result of which the increased secretion of glucocorticoids suppresses the activity of the immune system.

Hypothalamic-pituitary-thyroid system. The biological effect of thyroid hormones (TG) depends on the coordinated function and interaction of all components of *the hypothalamus-pituitary-thyroid gland-target tissue system* [1].

Thyroliberin secreted by neurons of the hypothalamus through the portal system of the pituitary gland, promotes the synthesis and release of thyroid-stimulating hormone (TSH) into the bloodstream. The secretion of both TSH and thyroliberin is regulated by a negative feedback mechanism from thyroxine (T4) and triiodothyronine (T3). TSH secretion is also corrected by other hormones, including glucocorticoids, growth hormones, and is suppressed by cytokines in the pituitary gland and hypothalamus [3].

The effects of thyroid hormones on the target tissue are a consequence of the activation of non-genomic regions - membranes, cytoplasm and mitochondria, but the main action of TG is manifested at the genomic level. TGs control the formation of heat, the rate of oxygen absorption, participate in maintaining the normal function of the respiratory center, have inotropic and chronotropic effects on the heart, increase the formation of erythropoietin, stimulate the motility of the gastrointestinal tract, and stimulate

the synthesis of many structural proteins in the body [1]. Thyroid hormones suppress the expression and inhibition of mitochondrial translocation of neuronal NOS (nNOS) [8].

The body's reactivity to physical stressors. The study of the mechanisms underlying the effect of physical stressors on the neuroimmunoendocrine response has led to the discovery of a cholinergic anti-inflammatory pathway involving the vagus nerve [44].

Chemoreceptors of the terminal part of the vagus nerve are sensitive to changes in pressure in internal organs and local changes in the chemical composition of the environment, namely, fluctuations in the concentration of IL-1, prostaglandins, TNF-α. In response to an increased level of inflammatory mediators in the organs innervated by the vagus nerve, the so-called "inflammatory reflex" is triggered [5]. This reflex is based on the transmission of information to the central nervous system, namely to the nucleus of the solitary pathway and then to the dorsal motor nucleus. All these nuclei receive information about the state of the immune system also through the chemoreceptor trigger zone of the most posterior field of the fourth ventricle [10, 42].

The efferent activity of the vagus nerve is manifested by the release of acetylcholine in close proximity to macrophages in the reticuloendothelial system, which leads to inhibition of the release of cytokines [39]. In turn, the sympathetic link of the autonomic nervous system innervates the spleen and activates T-lymphocytes, which leads to a decrease in the release of pro-inflammatory cytokines TNF-α and IL-1 by macrophages, while the synthesis of anti-inflammatory cytokines such as IL-10 does not change. Since the vagus nerve innervates the thymus and other lymphoid organs, in case of systemic inflammation, ChAT + T-lymphocytes and macrophages migrate from the thymus to the spleen, where they interact with sympathetic nerve endings, stimulating the release of norepinephrine [10]. Norepinephrine binds to β2-adrenergic receptors (β2AR) of CD4 + T-cells (T-helpers). CD4 + triggers the release of acetylcholine, which inhibits the secretion of inflammatory cytokines by macrophages through α7nAChR signaling [49].

Activation of the hypothalamic-pituitary-adrenal system by the cholinergic anti-inflammatory pathway. The afferent fibers of the vagus nerve terminate in the dorsal motor nucleus. Further, through the giant cell reticular nuclei, information about the imbalance between pro- and anti-inflammatory cytokines spreads to the blue spot of the pons, suture nuclei, amygdala, paraventricular nuclei of the hypothalamus, hippocampus and prefrontal cortex. The consequence of the activation of the hypothalamic-pituitary-adrenal axis is an increase in the concentration of corticosteroids in the blood plasma [10, 33]. In turn, glucocorticoids have a powerful anti-inflammatory effect by reducing the transcription of multiple cytokines such as tumor necrosis factor (TNF), IL-1 and IL-6. This effect is achieved by suppressing the transcriptional activity of the nuclear factor "kappa-bi". The nuclear factor "kappa-bi" is a universal transcription factor that controls the expression of genes for the immune response, apoptosis, and the cell cycle [14].

Glucocorticoids also cause a decrease in the number and change in the function of various immune cells such as T and B lymphocytes, monocytes, neutrophils and eosinophils at sites of inflammation. Another effect is to enhance the inhibition of macrophage migration, which makes a significant contribution to the regulation of the immune response to physical stressors [5]. Glucocorticoids also reduce the activity of inducible nitric oxide synthase, which has neurocytotoxicity [7, 30].

At the same time, corticotropin-releasing hormone inhibits endotoxin-stimulated production of IL-1 and IL-6 by monocytes, and ACTH suppresses the production of interferon beta-1b by human lymphocytes [46]. The fact that markers of inflammation can activate the hypothalamic-pituitary-adrenal system suggests a negative feedback loop to regulate the intensity of inflammation. But at the same time, this feedback-type reaction can have pathophysiological consequences, since chronic activation of the hypothalamic-pituitary-adrenal system by proinflammatory cytokines can lead to immunosuppression. In this case, this is a clear manifestation of the impact of pathological reactivity on the body with negative consequences [12, 36, 43].

At the same time, in critical conditions, a high level of cortisol is observed against the background of a suppressed level of ACTH. This fact is explained by the stimulating effect of cytokines on the adrenal glands. Hyperproduction of cortisol by the adrenal glands, in turn, suppresses by negative feedback the synthesis and secretion of ACTH. However, currently there is no direct evidence of the reasons for detecting high cortisol levels against the background of a decrease in ACTH levels. In addition, in some cases, there is glucocorticoid resistance, which is defined as a decrease or lack of sensitivity to the hormone, the absence or reduced effect of the hormone, despite its normal or increased level in blood [1, 28].

Activation of the hypothalamic-pituitary-thyroid system under the influence of physical stressors. Physical stressors are a determinant of TSH secretion, regardless of thyroid hormone levels [38]. Thus in the syndrome of euthyroid pathology, the low content of T3 and T4 does not cause a compensatory increase of TSH secretion. Inhibition of TSH secretion in the pituitary gland is caused by the influence of peripheral and local cytokines on the hypothalamus and, as a consequence, a decrease in the activity of the thyroid gland [24, 47].

Under stress conditions, the inhibitory effect of glucocorticoids on the secretory activity of TSH in the pituitary gland is also manifested. This influence is carried out through the expression of glucocorticoid receptors on the surface of pituitary thyrotropin-secreting neurons [20, 24].

Factors contributing to the development of pathological reactivity. The relationship between the immune system and the central nervous system when exposed to physical stressors, with the aim of returning homeostasis to its previous state, leads to stereotypical responses that include autonomic, endocrine and behavioral components. Long-term effects of cytokines on the central nervous system, activation of inducible nitric oxide synthase, hypoxia of brain tissues make a significant contribution to the development of pathological reactivity of the body [13].

Cytokines and CNS. The size of various cytokines at the periphery prevents them from entering the brain by passive diffusion. Three main mechanisms of the penetration of cytokines into the brain have been described. The first path is through areas devoid of the BBB (the most posterior field, pineal gland, neurohypophysis, vascular organ of the terminal plate, subforonic organ, subcommissural organ).

In the second pathway, cytokines pass through the BBB with the help of specific carriers, in the region of the vessels located close to the nuclei of the hypothalamus and the blue spot. Lipopolysaccharides can also enter the third ventricle from the cerebrospinal fluid, penetrating through the ependyma and acting on the projection of the small cell nuclei of the hypothalamus.

The third route of entry of cytokines is through receptor-mediated endocytosis. Further, cytokines penetrate into deeper areas of the brain, mainly into the nuclei of the hypothalamus, hippocampus,

amigdala, and autonomic nuclei of the brainstem and appear among the activators of the stress response [13].

Cytokines can also transmit signals to the central nervous system by stimulating the vagus nerve and activating areas of the brainstem [48]. Circulating pro-inflammatory cytokines such as IL-1, IL-6, TNF are the main activators of microglial cells and astrocytes [26]. Cytokines damage CNS neurons by activating microglial cells and astrocytes [45]. Directly activated by peripheral cytokines, microglial cells and astrocytes synthesize their own pro-inflammatory cytokines, thereby causing a vicious circle. It should be noted that the interaction between microglia and astrocytes is of paramount importance in the regulation of the inflammatory process in the central nervous system and communication with neurons [31].

Inducible nitric oxide synthase. Expression of IL-1 in the brain stimulates the synthesis of nitric oxide (NO) via an inducible isoform of NO synthase (iNOS) [7]. Nitric oxide blocks the mitochondrial respiratory chain in neurons, which can cause their premature death. The neurotoxic effect of NO on microglial cells suppresses the activity of the neuroendocrine response. Nitric oxide also causes apoptosis of neurons in the hypothalamic and autonomic nuclei, which suppresses the adequate stress response in critical conditions in the form of a decrease in corticotropin-releasing hormone, adrenocorticotropic hormone, vasopressin.

In addition, at low concentrations, NO inhibits the release of catecholamines from the adrenal glands and sympathetic nerve endings, leading to a limitation of the stress response [41].

Hypoxia. Damage to the nuclei of the central nervous system during stress is of a multifactorial nature and is not limited only to the influence of cytokines and nitric oxide. An essential role in the pathogenesis of the development of pathological reactivity is played by hypoxic-ischemic brain damage, leading to a violation of the synthesis of neurotransmitters - catecholamines and acetylcholine [3, 4, 27]. Moreover, one of the most vulnerable areas of the brain is the ancient cortex - the limbic system, in which the hippocampus plays a leading role. Consequently, damage to the pyramidal cells of the hippocampus leads to a violation of the formation of the stress-response strategy [6, 23].

Conclusion. At all stages of managing the constancy of the internal environment, there is a coordinated productive interaction of neurons of the limbic, hypothalamic and noradrenergic systems. In particular, the limbic system is capable of recognizing danger, analyzing, comparing with past experience, and choosing ways to overcome a critical state. At the same time, the hypothalamic and noradrenergic systems directly modulate metabolic, immune and hemodynamic reactions.

Physiological, and – when exposed to physical stressors – pathological reactivity of the body, is directed to the initial point of balance. Pathological reactivity when exposed to physical stressors can have both reversible and destructive effects on the body. The body's response to stress is formed on the basis of incoming information from the vagus nerve, peripheral cytokines that interact with the receptors of organs surrounding the cerebral ventricles, cerebral vessels, and local formation of cytokines in the central nervous system. The blood-brain barrier plays an important role in controlling the inflammatory process in neurons and glial cells. There is ample evidence that sepsis destroys the BBB, while the entry of pro-inflammatory mediators and other neurotoxic molecules (such as urea) into the brain becomes easier. In this case, the destruction of the BBB occurs under the influence of prolonged exposure to IL-1, TNF and NO [34, 40]. Cytokines, which are one of the main triggers of the stress response, stimulate the production of inducible NO synthase and lead to damage of the nuclei of the limbic, hypothalamic, and noradrenergic systems, thereby disrupting the neuroendocrine response. Further damage to DNA neurons in the hippocampus, hypothalamus, and the nuclei of the autonomic nervous system leads to depletion of the protective stress response, which leads to a critical state of the body.

Despite the extremely important role of neuroendocrine factors in the realization of critical conditions, their significance, as well as indications and measures of influence on them, have not yet been studied in detail.

Further study of the effect of physical stressors on the neuroendocrine system can be of practical use for creating algorithms for the diagnosis and treatment of endocrinopathies in critical conditions. The concept of endocrinopathies of critical conditions in the future can become the basis for assessing the endocrine status in order to resolve the issue of the need for substitution therapy.

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THYROID GLAND FUNCTION AND MAIL REPRODUCTIVE HEALTH

Over the past few decades, thyroid hormones have been well studied for their significance for male reproductive health. Hyperthyroidism and hypothyroidism affect testicular function and neuroendocrine regulation of reproductive functions, which can lead to decreased testosterone levels and poor sperm quality and compromise male fertility. Understanding these processes is more relevant than ever given the continuous decline in sperm count and quality that has been observed in humans over the past decades. The literature review presents a brief concept of the regulation of male reproductive function by thyroid hormones and a possible mechanism by which thyroid dysfunction affects testicular function.

Keywords: thyroid hormones, hypothyroidism, hyperthyroidism, steroidogenesis, spermatogenesis, infertility.

Thyroid hormones play an important role in the growth, development, and thermogenesis of mammals. The role of thyroid hormones in the development of the central nervous system, in the regulation of metabolism and physiology of the heart has been well studied [1, 12, 20]. However, the presence of receptors for thyroid hormones in most cell types and the effects observed by the researchers indicate a broad effect of these hormones on tissue. Several clinical and experimental studies have shown a close relationship between altered thyroid status and reproductive failure [24, 45].

Many works have been devoted to the study of the effect of thyroid hormones on the development and function of the testes [45], as well as the relationship between the altered status of the thyroid gland and infertility [44]. Normal thyroid function is essential for maintaining the reproductive system. Thyroid hormones, primarily the biologically more active triiodothyronine (T_3), regulate the maturation and growth of testes, controlling the proliferation and differentiation of Sertoli and Leydig cells during testes development, and stimulate steroidogenesis in rats and other mammalian species [28, 41].

Both hypothyroidism and hyperthyroidism are associated with changes in the concentration of sex-hormone-binding globulin (SHBG) and sex hormones (testosterone and estradiol) in both sexes, impaired ovulatory function in women and erectile dysfunction in men [13]. Hyperthyroidism causes disturbances in sperm motility, while hypothyroidism is associated with abnormalities in sperm morphology [24]. At the same time, thyroid hormone replacement therapy in patients with hypothyroidism returns the levels of SHBG and testosterone to normal concentrations [21] and eliminates sexual dysfunction [6].

Since normal thyroid function is important for maintaining male reproductive health, the purpose of this review was to discuss relevant information on the effects of hyper- and hypothyroidism on male fertility.

The mechanism of action of thyroid hormones. For a long time it was believed that the action of iodothyronines is regulated mainly by modulating the concentrations of their free fractions in the blood, the activity of nuclear receptors and intracellular destruction by a deiodinating enzyme. However, in the past decade, there has been some departure from this classic model. It is known that iodothyronines act both centrally, regulating sympathetic output, and peripherally, regulating metabolism in target tissues, while their central action can simultaneously alter the effects on peripheral tissues. At the present stage, scientists recognize that in addition to T3, thyroid hormone derivatives such as reverse T_3 (rT3) and diiodothyronine (T_2) have physiological activity, which can act both through traditional genomic transcription regulation pathways, acting on nuclear receptors, and through a more direct, a fast-acting non-genomic mechanism [25].

As derivatives of amino acid tyrosine, thyroid hormones require plasma membrane transporters to reach nuclear receptors. Thus, T_3 secreted by the thyroid gland into the bloodstream enters the target cell using specific cell membrane transporters, among which the monocarboxylate transporter 8 (MCT8), also present in testicular tissues, shows the highest affinity for T_3 [15]. MCT8 mutations in humans are associated with severe psychomotor retardation and elevated T_3 levels.

It was found that thyroid hormone nuclear receptors are expressed in embryonic and mature Sertoli cells [31]. Binding of triiodothyronine to its receptors in testicular cells activates gene transcription and protein synthesis, as well as proliferation and differentiation of Sertoli cells [16]. In addition to genomic effects, thyroid hormones also demonstrate non-genomic, which include the ability of iodothyronines to bind to non-nuclear receptors, affecting cell structure, metabolic rate and cell proliferation. It has been demonstrated that binding to non-nuclear receptors enhances the synthesis of cyclic adenosine monophosphate, calcium release and improved sperm kinetics [11].

In addition to nuclear receptors and transporters, the regulation of the thyroid hormone action in cells is provided by various patterns of iodothyronine metabolism. Iodothyronine deiodinases are a subfamily of selenoenzymes that selectively remove iodide from thyroxine (T_4) and its derivatives, thus activating or inactivating these hormones [29]. It is known that T_3 can be formed in peripheral tissues from T_4, which is produced by the thyroid gland in greater quantities than T_3 and is considered a prohormone, since its affinity for thyroid hormone receptors is 10 times less than that of T_3. The conversion of T_4 to T_3 is carried out by type 1 and type 2 deiodinases, whose activity determines the local availability of T_3, and also makes a significant contribution to the serum levels of thyroid hormones [17]. Type 2 deiodinase is present in the spermatids of the testes of neonatal and adult rats [43]. Type 3 deiodinase converts both T_3 and T_4 into metabolites with very low affinity for thyroid hormone receptors. Given this enzymatic activity, type 3 deiodinase is intended to reduce the availability of T_3 in the tissues in which it is expressed and, therefore, to reduce the local action of the thyroid hormone [35]. Type 3 deiodinase plays an important role in developing testis by maintaining the thyroid hormone availability within levels that are developmentally appropriate [40].

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Thus, the action of T_3 depends not only on the circulating levels of the hormone, but also on a set of a number of molecular determinants, including transporters, enzymes and receptors present in a particular cell or tissue. This set of factors is critical to the local bioavailability of thyroid hormones and can markedly increase or decrease the local action of thyroid hormones.

Influence of hyperthyroidism on sex hormones and sperm parameters. Thyroid dysfunction is one of the most common endocrine disorders observed in clinical practice. The prevalence of thyroid dysfunction varies by age, gender, ethnicity and area of residence due to differences in dietary iodine intake. Thyroid dysfunction has serious health consequences, including cardiovascular arrhythmias, metabolic and mental health problems [32]. The prevalence of hyperthyroidism in the general population is 1.3%, the *ratio* of *males to females* is 1:7. Infertile men with hyperthyroidism usually have decreased libido, erectile dysfunction, premature ejaculation, or symptoms of increased estrogen such as gynecomastia [10].

The effect of changes in thyroid hormone on the reproductive system has been extensively studied in animals and has generally shown that deviations from normal thyroid function lead to decreased sexual activity and fertility. The induction of hyperthyroidism in adult rats by L-thyroxine caused a significant decrease in serum levels of luteinizing hormone, follicle stimulating hormone and testosterone, along with a significant increase in serum estradiol levels compared to euthyroid rats [5]. In addition, sperm count and motility have decreased. After induction of hyperthyroidism there were also noted the increased concentrations of reduced glutathione, malondialdehyde and nitric oxide, along with a significant decrease in the activity of superoxide dismutase and catalase. The authors have suggested that hyperthyroidism may affect fertility by directly affecting the testes through oxidative stress mechanisms. It was found that hyperthyroidism is associated with increased mitochondrial activity and simultaneous release of electrons from the mitochondrial electron transport chain due to increased production of thyroxine [2].

In another study, conducted on rats after administration of L-thyroxine, it was demonstrated not only an increase in the levels of T_3 and T_4, but also in testosterone level. After that the simultaneous administration of antioxidants such as folic and ascorbic acids showed that the levels of thyroid hormones, testosterone, glutathione, as well as markers of oxidative stress approached values very close to normal ranges [7].

In human studies, hyperthyroidism has been associated with an increase in SHBG levels, which led to an increase in circulating levels of total testosterone and a decrease in the rate of its metabolic clearance [46]. These data are probably explained by the ability of thyroxine to increase the level of mRNA of SHBG by stimulating the transcription of the nuclear factor of hepatocytes 4α (HNF4α) [36]. In men with hyperthyroidism, the concentrations of total and free estradiol were increased; the levels of free testosterone were even lower than normal and below the value of the free testosterone / free estradiol ratio compared with euthyroid subjects [33, 38]. An increase in free estradiol in men with hyperthyroidism may contribute to a decrease in libido and a higher incidence of gynecomastia [27].

Clinical studies of the routine semen analysis have shown that an increase in the level of thyroid hormones is accompanied by astheno-, oligo-, teratozoospermia and a decrease in the volume of semen [17, 22]. Abalovich M. et al. investigating the effect of hyperthyroidism on spermatogenesis in 21 patients revealed the following *incidence* of abnormal semen parameters: asthenospermia 85.7%, hypospermia 61.9%, oligospermia 42.9%, necrospermia 42.9% and teratospermia 19.0% [18].

Krassas G.E. et al. studied semen parameters in a prospective study involving 23 men with hyperthyroidism, comparing data with 15 euthyroid men used as controls. The results showed a slight decrease in sperm density, changes in sperm morphology, and a significant decrease in sperm motility compared to controls. They have demonstrated an improvement in sperm count and sperm motility after treatment with methimazole alone or in combination with radioactive iodine [3].

Influence of hypothyroidism on sex hormones and sperm parameters. Hypothyroidism is a pathological condition of a low level of circulating T_4 and T_3 and an elevated thyroid-stimulating hormone level. Hypothyroidism in men is less common than in women, and has a less pronounced effect on reproductive function [14]. Hypothyroidism affects up to 5% of the general population; more than 99% of patients suffer from primary hypothyroidism. Globally, environmental iodine deficiency is the most common cause of all thyroid diseases, including hypothyroidism [8].

Primary hypothyroidism leads to a decrease in the concentration of SHBG, total and free testosterone [19], whose concentrations may increase after therapy with L-thyroxine [4]. Primary hypothyroidism is also associated with hyperprolactinemia and hypogonadotropic hypogonadism, which is reversible with thyroid hormone replacement therapy [27].

Among men with hypothyroidism, as in the case of hyperthyroidism, erectile dysfunction is widespread, and thyroid hormone replacement therapy restored normal erectile function [37]. Therefore, the authors of clinical trials *recommend screening for thyroid dysfunction* in *men* who present with *erectile dysfunction*.

Thyroid hormone deficiency during *early* stages of *testicular development affects* testicular maturation and reproduction later in life [42]. Thus, severe and prolonged hypothyroidism that occurs at an early age leads to a moderate failure of the secretion of gonadotropins by the pituitary gland, which, in turn, can affect the morphology and function of the testicles [26].

Sperm abnormalities associated with hypothyroidism are partially similar to those reported in hyperthyroidism [19]. In rats whose thyroid gland was blocked by antithyroid drugs, there was a significant decrease in the *epididymal sperm* count, which was accompanied by a significant increase in the percentage of damaged spermatozoa [9]. There was also a significant decrease in the weight of the seminal vesicles and the ventral prostate lobes the compared with euthyroid controls. Hypothyroidism also decreased total and daily sperm production and increased the transit time of sperm through the epididymis, while progressive sperm motility decreased [30]. This decrease in sperm viability may be the result of an imbalance between increased oxidative stress caused by lipid peroxidation and decreased antioxidant systems such as catalase and superoxide dismutase. According to a number of authors, thyroid hormones regulate the antioxidant defense of the testes, and any change in their level can affect the physiology of the testes due to oxidative stress. Thus, a decrease in the level of thyroid hormones can disrupt testicular function, especially spermatogenesis, by reducing the level of reduced glutathione in the testes, which plays an important role in the proliferation and differentiation of spermatogenic cells, protecting them from the harmful effects of reactive oxygen species [9].

In humans, teratozoospermia is the most common semen disorder in hypothyroid patients [23]. A decrease in the

proportion of progressive sperm cells has also been reported [34, 39]. Similar to hyperthyroidism, *semen* alterations during *hypothyroidism are reversible and mostly disappear* upon *achieving euthyroidism*.

Conclusion. The *recent* studies have significantly advanced our understanding of the mechanisms that regulate the action of thyroid hormones at the tissue and cellular levels. Research increasingly shows that the action of thyroid hormones depends not only on serum hormone concentrations, but also on the local set of transporters, deiodinases and receptors. The presence of thyroid hormone receptors in various types of testicular cells has been demonstrated in both animals and humans. Accordingly, hyperthyroidism and hypothyroidism have a marked effect on testicular function and, to a greater extent, on fertility. Hyperthyroidism and hypothyroidism are associated with changes that affect endocrine and reproductive function. Specifically, patients with hyperthyroidism have higher serum SHBG levels and lower free testosterone concentrations, higher levels of astheno-, oligo-, and teratozoospermia, and a higher prevalence of sexual dysfunctions such as premature ejaculation. In patients with hypothyroidism there are often observed teratozoospermia and a decrease in the proportion of sperm with progressive movement; hormonal changes are associated with a decrease in the levels of SHBG, total and free testosterone. Thyroid hormones also help maintain the redox status of testicular tissue by regulating the balance between reactive oxygen species and antioxidant defenses. Most patients with impaired thyroid function experience some sexual dysfunction that can be corrected by normalizing iodothyronine levels.

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GENES-MARKERS OF PEPTIC ULCER DISEASE

The review presents the analysis of the literature on genetic studies devoted to candidate genes for peptic ulcer disease. All the materials of these publications can be combined into two large groups: studies devoted to investigation of peptic ulcer inducer genes and studies devoted to protective genes. The main groups of ulcer inducer genes (*ABO, HLA, PSCA, IL-1B, IL1RN, IL-6, IL-8, IL-10, TNFα, TGF-b1, B1,2,3, CYP2C19, MMP-2, MMP-3, MMP-9, Toll,TLR4TLR9, MIF, MPO*) and protectors (*IL-1, IL-1RN, TNF, LTA, IL-1b, MMP-3*) were identified, but most of the results obtained to date are inconsistent, poorly reproduced in ethnically diverse populations, which makes it relevant to study this problem among different groups living in the Russian Federation.

Keywords: Peptic ulcer in women, peptic ulcer of the stomach and duodenum, genes, genes-markers of peptic ulcer disease, literature review.

Introduction. According to the world statistics, the prevalence of gastroduodenal ulcer is 5-15% of the world population [25]. Moreover, ulcer disease with localization in the duodenum is 4-13 times more common than gastric ulcers. Currently, there is an increase in the number of ulcer disease among women. The ratio of men and women in the incidence of duodenal ulcer is 1,9 : 1 in the USA, 2,2 : 1 in Europe and 3,6 : 1 in China. However, complicated forms ulcer diseases in women are observed 2-4 times less frequently than in men. Conspicuous is the fact that the highest incidence of Ulcer Disease in men is in their 20s with a gradual decrease by the age of 40 [8]. In women, the incidence rate is, on the contrary, higher with increasing age of the pathology [2].

It is commonly known that ulcerative defect of the mucous membrane of the stomach and duodenum occurs due to the predominance of aggression factors over protection factors. Nevertheless, later, during years of research, scientists discovered a bacterium unknown at that time, which was named H. pylori [2]. The microorganism was first isolated in 1982 by B. Marshall and R. Warren. They showed by their own example that this bacterium plays a fundamental role in the formation of gastric mucosa ulcers. Despite the fact that the cause of ulcers was "established" and experimentally proved, however, the question of differences in the frequency of ulcers in this or that category of people was still open. In addition to the infectious theory, inflammatory, gastric, peptic, vascular, spastic, mechanical, neurotrophic and cortico-visceral theories were considered as the ultimate cause of ulceration. However, none of these theories could explain the true nature of the ulcer. The question of Crouvellier (1835), "why does an ulcer arise in one place, while the rest of the mucosa remains intact," is still relevant today.

The possibility of determining disposition towards many multifactorial diseases has become a reality due to the development of molecular genetics. The results of treatment of these diseases can be determined by a specific set of polymorphic gene variants. The study of the genetic basis of these diseases allows not only to predict the course of the disease, but also prevents the occurrence of complications. Some genetic markers, such as blood group O (*ABO* gene, rs505922) [22], asecretory status, hyperpepsinogenemia (I/D)[19] and HLA antigens, polymorphic loci of the *PSCA* gene (prostate stem cell antigen, rs2294008) [19] have been described as associated with ulcer disease, although so far the results have been contradictory.

Due to the increasing incidence of ulcer disease and the frequent development of complications, the study of genes involved in the formation of ulcer disease is an extremely important task, the solu-

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tion of which will allow to formulate more accurate ideas about the pathogenesis of the disease.

The object of this research paper is to summarize the literature data on the results of genetic studies on ulcer disease and their subsequent systematization.

Discussion. Over the past decade, about 50 scientific studies have been conducted on various genes that cause pathology of the gastrointestinal tract, including gastric and duodenal ulcers. The analysis of both foreign and Russian literature on this topic showed that the most part of publications contains information on the study of gene polymorphism mainly from the point of view of oncological predisposition. All the materials of these published articles can be combined into two large groups: studies devoted to ulcer inducer genes and studies devoted to protector genes.

Ulceration inducer genes. Currently, there are several dozens of candidate genes for ulcer disease: *ABO, HLA, PSCA, IL-1B, IL1RN, IL-6, IL-8, IL-10, TNFa, TGF-b1, MMP, Toll, TLR4TLR9, MIF, MPO*.

It is known that the ability of the immune system to adequately respond to the existing pathological factors directly depends on the genetic structure of the microorganism. Cytokines, a group of polypeptide mediators, are of great importance in maintaining the body balance. They include interferons, colony-stimulating factors, interleukins, chemokines, transforming growth factors, a group of tumor necrosis factor and others [21]. With the help of blood cells, endothelium, connective tissue and epithelial cells, cytokines regulate the adequate response of local protective factors of the body to the effects of foreign agents. It is revealed that disturbance of cytokine synthesis, through cell damage, leads to the development of chronic gastroduodenal diseases. Particularly, a high level of cytokines leads to the activation of matrix metalloproteases and collagenases, which leads to increased destruction of carbohydrate-protein components of the connective tissue. Cytokine genes have a high degree of polymorphism. Cytokines possess the ability to activate and suppress themselves, other cytokines and their receptors, participating in the formation of a cytokine network. Genes encoding pro-inflammatory (IL-1, IL-6, IL-8, TNF-a) and anti-inflammatory cytokines (IL-10) directly affect the value of the cytokine response.

Interleukin -1B (IL-1B). As mentioned above, cytokines are actively involved in the body's defense against foreign agents. Such an agent in ulcer disease is mostly H. pylori. In response to H. pylori infection, the body reacts in the form of a sharp release of pro-inflammatory cytokines. Yet, if a macro organism has one of the polymorphic variants of the *IL-1B* gene (homo- or heterozygous for the high-producing allele), cytokine release occurs 2-4 times stronger than in ordinary people. IL-1ß is also one of the most powerful inhibitors of hydrochloric acid secretion - by 100 times stronger than proton pump inhibitors, and 6000 times stronger than H2 receptor antagonists. A less percentage of cytokines in the body potentiate an even greater inhibition of acid production of the gastric mucosa and the expansion of H. pylori colonization with the further development of inflammatory changes. In the longer term low acid production forms atrophy of the gastric mucosa. Some studies have shown that individuals with a combination of *IL-1B*-511*T and *IL-1B*-31*C or *IL-1RN* *2/*2 (2 repeats of 86 BP) which are classified as high - producing alleles are more vulnerable to the development of gastric atrophy, gastroduodenal ulcers and gastric cancer than those with the *IL-1B*-511*C, *IL-1B*-31*T or *IL-1RN**2 alleles [27,30]. But according to the results of a research study of children by Chinese scientists, no association was found between *IL-1* polymorphisms and H. pylori infection or gastric mucosal *IL-1* expression levels. Mostly, people (60.7%) with moderate or severe gastritis (stomach ulcer) had *IL-1B*-511TT/-31CC [27].

A research devoted to the study of polymorphic variants of *IL1ß* genes (interleukin 1-beta) (3953C>T, rs1143634), >*IL1RN*(receptor antagonist of interleukin 1) (VNTR, rs71941886), *IL8*(-251T>A, rs4073), >*IL10*(–627C>A, rs1800872) and >*TNFa* (–308G>A, rs1800629) in patients with gastroduodenal ulcer was conducted in the Republic of Bashkortostan. An increased risk of developing Ulcer Disease was associated only with the C allele (OR=2.87, p=0.006) and the CC genotype (OR=4.49, p=0.002) of the polymorphic variant rs1143634 (+3953C>T) of the *IL1B* gene among Bashkirs [1].

Interleukin -6 (IL-6). Interleukin-6 is a bidirectional cytokine that is important in host defense as an intermediary between innate and acquired immune systems, stimulating the production of IFN-γ, differentiation and maintenance of cytotoxic T cells, as well as promoting the secretion of immunoglobulin in activated B cells [7]. The levels of IL-6 in the gastric mucosa increase with associated gastritis and decrease after the infection is eliminated [27]. There were identified three polymorphisms of *IL-6* genes, which are located on chromosome 7p21, *IL-6*–174, -572 - [7]. It was revealed that *IL-6*-174 G and *IL-6*-572GG produce higher levels of IL-6 than carriers of the C/C genotype [28]. However, the connection between this polymorphism and Ulcer Disease remains unclear. The study reported that the frequencies of the *IL-6*–572 G/G genotype (P = 0.027) and the *IL-6*–572 G allele were lower in H. pylori-positive patients (P = 0.003) [27]. Moreover, the risk of gastric ulcer was significantly higher in carriers of the G/G genotype (OR= 58.86) and the G allele (OR = 33.10).

Interleukin-8 (IL-8). Interleukin - 8 is a pro-inflammatory cytokine that plays a significant role in the pathogenesis of acquired diseases. High production of interleukin-8 was detected in gastric epithelial cells during infection caused by the cag-PAI-positive strain of H. pylori. It is essential to the initiation, modulation and sustentation of inflammatory reactions of the gastrointestinal tract. High levels of IL-8 can increase the inflammatory response to H. pylori by activating neutrophils and monocytes, which leads to the formation of gastritis [28]. There are three polymorphic variants in the *IL-8* gene associated high produce of this protein: - A/T, - T/G and - C/T . The common single nucleotide polymorphism (SNP) at position -10 is associated with increased IL-8 production. The *T-to-A* mutation can affect the transcription and secretion of IL-8 [18].

Some research shown association between polymorph variants of *IL-8* and peptic ulcer disease. So, it was shown that H. pylori-positive patients with genotype A/A of the *IL-8* gene have an increased risk of developing Ulcer Disease (OR = 2.08) [17]. Similar results were obtained in a study of colleagues from Europe and Korea [24]. Among the Japanese population, the *IL-8*–251 A/A genotype is associated with a higher risk of developing Gastric Ulcer (OR 2.07) than the T/T genotype. Severe gastric atrophy is also significantly more common in the groups of patients carrying the A/A or A/T genotypes than in the group of patients carrying the T/T genotype [18].

Interleukin-10 (IL-10). Interleukin - 10 is an anti-inflammatory cytokine that suppresses the synthesis of IL-1B, TNF-α, interferon-γ and other pro-inflammatory cytokines. The effects of IL-10 on other cell types include inhibition of pro-inflammatory cytokine production by activated monocytes/macrophages. A relative deficiency of IL-10 can lead to a Th-1-induced hyper-inflammatory reaction

to H. pylori with progressive damage to the gastric mucosa. H. pylori can lead to an increase in IL-10 and suppression of the immune response, which contributes to the survival of bacteria [27]. Analyzing the *IL-10* gene, L.V. Volevach and L.V. Gabbasova found out that the genotype rs1800872*AA and the allele rs1800872*A of the *IL10* gene (-627C>A; rs1800872), p=0.017, OR=0.091 (CI95% (0.011-0.751) and p=0.025, OR=0.544 (CI95% (0.329-0.902)) are accompanied by a high risk of duodenal ulcers among Tatars [4]. Duodenal ulcer with a burdened hereditary history (rs1800872*AA and rs1800872*A) is characterized by a more severe clinical picture (pain syndrome) (84.72 ± 4.24%), progressive course with frequent annual exacerbations (more than 2-3 times a year in 72.22± 5.28%), high risk of complications (13.89).

TNF-a. Tumor necrosis factor (*TNF*) is a gene that encodes a multifunctional cytokine formed mainly by monocytes and macrophages. Present studies showed that among the five biallelic polymorphisms in the *TNF-A* promoter region, *TNF-A*-238 G/A and -308 G/A polymorphisms are associated with a high risk of ulcer disease [9]. Both-1031C and -863A have been found to be independent risk factors for the development of gastric and duodenal ulcers without intestinal metaplasia among people infected with H. pylori [18].

TGF-beta1. Transforming Growth Factor-beta1 (TGF-beta1) is an important cytokine that plays a role in cell proliferation, differentiation, tissue injury repair and ulcer healing. A research study by Russian scientists [6] in 2006 revealed that the combination of 10L/L25R/R-509C/C is more common in the group of patients with gastric ulcer, and the combination of 10P/P25R/P-509C/T is more common in patients with duodenal pathology.

Matrix metalloproteinases. Matrix metalloproteinases are a family of extracellular zinc-dependent endopeptidases capable of cleaving extracellular matrix components. They are involved in tissue remodeling, angiogenesis, cell proliferation, migration and differentiation, apoptosis, and inhibition of tumor growth. It is known that the presence of H. pylori infection increases the activity of MMP-2 and MMP-9, which are involved in the processes of tissue destruction.

The study of the polymorphic variant -468G/A of the *MPO* (myeloperoxidase) gene was carried out among the population of the island of Taiwan. The study included 115 patients with Duodenal Ulcer and 182 healthy people. The association of the allele A of the *MPO* gene with the development of the disease (OR=2.3, p=0.008) was established.

Toll-like receptor genes. The more active studied *Toll*-like receptor include polymorphisms *TLR4*+896A/G (rs4986790) and +1196C/T (rs4986791).

So, scientists from Iran also investigated single nucleotide gene substitutions of *Toll*-like receptors of type 4 *TLR4*+896A/G (rs4986790) (Asp299Gly), +1196C/T (rs4986791) (thr399ile) and +3725G/C (rs11536889). It was revealed that UD develops in carriers of CT+TT genotypes (rs4986791).

According to other authors, the risk of developing Duodenal Ulcer is associated with polymorphism of another gene of signaling peptides: *TLR9*+2848G>A (rs352140). The rs352140 A allele is associated with an increased risk of developing Duodenal Ulcer (OR=2.13, p=0.04) [11].

Genes of digestive enzymes. The role of hyperpepsinogenemia in the development of ulcer disease has been known for a long time. However, only in the second half of the 20th century, the American gastroenterologist M. Samloff found out that the concentration of pepsin proenzymes in blood serum is associated with the level of acid production of the stomach. [24].

Genes - protectors of the UD development. By reviewing the literature, we found that there are fewer works devoted to the study of "protective" genes. This circumstance is likely to be related to the difficulties in the selecting material for the study. There can be distinguished the following protectors of ulcer disease: *IL-1, IL-1RN, MMP-3.*

The scientist study [14] notice IL-1B and IL-1RN as an independent protective factor in duodenal ulcer. The explanation of this discovery may suggest that the carrier of these polymorphisms was associated with high production of IL-1b, which, due to its inhibitory effect of acid on the stomach, can reduce the risk of developing duodenal ulcer. However, it may increase the risk of developing gastric cancer. A study by E. Shaymardanova (2014) showed that the T allele (rs1143634) of *IL-1B* gene plays a protective role in the development of Ulcer Disease (OR=0.35, p=0.006) [6].

The genes of matrix metalloproteinases, in particular stromelysin-1 (*MMP-3*), are also considered as protective genes. Elevated levels of MMP-3 are recorded in patients with Gastric Ulcer. This endopeptidase is thought to play a protective role [2,16]. Another study suggests that melatonin suppresses the synthesis of MMP, leading to the healing of ulcers [16].

Conclusion. Summarizing all the information, we can say that the genetic basis of ulcer disease has not been studied enough. The main groups of ulcer inducer genes (*ABO, HLA, PSCA, IL-1B, IL1RN, IL-6, IL-8, IL-10, TNFα, TGF-b1, MMP, Toll, TLR4TLR9, MPO*) and protectors (*IL-1, IL-1RN, MMP-3*) were identified, but most of the results obtained to date are inconsistent, poorly reproduced in ethnically diverse populations, which makes it relevant to study this problem among different groups living in the Russian Federation.

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CORONAVIRUS INFECTION IN CHILDREN

Resume. A review of the literature of foreign and Russian studies on the course of a new coronavirus infection in children (SARS-CoV-2) is presented. Studies conducted over the past two years have shown a difference in the course of COVID-19 in children. The clinical picture of coronavirus infection in children is very diverse, from symptoms of respiratory infection to multisystem inflammatory syndrome. It was found that the frequency of severe coronavirus infection in children is lower. To fully understand the features of disease course and treatment of a new coronavirus infection, large-scale epidemiological studies are required.

Keywords: SARS-CoV-2, COVID-19, child population.

Introduction. Coronavirus disease 2019 (COVID-19) is a type of atypical pneumonia that broke out in December 2019, the causative agent of which was isolated and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2,3,5,9]. Due to the rapid spread of COVID-19, the World Health Organization and countries around the world have published relevant guidelines on the principles of prevention. Hundreds of millions of people have been infected in more than 200 countries, and it seems that the trend of increasing the number of infected will continue for a long time [1,2,4,11,12].

Coronaviruses (Coronaviridae) are a large family of RNA-containing viruses that can infect humans and some animals. In humans, coronaviruses cause a number of diseases: from mild forms of acute respiratory infection to severe acute respiratory syndrome (TOPC/SARS) [1,3,13,14]. According to the results of serological and phylogenetic analyses, coronaviruses are divided into alphacoronavirus, betacoronavirus and gammacoronavirus [17].

SARS-CoV-2 belongs to the betacoronovirus genus of viruses, which also includes viruses of severe acute respiratory syndrome and Middle East respiratory syndrome [7].

The maximum release of the virus from the patient occurs in the first 3 days from the onset of the disease. Virus isolation usually lasts up to 12-14 days in mild and moderate cases and more than 2 weeks in severe cases [19].

At the beginning of the spread of coronavirus infection, children were considered immune to COVID-19, but according to a survey published by the Centers for Disease Control (CDC) in April 2020 in the United States and China, children accounted for 2% of the total number of cases [11,16]. And by the end of 2021, children account for 17% of all COVID-19 cases. In addition, children have atypical symptoms of infection and cannot clearly describe their condition, which creates serious problems for the diagnosis and treatment of this population group. Infantile infections and features of clinical manifestations in COVID-19 in children required a more thorough study of clinical, laboratory and visual features of the course of coronavirus infection in children [6,10,15]. According to the results of a study by some authors, children who do not have chronic diseases, such as respiratory diseases or immunosuppression, have a low risk of developing a severe form of COVID-19. The authors attribute this to the anatomical and physiological features of the child's body and the way of life of children. However, some children face severe course of coronavirus infection. According to the Centers for Disease Control and Prevention, they may need hospitalization, treatment in an intensive care unit or a ventilator. In addition, children with other diseases, such as obesity, diabetes and asthma, may be at higher risk of severe COVID-19. Children with congenital heart defects, genetic diseases, diseases of the nervous system and metabolism can also get a severe form of COVID-19 [5,8,11,19,20].

Children under the age of 1 are also at high risk of severe coronavirus infection. This is likely due to the immaturity of the immune system and short airways, which are the cause of respiratory problems with respiratory viral infections [1,3,23,25,33].

While children and adults experience similar symptoms of COVID-19, symptoms in children tend to be milder and similar to seasonal viral disease. Most children recover within one to two weeks [2,4]. Possible symptoms may include: fever, cough that becomes productive, loss of taste and smell, changes in the skin, such as discoloration of skin areas on the hands and feet, sore throat, gastrointestinal symptoms - nausea, vomiting, abdominal pain, diarrhea, muscle pain, weakness, headache pain, nasal congestion [11,24,25].

Previous studies have shown that COVID-19 can be transmitted from person to person by airborne droplets and physical contact. The main susceptible population are people over the age of 50 [6,27,29]. The main symptoms are fever, cough, myalgia, headache and weakness. Laboratory tests usually show lymphopenia and leukocytosis [14,17,26,32].

According to the results of a study by some authors, lymphocytopenia, which is an important feature of adult COVID-19 and is considered one of the indicators for predicting the severity of the disease, was rare in children with COVID-19. Studies conducted in 2020 showed that SARS-CoV2 will cause a number of immune reactions after introduction into the body, which will cause an inflammatory reaction, leading to an increase in the inflammatory process and a decrease in the number of lymphocytes [31,33]. And in recent studies, leukopenia, high levels of C-reactive protein, increased erythrocyte sedimentation rate and high ALT were rarely indicated, which may indicate that the immune response in children with COVID-19 is weak [22,31]. Computed tomography data in 36% of children with COVID-19 did not reveal serious pathological changes in the lungs [28,30].

According to the results of studies conducted in 2021, we can say that the data on clinical symptoms, together with the results of laboratory tests and instrumental studies of children with COVID-19, show that the course of the disease is relatively easy for them. The authors indicate healthier respiratory tracts of children as possible causes of the mild course, because they are not exposed to cigarette smoke and polluted air for a long time, since these fac-

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tors contribute to the severe course of COVID-19 [13,19,20]. Also, many other types of viruses have been found in children in the upper respiratory tract and lungs, which can limit the growth of SARS-CoV2 through direct interaction and competition between viruses [18]. Some researchers consider the low number of mature angiotensin-converting enzymes-2 (ACE2) in lung receptors to be another factor of the mild course in children [14,21]. SARS-CoV2 uses ACE2 receptors on the cell surface to penetrate the epithelial cells of the human respiratory tract, and a limited number of ACE2 receptors increases the resistance of children to COVID-19 [14,28].

As it is known, the immune system of children is immature. Therefore, SARS-CoV2 infection will not cause a large number of inflammatory factors, severe damage to the autoimmunity of the lungs, heart, liver and other organs, and the possibility of a cytokine storm, which is the main cause of death in patients with severe COVID-19, will also decrease [8,30,32,33]. Therefore, the number of lymphocytes in the blood of children with COVID-19 is rarely reduced, and the indicators of inflammation are usually within the normal range or slightly increased.

Studies also indicate that since children are engaged in relatively limited outdoor activities, they tend to become infected in their families, and the virulence of these second or third generation infections may be lower [9].

The combination of all these factors, according to the researchers, leads to a mild course of COVID-19 in children. However, these children are carriers of the virus, and due to the latent mild or asymptomatic course, children can be a key link in the transmission of COVID-19 in the community. Thus, early detection and treatment of children with coronavirus infection is of great importance to prevent the spread of the disease [15].

The largest number of published foreign studies were conducted in the USA and China. In Russian medical publications, the largest number of publications on COVID-19 was in 2020. Thus, the Russian authors noted that there are fewer studies on the course of COVID-19 in children than in adults. It is noteworthy that all the studies conducted on the course of COVID-19 in children confirm the similarity of symptoms and laboratory data. The clinical picture in children was dominated by manifestations of respiratory viral infection of mild or moderate severity. Also, infants with COVID-19 are characterized by an atypical course of the disease.

To further study the course of coronavirus infection in children and to determine the best prevention and treatment strategy, it is necessary to conduct large-scale epidemiological studies.

Reference

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DISRUPTION OF TRANSPORT REGULATION OF IONS AND FLUID IN THE LUNGS WITH COVID-19

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The article discusses scientific data on impaired transport of ions and fluids in the lungs with COVID-19. The pathogenetic mechanism of impaired alveolar fluid clearance is indicated, which may represent one of the key factors in the pathophysiology of COVID-19-associated pneumonia and ARDS syndrome. Lung damage causes changes in the alveolar-capillary barrier, dysregulation of epithelial Na, K-ATPase, epithelial sodium channel (ENaC), and cystic fibrosis membrane conductance regulator (CFTR), which leads to the accumulation of alveolar fluid and impaired clearance. Thus, SARS-CoV-2 infection alters cellular processes that disrupt the function of ion transport proteins such as CFTR, ENaC, and Na+ / K+ -ATPase. This lesion further leads to hypoxia and hypercapnia, which further impairs the mechanisms of ion transport. Data on the involvement of TRPV4 (an osmotically activated channel associated with vanilloid receptor 4) in the pathogenesis of SARS-CoV-2 are presented. The study authors believe that inhibition of TRPV4 has important therapeutic benefits in COVID-19 patients. Inhibition of TRPV4 holds powerful promise for protecting the alveolar-capillary barrier in COVID-19 patients and even for regenerating the damaged barrier. A phase I of clinical trial using a selective TRPV4 inhibitor demonstrated a favorable safety profile in healthy control volunteers and in patients with cardiogenic pulmonary edema. The protection of the alveolar-capillary barrier with a selective TRPV4 inhibitor would also be useful in eliminating possible pulmonary fibrosis as a late consequence of COVID-19.

Keywords: COVID-19, ENaC, GPCR, SARS-CoV-2, TRPV4.

Introduction. The global COVID-19 pandemic continues to gain momentum and infect more and more of the world's population. The clinical picture of the new coronavirus infection is very diverse: from disorders of olfactory dysfunction (anosmia and hyposmia) [1] to severe acute respiratory distress syndrome (ARDS) requiring mechanical ventilation [4,16,26,35,46]. In some patients, the disease progresses in a very severe form associated with hyperactivation of proinflammatory cytokines, called "cytokine storm" due to dysregulation of the immune response, which can ultimately lead to multiple organ failure and death [27,36]. Speaking about the severity of the disease, it is necessary to remember about people at risk. The risk group for severe COVID-19 includes patients who have high expression of angiotensin-converting enzyme-2 in various tissues (diabetes mellitus (DM), cardiovascular diseases (CVD), chronic obstructive pulmonary disease (OPD) [2].

Pulmonary edema is the main clinical symptom of ARDS, characterized by impairment of the alveolar-capillary barrier, protein exudation, and migration of inflammatory cells to the focus [18]. The upper and lower respiratory epithelium are lined with a thin layer of fluid called airway surface fluid and alveolar lining fluid, respectively [32]. Their composition is supported by regulated processes of secretion and reabsorption mediated by ion channels and pumps of respiratory epithelial cells. Lung damage causes changes in the alveolar-capillary barrier, dysregulation of epithelial Na, K-ATPase, epithelial sodium channel (ENaC) and cystic fibrosis membrane conductance regulator (CFTR), which leads to the accumulation of alveolar fluid and impairment of its clearance [5, 6, 28, 32, 33, 43]. In this article, we critically discuss the available evidence on the role of transepithelial ion transport in SARS-CoV-2 respiratory tract infection.

The authors of the publication Abdel Hameid R. et al. [3] suggest that SARS-CoV-2 can change the evolutionary signaling cascades of the messenger by activating G-protein-coupled receptors (GPCR) or by direct modulation of G-protein signaling. Based on the well-known relationship between ENaC and CFTR [29, 37], scientists hypothesize that stimulation of GPCR signaling leads to activation of CFTR-mediated chlorine ion transport, which can suppress absorption pathways such as ENaC-dependent Na^+ uptake. This process could trigger a pathophysiological cascade of reactions leading to the development of pulmonary edema, which is observed in severe cases in patients with COVID-19 and ARDS. CFTR is regulated by the activation of cAMP / protein kinase A [30], which are known to be involved in the pathogenesis process during infection with Vibrio cholerae, activating adenylate cyclase and triggering the secretion of chlorine ions through CFTR [7]. The authors also propose the role of a candidate protein (exchange factor of directly activated cAMP 1) - EPAC1, which is an alternative effector of cAMP interacting with CFTR via Na^+ / H^+ antiporter 3-regulator-1 (NHERF1) [25]. Previously, it was reported that the EPAC1 pathway plays a role in infections with MERS-CoV (Middle East respiratory syndrome coronavirus) and SARS-CoV [41]. However, it is well known that viral infections cause inhibition of ENaC by mechanisms other than GPCR activation. For example, the influenza M 2 protein, which functions as a proton ion channel, reduces the activity of ENaC and CFTR, causing the degradation of these transport proteins [24]. In this case, only ENaC will contribute to the disruption of fluid homeostasis. The main significant drawback of this work is the lack of evidence by the authors of any association between SARS-CoV-2 infection and levels of function and / or expression of CFTR.

The study by Kryvenko V and Vadász [21] focuses on the effect of Na^+ / K^+ -ATPase on lung damage, including COVID-19 infection. There is significant evidence that downregulation of Na^+ / K^+ -ATPase is associated with alveolar barrier disruption in experimental models of lung injury, since this ion carrier is required for normal alveolar epithelium function [5, 13, 33, 42, 43, 44]. Therefore, the authors suggest that a decrease in the concentration of Na+ / K+ -ATPase on the plasma membrane of alveolar epithelium cells contributes to dysfunction of the alveolar epithelium due to infection with SARS-CoV-2. In addition, scientists suggest that disruption of the alveolar-capillary barrier leads to permanent damage to the lungs, which correlates with the extrapulmonary

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manifestations of COVID-19. Several foreign publications report a decrease in the level of mRNA and protein subunits of Na^+ / K^+ -ATPase in cells infected with SARS-CoV-2 and in postmortem autopsy samples of lung tissue from patients with COVID-19 [8, 9, 12, 19]. These data indicate a decrease in transcription and translation of Na^+ / K^+ -ATPase upon infection with SARS-CoV-2. In addition, a convincing analysis of cellular processes influenced by SARS-CoV-2 infection showed that maturation of Na^+ / K^+ -ATPase molecules and their delivery to the plasma membrane of the cell may be impaired. In particular, there is evidence that infection with SARS-CoV-2 causes stress to the endoplasmic reticulum (ER) [10, 19, 22, 38] and disrupts the folding of transmembrane proteins using a chaperone, including the key molecule Na^+ / K^+ -ATPase in lumen of the ER. In addition, molecular docking has shown that the SARS-CoV-2 spike protein is highly glycosylated and disrupts the mechanism of glycosylation and glycan-dependent folding of host proteins. This can disrupt the formation of Na, K-ATPase, which critically depends on the glycosylation of one of its subunits [45]. In addition, the pathogen SARS-CoV-2 disrupts the signaling cascades that usually regulate the content of Na^+ / K^+ -ATPase in the plasma membrane, promoting the penetration of the pathogen through clathrin-dependent endocytosis.

The Role of Cytokine Storm in Pulmonary Epithelial Damage. The authors of two articles discuss the potential contribution of ion transport proteins to the pathophysiology of acute lung injury and ARDS in patients with severe COVID-19. However, they did not indicate that in severe cases of COVID-19, a so-called cytokine storm develops, which can lead to increased cell death (apoptosis), causing a condition of the type of "leaky" epithelium [31,39]. In the literature, it has been described that the concentration of cytokines such as IL-1β, IL-6 and TNFa (tumor necrosis factor alpha) increases in the lungs of patients with COVID-19 and can lead to destabilization of CFTR, ENaC and Na^+ / K^+ -ATPase [37].

In medicine, the glucocorticosteroid dexamethasone has been used for decades, which has many pharmacological effects: anti-inflammatory, anti-allergic, immunosuppressive, anti-shock. Due to such a wide pharmacological spectrum, dexamethasone is still used in the treatment of COVID-19, since its use in multicenter studies has shown an improvement in patient outcome [20]. It is known that dexamethasone regulates ion transport proteins, including ENaC, CFTR and Na^+ / K^+ -ATPases [11,14,34], which indicates the role of ion transport mechanisms in the pathophysiology and outcome of patients with ARDS in the presence of SARS-CoV-2 infection.

As mentioned above, during viral pneumonitis and ARDS, damage to the alveolar epithelial barrier occurs, associated with generalized death of alveolocytes and epithelial cells, as well as dysregulation of ion transport in the lungs [40]. Thus, it can be concluded that SARS-CoV-2 infection alters cellular processes that disrupt the function of ion transport proteins such as CFTR, ENaC, and Na^+ / K^+ -ATPase. This violation further leads to hypoxia and hypercapnia, which further impairs the mechanisms of ion transport [31, 39]. A promising role for a TRPV4 inhibitor in the treatment of COVID-19.

In the original study, the authors investigated the role of TRPV4 (an osmotically activated channel associated with vanilloid receptor 4) in the pathogenesis of COVID-19. The researchers point out that inhibition of (TRPV4) permeable to Ca^{2+} ions as a strategy to address this problem, based on the fact that inhibition of TRPV4 was protective in various preclinical models of pulmonary edema, and that TRPV4 hyperactivation potentially damages the alveolar-capillary barrier with fatal outcome. TRPV4 are activated multimodal Ca^{2+} sensitive ion channels that have been identified as important regulators of the alveolar-capillary barrier. These channels are closely related to type I and II alvelocytes, as well as alveolar capillary endothelial cells [47]. In addition, TRPV4 are expressed and regulate the activation of innate immune cells, such as alveolar macrophages and neutrophilic granulocytes, which contribute to the destruction of the alveolar-capillary barrier through the release of proteases, cytokines and reactive oxygen species [15].

Thus, inhibition of TRPV4 holds powerful promise for protecting the alveolar-capillary barrier in COVID-19 patients and even for regenerating the damaged barrier. A phase I clinical trial using a selective TRPV4 inhibitor demonstrated a favorable safety profile in healthy control volunteers and in patients with cardiogenic pulmonary edema. Also in clinical practice, it is known about the late consequences of COVID-19 in the form of the development of pulmonary fibrosis, which is assumed to depend on the enhancement of TRPV4 function in pulmonary fibroblasts [17]. Thus, the protection of the alveolar-capillary barrier with a selective TRPV4 inhibitor would also be useful in eliminating possible pulmonary fibrosis as a late consequence of COVID-19.

Conclusions. With little data on the mechanisms regulating lung recovery after the acute phase of COVID-19, it can be assumed that these mechanisms will be similar to lung recovery after influenza pneumonitis or other serious causes of lung injury, where ion transport mechanisms are of paramount importance. If the lung is overwhelmingly intact, the alveolar epithelium should restore normal function after the alveolar-capillary barrier is disturbed by the pathogen SARS-CoV-2.

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POINT OF VIEW

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ALLERGIC MECHANISMS AS NEW TRIGGERS FOR PSORIASIS DEVELOPMENT

Introduction. Psoriasis and atopic dermatitis combine signs of a systemic inflammatory process with damage not only in the skin, but also in other organs and systems with the formation of severe forms of the disease, the so-called "psoriatic disease" and "atopic march". The question of the causal relationship between allergy and psoriatic disease and the peculiarities of the spectrum of sensitization to allergens in psoriasis is relevant, and its study can lead to the discovery of new triggers for the development and progression of pathology.

The purpose of the study: to analyze the spectrum of sensitization to pollen, household, fungal and epidermal allergens in patients with psoriasis in order to identify new triggers of psoriatic disease.

Materials and methods. Patients with psoriasis (Group 1, n=41) aged 18 to 66 years were examined. Patients with atopic dermatitis (Group 2, n=20) were examined as a comparison group. The control group consisted of practically healthy people matched by sex and age (group 3, n=19). Specific allergological examination included collection of an allergic history, determination of the spectrum of sensitization by analyzing the concentration of total immunoglobulin E (IgE) and allergen-specific IgE to pollen, household, fungal and epidermal allergens by the method of enzyme-linked immunosorbent assay. The calculation and analysis of the obtained data was carried out using the Statistica 8.0 software package.

Results and discussion. In a comparative analysis of the spectrum of sensitization to pollen allergens between groups of patients, it was noted that in atopic dermatitis, sensitization to pollen from trees, meadow grasses and weeds was statistically significantly more frequent in comparison with psoriasis. In the group of patients with psoriasis, monovalent sensitization was statistically significantly more frequent in comparison with the group of patients with atopic dermatitis, in which, on the contrary, polyvalent sensitization was more often determined.

Conclusion. The data obtained in the course of this study confirm the concept that atopic mechanisms are characteristic of psoriasis, but to a lesser extent than for atopic dermatitis and are protective against the development of autoimmune mechanisms, which is consistent with literature data. Consequently, further study of psoriasis and allergies from the standpoint of comorbidity should be carried out in the direction of investigating both atopic and non-atopic mechanisms of triggering allergic reactions involved in the immunopathogenesis of psoriatic disease.

Keywords: psoriasis, atopic dermatitis, sensitization, allergens, immunoglobulin E, immunopathogenesis.

Introduction. Psoriasis (PS) and atopic dermatitis (AD) are chronic inflammatory skin diseases, in the pathogenesis of which the cells of the immune system play a key role [3,4,10]. PS and AD combine signs of a systemic inflammatory process with damage not only in the skin, but also in other organs and systems with the formation of severe forms of the disease, the so-called "psoriatic disease" and "atopic march" [1,2,7]. PS and AD are genetically determined diseases, the development and course of which is associated with the influence of numerous environmental factors: mechanical and physical effects, insolation, microorganisms, allergens and others [3,4,6]. Defects of the epidermal barrier in psoriasis and atopic dermatitis promote the penetration of various antigens through the epidermis with the development of sensitization and subsequent activation of allergic mechanisms of skin damage [7,14].

It is worth noting that the link between autoimmune diseases and atopy is actively discussed in modern research. Previously, it was believed that diseases caused by mutual counter-regulation of immunopathological responses of Th1 and Th-2 types cannot occur simultaneously in the same person. However, in modern studies, data on the combination of psoriasis and atopy are increasingly found [10,12,15].

Atopic dermatitis is a classic example of atopy, in which the predominance of the Th2-type immune response is noted and the key role of IgE-mediated mechanisms has been proven [6]. Whereas psoriasis, in contrast to atopic dermatitis, is characterized by the formation of a Th1/Th17-type immune response [4]. For a long time it was believed that the presence of psoriasis in a patient is "protective" in relation to the development of allergies. Therefore, allergy can be one of the triggers of psoriasis. Evidence in favor of this hypothesis is provided by the results of studies indicating that a long course of inflammatory reactions in PS leads to an increase in the concentration of B-cells in psoriatic plaques with a deviation of the immune response from Th1 to Th2 type [9]. This opinion is supported by data on the confirmed role of Th17 and Th1 lymphocytes both in psoriasis and in some forms of AD [6]. There is evidence of an increase in the production of immunoglobulin E by B-lymphocytes under the action of IL-17a, a key cytokine involved in the development of PS [11].

Thus, the fundamental scientific problem to be solved by this research is to study the role of atopic immunopathological mechanisms of allergic reactions in the development of psoriatic disease based on the analysis of the concentration of specific IgE to pollen, household, fungal, epidermal allergens. Comparative analysis of data from specific allergological examination of patients with psoriasis and atopic dermatitis is aimed at identifying new specific markers of psoriatic disease that can be used for a personalized approach to the diagnosis and treatment of psoriatic disease. **Purpose of the study**: to conduct a comparative analysis of the spectrum of sensitization to pollen, household, fungal and epidermal allergens of patients with psoriasis and atopic dermatitis in order to determine new specific markers of psoriatic disease..

Materials and methods. Patients with psoriasis were examined (Group 1, n=41). The age of patients varied from 18 to 66 years, the average age of patients with PS was 40,0±2.1 years. Patients with atopic dermatitis (Group 2, n=20) were examined as a comparison group, since AD is a classic example of atopic allergic disease. The average age of AD patients was 30,5±2,7 years. In both groups of patients, women were more common: in the group of patients with PS – 60,9% (n=25) of cases, in the group of patients with AD - in 60,0% (n=12). The control group

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consisted of practically healthy people matched by sex and age (group 3, n=19). All subjects signed informed consent to participate in the study. The survey protocol was approved by the local ethics committee. The severity of the clinical course of PS was assessed by calculating the PASI index (Psoriasis area and severity index). The average value of the PASI index in the group of patients with PS was 9,9 [5,8; 14,3].

Specific allergological examination included collection of an allergic history, determination of the spectrum of sensitization using the analysis of the concentration of total immunoglobulin E (IgE), eosinophilic cationic protein and allergen-specific IgE to pollen, household, fungal and epidermal allergens in the blood serum by the method of enzyme-linked immunosorbent assay by semi-assay Scientific Multiskan FC. Reagents were used to determine allergen-specific IgE to the following allergens: a mixture of meadow grasses (hedgehog, meadow fescue, perennial ryegrass, timothy grass, meadow bluegrass), a mixture of tree allergens (ash-leaved maple, gray alder, warty birch, hazel, oak, plane tree maple-leaved, willow, triangular poplar), a mixture of weeds (wormwood, plantain, white gauze, goldenrod, stinging nettle), a mixture of fungal allergens (*Penicillium notatum, Cladosporium herbarum, Aspergillus fumigates, Mucor racemosus, Alternaria alternata*), a mixture (house dust, *Dermatophagoides pteronyssinus, Dermatophagoides farinae*, cockroach), a mixture of epidermal allergens (cat epithelium, dog epithelium, horse dander, cow dander). According to the manufacturer's instructions (AlkorBio, Russia), the concentration of IgE≥0.35 kE/l indicated a positive reaction.

The calculation and analysis of the obtained data was carried out using the Statistica 8.0 software package. In the comparative analysis of qualitative characteristics, Fisher's exact test was used. Indicators were considered statistically significant at p<0,05. The analysis of qualitative traits was carried out by assessing the relative frequency of the trait (prevalence) P and determining the average error in the proportion of m.

Results and discussion. Analysis of allergological anamnesis data showed that in 43,9% (n=18) of cases, PS patients previously noted episodes of food, insect and drug allergies, manifested by urticaria and dermatitis. Seasonal manifestations of allergy were observed in 9,8% (n=4) of patients with PS. A burdened hereditary allergic history (the presence of allergic reactions and / or diseases in close relatives) was revealed in 17,1% (n=7) of patients with PS. A burdened hereditary history (the presence of psoriasis in close relatives) was noted in 39,0% (n=16) of cases. According to the allergological anamnesis, in the group of patients with atopic dermatitis in 95% (n=19) of cases there were episodes of food, insect and drug allergies, manifested by urticaria and dermatitis. Seasonal manifestations of allergy were observed in 60% (n=12) of patients with AD. A burdened hereditary allergic history (the presence of allergic reactions and / or diseases in close relatives) was detected in 55% (n=11) of cases. Therefore, in the present study, it was found that the incidence of aggravated allergic anamnesis in patients with PS is less than in patients with AD, but more often than in controls, which is consistent with the literature data [14].

The duration of symptoms of the disease in the group of patients with psoriasis was 11,0±1,8 years, the onset of psoriasis at the age of 25,0±2,5 years, the onset of articular syndrome was 46,0±3,0 years. The duration of the disease in the group of patients with atopic dermatitis was 10,0±1,7 years, the onset of the disease in childhood in the form of exudative-catarrhal diathesis, neurodermatitis with transformation into AD at the age of 20,0±2,7 years. In the group of AD patients, a combination of skin rashes and allergic rhinitis (dermato-respiratory syndrome) was observed in 100% (n=20) cases. The average age of onset of allergic rhinitis was 21,0±3,3 years.

The concentration of total immunoglobulin E in the blood serum was statistically significantly higher in the group of patients with atopic dermatitis in comparison with the group of patients with psoriasis and the control group: 210,4 IU/ml [56,2; 1000,0] relative to 63,0 IU/ml [30,4; 133,8] and 45,1 IU/ml [23,4; 144,0], respectively, $p_{1,2}$=0,005, $p_{2,3}$=0,001, $p_{1,3}$=0,4. In the group of AD patients, a high level of total IgE was found in 60,0% (n=12) cases, in the group of PS patients - in 34,1% (n=14) cases. The concentration of eosinophilic cationic protein in the blood serum was statistically significantly higher in the group of patients with atopic dermatitis in comparison with the group of patients with psoriasis and the control group: 28,7 ng/ml [13,9; 37,1] relative to 8,6 ng/ml [4,8; 17,.2] and 7,9 ng/ml [4,6; 27,1], respectively, $p_{1,2}$=0,005, $p_{2,3}$=0,003, $p_{1,3}$=0,8.

The features of the spectrum of sensitization of patients with psoriasis and atopic dermatitis have been determined. In the group of patients with psoriasis, sensitization to pollen, household, fungal and epidermal allergens was statistically significantly less frequent in comparison with the group of patients with AD: 36,6% of cases relative to 75,0% of cases, $p_{1,2}$=0,005 (Table 1), which is consistent with the literature data [5].

When assessing the spectrum of sen-

Comparative characteristics of the spectrum of sensitization to pollen, household, fungal and epidermal allergens in patients with psoriasis and atopic dermatitis, % (n)

Allergen	1st group PS (n=41)	2nd group AtD (n=20)	p
The presence of sensitization to the studied allergens	36.6%±7.5 (n=15)	75.0%±9.9 (n=15)	$p_{1.2}$=0.005 $p_{1.3}$=0.002 $p_{2.3}$<0.001
A mixture of meadow grasses	7.3%±4.1* (n=3)	35.0%±11.8 (n=7)	$p_{1.2}$=0.006 $p_{1.3}$=0.2 $p_{2.3}$=0.003
A mixture of tree allergens	9.8%±4.6 (n=4)	35.0%±11.8 (n=7)	$p_{1.2}$=0.02 $p_{1.3}$=0.1 $p_{2.3}$=0.003
A mixture of weeds	4.9%±3.4* (n=2)	40.0%±11.2 (n=8)	$p_{1.2}$=0.0005 $p_{1.3}$=0.3 $p_{2.3}$=0.001
A mixture of allergens of house dust	12.2%±5.1 (n=5)	45.0%±11.4 (n=9)	$p_{1.2}$=0.004 $p_{1.3}$=0.1 $p_{2.3}$=0.0006
A mixture of fungal allergens	4.9%±3.4* (n=2)	15.0%±8.2* (n=3)	$p_{1.2}$=0.2 $p_{1.3}$=0.3 $p_{2.3}$=0.07
A mixture of epidermal allergens	4.9%±3.4* (n=2)	35.0%±11.8 (n=7)	$p_{1.2}$=0.002 $p_{1.3}$=0.3 $p_{2.3}$=0.003

Note. % (n) – relative and absolute number of sensitized patients. *p>0,05. Sensitization to the studied allergens was not detected in the control group.

sitization to household allergens of patients with PS, the highest frequency of occurrence of sensitization to a mixture of house dust allergens was found in comparison with other types of allergens. When studying pollen sensitization in PS patients, sensitization to a mixture of trees prevailed in comparison with other types of pollen allergens. The highest concentration of allergen-specific IgE in psoriasis is determined to house dust allergens. In the group of AD patients, the highest incidence of sensitization was revealed to weed pollen - 40% of cases. Sensitization to pollen from trees and meadow grasses was noted in 35% of cases. The presence of sensitization to epidermal allergens in AD patients was revealed in 35% of cases. The lowest incidence of allergen-specific IgE was found in the group of patients with AD to a mixture of mold allergens - in 15% (n=3) cases.

In the group of AD patients, sensitization to pollen, household fungal and epidermal allergens was found statistically significantly more often in comparison with the group of patients with psoriasis, $p_{1,2}$=0,005. In a comparative analysis of the spectrum of sensitization to pollen allergens between the groups of patients, it was noted that with AD, sensitization to pollen from trees, meadows and weeds was statistically significantly more frequent in comparison with psoriasis, $p_{1,2}$=0,02, $p_{1,2}$=0,006, $p_{1,2}$=0,0005, respectively. In addition, in the group of AD patients, sensitization to house dust and epidermal allergens was found statistically significantly more often in comparison with PS, $p_{1,2}$=0,004, $p_{1,2}$=0,002. There were no intergroup differences in sensitization to mold allergens.

In the group of patients with PS, monovalent sensitization was statistically significantly more frequent in comparison with the group of patients with AD: 93,3% (n=14) and 26,7% (n=4), respectively, $p_{1,2}$<0,001. In turn, in the group of patients with AD, polyvalent sensitization to allergens was statistically significantly more frequent in comparison with the group of patients with PS: 53,3% (n=8) and 0%, respectively, $p_{1,2}$=0,0009. Data on the nature of sensitization in patients with PS are few and contradictory. Thus, an increase in the level of specific IgE to inhalation allergens has been reported in patients with PS in comparison with the group of healthy people and patients with psoriatic arthritis [10]. In another study, sensitization to allergens of birch pollen, timothy grass, rye, potatoes, and carrots was found in patients with PS [5]. There are data on the absence of statistically significant differences in the concentration of specific IgE to household allergens (*Dermatophagoides pteronyssinus, Dermatophagoides farinae*) in the blood serum in the groups of PS patients relative to the group of healthy people [9]. The literature data on the concentration of total IgE in patients with PS are contradictory. In some studies, an increased level of total IgE was found in comparison with the control [8,9,11,12]. In another study, on the contrary, there were no statistically significant differences in the concentration of total IgE in the groups of patients with PS and controls [15].

Our previous studies, based on skin testing, showed the features of the spectrum of sensitization to food, household, pollen, fungal allergens in patients with psoriasis. So, in the group of patients with psoriasis in more than 50% of cases, the prick-testing method revealed sensitization to pollen and fungal allergens.

Conclusion. Thus, in the study, new triggers of psoriasis were identified. The features of the spectrum of sensitization to pollen, household, fungal and epidermal allergens in patients with psoriasis have been established. The data obtained in the course of this study based on the study of the concentration of general and specific IgE on a lower frequency of occurrence (36.6%) of sensitization to pollen, household, fungal and epidermal allergens in PS may be associated with the fact that in psoriatic disease, participation of either reagins of a different class (IgG4), or other immunopathological mechanisms of triggering allergies (II, III, IV type according to the Gell & Coombs classification) are the basis. The results obtained in the course of this study confirm the concept that atopic mechanisms are characteristic of psoriasis, but to a lesser extent than for atopic dermatitis and are protective against the development of autoimmune mechanisms. Consequently, further study of psoriasis and allergies from the standpoint of comorbidity should be carried out in the direction of investigating both atopic and non-atopic mechanisms of triggering allergic reactions involved in the immunopathogenesis of psoriatic disease.

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FREQUENCY OF INTERICTAL EPILEPTIFORM DISCHARGES IN SLOW SLEEP WITH RELAPSE OF TONIC-CONICAL SEIZURES IN ADULTS WITH GENERALIZED EPILEPSY AFTER WITHDRAWAL OF ANTIEPILEPTIC DRUGS

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Interictal epileptiform discharge rates (IED) were studied in slow-wave sleep phases (NREM) with recurrent tonic-clonic seizures with generalized onset (GTCS) in adults after withdrawal from antiepileptic drugs (AED) with the debut of idiopathic generalized epilepsy (IGE) before the onset of adult age (group A). The control group consisted of IGE patients with non-drug-induced remission of GTCS for more than 5 years (group B). Patients who had presented information on myoclonic seizures in adolescence constituted group 1, patients with isolated GTCS - group of probable IGE GTCS (group 2). Patients with febrile and absence seizures in the disease history, structural alterations on MRT, myoclonic, and absence seizures at the time of the study were excluded. All patients underwent polysomnographic investigation (PSG) on the device "Neuron-Spectr-4VP" of the firm "Neurosoft" in the period of physiological nocturnal sleep. Visual identification of sleep phases was carried out in accordance with the guidelines of the American Academy of Sleep Medicine. IEDs were revealed during visual evaluation of the native EEG, and manual counting of the absolute number of discharges in NREM was performed. The IED generation rates were calculated as a ratio of the absolute number of IED to the summarized duration of every phase in the parts without artefacts. The comparison of the rates of IED in NREM in study groups was conducted. Statistical processing was performed with the Statistica 6.0 toolkit. The study used parametric and nonparametric methods of comparison. For the entire period of registration of the slow wave sleep phase, the absolute number and rates of IED per hour of recording were higher in patients with recurrent GTCS and myoclonic seizures in the illness history compared to other groups. In patients with recurrent GTCS and myoclonic seizures in the history of the disease, the persistent increase in IED rates per hour to the deep wave sleep phase was observed compared to the other group of patients with IGE. The evaluation of the IED rates in the slow wave sleep phase can be performed in patients with IGE for the prediction of recurrent GTCS and the solution of the question of withdrawal from the AED.

Keywords: interictal epileptiform discharges, slow wave sleep phases, generalized tonic-clonic seizures, idiopathic generalized epilepsy.

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Introduction. The literature accumulated sufficient data comprising long-term follow-ups of electroclinical dynamics with some syndromes of idiopathic generalized epilepsy (IGE) with a variable phenotype, however, rates of interictal epileptiform discharges (IED) in slow wave sleep phases (NREM) with recurrent tonic-clonic seizures with a generalized onset (GTCS) in patients with IEG debut prior to onset of the adult age after withdrawal from AED were studied inadequately. GTCS are of major medico-social importance in adults with idiopathic generalized epilepsy (IGE) with a variable phenotype [1, 2]. The continuum of IGE is characterized by variety of generalized seizures and comprises juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with isolated GTCS (IGE GTCS) [3,4]. Favorable prediction of IGE is associated with reduction in rates and duration of IED, however, methodological heterogeneity of the studies explains contradictory character of results, which are reported about predictive value of the EEG in IGE and is in need of further research [5]. As a whole, type of the seizure and registration of IED after withdrawal from AED is considered as a predictor of the recurrent seizures into the remission of an unspecified syndrome of IGE [6]. In its turn, a higher density and major duration of IED may be retrospectively associated with a shorter remission which supposes potential possibility of the use of EEG as a biomarker of the prediction in IGE and makes clinical research in this direction relevant [7].

The purpose of the study was to investigate the rates of IED in NREM with recurrent GTCS in adults after withdrawal from AED with the IGE debut prior to the onset of adult age.

Materials and Methods. During the elaboration of the research protocol, a 'case-control' design was used to compare records of patients with IGE and recurrent GTCS (group A) and patients with a remission duration of more than 5 years (group B). The duration of remission was evaluated based on the clinical questionnaire according to guidelines [8]. Seizures were defined as GTCS according to the guidelines [9]. The reconstruction of IGE syndrome was conducted based on illness history information (detection of other types of generalized attacks in the debut of the disease) in the accordance with the guidelines [10]. Patients who gave the information on their myoc-

lonic attacks at adolescence constituted the group of probable JME (group 1), patients with isolated GTCS – the group of probable IGE GTCS (group 2). All patients underwent EEG monitoring in the period of physiological sleep in the laboratory Video-EEG-monitoring of the Department of Neurology and Neurosurgery of SibSMU. Criteria of inclusion: observation in the outpatient network with the diagnosis IGE; age from 18 to 50 years, absence of epileptic attacks during 10 days prior to investigation, withdrawal from AED not less than 12 months prior to the study. Criteria of exclusion: actual physical and neurological pathology, febrile and absence attacks in the history of the disease, structural alterations in MRT, gravida period and lactation, mental disorders, myoclonic (including myoclonus of eyelids with absences) and absence attacks at the time of study, documented GTCS during neurophysiological investigation. The study included 78 patients with IGE. Of them, 54 women and 24 men aged 18 to 51 years. The mean age was 25.07±6.05 and 24.83±7.15, respectively (p= 0.87). The main group (group A) included 60 patients, complaining of recurrent GTCS within 1 to 8 years. The average duration of the previous remission was 2.46±1.44 years. The control group (group B) included 18 patients with remission of attacks from 5 to 8 years. The average duration of remission was 6.2±1.1 years. The myoclonic attacks in the illness history were revealed in 40 patients (group 1), the remaining patients entered group 2. The comparison was carried out in homogeneous groups formed according to sex and age among patients with IGE with variable phenotype with myoclonic attacks in the history of the disease and isolated GTCS after withdrawal from AED in the subgroups according to the course of the disease.

Protocol of neurophysiological investigation. All patients underwent polysomnographic investigation (PSG), including electroencephalography (in leads F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, 2 with the use of the standard position of the electrodes according to the system 10–20), electro-oculography (2 channels), electrocardiography (1 lead), electromyography of the mental muscles (2 channels), on the device “Neuron-Spektr-4VP” of the firm “Neurosoft” in the period of physiological nocturnal sleep. Visual determination of sleep phases was performed according to the guidelines of the American Academy of Sleep Medicine [31]. Some IEDs (complexes peak-wave, polypeak-wave) were revealed during visual evaluation of the native EEG according to the conventional classification [32]. In patients with documented IEDs in the first, second and third NREM of the first cycle of the sleep, a manual counting of the absolute number of discharges was conducted. The description of the quantity of IEDs was carried out according to the guidelines [33]. The rates of generation of IEDs were calculated as a ratio of the absolute number of the IEDs to the summarized duration of every phase in the parts without artefacts in all cycles of the sleep. Comparison of IED rates in NREM was conducted in the study groups. Statistical processing was performed with the use of the Statistica 6.0 toolkit. The study used parametric and nonparametric methods of the comparison, Mann-Whitney, Freedman, Kruskal-Wallis test, Shapiro-Wilk, t-test (Student). For the reliable level, the level of significance $p<0.05$ was accepted. Data were presented as mean and standard deviation (M±SD), median (Me) and quartiles (q1; q3) – Me (q1; q2).

Results and Discussion. In the structure of IGE, recurrent GTCS in adults can be observed in IGE GTCS and JME. Both IGE syndromes are not referred to as self-resolved, but may have a tendency to a benign course, including spontaneous long-term remissions irrespective of AED intake [19]. In the formed sample of patients with IGE, illness history information on the presence of myoclonic attacks at adolescence did not allow concluding about prediction of recurrent GTCS: breakage of remission was documented in 72.5% of patients with myoclonic attacks in the illness history and in 81.6% with isolated seizures (p=0.34148).

The incidence rates of IED in NREM in study groups of patients with IGE depending on the course of the disease are presented in Figure 1. In adult patients with IGE, very frequent (more often than 1 per 10 seconds) IEDs were not documented. The frequent (more frequent than 1 per one minute but more rarely than 1 per 10 seconds) ones were predominantly documented in group A1, whereas in groups A2 and B, rare (more rarely than once an hour) IEDs. The presented data correspond to the formed in the literature notions about major rates of IED in patients with JME in comparison with IGE GTCS and higher risk of recurrent JME during frequent IEDs [7,11].

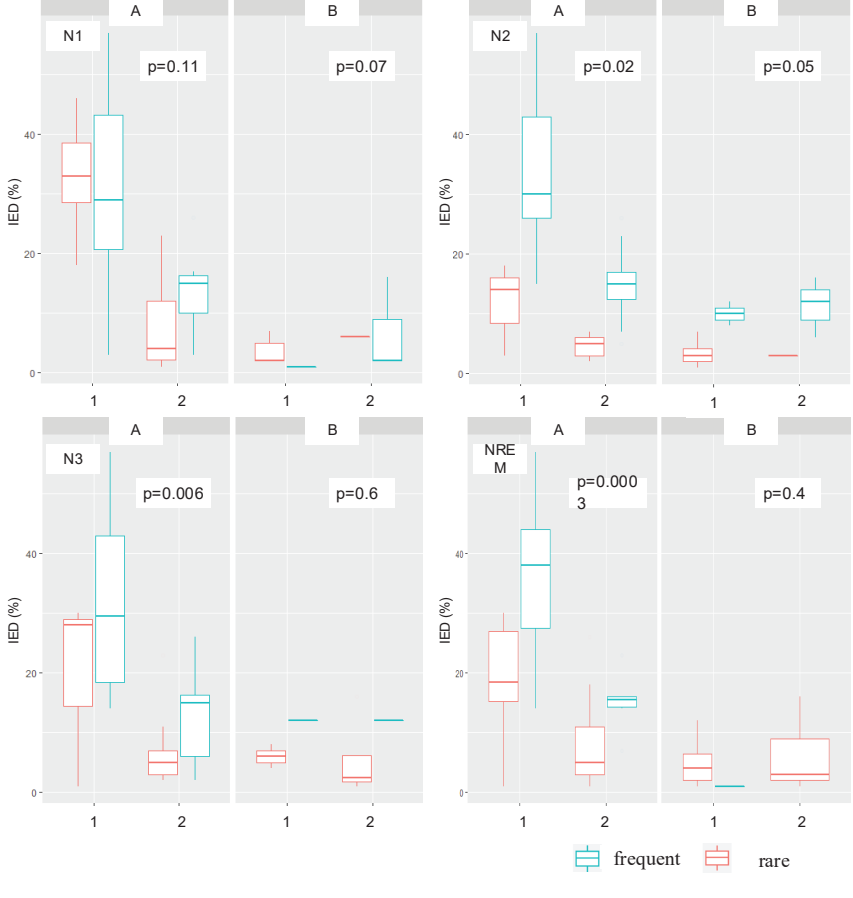

Fig. 1. IED incidence rates in NREM in study groups of patients with IGE
Note: IED – interictal epileptiform discharges: frequent rare
N1 – stage 1 of NREM, N2 – stage 2 of NREM, N3 – stage 3 of NREM, NREM – stages 1-3 of NREM

As a whole, despite of that in the adult patients with IGE, rare IED were documented more often, diagnostically relevant duration of EEG monitoring corresponded to data [14].

The frequency of documenting the IEDs in NREM in study groups of patients with IGE taking AED is presented in table 1. Duration of parts of the EEG without artefacts in NREM did not differ in the study groups.

For the entire period of documenting the slow wave sleep, the absolute quantity and rates of IED per hour were higher in patients with recurrent GTCS and myoclonic attacks in the illness history compared to other groups. The effect of the pronounced reduction in absolute amount and IED rates per hour in patients with JME remission is shown during the outpatient EEG with long-term accumulation of pathological graph elements [11]. According to common notions, a stable decrease in rates and the absence of epileptiform patterns with JME may be considered as a neurophysiological predictor of remission of the disease [5]. However, alongside with increase of the duration of documenting the EEG, in literature there is another trend based on the evaluation of the interaction of the physiological and pathological activity in IGE. In IGE during slow wave sleep and specifically in the second phase of NREM, conditions are created for synergy of physiological and pathological activity that leads to increased frequency of IEDs [5, 15]. It is shown that variants of the correlations between physiological patterns of the sleep and IEDs may be considered during prediction of the JME remission [16]. In patients with recurrent GTCS and myoclonic attacks in the history of the illness, the absolute number and IED rates per hour of recording in phase 2 of NREM exceeded the corresponding values in other study groups, which is consistent with the available data in the literature.

In recent years, the diagnostic significance of the documenting the IED in delta-sleep is studied [17]. In patients with recurrent GTCS and myoclonic attacks in the history of the disease, the absolute number and IED rates per hour of recording in deep-wave sleep exceeded the corresponding values in other study groups, which can be considered as a neurophysiological indicator of unstable IGE remission. It should be agreed with the proposition [17], that despite the patterns of distribution of IEDs with different courses of IGE revealed in many works, the attitude towards the practical application of the findings of EEG investigations remains sceptic due to the heterogeneity of the groups and methods used. In the next stage of the work, the evaluation of the dynamics of IEDs in NREM in study groups of patients with IGE (Figure 2).

In patients with recurrent GTCS and myoclonic attacks in the history of the illness, a persistent increase in IED rates per hour to deep-wave sleep phases was documented compared to other groups of patients with IGE.

Quantity of interictal epileptiform discharges in slow wave sleep in study groups of patients with IGE - (q1; Me; q2) n

Studied indicators		A1	A2	B1	B2	Level of reliability of differences (p)
Stage 1	Duration of the documenting (without artefacts, hour)	(0.17;0.51;0.71) 29	(0.37;0.7;1.08) 31	(0.14;0.29;0.76) 11	(0.08;0.37;1.25) 7	0.094078
	Quantity of IED	(1;2;4) 23	(1;2;3) 18	(1;1;1) 6	(1;1.5;3) 4	0.336655
	Rates (incidence rates) of IED (number per hour)	(3.33;5.88;12.94) 23	(2.16;2.485;5.56) 18	(1.72;2.17;3.45) 6	(1;1.5;3) 4	0.139856
Stage 2	Duration of the documenting (without artefacts, hour)	(0.61;1.89;3.54) 29	(0.64;2.18;3.71) 31	(0.84;0.99;3.66) 11	(0.79;1.38;2.12) 7	0.729974
	Quantity of IED	(6.5;13;23.5) 28*.**	(2;5.5;8) 24*	(1;2;5) 10**	(3.5;6;7.5) 4	0.001424* 0.000590**
	Rates (incidence rates) of IED (number per hour)	(3.2;6.85;20.09) 28*.**	(1.53;3.445;7.025) 24*	(1.01;1.175;2.19) 10**	(3.025;4.37;5.35) 4	0.003899* 0.003282**
Delta-sleep	Duration of the documenting (without artefacts, hour)	(0.32;0.5;1.02) 26	(0.5;0.75;1.27) 27	(0.31;0.71;1.22) 8	(0.47;0.95;1.35) 6	0.430172
	Quantity of IED	(4;9;14) 25*	(1;2;7) 23*	(2;3;4) 3	(1;1;4) 5	0.001053*
	Rates (incidence rates) of IED (number per hour)	(8.82;16.05;26.92) 25*	(2;3.23;6.18) 23*	(1.47;1.91;3.13) 3	(2.13;2.45;3.03) 5	0.000387*
All stages	Duration of the documenting (without artefacts, hour)	(1.31;2.67;5.53) 29	(1.32;4.43;5.55) 31	(1.48;1.56;5.66) 11	(1.34;2.1;4.75) 7	0.678822
	Quantity of IED	(18;29;43) 29*.**.***	(3;7;15) 31*	(2;4;7) 11**	(2;3;12) 7***	0.000149* 0.000149** 0.000150**
	Rates (incidence rates) of IED (number per hour)	(4.66;10.69;22.31) 29*.**.***	(1.07;2.59;4.55) 31*	(1;1.28;2.01) 11**	(0.75;2.11;2.86) 7***	0.000151* 0.000211** 0.001618***

Note. Duration of registration – the total duration of non-abstract EEG sections in the studied nREM stage per hour; number of IER – the absolute number of IER in the studied nREM stage; frequency of IER – the number (occurrence) IER per hour; pairs of signs with statistically significant differences were marked with the same number of asterisks.

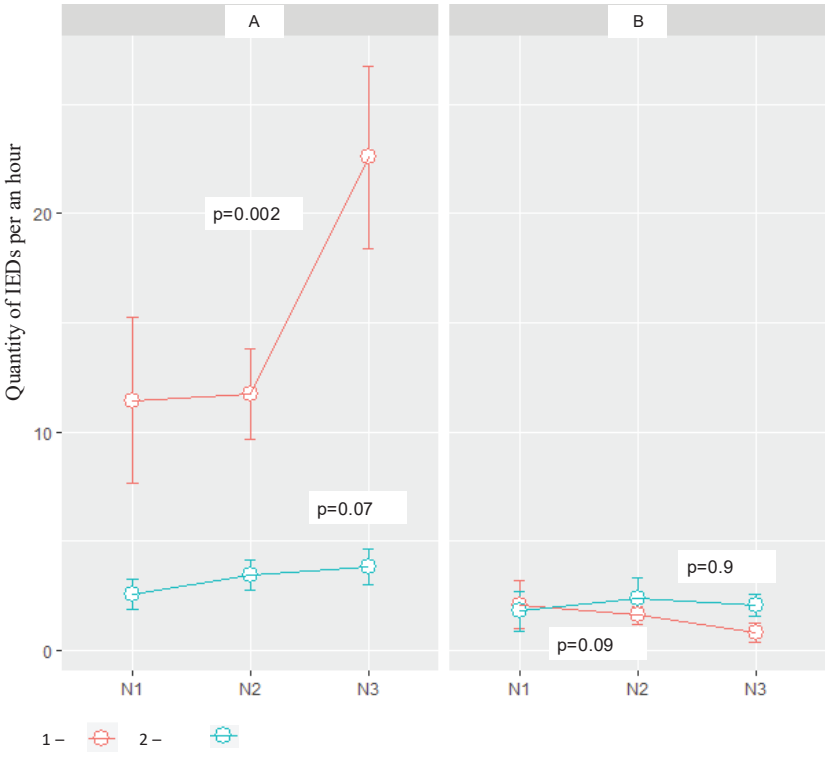

Fig. 2. Dynamics of IED rates in NREM in study groups of patients with IGE
Note: N1 – stage 1 of NREM, N2 – stage 2 of NREM, N3 – stage 3 of NREM, NREM – stages 1-3 of NREM

Conclusions However, the clinical importance of the findings is in need of further sophistication with the accumulation of data; the following is practically applicable: during the registration of frequent IEDs in patients with remission of IGE in combination with myoclonic attacks in the history of the disease, the question of withdrawal from AED should be solved regardless of the duration of the remission taking into account the dynamics of reduction of pathological activity in the EEG; the increase in the rates of IEDs per hour in the deep-wave sleep phases may be considered as an unfavorable predictive factor of recurrent GTCS in the individual clinical case.

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CLINICAL CASE

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VISUAL AND SEMANTIC MEMORY FOR PARKINSON'S DISEASE: CLINICAL CASE ANALYSIS

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The aim of the work is to specify the mechanisms of transformation of the content to be memorized in the process of consolidation and reconsolidation in patients with Parkinson's disease (PD).

Materials and methods. The study involved three patients with PD (disease duration no more than three years; second stage) without cognitive impairment with mixed (akinetic-rigid-tremor), akinetic-rigid and tremulous forms of the disease. When studying the processes of consolidation-reconsolidation of visual-figurative and semantic memory in PD patients, a symbolic image and a text from the epic of the Indians of Canada were proposed as a stimulating material for memorization. The study of the processes of consolidation-reconsolidation was carried out sequentially: direct reproduction after presentation, reproduction after 40 minutes, after 4 hours, after 36 hours.

Results. When extracting visual-shaped information already at the stage of copying (storing information), a tendency appears to transform the symbol into a specific image ("bird", "owl"), which increases from stage to stage. As a result, there are not only distortions of the reproduced information up to its complete loss, but also simplification. The number of image details decreases, the accuracy of their reproduction decreases, and new elements that are absent in the original image are drawn. When the semantic content was reproduced immediately after presentation, the content loss was 25-27%. When playing text content after 40 minutes, the loss of semantic units was 50-52%. After 4 hours, the patients were able to reproduce 22-25% of the semantic content of the heard text. Revealed the suppression of verbal information in PD.

Conclusion. The presence of neurodegenerative changes due to a pathological process in PD significantly changes the quality (volume and accuracy) of the information retrieved or leads to its complete loss. In patients, regardless of the form of the disease (trembling, akinetic-rigid or mixed), a significantly smaller amount of information (both auditory-verbal and visual-shaped) is consolidated. This tendency is correlated with a pronounced distortion in the process of information extraction.

Keywords: visual-shaped memory, semantic memory, consolidation, reconsolidation, Parkinson's disease.

The main place in the clinical picture of Parkinson's disease (PD) is occupied by motor disorders (muscle rigidity, hypokinesia and rest tremor). However, non-motor manifestations also fall into the field of research interest: in particular, vegetative disorders, sensory disorders, pain, olfactory disturbances, increased sweating, changes in body mass index, gastrointestinal disorders, sleep disorders. Also, non-motor manifestations of PD include pain syndrome, cognitive and affective disorders [3,4,5,7,8].

The study of cognitive functions of people suffering PD, as well as specifically mnestic functions that are associated with the concept of non-motor symptoms, are presented in the works of Tweedy, J., Langer, K., McDowell, F. (1982); Flowers, K. A., Pearce, I. and Pearce, J. M. S. (1984); Weingartner H., Burns S., Diebel R., Le Witt P. A. (1984); Brown R.G., Marsden C.D. (1990); Gabrieli J. D. E., Singh J., Stebbins G.T., Goetz Ch.G. (1996); Hou J.-G.G., Lai E.C., (2007); Brefel-Courbon C., Ory-Magne F., Thalamas C., Payoux P., Rascol O., (2013); Barone P. et al. (2009); Berganzo K., Tijero B., González-Eizaguirre A., Somme J., Lezcano E., Gabilondo I., Fernandez M., Zarranz J.J., Gómez-Esteban J.C., (2016); Nikishina V.B., Shuteeva T.V., Zapesotskaya I.V., Petrash E.A. (2017); Siciliano M. et all (2021); Pourzinal D. et all (2021); Schmidt N. (2021).

According to the available data, cognitive impairment of people suffering PD significantly reduces the quality of their life [4]. The data from the study of non-motor symptoms in patients with PD indicate that there is no relationship between cognitive status (on the MMSE scale) and difficulties with attention and memory, which patients complained about. Patients noted violations of short-term memory, difficulty concentrating, as well as forgetting in everyday affairs. In tests for the study of memory, it was found that patients suffer more from difficulties of recall than recognition [7]. Unlike remembering and memorizing, recognition is a variant of "passive memory", when a person does not need to carry out purposeful activities in relation to the material. It is only necessary to make a choice between the available alternatives. Consequently, the greatest difficulties arise when active participation is required from the subject [8]. Recall is an active process, although it is also based on passive recognition [16]. It was also found that memory disorders in PD are similar to memory disorders in frontal lesions, which may be due to two factors. Firstly, a possible lesion of the frontal parts of the brain in PD. Secondly, there is a similar mechanism of dopamine deficiency in PD and in frontal localization of the defect [9]. Underestimation of cognitive functions in PD is associated with the severity of asthenization and depressive symptoms, but not with demographic or clinical features. Overestimation of cognitive functioning is associated with impaired frontal functioning [12].

A number of authors also note the connection of episodic memory impairment in PD with a violation in the functioning of hippocampal structures [11]. A general lack of the ability of patients with PD to use semantic signals as memory aids was also found [15]. Ann E. Taylor (1990) in his research indicates that patients with PD demonstrated a number of specific memory deficiencies: spontaneous organization of memorized material and increased sensitivity to interference during learning [14]. According to Schmidt N. (2021), there is an improvement in verbal and nonverbal memory 6 months after the start of cog-

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nitive training in patients with PD [13].

Thus, patients with PD have violations in all parameters of strategic memory – free recall, self-ordered indication and temporary ordering. The patients had no violations in terms of non-strategic declarative memory (memory recognition test) and semantic memory (vocabulary tests and fluency of speech). It is noted that the use of associations significantly increases the percentage of recall.

Cognitive declines that can be observed in PD are due to a decrease in the amount of working memory, as well as a violation of the work of strategic memory. It is noted that a slowdown in perceptual-motor processing can lead to a decrease in the volume of working memory, which, in turn, is the result of dopaminergic insufficiency [12]. However, the question of the hierarchy of this system remains debatable.

The methodological foundations of our understanding of the processes of consolidation-consolidation of visual-figurative and semantic memory in PD were the provisions of the concept of working memory by B.B. Velichkovsky (2015). According to this concept, working memory is a system of cognitive processes that provide operational storage and processing of information. It has a heterogeneous structure, including components of operational storage and processing of information with various functional characteristics, as well as a system of functional mechanisms. Working memory is a multicomponent system, the functional organization of which ensures the implementation of the functions of storing and processing information [1,2].

The scheme of consolidation processes-consolidation of visual-figurative and semantic information is presented in Fig. 1.

The first stage is processing and storing information in working memory. Procedurally, the process of processing and initial preservation of information (both visual-figurative and semantic) is carried out through its direct reproduction. Visual-figurative information is reproduced through copying; semantic information is reproduced through oral reproduction of the text immediately after presentation by ear. In the process of processing, information is transformed into a primary mystical image (visual-figurative information) and semantic content (textual information). At the same time, it is natural to "collapse" the initial information while preserving its main (identifying) features. The storage of information in the RP is carried out using both short-term and long-term storage mechanisms. Short-term storage mechanisms are used for operational storage of information of particular importance for solving the current cognitive task.

After processing the information in the working memory system, it is stored in the form of transformed images in the structure of short-term memory. At the same time, it should be noted that short-term memory in this case acts as a kind of "transit" linking the stages of processing the initial information and its subsequent storage.

In the process of consolidation, which ensures the transition from short-term memory to long-term memory, there is also a transformation of stored information (both visual and semantic) in accordance with existing experience. The newly saved information is compared with the information already available in the long-term information storage. The result of the comparison is the fixation of key (object about significant identification) features in relation to the information already available in the experience (long-term storage). Long-term storage mechanisms are used to store information activated when solving a current cognitive task.

The subsequent extraction of information (referred to as the process of reconsolidation) is carried out from a long-term storage. At the same time, the information strengthened in the previous experience (both visual-figurative and semantic) is initially reconsolidated, which is transformed in the process of extraction taking into account the fixed object-significant identification features.

Any violations of working memory lead to a reduction in a person's ability to process information, make suboptimal decisions and, in general, to a decrease in adaptive potential.

Despite the fact that the analysis of clinical cases illustrates only the motor segment of this nosology (differentiation of the forms of the disease by the predominant clinical manifestations of motor disorders), it is in this segment that the presence of cognitive and mnemic features has not been investigated.

The aim of the study is to specify the mechanisms of transformation of the content to be memorized in the process of consolidation and reconsolidation in patients with PD.

Organization and methods of research. Under observation were 3 patients diagnosed with G20 "Parkinson's disease" (according to ICD-10), the average duration of the disease was 3.2 ± 0.29 years. All patients had secondary vocational education (technical profile). Levodopa preparations were received as a basic treatment (the average daily dose was 594.2+ 236.2 mg). The criteria for selecting patients for the analysis of specific clinical cases were: the age of patients from 60 to 65 years (the average age was 63.4 ± 1.49 years); male patients; the duration of the disease is not more than three years; clinical manifestations at the time of the study correspond to the second stage of PD (according to the Hen

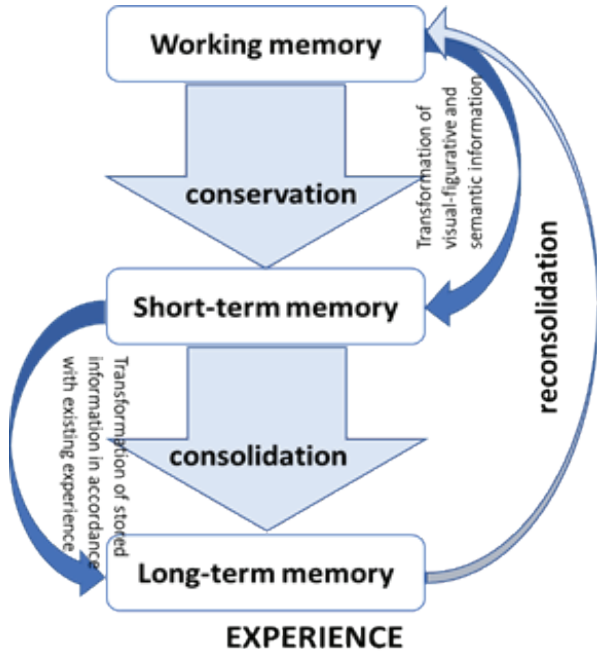

Fig. 1. Scheme of consolidation-deconsolidation processes of visual-figurative and semantic information

and Yara scale); absence of pronounced cognitive disorders (which in quantitative terms corresponds to indicators of at least 23 points on the MMSE scale). The PSP patient was diagnosed with a mixed (akinetic-rigid-tremulous) form of PD. The GAB patient was observed with an akinetic-rigid form. A tremulous form of PD was detected in an LNP patient.

At the first stage, the clinical examination included an assessment of somatic and neurological status. The degree of cognitive disorders was determined using the scale of a brief study of mental status (Mini-mental State Examination -MMSE).

The neuropsychological status was assessed by the neuropsychological research procedure, which includes a qualitative and quantitative analysis. The quantitative assessment was carried out according to the developed 0-3 scale (L. I. Wasserman, S. A. Dorofeeva, Ya. A. Meerson, 1997). The quantitative assessment was carried out according to the indicators "pace", "accuracy", "differentiation", where the dynamic component of activity was evaluated in the indicator "pace", in the indicator "accuracy" – operational, and in the indicator "differentiation" – motivational.

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The image and text from the epic of the Indians of Canada were offered as incentive material.

The reason for choosing the image (Fig. 2) was the reliable absence of this material in previous experience (a letter of the ancient Greek alphabet resembling an owl). The symbolic image (symbol) included four parts: "head", "trunk with leg", "wing", "leg". Elements were highlighted in each part of the symbolic image (for example, the "head" part contains two elements - the head itself and the inner part in the form of a "tick").

The instruction sounded as follows: when examining the image memory at the copying stage: "You have a certain image in front of you. Please copy it according to the sample." Then (after 40 minutes, 4 hours, 36 hours) the patients were given a deaf instruction: "Remember, we copied the image with you, draw it now, please, as you remember, as close as possible to the original. The evaluation of figurative memory was carried out according to four criteria: the integrity of the figure, the number of losses, the number of distortions, the number of stored elements.

The text from the epic of the Indians of Canada, presented in Russian, contained 79 semantic units (33 sentences, 1427 characters, 295 words). Semantic units are grammatical forms characterized by semantic content and implemented in various combinations of nouns as the main linguistic form with other forms (adjectives, verbs, pronouns). In the study of semantic memory, patients were offered the following instruction: "Now I will read the text to you. Listen to it and retell it as close to the text as possible." When the patient repeated the instruction, the text was not offered, it was suggested to recall the text without additional reliance on the stimulus. The evaluation of semantic memory takes place according to the criteria: the number of preserved sentences, the number of preserved semantic units, the number of distortions of sentences, the number of distortions of semantic units, the number of violations of the sequence of sentences, the number of violations of the sequence of semantic units. The following categories were taken as semantic units: object and attribute (who), object and time (when), object and action (what they did), object and place (where), as well as cause-and-effect relationships. To register the received data, a semantic map was developed and used, which made it possible to qualify errors in more detail and visually (two forms of errors were distinguished: replacement errors and loss errors).

The research results. As a result of the study of the processes of consolidation, deconsolidation of figurative memory, the following features were identified.

At the stage of copying a symbolic image, the transformation from a symbolic image to a figurative one is recorded as a general trend, regardless of the types of PD. The transformation of a symbolic image into a figurative one at the stage of memory preservation leads to the fact that a distorted image is initially fixed.

Minimal distortions of the visual image during copying were revealed in the akinetic-rigid form of PD (the GAB patient) (Fig. 3A). The patient correctly reproduces the number of image details, their size and relative location relative to each other. At the same time, it should be noted the overlap of lines, which is a specific feature of this particular form of PD (due to the general rigidity at the level of the graphical function, the patient repeatedly draws one line). In an LNP patient with a tremulous form of PD (Fig. 3B) already during rendering, there is a loss of image elements and distortion of their size. At the same time, the general outline of the image is preserved. In a patient with a mixed form of PD (Fig. 3B), we note already at the stage of drawing both the distortion of the silhouette as a whole and its individual details. A characteristic feature of rendering in this form is the repeated tracing of each of the image lines and the introduction of new image details that are absent in the original stimulus material.

At the next stage, when reproducing the visual image from memory 40 minutes after presentation, further distortion of the stored concretized image was revealed, mainly concerning the number of elements. As a general trend in three patients, regardless of the form of the disease, a simplification of the image was revealed, characterized by distortion of parts of the image with a decrease in the number of elements. All three patients revealed new (introduced) elements located mainly in the lower part of the image. Patients draw new elements in parts of the image, while the original elements present in the stimulus image are absent in the drawings of patients with PD (Fig. 4-I).

In the akinetic-rigid form of PD (GAB patient), new introduced elements are fixed in the form of additional lines partially or completely superimposed on each other (Fig. 4-I-A). These manifestations (overlapping image lines with each other under strong pressure) are a consequence of the manifestation of rigidity. With the tremulous form of PD (LNP patient), simplification of elements and their row-by-row arrangement is noted (simplified elements are depicted next to each other). The lines of the image partially intersect. As a result of the tremor, attempts to overlay lines lead to their multiplicity – some elements are drawn with a multiple

Fig. 2. Stimulus image for the study of implicit memory

line (Fig. 4-I-B). With a mixed form of PD (PSP patient), the patient adds new elements to the image, bringing them from the already existing image of the bird's memory. At the same time, parts of the image are clearly highlighted, such as the head, ears, beak and eyes, wing, paws (with an emphasis on the fingers) (Fig. 4-I-C). The pressure is uneven.

Memory reproduction of a figurative stimulus after 4 hours by patients with different forms of PD indicates that there is a transformation of the memory image (its reconstruction, according to Bartlett's terminology) with the loss of the original elements: combining several elements into one (with a tremulous form in a patient with LNP); introducing new additional elements (with akinetic-rigid and tremulous forms of PD). As a general trend in three patients, regardless of the form of the disease, a simplification of the image was revealed, characterized by a decrease in the number of parts with an increase in the number of elements: an increase in the number of lines that significantly enhance the boundaries of the image details (Fig. 4-II).

With a mixed form of PD, the simultaneous superimposition of new image elements that are absent in the original stimulus is clearly recorded (Fig. 4-II-B).

After 36 hours, regardless of the shape of the PD, there is a complete loss of the shape of the original symbolic information: the number of parts decreases to one (the figure itself); the number of parts also decreases to 1-2 (Fig. 4-III). At the same time, the trends identified during previous reproductions are preserved: layering of lines in akinetic-rigid (GAB patient) and mixed (PSP patient) forms of PD, one-linearity of the image in the tremulous form of PD (LNP patient). At the same time, it should be noted that in a patient with GAB and LNP, the number of details of the reproduced image is reduced to one (Fig. 4-III-A, 4-III-B), the patient has PSP - up to two (Fig. 4-III-C).

Thus, when extracting figurative information in patients with PD, regardless of the form of the disease (tremulous, akinetic-rigid, mixed), the transformation of the image into a specific image was established. It is established that already at the stage of copying (reproducing a symbol according to a visual pattern), characterizing the process of preserving information, there is a tendency to transform the symbol into a specific image ("bird", "owl"), which increases from stage to stage. As a result, there are not only distortions of the reproduced information up to its complete loss, but also simplification. There is a decrease in the number of image details, the accuracy of their reproduction decreases (the number of elements; their location both in the overall composition of the image and relative to each other; the shape and size of the elements are distorted), new elements that are missing from the original image are drawn.

When studying the processes of consolidation, deconsolidation of semantic memory in patients with PD, a text evaluation map was built for each patient, reflecting the quality of reproduction of semantic units in relation to their distribution according to text sentences (Fig. 5).

As a result of studying the processes of consolidation, reconsolidation of semantic memory in patients with PD, a complete loss of the semantic content of verbal information was revealed. When directly reproducing the text, a GAB patient with an akinetic-rigid form of PD significantly reduced the original text presented, while retaining its main idea. The loss of semantic content was 25%. It should also be noted that there are no distortions in the retelling of the text immediately after its presentation. In an LNP patient with a tremulous form of PD, when reproducing the text immediately after presentation, the loss of semantic content was 26.2%. The main idea of the text was also conveyed. During reproduction, the patient built simple short, mostly single-base sentences consisting of no more than four words. Distortions of semantic content were also not revealed. A PSP patient with a mixed form (akinetic-rigid-tremulous) PD during direct reproduction of the text demonstrated distortion of some semantic units (24 out of 79 original ones with adequate transmission of the general meaning of the reproduced text. At the same time, the loss of semantic content was 27%. It should also be noted, as with the tremulous form, the simplification of language structures: the patient retells the test using simple non-extended sentences, which, in turn, makes it difficult to convey semantic content.

40 minutes after the presentation of the text to patients, regardless of the form of PD, further loss of semantic content should be indicated. The number of semantic units was: in a PSP patient - 50.4%; in a GAB patient - 51.7%; in an LNP patient - 51.4%. With a mixed form of PD (patient PSP), the semantic content of only part of the sentences that make up the retelling reflected the semantic content of the original text (6 sentences). The remaining semantic units, describing mainly objects and actions occurring with them, have been distorted or replaced. A GAB patient with an akinetic-rigid form of PD in the process of retelling retained the original semantic content of the reproduced text in 11 sentences. But at the same time, it should be noted the repeated (two or three times) perseverative repetition of sentences. With the tremulous form of PD (LNP patient), the number of sentences in the retelling is 10, while descriptions of objects are predominant with minimal indication of their actions. The causal relationship is indicated by the patient only once. Distortions and substitutions of semantic content are recorded.

After 4 hours, patients, regardless of the form of PD, were able to reproduce 22-25% of the semantic content of the text they heard (PSP - 22.7%; GAB - 23.4%; LNP - 24.8%). At the same time, the enumeration of objects and their actions prevailed in the retelling. The substitution of objects presented in the source

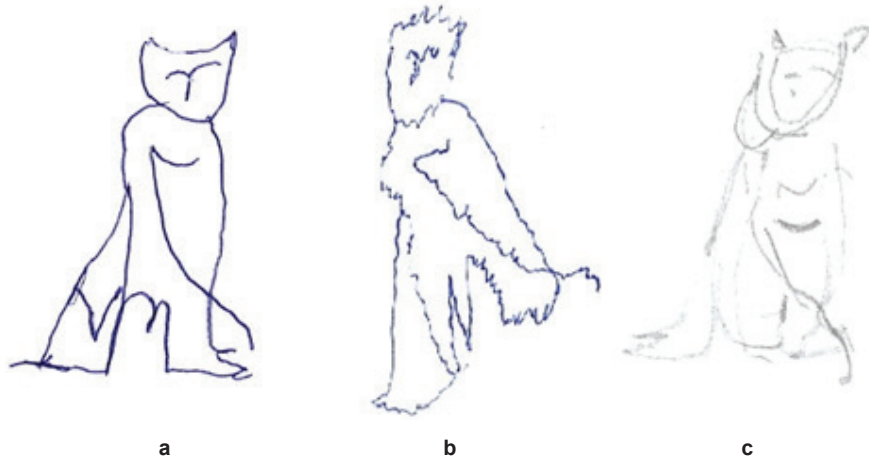

Fig. 3. Images of patients with PD in sketches. In Fig. 3 and 4: a - a GAV patient (an akinetic-rigid form of PD); b - a LDL patient (a tremulous form of PD); c - a PSP patient (a mixed form of PD)

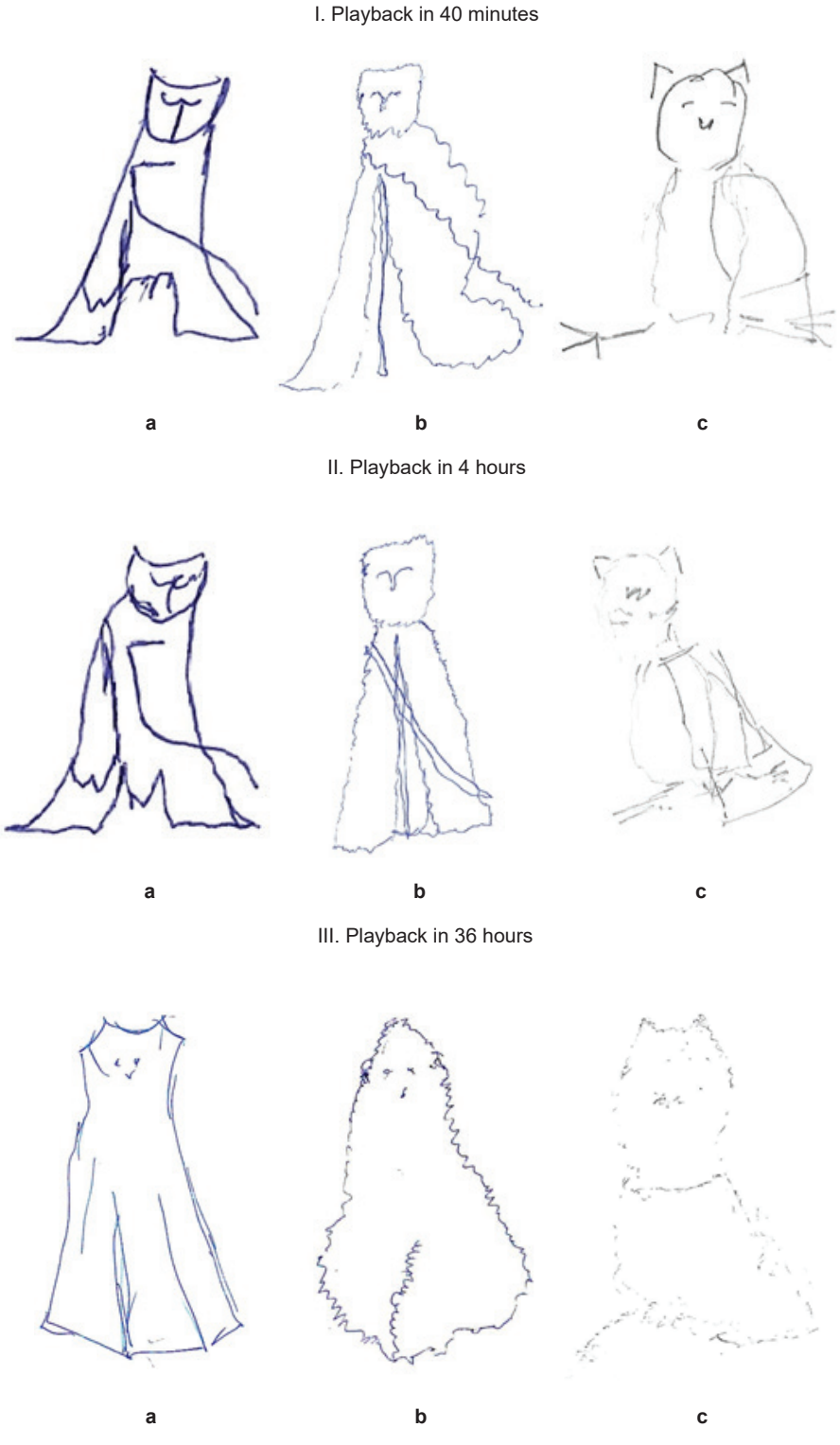

Fig. 4. Images of patients with PD in 40 min, 4h, 6h

text with their own content was clearly recorded in all three patients. The texts of the patients' retelling consist of simple monosyllabic sentences, including only the subject and predicate. At the same time, the construction of sentences is also not grammatically correct: inconsistency of sentence members is noted. With mixed (PSP) and akinetic-rigid (GAB) forms of PD, a perseverative tendency was revealed. When reproducing the text, patients repeatedly reproduce the composed sentences (the multiplicity is up to four repetitions). There were no causal relationships in full.

After 36 hours, all three patients with PD had a complete loss of semantic content. A PSP patient with a mixed form of PD as a retelling presented a text containing 8 simple, non-expanded single-base sentences that have nothing in common with the original text. 4 new objects have been introduced, and proposals have been submitted for their actions. There are no causal relationships in the retelling. In the akinetic-rigid form of PD (GAB patient), the text of the retelling contained 11 sentences, three of which were repeated twice each. The sentences were also simple, but, unlike the mixed form, had minor terms and were common. At the same time, there were no semantic units represented in the source text. There are also no causal relationships. With the tremulous form of PD (LNP patient), the volume of retelling was 9 simple monosyllabic unrolled sentences, with a minimal description of the actions of objects. At the same time, the semantic content of the source text in the retelling is missing in full. However, it should be noted the replacement (distortion) of the semantic content of the source text. Unlike the previous two patients, LNP describes three causal relationships in its retelling.

At the first stage, immediately after the presentation, the loss of content was 25-27%. Patients lost a significant part of semantic units when retelling the text. When reproducing text content after 40 minutes, the loss of semantic units was 50-52%. After 4 hours, patients were able to reproduce only 22-25% of the semantic content of the text they heard. At the same time, the enumeration of objects and their actions prevailed in the retelling. There were no causal relationships in full. After 36 hours, we can state the complete loss of 100% of the semantic content. The errors of substitutions were predominant in this case. To present a retelling, patients "invented" objects, described their actions and built causal relationships. But even when reproducing the "invented" text, the number of words (82 compared to the original 295) and semantic units (22 compared to the original 79) was significantly less than the original version. Patients demonstrated monosyllabic recollection, unrelated to the text. The results obtained indicate the suppression of verbal information in patients with PD.

Thus, the described clinical cases in the aspect of the peculiarities of the implementation of the process of consolidation-reconsolidation of visual-figurative and semantic memory allow us to identify and describe general and specific trends, taking into account the form of the disease in PD (Fig. 6).

As a general trend, in three patients with PD, regardless of the form of the dis-

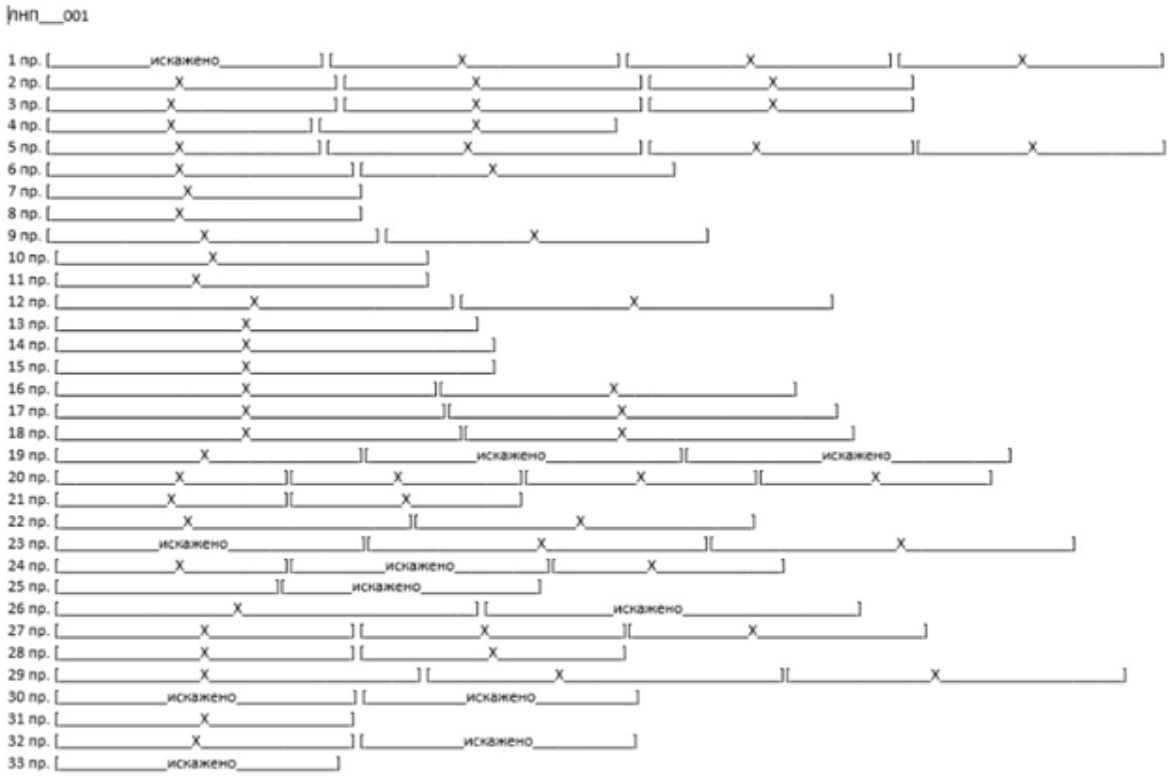

Fig. 5. An example of the text evaluation card (playback in 36 hours)

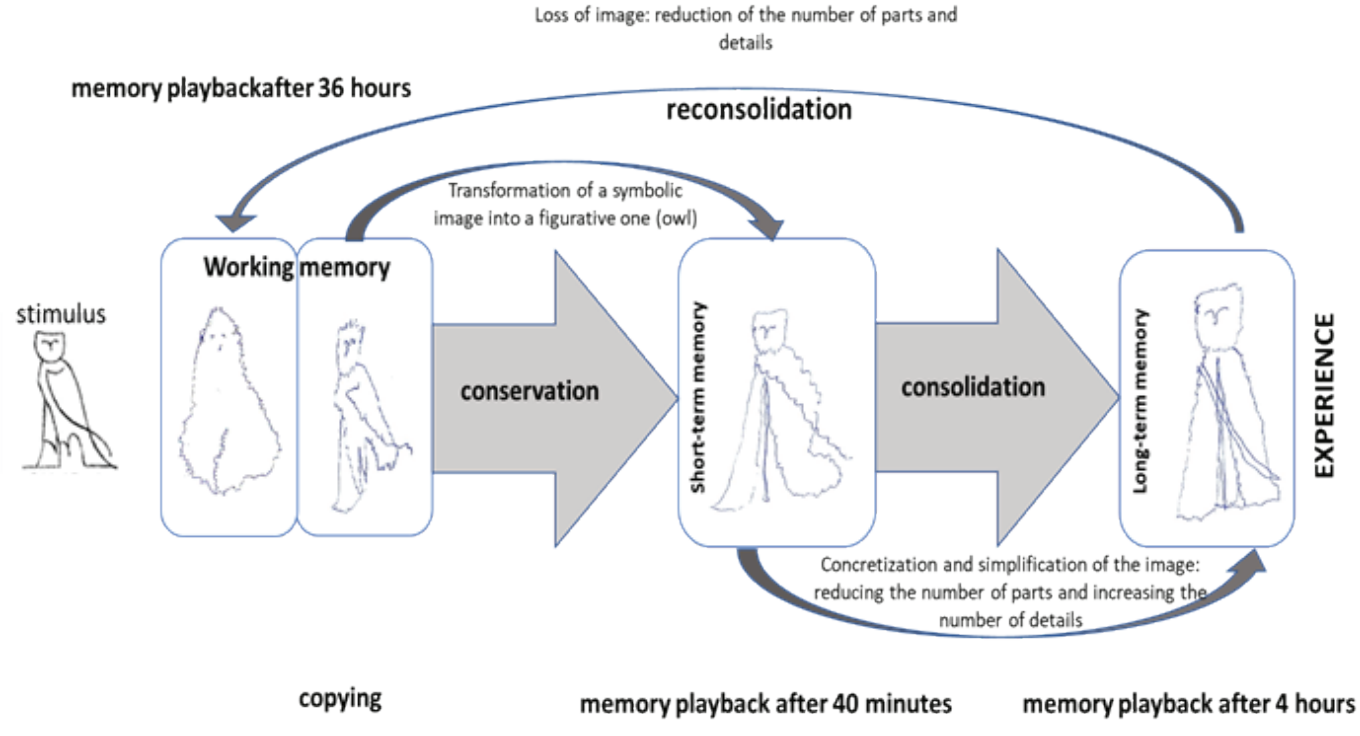

Fig. 6. The scheme of the study of consolidation processes-consolidation of visual-figurative and semantic information in PD

ease, in the absence of cognitive impairment, a complete loss of both figurative and semantic content is recorded. This indicates a violation of the processes of consolidation-reconsolidation of memory traces in PD. This trend may be due to the fact that already at the stage of information preservation (when copying a symbol from a visual sample, as well as when directly reproducing textual semantic content), its distortion occurs. A symbolic image is reduced to a specific image based on the principle of finding similarities with images of representations already available in experience and stored in long-term memory. Semantic content is also distorted by substitution of objects and transformation.

The presence of neurodegenerative changes due to the pathological process in PD significantly changes the quality (volume and accuracy) of the extracted information or leads to its complete loss. In patients, regardless of the form of the disease (tremulous, akinetic-rigid or mixed), a significantly smaller amount of information (both auditory and visual-figurative) is consolidated. This trend is correlated with a pronounced distortion in the process of extracting information. Taking into account the level and profile of education of the described patients, as well as the duration of their involvement in professional activity (the duration of the period from the moment of receiving vocational education to the manifestation of PD), it should be noted that manual (motor) memory is mainly activated during secondary vocational education of a technical profile. Consequently, this type of memory, which is specialized, was not included in the study.

In practical terms, the results obtained should be considered as tasks for inclusion in the processes of social rehabilitation of the mnemic component in the processes of consolidation and reconsolidation.

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